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Drugs for the treatment of secondary hyperparathyroidism and hyperphosphataemia

Targeted Literature Review

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Contents

Summary

This summary is not a position statement and does not represent recommendations from the NSW Therapeutic Advisory Group. It is a summary of the main points from the reviews, guidelines and articles identified in a targeted review of the published literature and presented in the main text of this document.

Background

Elevated parathyroid hormone (PTH) levels from secondary hyperparathyroidism (SHPT) are seen in around 40% of patients on dialysis for chronic renal failure. Very high levels of PTH develop in 1 in 10 patients on dialysis, defined as uncontrolled hyperparathyroidism (>800 pg/mL), with nodular hyperplasia of the parathyroid glands. In such cases, parathyroidectomy may be considered. Elevated PTH leads to high turnover bone disease (including the typical features of osteitis fibrosa) and may be present in up to 75% of people on dialysis resulting in raised serum calcium, phosphorus and calcium-phosphorus product (calcium-phosphate product). Fracture risk may be increased. Secondary hyperparathyroidism (SHPT) may also be complicated by calcification at a range of sites, including cardiovascular calcification. Left ventricular hypertrophy and dysfunction may also result from raised PTH levels. Such effects contribute to the increased overall and cardiovascular mortality noted in people with chronic kidney disease (CKD).

Prophylaxis is considered appropriate in asymptomatic patients with hyperparathyroidism. International guidelines suggest target levels for serum PTH, calcium and phosphate concentrations. The main treatment approaches are to reduce serum phosphate by using phosphate binding agents (and dietary restriction) and to reduce PTH by supplementation of vitamin D. The optimum choice of phosphate binding agent is unclear. Aluminium-containing agents may contribute to increased aluminium toxicity and are discouraged. Calcium-containing binders were the mainstay of treatment until concerns about associated risk of vascular calcification in people on haemodialysis arose. (Adapted from http://www.hta.ac.uk/project/1499.asp)

Cinacalcet

Cinacalcet (Sensipar™) is approved by the TGA for treating the biochemical manifestations of SHPT in patients with end-stage renal disease (ESRD) receiving dialysis. It operates by increasing parathyroid sensitivity to serum calcium thus reducing secretion of PTH, which, in turn, reduces serum calcium.

Treatment recommendations

A Cochrane review (2006) of 8 randomised controlled trials (RCTs - all presented in the Clinical Studies section of this document) concluded that calcimimetic treatment of SHPT leads to significant improvements in biochemical parameters associated with increased mortality, cardiovascular risk and osteitis fibrosa. They state it can be considered of potential but currently unproven benefit to patient-based outcomes including cardiovascular mortality, renal osteodystrophy and fracture.

CARI (Caring for Australasians with Renal Impairment) guidelines (April 2006) state that cinacalcet should be used in conjunction with standard therapies to improve the proportion of dialysis patients who achieve target serum levels of PTH, calcium, phosphate and calcium-phosphate product. They note however, that rates of treatment withdrawal and the incidence of nausea and vomiting are higher for cinacalcet than for placebo.

CARI guidelines also state that cinacalcet therapy of SHPT may reduce rates of parathyroidectomy and fracture but has not been shown to influence hospitalisation, cardiovascular mortality, all-cause mortality or quality of life. Clinical Evidence (2007) adds that a pooled analysis found cinacalcet reduced the risk of cardiovascular hospitalisation, fracture, and parathyroidectomy compared with placebo. It found no significant difference in overall mortality between cinacalcet and placebo though safety outcomes were not primary

outcomes of interest in the studies (see Cunningham et al 2005 abstract).

CARI guidelines add that cinacalcet should be available for use by patients who require, but are medically unfit for parathyroidectomy or are waiting for elective parathyroidectomy.

The National Institute for Health and Clinical Excellence (NICE) [2007 review] do not recommended cinacalcet for the **routine treatment** of SHPT in patients with ESRD on maintenance dialysis therapy. They do recommend it for the treatment of **refractory SHPT** in patients with ESRD (including those with calciphylaxis) who have 'very uncontrolled' plasma levels of intact PTH (defined as greater than 85 pmol/litre [800 pg/ml]) that are refractory to standard therapy, and a normal or high adjusted serum calcium level, **and** in whom surgical parathyroidectomy is contraindicated (in that the risks of surgery are considered to outweigh the benefits). They add that response to treatment should be monitored and treatment continued only if a reduction in iPTH of 30% or more is seen within 4 months of treatment.

Cochrane, CARI and NICE all state that many other studies are required including RCTs over longer time periods to assess efficacy and safety of cinacalcet in ESRD. Trial endpoints should include cardiovascular and all-cause mortality, hospitalisation, fracture and bone mineral density and the relationship between biochemical disruption in SHPT and these clinical outcomes needs to be elucidated.

The NICE review did not identify any cost-effectiveness studies but they did review unpublished economic models, which showed incremental cost-effectiveness ratios (ICERs) of £35,600 to £61,900 per quality-adjusted life year (QALY) gained (see body text for specifics). NICE concluded that cinacalcet was unlikely to be a cost-effective use of NHS resources in the treatment of SHPT in patients with ESRD.

Use in children

No evidence was found for the use of cinacalcet in children.

Phosphate Binders

Sevelamer (Renagel™) is approved by the TGA for the management of hyperphosphataemia in adult patients with stage 4 and 5 CKD. It is a non-calcium containing phosphate binder which also reduces serum lipid levels.

Lanthanum (Fosrenol™) is approved by the TGA for the treatment of hyperphosphataemia in adults with chronic renal failure (CRF) on haemodialysis or continuous ambulatory peritoneal dialysis.

Treatment recommendations

CARI guidelines (2006), based on National Health and Medical research Council (NHMRC) levels of evidence, recommend the use of sevelamer when levels of calcium are above the target range or when levels of PTH are below the target range, but this is only based on opinion – ie, low level of evidence. They cite RCTs, which are included in the more comprehensive Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review published in 2006. This review included 10 RCTs in its assessment with a total of 3,025 participants. They found no convincing evidence that substituting sevelamer for calcium-based binders reduced all-cause mortality, cardiovascular mortality, hospitalisation, or the frequency of symptomatic bone disease, and no evidence that sevelamer improved quality of life. While sevelamer therapy resulted in a smaller decrease in phosphate levels, and fewer episodes of hypercalcaemia, compared with calcium-based phosphate binders, the clinical significance of this is still unknown. CARI comment that, in patients prone to hypercalcaemia, there may be a role for sevelamer but it is still unclear whether sevelamer is associated with less calcification in such cases and whether the reduction in vascular calcification is due to lower calcium levels or by concomitant improvement in lipid profile. They state that recent Japanese studies have shown good

phosphate control and patient tolerability with a combination of sevelamer and $CaCO_3$ (see Koiwa et al 2005 abstract)

CADTH state that the cost effectiveness of sevelamer is still uncertain. A cost per QALY gained ranging from $127,000 to $278,100 was calculated, and the authors suggested a possible restriction to patients ≥65 years old.

CARI comment that lanthanum is an effective binder of dietary phosphate compared with placebo (Joy & Finn 2003) and similar to CaCO3, with no trend towards adynamic bone disease (D'Haese et al 2003). There are no RCTs comparing lanthanum with sevelamer. A recent Prescrire review states that lanthanum is no more effective than other phosphate binders in terms of effects on mortality, incidence of fractures, or blood phosphorus level. In trials, adverse events were more frequent with lanthanum than with the other phosphorus chelators (gastrointestinal disorders, headaches, seizures, and encephalopathy). Longer-term studies suggest lanthanum is well tolerated (see Altmann et al 2007, Finn 2006, Finn & Joy 2005). The Scottish Medicines Consortium (2007 review) adds that lanthanum carbonate takes more than ten years to reach steady state in bone and that accumulated lanthanum would be cleared slowly if discontinued. Prescrire conclude that when a phosphorus chelator is needed to treat hyperphosphataemia in dialysis patients with CRF, calcium carbonate is the first choice and sevelamer remains the best alternative.

CARI suggest that future research needs to include mortality studies with sevelamer and lanthanum in comparison with calcium salts. Also, a cost-benefit analysis of sevelamer vs. calcium salts should be undertaken as well as bone biopsy studies of patients treated long-term with lanthanum to satisfy safety concerns.

Use in children

Published studies on the use of phosphate binding agents in children are scarce. In general, the evidence from adult studies is not necessarily directly applicable to paediatric age groups (especially younger ages). The need for longer-term effectiveness and safety data on relevant clinical (eg, bone disease, vascular calcification, mortality) versus surrogate (eg, calcium and phosphate levels) outcomes is even more relevant in paediatrics because of the likelihood of a different (and, currently, largely unknown) adverse effect profile compared with adults and the fact that younger patients will be on treatment for a relatively longer time. Civilibal et al showed that that serum phosphorus and the cumulative exposure to calcium-containing phosphate binders were the most significant independent predictors in the development of coronary artery calcification in children with ESRD. Thus, non-calcium based phosphate binders might have an advantage in this regard; however, the small study by Pieper et al showed that sevelamer may increase metabolic acidosis compared with calcium acetate. The clinical significance of this on factors such as growth and development are as yet unknown and larger controlled trials are required.

Introduction

This document contains summary data from published reviews, guidelines and articles to help drug and therapeutic committees make decisions about use of cinacalcet, sevelamer and lanthanum. It is not a *Position Statement* and does not represent recommendations from the NSW Therapeutic Advisory Group.

The data was collated after searching websites of organizations/publications including Cochrane, National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), The Canadian Agency for Drugs and Technologies in Health (CADTH), Clinical Evidence, National Heath Service Health Technology Assessment Programme (NHS HTA Programme), National Guideline Clearing House (NGC), Scottish Medicines Consortium (SMC), Medical Journal of Australia (MJA), National Health and Medical research Council (NHMRC) and Medscape (March 2007). Specialist nephrology guidelines were also sourced: Caring for Australiasians with Renal Impairment (CARI), Kidney Disease Outcomes Quality Initiative (K/DOQI), British Renal Association, Canadian Society of Nephrology, European Best Practice Guidelines (all accessible from www.kdigo.org).

An Embase search (1996 to 2007 week 15) was also performed using the following MESH terms:
a. “kidney disease” or “chronic kidney disease” or “hyperphoshphatemia” or “secondary hyperparathyroidism” (24764 results).
b.”cinacalcet” or “calcimimetic agent” or “r568” or “calcium channel stimulating agent” or “amg073” or “N[3(2 chlorophenyl)propyl] 1(3 methoxyphenyl)ethylamine” or “calcimimetic agent” or n (3[2 chlorophenyl]propyl) alpha methyl 3 methoxybenzylamine” (1016 results)
c. a and b combined (299 results)
d. “sevelamer” or “lanthanum carbonate” or “lanthanum” (2095 results)
e. a and d combined (389 results)
f. “case control studies” or “cohort analyses” (50889 results).
g. (a or e) and f combined (11 results – this search was performed to locate additional safety information not otherwise found in the other searches).
h. (b or d) and (child or adolescent or infant) – this search was conducted to find any paediatric studies with cinacalcet or lanthanum or sevelamer. It yielded no more results than those identified in the other searches).
All of the results were assessed, and abstracts of the selected papers are presented in this document.

Summaries of systematic reviews and guidelines are reproduced verbatim where possible, but may have been edited for conciseness. The abstracts of review articles and clinical studies are taken verbatim from Embase (background information may have been deleted) and are presented chronologically (latest studies first). Full references are given so that readers may consult these if required.

Systematic Reviews and Guidelines

Cinacalcet

Clinical Evidence (2007 edition)

Source: Hall YN, Chertow GM. End stage renal disease. Available at Books @ OVID, http://gateway.ut.ovid.com/gw1/ovidweb.cgi

Summary of main findings:

Two randomized controlled trials (RCTs) found that cinacalcet improved control of secondary hyperparathyroidism (SHPT) compared with placebo at 26 weeks.

Benefits

Cinacalcet versus placebo: The first RCT (Block et al 2004) compared cinacalcet versus placebo for 26 weeks (efficacy was measured from week 13 to week 26). It found that cinacalcet significantly improved control of SHPT compared with placebo. The second RCT (Lindberg et al 2005) found that cinacalcet significantly improved control of SHPT compared with placebo.

Harms

Cinacalcet versus placebo: The first RCT found that adverse events were common and occurred at a similar frequency with cinacalcet and with placebo. The second RCT reported a higher incidence of gastrointestinal side effects in people receiving cinacalcet compared with placebo

Comment

The second RCT found that the efficacy of cinacalcet was similar for peritoneal dialysis and haemodialysis. We identified one pooled analysis of safety data (Cuningham et al 2005) from four RCTs, two of which were phase II trials and had participant overlap with the two RCTs described in the benefits section above, and therefore are not reported separately. The pooled analysis (1184 adults with end-stage renal disease [ESRD] receiving dialysis) found that cinacalcet reduced the risk of cardiovascular hospitalisation, fracture, and parathyroidectomy compared with placebo. It found no significant difference in overall mortality between cinacalcet and placebo. Such results should be interpreted with caution because the safety outcomes were not primary outcomes of interest in the studies. Further prospective studies will be needed to evaluate whether reductions in PTH, calcium, and phosphorus concentrations favourably influence cardiovascular health and overall survival.

NICE

Source: www.nice.org.uk Cinacalcet for the treatment of SHPT in patients with ESRD on maintenance dialysis therapy. January 2007.

Summary of main findings:

Guidance

1. Cinacalcet is not recommended for the routine treatment of SHPT in patients with ESRD on maintenance dialysis therapy.
2. Cinacalcet is recommended for the treatment of refractory SHPT in patients with ESRD (including those with calciphylaxis) only in those: who have 'very uncontrolled' plasma levels of intact PTH (defined as greater than 85 pmol/litre [800 pg/ml]) that are refractory to standard therapy, and a normal or high adjusted serum calcium level, **and** in whom surgical parathyroidectomy is contraindicated, in that the risks of surgery are considered to outweigh the benefits.
3. Response to treatment should be monitored regularly and treatment should be continued only if a reduction in the plasma levels of intact PTH of 30% or more is seen within 4 months of treatment, including dose escalation as appropriate.

Clinical effectiveness

Seven RCTs in people with hyperparathyroidism secondary to ESRD who were receiving dialysis were found. Significant improvements in mean levels of PTH, calcium, phosphorus and the calcium-phoshporus product (calcium-phosphate product) with cinacalcet were found in most of the studies. A pooled analysis of the 3 largest RCTs (n = 1136) showed that target mean intact PTH levels (<26.5 pmol/litre [250 pg/ml]) were reached in 40% of

patients randomised to cinacalcet, compared with 5% of patients receiving placebo ($p < 0.001$). Significantly more patients who were treated with cinacalcet had a reduction of at least 30% in mean intact PTH levels compared with those receiving standard care alone in all RCTs. A post-hoc analysis of pooled data from 4 RCTs designed to investigate changes in biochemical markers (n = 1184) assessed the effects of cinacalcet compared with placebo on the clinical outcomes of fracture, cardiovascular hospitalisation, all-cause hospitalisation, parathyroidectomy and mortality. No statistically significant differences were seen in overall mortality or all-cause hospitalisation. However, statistically significant differences were observed in fracture, cardiovascular hospitalisation, and parathyroidectomy based on follow-up of 6–12 months. This analysis also reported HRQOL improvements.

Consideration of the evidence

The clinical trials of cinacalcet showed that it was effective in reducing levels of PTH and other biochemical markers, including serum calcium and phosphorus. A reduction in adverse clinical outcomes associated with raised PTH levels, such as bone fracture and cardiovascular hospitalisation, had been observed in a post-hoc analysis of pooled safety data from several trials. However, these trials were not designed to demonstrate the clinical benefits of treatment in terms of a reduction in adverse events, and there was a lack of data relating to long-term treatment with cinacalcet. The Committee was aware of observational evidence to suggest that there is a relationship between levels of PTH, calcium and phosphate, and adverse clinical outcomes. However, it noted that there is considerable uncertainty about the extent to which intervening to correct derangements in the levels of PTH, calcium and phosphate (in particular by lowering PTH levels) is effective in reducing the risk of the adverse outcomes. The Committee also noted that many other factors relating to ESRD and its underlying causes contribute to the increased risk of serious adverse events for people on dialysis, and that these add to the uncertainty in predicting clinical benefits from changes in surrogate markers. Although cinacalcet can reduce the severity of major adverse events associated with raised PTH levels, it does not replace the need for dietary restrictions and the use of other medications such as phosphate binders and vitamin D sterols.

Recommendations for further research

The Committee identified a need for long-term clinical studies that are designed to evaluate the effects of cinacalcet on clinical outcomes (in particular, fracture and cardiovascular events) in people with ESRD. Studies to establish the multivariate relationship between biochemical disruption in SHPT and these clinical outcomes are also recommended. The Committee also noted that more research is needed on the effects of cinacalcet in people with ESRD with particular clinical needs, specifically people with refractory secondary (or tertiary) hyperparathyroidism, people awaiting kidney transplants from living donors, people with calciphylaxis, people with recurrent hyperparathyroidism after parathyroidectomy, and people in whom surgical parathyroidectomy is contraindicated.

Cost effectiveness

The systematic review did not identify any published cost-effectiveness studies. An economic model and separate cost–consequence analysis were submitted by the manufacturer of cinacalcet, and the Assessment Group developed its own economic model. The manufacturer's model resulted in an incremental cost-effectiveness ratio (ICER) of £35,600 per quality-adjusted life year (QALY) gained. The Assessment Group's approach differed and they calculated the ICER for cinacalcet at £61,900 per additional QALY, though 2 further scenarios produced ICERs of £43,000 and £38,900 per QALY gained, excluding dialysis costs. Other analyses looked at the cost effectiveness of two strategies for discontinuing cinacalcet in people whose PTH levels were not controlled by treatment, and produced ICERs of £44,000 and £57,400 per QALY. The manufacturer also refined their analysis based on strategies for adjusting dosage according to PTH levels and treatment discontinuation. The Committee concluded that cinacalcet was unlikely to be a cost-effective use of NHS resources in the treatment of SHPT in patients with ESRD.

Also, they were not persuaded that these treatment strategies were clinically practicable, and did not consider them an acceptable approach to maximising the clinical and cost effectiveness of treatment with cinacalcet.

Cochrane

Source:
www.mrw.interscience.wiley.com/cochrane
Strippoli GFM, Tong A, Palmer SC, et al. Calcimimetics for SHPT in chronic kidney disease patients. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD006254.

Summary of main findings:

Main results
This review evaluated the benefits and harms of calcimimetics for the prevention of secondary hyperparathyroid bone disease (including osteitis, fibrosa cystica and adynamic bone disease) in dialysis patients with CKD. Eight studies (1429 patients) were identified, which compared a calcimimetic agent plus standard therapy to placebo plus standard therapy. The end of treatment values of PTH (pg/mL) (MD -290.79, 95% CI -360.23 to -221.34), serum calcium (mg/dL) (MD -0.85, 95% CI -1.14 to -0.56), serum phosphorus (mg/dL) (MD -0.29, 95% CI -0.50 to -0.08) and the calcium-phosphate product (mg^2/dl^2)(MD -7.90, 95% CI -10.25 to -5.54) were significantly lower with calcimimetics compared to placebo. There was no statistically significant reduction in the risk of all cause mortality with calcimimetics compared to placebo/no treatment (5 trials, 1285 patients: RR 0.75, 95% CI 0.30 to 1.88). There was a significant increase in achieving a greater or equal to 30% decrease in mean PTH level with calcimimetics compared to placebo/no treatment (4 trials, 1284 patients: RR 4.49, 95% CI 3.04 to 6.64). There were no reported episodes of fractures in the included studies. There was no statistically significant increase in the risk of hypocalcaemia with calcimimetics compared to placebo/no treatment (4 trials, 868 patients: RR 2.89, 95% CI 0.71 to 11.73). There was no statistically significant reduction in the risk of parathyroidectomy with calcimimetics compared to placebo/no treatment (*analysis 01.11* (1 trial, 395 patients): RR 0.07, 95%CI 0.00 to 1.43). No other significant effects on patient-based endpoints were demonstrated except for the risk of hypotension which was significantly reduced with calcimimetics compared to placebo (RR 0.53, 95%CI 0.36 to 0.79).

Conclusions
The authors concluded that calcimimetic treatment of SHPT leads to significant improvements in biochemical parameters that observational studies have shown to be associated with increased mortality, cardiovascular risk and osteitis fibrosa. The authors stated several reservations relating to the current RCTs (including trial design, duplicate publication and study duration) and said that calcimimetic therapy of SHPT can be considered of potential but currently unproven benefit to patient-based outcomes including cardiovascular mortality, renal osteodystrophy and fracture. RCTs with adequate power and longer treatment duration are required to determine the most appropriate use of this important new class of drugs.

Surrogate validation
The argument in favor of calcimimetic use hinges on the acceptance of improvements in Ca-P metabolism and levels of PTH as valid surrogates of clinically important outcomes such as mortality. However, not all surrogates are valid proxies of clinically important patient-centered outcomes. In order for a surrogate to be valid, two criteria must be met. First, there must be a strong, independent and consistent association between the surrogate and the clinically important outcome, which comes from observational studies. For calcium, phosphorus and PTH this criterion has been met from a number of large-scale cohort and cross sectional studies. Second, and more importantly, for a surrogate to be valid there must also be evidence that using an intervention changes a surrogate (eg, reduction of PTH with a calcimimetic) and results in an expected change in the patient-based outcome distal to the surrogate in the same causal pathway for the disease in question (e.g. reduction of deaths with a calcimimetic). This criterion requires a RCT, which measures both the surrogate and the hard endpoint. Our study has shown that the second criterion has not yet been met for

calcimimetics. Critics of the second criterion argue that it is too stringent and will mean potentially life-saving interventions will be withheld. Proponents invoke the usual arguments for superiority of RCTs compared with observational studies (selection bias and unmeasured confounders) to estimate the true effects of interventions. In addition some interventions that positively affect a surrogate have been reported to have possible harmful effects on the major patient-based outcome. A recent example is that high dose erythropoietin increases hemoglobin levels in patients with metastatic breast cancer but has also been associated with an increase in the risk of death and disease progression in this population. Such results suggest that validation of surrogates in disease specific populations, should be mandatory when adopting novel interventions and that trial results based on unvalidated surrogates should be used cautiously.

CARI (Caring for Australasians with Renal Impairment)

Source: www.cari.org.au Use of calcimimetic drugs (2006).

Guidelines (NHMRC levels of evidence):

a. Treatment with cinacalcet reduces levels of PTH, calcium, phosphate and the calcium-phosphate product in patients with SHPT due to dialysis-dependent CKD. (Level II evidence)
b. Treatment with cinacalcet is not reported to influence requirements for standard drug therapy of SHPT. However, a greater proportion of patients treated with the addition of cinacalcet achieve K/DOQI and CARI target levels of PTH, calcium, phosphate and the calcium-phosphate product. (Level II evidence)
c. When using cinacalcet, patients on dialysis with mild or moderate SHPT are more likely to achieve target levels of PTH, calcium, phosphate and the calcium-phosphate product than patients with severe SHPT. (Level II evidence)
d. Rates of treatment withdrawal and the incidence of nausea and vomiting are higher for cinacalcet than for placebo. (Level II evidence)

Suggestions for clinical care (based on Level III and IV evidence):

The use of cinacalcet in patients on dialysis is associated with a reduction in bone turnover and bone marrow fibrosis. (Level III evidence)
Cinacalcet should not be used in patients on dialysis with intact-PTH levels below the target range (Opinion). The use of cinacalcet may be associated with development of adynamic bone disease when iPTH values are < 10.6 pmol/L (< 100 pg/mL). (Level III evidence)
Cinacalcet therapy of SHPT may reduce rates of parathyroidectomy and fracture but has not been shown to influence hospitalisation, cardiovascular mortality, all-cause mortality or quality of life. (Post-hoc analysis of Level II evidence)
A therapeutic trial of cinacalcet is warranted for dialysis-dependent patients with SHPT when sustained levels of iPTH and the calcium-phosphate product remain above target levels despite optimal standard therapy. (Opinion)
Parathyroidectomy should be considered for patients given a therapeutic trial of cinacalcet who do not achieve target levels of PTH, calcium, phosphate or the calcium-phosphate product. In particular, parathyroidectomy should be considered for patients with sustained levels of iPTH > 85 pmol/L (> 800 pg/mL), or sustained levels of iPTH > 50 pmol/L (> 470 pg/mL) in addition to levels of corrected serum calcium, phosphate or the calcium-phosphate product above the target ranges. (Opinion)
Cinacalcet should be available for use in patients who require but are medically unfit for parathyroidectomy, or who are waiting for elective parathyroidectomy. (Opinion)

Implementation and audit

In Australia and New Zealand, the use of cinacalcet will depend on availability and the cost to dialysis patients. Cinacalcet should be used in conjunction with standard therapies to improve the proportion of dialysis patients who achieve target serum levels of PTH, calcium, phosphate and the calcium-phosphate product, as described elsewhere in the guidelines. Cinacalcet

should be available for use by patients who require, but are medically unfit for parathyroidectomy or are waiting for elective parathyroidectomy (see Suggestions for Clinical Care).

Suggestions for future research:

RCTs over longer time periods are needed to assess the continuing efficacy and safety of cinacalcet. Trial endpoints should include cardiovascular and all-cause mortality, hospitalisation, fracture and bone mineral density. A longer study with larger patient numbers is required to assess influences of cinacalcet on bone histomorphometry. The potential for cinacalcet to be used at earlier stages of CKD and following renal transplantation requires evaluation. To date, calcimimetics have been evaluated as an addition to standard therapy but studies to assess cinacalcet plus lower dose vitamin D are underway. An evaluation of cinacalcet versus standard therapies would be useful, particularly in early CKD when cinacalcet may reduce progression of parathyroid hyperplasia in addition to improving the attainment of biochemical targets.

NHS Health Technology Assessment Programme

Source: http://www.hta.ac.uk/project/1499.asp
The clinical and cost-effectiveness of cinacalcet hydrochloride for the treatment of SHPT in patients with ESRD on maintenance dialysis therapy.

Details:

This report is due to be published in May 2007. It has been commissioned by the HTA programme on behalf of NICE on a call-off contract basis. This project will draw together all relevant evidence on cinacalcet in a systematic review. It will also assess whether the introduction of cinacalcet is likely to represent good value for money to the NHS.

KDIGO (Kidney Disease: Improving Global Outcomes)

Source: www.kdigo.org Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease-Related Mineral and Bone Disorders (CKD-MBD).

Details:

This report is due to be published in 2008. The major issues to be addressed will be to find: the most sensitive and specific biochemical, bone and calcification tests for diagnosis of CKD-MBD; target levels for biochemical measures of CKD-MBD; the prevalence of CKD-MBD at various stages of CKD; the validity of the classification of CKD-MBD in predicating morbidity and mortality; the most efficacious and safe treatment options for the various components of CKD-MBD.
Treatment options to be assessed will be:
A. Treatment strategies for hyperphosphatemia
Which therapy is best for the control of hyperphosphatemia?
What are the major side effects of oral phosphate binders?
What role do non-binder therapies play?
B. Treatment strategies for hyperparathyroidism
Which therapy (oral calcium supplements, vitamin D oral vs. IV vs. type, calcimimetics, direct parathyroid injection of active vitamin D compounds, parathyroidectomy) is best for lowering elevated PTH, avoiding over-suppressed PTH, [minimizing] side effects?
C. Treatment strategies for bone:
What is the efficacy of standard anti osteoporotic therapies including bisphosphonates, calcitonin, estrogen, SERMs, and intermittent PTH on bone mineral density by DEXA, qCT and on bone fractures?
What impact do therapies for control of serum phosphorus, calcium, and PTH have on bone as assessed by histology, DEXA, or qCT, on bone fractures and strength?
D. Treatment strategies for vascular calcification:
What impact do therapies for control of serum phosphorus, calcium, and PTH have on vascular calcification?
What impact do traditional therapies for atherosclerosis (i.e. statins) have on vascular calcification?

Phosphate Binders

Clinical Evidence (2007 edition)

Source: Hall YN, Chertow GM. End stage renal disease. Available at Books @ OVID, http://gateway.ut.ovid.com/gw1/ovidweb.cgi

Summary of main findings:

One RCT found that sevelamer reduced the progression of coronary artery and aortic calcification compared with calcium salts at 52 weeks. One crossover RCT found no difference in reduction of serum phosphorus between sevelamer and calcium acetate. The two RCTs found that sevelamer reduced serum low density lipoprotein cholesterol levels and the incidence of hypercalcaemia compared with calcium salts. We found no RCTs comparing sevelamer versus aluminium or lanthanum carbonate.

Benefits

Sevelamer versus calcium: We found two RCTs. The first multicentre RCT (open label; 200 adults with ESRD) compared sevelamer versus calcium salts (calcium carbonate and calcium acetate) for 52 weeks. It found that sevelamer significantly reduced the progression of coronary artery and aortic calcification (as measured by electron beam tomography) compared with calcium salts at 52 weeks. It also found that serum low density lipoprotein (LDL) cholesterol levels significantly decreased with sevelamer compared with calcium salts after 52 weeks. The second RCT (open label, crossover trial with 2 week hout period; 83 adults on maintenance haemodialysis) compared sevelamer versus calcium acetate for 8 weeks. The study did not present the results before crossover. It found no significant difference between groups in the reduction of serum phosphate from baseline at the end of treatment. In addition, serum LDL cholesterol levels decreased significantly more with sevelamer than with calcium acetate. We found no RCTs.

Sevelamer versus lanthanum carbonate: We found no RCTs.

Harms

Sevelamer versus calcium: The first RCT found that both sevelamer and calcium salts were well tolerated. Significantly more people experienced at least one hypercalcaemic episode with calcium salts compared with sevelamer over 52 weeks. Serum bicarbonate concentrations were significantly higher in the calcium treated group. There was no significant difference between groups in the risk of hospital admission and the number of days spent in hospital. The causes of hospital admission were not reported. Post hoc analysis of this RCT found that calcium salts significantly reduced vertebral bone mineral density compared with sevelamer. The second RCT reported no serious adverse effects with either treatment. There was no significant difference between groups in gastrointestinal complaints. It found that serum alkaline phosphatase was significantly increased from baseline with sevelamer. During treatment with sevelamer, 18/80 (23%) people required an evening dose of calcium carbonate to maintain serum calcium concentrations, and 15/80 (18%) people developed hypocalcaemia (serum calcium).

Sevelamer versus aluminium: We found no RCTs.

Sevelamer versus lanthanum carbonate: We found no RCTs.

Comment

Traditional risk factors for coronary artery disease account for only a portion of the remarkable increase in cardiovascular mortality observed in people receiving dialysis. Disorders of mineral metabolism (i.e. abnormalities of calcium, phosphorus, PTH, and vitamin D) may play an important role in the accelerated atherosclerosis unique to the dialysis population. Since the late 1980s, calcium salts have served as the conventional treatment for controlling hyperphosphataemia. Several observational studies have shown a direct correlation between elevated levels of serum phosphorus and calcium, and higher coronary artery calcification scores and mortality in people receiving chronic haemodialysis. In clinical practice, elevations in serum calcium and phosphorus often limit the use of conventional calcium salts and vitamin D analogues in controlling abnormalities of mineral metabolism seen in patients with ESRD. Thus, recent attention has focused on the effects of non-calcium-containing phosphate binders. Sevelamer is also known to act as a bile acid sequestrant. Hence, it is unclear whether the effects of

sevelamer on serum LDL cholesterol contributed significantly to the beneficial effects on vascular calcification. Further studies investigating the effects of sevelamer on all-cause mortality and cardiovascular events are currently in progress. Studies investigating the effects of lanthanum carbonate on bone and mineral metabolism are currently in progress.

Scottish Medicines Consortium

Source: www.scottishmedicines.org.uk Lanthanum carbonate 500, 750, 1000mg chewable tablets (Fosrenol®).March 2007

Summary of main findings:

Advice to NHS boards in Scotland: (Note, the SMC advises that the whole document be read at their website rather than summarised.) Lanthanum carbonate is accepted for restricted use within NHS Scotland as a phosphate-binding agent for use in the control of hyperphosphataemia in chronic renal failure (CRF) patients on haemodialysis or continuous ambulatory peritoneal dialysis. Lanthanum carbonate is as effective as calcium carbonate in reducing phosphate to target levels. It is restricted to use as a second-line agent in patients where a non-aluminium, noncalcium phosphate binder is required.

Summary of clinical effectiveness:

The practical advantages of this new treatment are that the tablets are taste neutral, can be taken without fluid and potentially fewer tablets may be required. There are no head to head studies with the only other non-aluminium, non-calcium phosphate binder, sevelamer. In the 24 month, comparative study of tolerability with standard treatment there was a higher number of withdrawals in the lanthanum arm compared to standard treatment (see Finn 2006 in the Safety section). Patients on standard therapy were allowed to switch to a different phosphate binder and still remain in the study while no switching could be allowed for patients on lanthanum and therefore they could only discontinue from the study. This was the explanation given for the higher discontinuation rates. The discontinuation rates in other studies were also quite significant, however tolerability of phosphate binder therapy is problematic and patients who had discontinued during the early parts of the studies did have the option to re-titrate their lanthanum carbonate dose and re-enter the long-term extension phases. Long-term effects on bone have still to be fully established. There is experience of lanthanum carbonate use out to six years but only in a small number of patients. Lanthanum carbonate takes more than ten years to reach steady state in bone therefore it has not yet reached steady state in patients who have been treated so far and there is still some concern over the effects of long-term treatment on bone and other tissue toxicity. Once lanthanum treatment has been discontinued, accumulated lanthanum is cleared slowly from bone which potentially could prolong the time to resolution of adverse effects.

CADTH

Source: www.cadth.ca Manns B, et al. Sevelamer in patients with ESRD: a systematic review and economic evaluation [Technology Report no 71]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.

Summary of main findings:

We did a systematic review to identify relevant literature. Evidence of efficacy was determined from randomized controlled trials (RCTs). Evidence of harm was determined from trials or registries where data was gathered prospectively. Ten RCTs with a total of 3,025 participants were included in the efficacy analysis; 28 prospective trials with a total of 3,983 participants were identified and eligible for the review of harm. One unpublished, randomized, unblinded study of 2,103 dialysis patients was designed to measure overall survival and cardiovascular mortality.

Sevelamer was found to have no demonstrated effect on health outcomes compared with calcium-based phosphate binders. There was no convincing evidence that substituting sevelamer for calcium-based binders reduced all-cause mortality, cardiovascular mortality, hospitalisation, or the frequency of symptomatic bone disease, and no evidence that sevelamer improved quality of life. Sevelamer therapy resulted in

a smaller decrease in phosphate levels, and fewer episodes of hypercalcaemia of unknown clinical significance, compared with calcium-based phosphate binders.
There is uncertainty regarding the cost effectiveness of sevelamer. Even if sevelamer is assumed to be more effective than calcium-based phosphate binders, it is associated with a cost per quality-adjusted life year gained ranging from $127,000 to $278,100. It is possible that sevelamer use, restricted to patients ≥65 years old, might be more economically efficient, but improved effectiveness in this group requires confirmation from future studies.
Funding sevelamer will require additional resources. The difference in cost per patient between calcium carbonate and sevelamer at usual daily doses is $4,127 annually. Substituting sevelamer for calcium carbonate for all patients with ESRD in Canada would increase expenditures by $70,620,616 annually. Restricting access to those ≥65 years old, or based on biochemical criteria, results in increased expenditures between $14,712,628 and $36,016,514.

COCHRANE

Source:
www.mrw.interscience.wiley.com/cochrane
Navaneethan SD, Chaukiyal P, Strippoli GF, et al. Phosphate binders for preventing and treating bone disease in chronic kidney disease patients. (Protocol) Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD006023.

Protocol:

This is the protocol for a review only – no results are yet available. The objectives are as follows:
1) The efficacy of the available aluminium salts, calcium salts, sevelamer hydrochloride, lanthanum carbonate, iron salts and magnesium-based phosphate binders in treatment of hyperphosphataemia.
2) To assess their impact on the development of SHPT or low bone turnover based on surrogate markers (PTH, bone specifi alkaline phosphatase, osteocalcin or other bone turnover markers) and the serum calcium, phosphate, the calcium-phosphate product, PTH levels. In addition, the influence of these drugs would be assessed in relation to lipid profie, tissue calcifiation and common symptoms such as pruritis and bone or muscle pain.
3) To study the impact of these agents on BMD assessed by dual-energy X-ray absorptiometry (DXA) or quantitative computerized tomography (QCT) and on bone turnover and mineralization based on histomorphometry and fracture rates.
4) To assess other patient-based 'hard' endpoints such as incidence of cardiovascular events, number of hospital admissions and all-cause mortality rates.
5) To assess the impact of various phosphate binders on metastatic calcifiation rates.
6) To assess cost effectiveness and quality of life.
7) Patient compliance with therapy and the incidence and nature of side effects.

CARI (Caring for Australasians with Renal Impairment)

Source: www.cari.org.au Use of phosphate binders in chronic kidney disease (2006).

Guidelines (NHMRC levels of evidence):

a. Calcium-containing phosphate binders are effective. (Level II evidence)
b. Calcium acetate (CA) is more effective than calcium carbonate. (Level I evidence)
c. Calcium salt-based binders should be minimised when serum calcium is above the target range (2.4 mmol/L) or serum PTH is below the upper limit of the reference range. (Level II evidence)
d. Sevelamer is an effective phosphate binder. (Level II evidence)
e. Lanthanum is an effective phosphate binder. (Level II evidence)

Suggestions for Clinical Care (based on Level III and IV evidence):

Factors influencing the choice and effectiveness of a phosphate binder include serum PTH, tendency towards hypercalcaemia, side effects, diet and compliance of the patient. (Opinion)
Initial management of serum phosphate levels above the target range (> 1.6 mmol/L) should include optimization of dialysis, when

possible, by increasing the duration and/or the number of treatments (Level III evidence), dietary advice and efforts to ensure patient compliance with medications. (Opinion)

Calcium-containing phosphate binders should be the initial choice in patients with levels of serum calcium < 2.4 mmol/L and PTH in the target range (Opinion), but should be avoided when levels of PTH are below the target range. (Level lll evidence)

Calcium carbonate ($CaCO_3$) should be taken before or with meals and may be less effective than CA when used with inhibitors of gastric acidity. (Level III evidence)

Aluminium salts should be avoided when PTH is below the target range (Level lll evidence). Aluminium use is associated with an increased risk of low bone turnover and abnormal bone mineralisation and should be avoided in at-risk patients, including children. (Level III evidence)

Monitoring of serum aluminium levels at regular intervals is suggested when aluminium-containing binders are used. If no aluminium-containing binders are used, it is sufficient to monitor reverse osmosis water supplies for heavy metal contamination, and perform serum aluminium levels and desferrioxamine testing in patients when the clinical state suggests that aluminium toxicity is possible.

Calcium citrate may increase aluminium absorption and should be avoided (Level III evidence)

The use of sevelamer should be considered when levels of calcium are above the target range. (Opinion)

The use of sevelamer should be considered when levels of PTH are below the target range. (Opinion)

Compared with calcium, magnesium-containing salts are an alternative but less efficient phosphate binder. (Level III evidence)

There are few long-term studies of safety. If used, serum magnesium levels should be monitored. Consider the use of low magnesium dialysate (Opinion)

Care should be taken to avoid hypercalcaemia when calcium salts are used in conjunction with calcitriol or vitamin D analogues. (Opinion)

A maximum daily dose of calcium salts to be used in CKD is not suggested in this guideline.

Summary of the evidence (sevelamer and lanthanum only):

Sevelamer is a newer agent recently available in Australia. Available trial data suggests that sevelamer is an equivalent but not better binder of phosphate, compared with calcium salts. There is evidence that sevelamer use leads to less hypercalcaemia than calcium salts. Sevelamer also lowers LDL cholesterol. It is associated with a lower serum bicarbonate level in kidney disease patients. One trial examined vascular calcification over a 1-year period and found less calcification with sevelamer than with $CaCO_3$ (Chertow et al 2002). Mortality data is awaited. Another major study is the CARE study (Qunibi et al 2004), an RCT of 98 patients randomised to CA or sevelamer. This well-conducted study showed that CA was able to control serum phosphate and the calcium-phosphate product better than sevelamer, at less cost. In patients prone to hypercalcaemia, there may be a role for sevelamer. Less coronary calcification progression over 52 weeks was seen for sevelamer (+ 6% increase) vs $CaCO_3$ (+ 23% increase) in the study by Chertow et al (2002). Calcification score is a surrogate marker for cardiovascular events and hard endpoint data is awaited. Some studies with sevelamer have required the use of supplemental calcium to maintain serum calcium levels. It is unclear whether sevelamer is associated with less calcification in such cases and whether the reduction in vascular calcification is due to lower calcium levels or by concomitant improvement in lipid profile. Recent Japanese studies have shown good phosphate control and patient tolerability with a combination of sevelamer and $CaCO_3$ (Koiwa et al 2005).

Lanthanum is a new rare metal salt, phosphate binder. There is evidence that lanthanum is an effective binder of dietary phosphate compared with placebo (Joy & Finn 2003). A 12-month clinical study in humans showed no trend towards the development of adynamic bone disease with this salt, although rat studies had suggested that this may occur (Behets et al 2004). The same study showed lanthanum equivalence with $CaCO_3$ in the control of serum phosphate (D'Haese et al 2003). Serum and bone levels of lanthanum did increase over

the 12 months in the lanthanum-treated group, although not to a large degree. The $CaCO_3$ group had more episodes of hypercalcaemia compared with the lanthanum group, although mean serum calcium levels were not significantly different.

Implementation and audit:

Implementation should be on the basis of achieving target serum levels of calcium (< 2.4 mmol/L), phosphate (< 1.6 mmol/L) and PTH (not less than the upper limit of the reference range). As episodes of hypercalcaemia may be a marker for vascular calcification, dialysis units should review blood results monthly in order to minimize hypercalcaemic episodes and improve serum phosphate control. The number of patients with levels out of range could be used as a performance indicator.

Suggestions for future research

1. Mortality studies with newer agents – sevelamer and lanthanum – in comparison with calcium salts are urgently required.
2. An audit of serum aluminium levels. Follow-up data on patients with elevated levels should be collected.
3. Cost-benefit analysis of sevelamer vs. calcium salts should be undertaken as the dose of sevelamer needed to control phosphate will add considerably to the cost of treating end-stage kidney disease.
4. Bone biopsy studies of patients treated long-term with lanthanum should be undertaken to satisfy safety concerns.

National Kidney Foundation (US)

Source:
www.kidney.org/professionals/KDOQI
K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Guideline 5. Use of Phosphate binders in CKD (2004).

In CKD Patients (Stages 3 and 4):

1. If phosphorus or intact PTH levels cannot be controlled within the target range, despite dietary phosphorus restriction, phosphate binders should be prescribed. (OPINION)
2. Calcium-based phosphate binders are effective in lowering serum phosphorus levels (EVIDENCE) and may be used as the initial binder therapy. (OPINION)

In CKD Patients with Kidney Failure (Stage 5):

3. Both calcium-based phosphate binders and other noncalcium-, nonaluminum-, nonmagnesium-containing phosphate-binding agents (such as sevelamer HCl) are effective in lowering serum phosphorus levels (EVIDENCE) and either may be used as the primary therapy. (OPINION)
4. In dialysis patients who remain hyperphosphatemic (serum phosphorus >5.5 mg/dL [1.78 mmol/L]) despite the use of either of calcium-based phosphate binders or other noncalcium-, nonaluminum-, nonmagnesium-containing phosphate-binding agents, a combination of both should be used. (OPINION)
5. The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg/day (OPINION), and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day. (OPINION)
6. Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcemic (corrected serum calcium of >10.2 mg/dL [2.54 mmol/L]), or whose plasma PTH levels are <150 pg/mL (16.5 pmol/L) on 2 consecutive measurements. (EVIDENCE)
7. Noncalcium-containing phosphate binders are preferred in dialysis patients with severe vascular and/or other soft tissue calcifications. (OPINION)
8. In patients with serum phosphorus levels >7.0 mg/dL (2.26 mmol/L), aluminum-based phosphate binders may be used as a short-term therapy (4 weeks), and for one course only, to be replaced thereafter by other phosphate

binders. (OPINION) In such patients, more frequent dialysis should also be considered. (EVIDENCE)

Other reviews

Cinacalcet

Johnson DW, Craven A-M, Isbel NM.
Modification of cardiovascular risk in hemodialysis patients: An evidence-based review. Hemodialysis International. Vol. 11(1)(pp 1-14), 2007.

Cardiovascular disease accounts for 40% to 50% of deaths in dialysis populations. Overall, the risk of cardiac mortality is 10-fold to 20-fold greater in dialysis patients than in age and sex-matched controls without CKD. The aim of this paper is to review critically the evidence that cardiac outcomes in dialysis patients are modified by cardiovascular risk factor interventions. There is limited, but as yet inconclusive controlled trial evidence that cardiovascular outcomes in dialysis populations may be improved by antioxidants (vitamin E or acetylcysteine), ensuring that hemoglobin levels do not exceed 120 g/L (especially in the setting of known cardiovascular disease), prescribing carvedilol in the setting of dilated cardiomyopathy, and by using cinacalcet in uncontrolled SHPT. Similarly, there are a number of negative controlled trials, which have demonstrated that statins, high-dose folic acid, angiotensin-converting enzyme inhibitors, multiple risk factor intervention via multidisciplinary clinics, and high-dose or high-flux dialysis are ineffective in preventing cardiovascular disease. Although none of these studies could be considered conclusive, the negative trials to date should raise significant concerns about the heavy reliance of current clinical practice guidelines on extrapolation of findings from cardiovascular intervention trials in the general population. It may be that cardiovascular disease in dialysis populations is less amenable to intervention, either because of the advanced stage of CKD or because the pathogenesis of cardiovascular disease in dialysis patients is different from that in the general population. Large, well-conducted, multicenter randomized-controlled trials in this area are urgently required.

Cannella G, Messa P.
Therapy of secondary hyperparathyroidism to date: Vitamin D analogs, calcimimetics or both? Journal of Nephrology. Vol. 19(4)(pp 399-402), 2006.

Therapy with i.v. calcitriol (CLT), that had been the mainstay of the cure of severe SHPT for many years, is often hindered by the occurrence of hypercalcemia, that requires discontinuation of the drug with consequent rebounding of the PTH oversecretion. To circumvent this shortcoming, CLT-analogs with less calcemic effects with respect to CLT have been developed. One of these analogs, paracalcitol (PCLT), proved to be at least as powerful as CLT in decreasing serum PTH, but it still remains endowed with some calcemic effect as the parent compound. Meanwhile, calcimimetics (CaMs) drugs targeting the calcium-sensing receptors on the PTG, have been marketed woldwide. Cinacalcet (CNC) is a CaM endowed with the unique prerogative to significantly decrease serum PTH while aldecreasing serum calcium. Thus, one may attempt to speculate that CaMs may completely replace vitamin D derivatives from the therapeutic arena. Uremic patients, however, suffer from severe deprivation of biological vitamin D effects, that puts them in need of highly dosed vitamin D in order to both ameliorate their bone status and to preserve their general and cardiovascular health. Thus, a combination therapy with PCLT, which has a significant patient-survival advantage over CLT, and CNC seems to be more appropriate than only-one-drug based therapy for SBPT. Such a combination will hopefully result in a better control of SHPT, avoidance of cumbersome hypercalcemia and higher life expectancy for uremic patients than ever before.

Gal-Moscovici A, Sprague SM.
The role of calcimimetics in chronic kidney disease. Kidney International. Vol. 70(SUPPL. 104)(pp S68-S72), 2006.

SHPT develops in CKD as a consequence of impaired phosphate, calcium, and vitamin D homeostasis. Treatment strategies directed to reduce the PTH concentrations have included phosphate binders and active vitamin D compounds. The over zealous use

of these agents may result in hypercalcemia or overt calcium overload. Severe SHPT, hyperphosphatemia, and total body calcium overload have been implicated in the pathophysiology of skeletal and extraskeletal calcification and associated with increased morbidity and mortality among the dialysis population. Cinacalcet, the recently approved agent to lower PTH, activates the calcium-sensing receptor of the parathyroid gland amplifying the glands' sensitivity to extracellular ionized calcium concentration resulting in suppression of PTH secretion. Several clinical studies conducted in dialysis patients, have shown that cinacalcet in doses from 30 to 180 mg/day, significantly reduce PTH concentrations while simultaneously lowering calcium and phosphate levels. Respective to the National Kidney Foundation-Kidney Disease Outcomes and Quality Initiative (NKF-K/DOQI) recommended targets for bone and mineral metabolism, 41% of cinacalcet-treated patients achieved both PTH and calcium-phosphorus targets. The ability of cinacalcet to reduce PTH secretion, along with reductions in the serum calcium, phosphorus, and calcium-phosphate product provide an alternative to the traditional treatment paradigm, and should be a welcomed addition to our therapeutic strategy in the management of SHPT.

Lindberg JS.
Calcimimetics: A new tool for management of hyperparathyroidism and renal osteodystrophy in patients with chronic kidney disease. Kidney International. Vol. 67(SUPPL. 95)(pp S-33-S-36), 2005.

Epidemiologic, clinical, and basic scientific studies led to an explosion in our understanding of disorders of mineral metabolism in the CKD patient. These advances are not always translated into improved care of renal osteodystrophy in CKD-5 patients. The introduction of a new class of drugs, calcimimetics, allows improved control of abnormal calcium/phosphorus metabolism. The calcimimetics compliment, rather than replace, current treatment options for SHPT in the chronic disease patient.

Ogata H, Koiwa F, Ito H, et al.
Therapeutic strategies for secondary hyperparathyroidism in dialysis patients. Therapeutic Apheresis & Dialysis. Vol. 10(4)(pp 355-363), 2006.

SHPT leads not only to bone disorders, but also cardiovascular complications in long-term dialysis patients. Conventional treatment with calcium (Ca) supplement, phosphate (P) binders and active vitamin D analogs lead in part to amelioration of SHPT, but are simultaneously associated with unacceptable side-effects, including hypercalcemia, hyperphosphatemia, and increased calcium-phosphate products, which are the risk factors for cardiovascular disease in dialysis patients. Conventional treatment has been unable to facilitate the attainment of optimal management of SHPT proposed in the K/DOQI guidelines. Cinacalcet HCl (cinacalcet), a novel calcimimetic compound, restores the sensitivity of the Ca-sensing receptor in parathyroid cells, and decreases serum PTH without introducing hypercalcemia or hyperphosphatemia. Cinacalcet treatment enables a significant number of patients to achieve the K/DOQI guideline. Based on experimental data, calcimimetics could ameliorate cardiovascular calcification and remodeling in uremic rats with SHPT. Clinical trials have shown that cinacalcet significantly reduced the risks of parathyroidectomy, fracture and cardiovascular hospitalization among long-term dialysis patients with SHPT. Parathyroid intervention therapy (parathyroidectomy and percutaneous direct injection) is ala useful alternative. In the present article, we review novel therapeutic strategies for SHPT.

Ix JH, Quarles LD, Chertow GM.
Guidelines for disorders of mineral metabolism and secondary hyperparathyroidism should not yet be modified. Nature Clinical Practice Nephrology. Vol. 2(6)(pp 337-339), 2006.

This brief article is a response to the article by Monge et al. on page 326 entitled Reappraisal of 2003 NKF-K/DOQI guidelines for management of hyperparathyroidism in CKD patients. We contend that there is insufficient evidence to

support the changes to clinical practice and clinical practice guidelines proposed by Monge and colleagues. We recommend that clinical trials be conducted to resolve these points of contention and other critical issues in the management of disorders of mineral metabolism in CKD, including SHPT. The focus should be on evaluating the effects of alternative strategies on survival, as well as clinical manifestations of cardiovascular and bone disease.

Shahapuni I, Monge M, Oprisiu R, et al.
Drug insight: Renal indications of calcimimetics. Nature Clinical Practice Nephrology. Vol. 2(6)(pp 316-325), 2006.
Calcimimetics suppress the secretion of PTH by sensitizing the parathyroid calcium receptor to serum calcium. Cinacalcet (Sensipar/Mimpara, Amgen Inc., Thousand Oaks, CA), the first-in-class calcimimetic agent approved for treatment of SHPT in dialysis patients, is, in association with higher dose of a calcium-based oral phosphate binder, a well-tolerated and effective alternative to standard treatments such as vitamin D derivatives in association with a non-calcium-based oral phosphate binder. Here, we present an overview of evidence in support of this assertion. We extend our discussion to encompass other indications for calcimimetics - SHPT in predialysis CKD patients, hypercalcemic hyperparathyroidism in renal transplant recipients, primary hyperparathyroidism, and hypercalcemia associated with parathyroid carcinoma - as well as providing guidance on optimal usage of this drug.

Anonymous.
Cinacalcet. Secondary hyperparathyroidism: Where are the clinical data? Prescrire International. Vol. 15(83)(pp 90-93), 2006.
Patients who require dialysis for CRF develop phosphocalcium metabolic disorders that often lead to SHPT. Standard treatment consists of a phosphate chelator and vitamin D, along with the use of an appropriate calcium concentration in the dialysis bath, but is difficult to manage. Parathyroid cancer is a rare malignancy frequently associated with hypercalcaemia. Cinacalcet is a calcimimetic agent that reduces the parathormone level. Clinical evaluation includes more than a dozen dose-finding studies and clinical trials. The optimal dose seems to range from 30 to 180 mg/day and varies widely from one patient to another. 3 double- blind placebo-controlled trials, lasting for a maximum of one year and involving a total of 1136 dialysis patients with CRF, showed no improvement in quality of life with cinacalcet. The target parathormone level was reached by 40% of patients on cinacalcet versus 5% of patients on placebo, while the effects of cinacalcet on calcium levels (-7%) and phosphate levels (-8%) were modest. No impact on bone complications is mentioned in available reports. The assessment of treatment of parathyroid cancer is limited to one ongoing non comparative trial involving 21 patients. * During clinical trials, 11% of dialysis patients had low parathormone levels, creating a risk of adynamic bone disease and fractures, but available data are sparse. Two-thirds of patients receiving cinacalcet have episodes of hypocalcaemia, which may in part account for reports of seizures (1.4% of patients), nausea (31%) and vomiting (27%). Many adverse effects seen in animal studies have not been adequately investigated in the clinical setting, such as an increase in the QT interval, thyroid disorders, and sexual dysfunction. Cinacalcet is a powerful CYP 2D6 inhibitor and is almetabolised by isoenzymes CYP 3A4 and CYP 1A2, creating an increased risk of drug interactions. In practice, treatment with cinacalcet seems difficult to manage and to provide only limited benefits. Available assessment reports leave many questions unanswered, and this is a further reason not to use this product outside of clinical trials, either after failure of phosphate chelator and vitamin D therapy (especially as an alternative to surgery) or in parathyroid cancer.

Strippoli GFM, Palmer S, Tong A, et al.
Meta-Analysis of Biochemical and Patient-Level Effects of Calcimimetic Therapy. American Journal of Kidney Diseases. Vol. 47(5)(pp 715-726), 2006.
Background: Many randomized trials have now evaluated the effects of calcimimetics in patients with CKD and SHPT on standard therapy with vitamin D and/or phosphate

binders. We conducted a meta-analysis to evaluate outcomes of therapy with these novel agents. Methods: MEDLINE, EMBASE, the Cochrane Controlled Trials Register, and conference proceedings were searched for randomized controlled trials evaluating any calcimimetic against placebo or another agent in predialysis or dialysis patients with CKD. Data were extracted for all relevant patient-centered and surrogate outcomes. Analysis was by means of a random-effects model, and results are expressed as relative risk or weighted mean difference (WMD) with 95% confidence intervals (CIs). Results: Eight trials (1,429 patients) were identified that compared a calcimimetic agent plus standard therapy with placebo plus standard therapy. End-of-treatment values for PTH (4 trials; 1,278 patients; WMD, -290.49 pg/mL; 95% CI, -359.91 to -221.07), serum calcium (3 trials; 1,201 patients; WMD, -0.85 mg/dL; 95% CI, -1.14 to -0.56), serum phosphorus (3 trials; 1,195 patients; WMD, -0.29 mg/dL; 95% CI, -0.50 to -0.08), and calcium-phosphate product (3 trials; 1,194 patients; WMD, -7.90 mg^2/dL^2; 95% CI, -10.25 to -5.54) were significantly lower with calcimimetic therapy compared with placebo. No significant effects on patient-based end points were shown. Conclusion: Calcimimetic treatment of patients with SHPT leads to significant improvements in biochemical parameters that observational studies have associated with increased mortality, cardiovascular risk, and osteitis fibrosa, but patient-based benefits have not yet been shown. For patients with SHPT, the benefits of calcimimetics over standard therapy remain uncertain until additional randomized trials become available.

Reichel H.
Current treatment options in secondary renal hyperparathyroidism. Nephrology Dialysis Transplantation. Vol. 21(1)(pp 23-28), 2006.
No abstract available.

Goodman WG.
Calcimimetics: A remedy for all problems of excess parathyroid hormone activity in chronic kidney disease? Current Opinion in Nephrology & Hypertension. Vol. 14(4)(pp 355-360), 2005.
Purpose of review: Cinacalcet is a calcimimetic agent that is now available for use clinically to manage SHPT among patients undergoing dialysis regularly. It acts as an allosteric activator of the calcium-sensing receptor, the molecular mechanism that controls PTH secretion. This mechanism of action differs fundamentally from that of the vitamin D sterols, which heretofore have been the only definitive pharmacological intervention for treating SHPT. Recent findings: The ability of calcimimetic agents to enhance signaling through the calcium-sensing receptor in parathyroid cells affects several important components of parathyroid gland function. Results: from several large clinical trials demonstrate that cinacalcet effectively lowers plasma PTH levels in dialysis patients with SHPT when used either alone or together with vitamin D. Unlike the vitamin D sterols, which generally raise serum calcium and phosphorus levels, treatment with cinacalcet is associated with modest reductions in serum calcium and phosphorus concentrations. The impact of these biochemical changes on renal bone disease and on soft-tissue and vascular calcification during long-term treatment has yet to be characterized fully. Cinacalcet diminishes PTH gene expression, and studies in experimental animals indicate that its use retards the progression of parathyroid gland hyperplasia and increases bone mass. If confirmed in future clinical trials in patients with SHPT, these features represent potentially important ancillary therapeutic benefits. Summary: Calcimimetic agents have diverse effects on parathyroid gland function that may enhance the overall medical management of SHPT in patients undergoing dialysis regularly.

Byrnes CA, Shepler BM.
Cinacalcet: A new treatment for secondary hyperparathyroidism in patients receiving hemodialysis. Pharmacotherapy. Vol. 25(5 I)(pp 709-716), 2005.
Cinacalcet is the first calcimimetic drug approved by the United States Food and Drug Administration for the treatment of SHPT in patients with chronic kidney disease. A literature search, performed by

using PubMed and MEDLINE from January 1997-June 2004, identified articles concerning the efficacy and safety of cinacalcet in this patient population. Currently, Vitamin D and its analogs are considered first-line therapy for SHPT. However, use of these agents is often accompanied by an increase in serum calcium and phosphorus concentrations, a problem that often limits their use. Cinacalcet's mechanism of action decreases PTH, calcium, and phosphorus levels, offering potential advantages over the other treatments for SHPT. Additional clinical trials are needed to evaluate the long-term safety and efficacy of the drug as a first-line agent.

Phosphate Binders

Anonymous (2007).
Lanthanum: new drug. Hyperphosphataemia in dialysis patients: more potential problems than benefits. Prescrire Int 16(88): 47-50, 2007.

In dialysis patients with CRF, hyperphosphataemia can cause osteorenal dystrophy, leading to bone pain, fractures and excess cardiovascular mortality. In addition to a low-phosphorus diet and dialysis, phosphorus chelators are usually needed to control blood phosphorus levels. The first choice is calcium carbonate, and sevelamer is an alternative. Lanthanum carbonate, a phosphorus chelator, is now also licensed for the treatment of hyperphosphataemia in dialysis patients with CRF. In addition to three dose-finding placebo-controlled studies, clinical evaluation includes 2 comparative randomised unblinded trials: one 6-month trial versus calcium carbonate and a 2-year trial versus other phosphorus chelators. During these trials, lanthanum was no more effective than the comparators in terms of effects on the mortality rate, incidence of fractures, or blood phosphorus level. During these trials, adverse events attributed to treatment were more frequent with lanthanum than with the other phosphorus chelators. The main problems were gastrointestinal disorders (nausea, vomiting, diarrhoea, constipation and abdominal pain), headaches, seizures, and encephalopathy. The accumulation of lanthanum in the bones and brain is troubling. The known long-term adverse effects of aluminium, another trivalent cation with weak gastrointestinal absorption, suggest that caution is also required with lanthanum. In practice, when a phosphorus chelator is needed to treat hyperphosphataemia in dialysis patients with CRF, calcium carbonate is the first choice and sevelamer remains the best alternative.

Freemont AJ.
Lanthanum carbonate. Drugs of Today. Vol. 42(12)(pp 759-770), 2006.

Controlling hyperphosphatemia in patients with CRF on renal dialysis is a major problem. None of the available calcium- or aluminum-based phosphate binders match the requirements for an ideal agent, each having its own limitations. The introduction of sevelamer hydrochloride represented a step change in management. Lanthanum carbonate is an alternative nonaluminium, noncalcium phosphate binder. Taken with food, it is well tolerated. It is poorly absorbed and does not require functioning kidneys to be removed from the body. There is no evidence from current studies that it accumulates to biologically significant levels in tissues, but despite the large numbers of patients included in clinical trials, experience with long-term dosing is limited and, as with every new drug used in this type of clinical setting, patients should be carefully monitored as experience with the drug increases. Lanthanum carbonate binds phosphate effectively across the physiological pH range of the upper gastrointestinal tract, and has no detrimental effect on calcium, vitamin D or PTH metabolism. From the extensive trial data it seems that lanthanum carbonate is an effective and practical phosphate binder. Lanthanum carbonate and sevelamer are two new oral phosphate binding agents that with others currently in preclinical trials, such as stabilized polynuclear iron idroxide, could well represent a significant breakthrough in the management of hyperphosphatemia in patients with CRF in whom dietary phosphate restriction and cheaper oral phosphate binding agents prove unsatisfactory. Comparative trials and enhanced clinical experience are needed before the exact place of these competing

and complementary therapies can be properly identified in patient management.

Cozzolino M, Brancaccio D.
Lanthanum carbonate - New data on parathyroid hormone control without liver damage. Nephrology Dialysis Transplantation. Vol. 22(2)(pp 316-318), 2007.
No abstract available.

Brancaccio D, Cozzolino M.
Lanthanum carbonate: Time to abandon prejudices? Kidney International. Vol. 71(3)(pp 190-192), 2007.
Since lanthanum carbonate has become available there has been much interest in its use as a non-calcium-containing phosphate binder, but also much speculation among scientists about possible aluminum-like toxicity. This Commentary focuses on the major aspects of this scientific controversy, confirming the safety and efficacy of this new phosphate binder

Nikolov IG, Joki N, Maizel J, et al.
Pleiotropic effects of the non-calcium phosphate binder sevelamer. Kidney International. Vol. 70(SUPPL. 105)(pp S16-S23), 2006.
The number of CKD patients and related adverse outcomes has dramatically increased worldwide in the past decade. Therefore, numerous experimental and clinical studies have recently addressed the underlying mechanisms, in particular the marked increase in cardiovascular mortality. Hyperphosphatemia is a major problem in these patients with advanced stage of CKD. Its control by calcium-containing phosphate binders is effective, but at the price of potentially noxious calcium overload. Sevelamer hydrochloride is a phosphate binder that offers an effective control of hyperphosphatemia as calcium-rich binders but without increase of calcium load. Beyond the control of phosphate, sevelamer seems to exert pleiotropic effects which include the correction of lipid abnormalities and the clearance of some uremic toxins.

Nolan CR, Qunibi WY.
Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis. Kidney International. Vol. 67(SUPPL. 95)(pp S-13-S-20), 2005.
Hyperphosphatemia in patients with ESRD leads to SHPT, renal osteodystrophy, and is independently associated with mortality risk. The exact mechanism by which hyperphosphatemia increases mortality risk is unknown, but it may relate to enhanced cardiovascular calcification. National Kidney Foundation K/DOQI bone metabolism and disease guidelines recommend maintenance of serum phosphorus (P) below 5.5 mg/dL, and calcium-phosphate product less than 55 mg^2/dL^2. Although calcium-based phosphate binders (CBPB) are cost effective, long-term safety concerns relate to their postulated role in progression of cardiovascular calcification. Sevelamer hydrochloride has been recommended as an alternative noncalcium phosphate binder. Results from the Calcium Acetate Renagel Evaluation (CARE study) indicate that calcium acetate is more effective than sevelamer in controlling serum phosphorous and calcium-phosphate product in hemodialysis patients. In the Treat-to-Goal study, dialysis patients treated with sevelamer had slower progression of coronary and aortic calcification than patients treated with CBPB. The mechanism underlying the beneficial effect of sevelamer is unknown, but may relate to decreased calcium loading or to dramatic reductions in LDL cholesterol in sevelamer-treated patients. At present, evidence incriminating CBPB in the progression of cardiovascular calcification in ESRD remains largely circumstantial. As calcium acetate is more efficacious and cost effective than sevelamer, it remains an accepted first-line phosphate binder. In this review, we will examine these issues and provide rational guidelines for the use of calcium-based phosphate binders in patients on maintenance hemodialysis.

Monge M, Shahapuni I, Oprisiu R, et al.
Reappraisal of 2003 NKF-K/DOQI guidelines for management of hyperparathyroidism in chronic kidney disease patients. Nature Clinical Practice Nephrology. Vol. 2(6)(pp 326-336), 2006.
The 2003 guidelines for the management of hyperparathyroidism in CKD compiled by the

Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation (NKF-K/DOQI) were formulated on the basis of work published up until 2001. Since then, new drugs (e.g. calcimimetics and lanthanum carbonate) have become available, and others (e.g. sevelamer, nicotinamide and paricalcitol) have been more stringently clinically evaluated. Because of these advancements, a reappraisal of the 2003 guidelines is justified. In this article we critically review the following recommendations of the NKF-K/DOQI: (i) routine use of 1.25 mmol/l (5.0 mg/dl) dialysate calcium and 1aOH-vitamin D derivatives; (ii) limitation of the maximal daily dose of calcium-based oral phosphate binders to 1.5 g of elemental calcium; and (iii) not correcting vitamin D insufficiency in dialysis patients.

Albaaj F, Hutchison AJ.
Lanthanum carbonate (Fosrenol): A novel agent for the treatment of hyperphosphataemia in renal failure and dialysis patients. International Journal of Clinical Practice. Vol. 59(9)(pp 1091-1096), 2005.
Approximately 70% of patients with ESRD and dialysis have hyperphosphataemia, which is associated with renal osteodystrophy, metastatic calcification and increased mortality and morbidity. Despite dietary restriction and dialysis, most patients will require a phosphate-binding agent to treat this condition. However, phosphate control has not significantly improved over the last two decades, mainly because of the lack of an ideal phosphate-binding agent. Aluminium-based and calcium-based agents are associated with major side-effects despite their efficacy. Although sevelamer hydrochloride represents a step forward in the management of hyperphosphataemia, it has drawbacks and therefore is not the ideal phosphate binder. Lanthanum carbonate is a non-calcium, non-aluminium phosphate-binding agent. It has shown to be effective, well-tolerated and has a positive effect on bone histology.

Nadin C.
Sevelamer as a phosphate binder in adult hemodialysis patients: An evidence-based review of its therapeutic value.Core Evidence. Vol. 1(1)(pp 43-63), 2005.
Introduction: Patients on hemodialysis require phosphate binders to reduce dietary phosphate absorption and control serum phosphate. The standard therapy, calcium salts, can be associated with elevated serum calcium (hypercalcemia). Concern has been raised that hypercalcemia, especially combined with elevated serum phosphate, may be associated with arterial calcification, and this may contribute to increased risk of cardiovascular mortality and morbidity. Sevelamer is a nonmetal, nonabsorbed phosphate binder. Aims: This review assesses the evidence for the therapeutic value of sevelamer as a phosphate binder in adult hemodialysis patients. Evidence review: Strong evidence shows that sevelamer is as effective as calcium salts in controlling serum phosphate and calcium-phosphate product, has less risk of inducing hypercalcemia and is more effective at lowering lipid levels. Some evidence indicates that sevelamer reduces arterial calcification progression and loss of bone mineral density, but it may be more likely to induce metabolic acidosis, compared with calcium salts. Sevelamer-containing regimens may improve calcific uremic arteriolopathy, although the evidence is weak. Evidence is divided on whether the incidence of gastrointestinal adverse events with sevelamer is similar to or higher than that with calcium salts. Retrospective and modeling studies suggest lower cardiovascular morbidity and mortality with sevelamer than with calcium salts, with incremental cost-effectiveness of $US1100-2200 per life-year gained. Further direct evidence is needed on mortality, quality of life, and cost-effectiveness. Place in therapy: Sevelamer is effective in controlling serum phosphate and lowering lipid levels in hemodialysis patients without inducing hypercalcemia, and may have beneficial effects on arterial calcification.

Cheng CM.
Lanthanum carbonate treatment of hyperphosphatemia in end-stage renal disease. Journal of Pharmacy Technology. Vol. 22(2)(pp 99-104), 2006.
Objective: To review the literature on the safety and efficacy of lanthanum carbonate

for the treatment of hyperphosphatemia in patients with ESRD (ESRD). Data Sources: Primary literature was obtained through a PubMed search (1966-September 2005) using the key terms Fosrenol and lanthanum carbonate. The FDA review, manufacturer-provided data, and published abstracts on lanthanum carbonate were also reviewed and evaluated. Study Selection and Data Extraction: Human studies in which lanthanum carbonate was compared with placebo or active control for the treatment of hyperphosphatemia secondary to renal disease were included. Dose-titration studies were excluded. Data Synthesis: Phosphate-lowering agents and dietary phosphate restriction are currently the first-line therapies for initial treatment of hyperphosphatemia associated with ESRD. Lanthanum carbonate is a highly effective non-aluminum, non-calcium-containing phosphate binder. It is the only FDA-approved phosphate binder that is available as an unflavored chewable tablet that may be taken without water. Conclusions: Clinical studies demonstrate that lanthanum carbonate is more effective than placebo but as or less effective than standard therapies in lowering serum phosphate to target levels. When compared with calcium salts, lanthanum carbonate had a lower incidence of hypercalcemia and a lower risk of patients developing bone disease. However, in clinical trials, patients receiving lanthanum carbonate had greater discontinuation rates, some due to adverse events. The long-term safety data (>5 y), including the potential for lanthanum accumulation in the bone with subsequent development of osteodystrophy, remain unknown.

Joy MS, Kshirsagar A, Candiani C, et al.
Annals of Pharmacotherapy. Vol. 40(2)(pp 234-240), 2006.

OBJECTIVE: To review the pharmacology, pharmacokinetics, clinical efficacy, and safety profile of lanthanum carbonate, a phosphate binder for CKD. DATA SOURCES: Information was selected from PubMed (1965-October 2005). All studies presented as scientific posters and abstracts from nephrology meetings from 1999 to 2005 were also included. STUDY SELECTION AND DATA EXTRACTION: All published articles regarding lanthanum carbonate were included. In addition, abstracts and presentations from scientific meeting symposia were also considered for inclusion. DATA SYNTHESIS: Lanthanum carbonate has been recently approved as non-calcium-based therapy for phosphate reduction in patients with stage 5 CKD requiring dialysis. The recommended dose is 250-500 mg with meals, for a maximum of 1500 mg daily. Clinical studies have shown short- and long-term safety with lanthanum carbonate administration. Adverse effects were primarily gastrointestinal in nature. Clinical trials have also shown reductions in serum phosphorus to target concentrations, reductions in associated calcium-phosphate product, and minimal effects on serum calcium and PTH concentrations. CONCLUSIONS: Lanthanum carbonate is an effective phosphate-binding agent without significant risk of hypercalcemia or worsening metabolic acidosis. Lanthanum carbonate is a safe and effective drug for reduction of elevated serum phosphorus levels associated with stage 5 CKD. The role of lanthanum carbonate relative to other phosphate-binding drugs, such as calcium salts and sevelamer, remains to be determined.

Qunibi WY, Nolan CR.
Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis: Results of the CARE study. Kidney International - Supplement. Vol. 66(90)(pp S33-S38), 2004.

Most patients with ESRD develop hyperphosphatemia because their dietary intake exceeds phosphorus elimination by intermittent thrice-weekly dialysis. Inadequately treated hyperphosphatemia plays a central role in the pathogenesis of SHPT and extraosseous calcification. Moreover, in the last 15 years, this biochemical abnormality has become increasingly important following the publication of two epidemiologic studies that demonstrated an association between elevated serum phosphorus and increased mortality risk in patients with ESRD. As a result, the National Kidney Foundation Kidney Disease Outcome and Quality Initiative (K/DOQI) Bone Metabolism and Chronic Kidney Disease Guidelines recommend that serum phosphorus levels be maintained between 3.5 and 5.5 mg/dL.

Unfortunately, cross-sectional studies have shown a mean serum phosphorus of 6.2 mg/dL in the maintenance hemodialysis population in the United States. An alarming 60% of patients have serum phosphorus in excess of the 5.5 mg/dL level recommended by K/DOQI guidelines. In order to achieve this new target for serum phosphorus, the most efficacious and cost-effective phosphate binders currently available should be utilized. In this review, we discuss the results of the Calcium Acetate Renagel Evaluation (CARE study), which clearly demonstrated the superiority of calcium acetate over sevelamer hydrochloride for controlling serum phosphorus and calcium-phosphate product to the levels recommended by the K/DOQI guidelines.

Pai AB, Smeeding JE, Brook RA.
The role of sevelamer in achieving the kidney disease outcomes quality initiative (K/DOQI) guidelines for hyperphosphatemia. Current Medical Research & Opinion. Vol. 20(7)(pp 991-999), 2004.

Disregulation of mineral metabolism (principally hyperphosphatemia and hypercalcemia) contributes to substantial morbidity and mortality. Accordingly, new and more-aggressive Kidney Disease Outcomes Quality Initiative (K/DOQI) Guidelines from the National Kidney Foundation promote lower serum phosphorus (3.5-5.5 mg/dL), lower calcium (8.4-9.5 mg/dL), and lower calcium-phosphate product (< 55 mg^2/dL^2) targets. Review findings: Traditional calcium-based and metal-based phosphate binders are effective but are associated with side effects and toxicity that limit their use. Achieving rigorous K/DOQI goals demands higher therapeutic doses of phosphate binders and may require more-aggressive use of calcium-free and metal-free phosphate binders. Sevelamer hydrochloride is a calcium- and metal-free polymer that binds phosphate effectively without contributing to calcium load or metal accumulation. In the Treat-to-Goal trial, sevelamer-treated dialysis patients had less progression of coronary and aortic calcification than patients treated with calcium-based binders. This offers the potential promise of reducing cardiovascular morbidity and mortality. The 800mg tablet (Renagel*) increases the daily sevelamer dose while reducing the number of tablets required per meal. Nine of the 800mg tablets per day (3 x 800mg tablets tid with meals) of sevelamer monotherapy have been shown to achieve K/DOQI serum phosphorus and calcium-phosphate product targets. Conclusion: In summary, this review of the current evidence-base concludes that the new, more-aggressive, K/DOQI goals limit the use of metal-based and calcium-based phosphate binders. Sevelamer offers the advantages of lowering serum phosphorus without the risks of calcium or metal accumulation - and offers the promise of slowing the progression of vascular calcification and potentially reducing the morbidity and mortality of hemodialysis patients.

Swainston Harrison T, Scott LJ.
Lanthanum carbonate. Drugs. Vol. 64(9)(pp 985-996), 2004.

Lanthanum carbonate (elemental lanthanum 375-3000 mg/day) reduced serum phosphorus levels compared with placebo in two randomised, double-blind, multicentre 4-week trials in patients with CRF receiving regular haemodialysis. In two large, randomised trials in patients with CRF requiring haemodialysis, lanthanum carbonate (elemental lanthanum 375-3000 mg/day) was as effective as calcium carbonate and/ or other conventional phosphate binders in reducing and maintaining serum phosphorus levels (≤5.6 mg/ dL over 6 months and ≤5.9 mg/dL over 2 years). Lanthanum carbonate was generally well tolerated. Most adverse events were mild-to-moderate in severity, with gastrointestinal events being the most common. The tolerability profile of lanthanum carbonate was similar to those of conventional phosphate binders; however, hypercalcaemic episodes occurred significantly less frequently over 6 months with lanthanum carbonate than with calcium carbonate. In a randomised 1-year trial, numerically fewer lanthanum carbonate (elemental lanthanum ≤3750 mg/day) recipients had renal bone disease at study end than at baseline; however, in the calcium carbonate 59000 mg/day group, numerically more patients had renal bone disease at study end compared with baseline.

Clinical Studies

Cinacalcet

Efficacy

RCTs

Lindberg JS, Culleton B, Wong G, et al. Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: A randomized, double-blind, multicenter study. Journal of the American Society of Nephrology. Vol. 16(3)(pp 800-807), 2005.

This phase 3, multicenter, randomized, placebo-controlled, double-blind study evaluated the efficacy and safety of cinacalcet in hemodialysis (HD) and peritoneal dialysis (PD) patients with PTH ≥300 pg/ml despite traditional therapy. A total of 395 patients received once-daily oral cinacalcet (260 HD, 34 PD) or placebo (89 HD, 12 PD) titrated from 30 to 180 mg to achieve a target intact PTH (iPTH) level of ≤250 pg/ml. During a 10-wk efficacy assessment phase, cinacalcet was more effective than control for PTH reduction outcomes, including proportion of patients with mean iPTH levels ≤300 pg/ml (46 versus 9%), proportion of patients with ≥30% reduction in iPTH from baseline (65 versus 13%), and proportion of patients with ≥20, ≥40, or ≥50% reduction from baseline. Cinacalcet had comparable efficacy in HD and PD patients; 50% of PD patients achieved a mean iPTH ≤300 pg/ml. Cinacalcet alsignificantly reduced serum calcium, phosphorus, and calcium-phosphate product levels compared with control treatment. The most common side effects, nausea and vomiting, were usually mild to moderate in severity and transient. Once-daily oral cinacalcet was effective in rapidly and safely reducing PTH, Ca P, calcium, and phosphorus levels in patients who received HD or PD. Cinacalcet offers a new therapeutic option for controlling SHPT in patients with CKD on dialysis.

Charytan C, Coburn JW, Chonchol M, et al. Cinacalcet hydrochloride is an effective treatment for secondary hyperparathyroidism in patients with CKD not receiving dialysis. American Journal of Kidney Diseases. Vol. 46(1)(pp 58-67), 2005.

This phase 2 study evaluated the effects of the oral calcimimetic cinacalcet hydrochloride in patients with CKD not on dialysis therapy. Methods: A randomized, double-blind, placebo-controlled, 18-week study enrolled adults with an estimated glomerular filtration rate of 15 to 50 mL/min/1.73 m^2 (0.25 to 0.83 mL/s/1.73 m^2) and an intact PTH (iPTH) level greater than 130 pg/mL (ng/L). Cinacalcet (or placebo) was titrated from 30 to 180 mg once daily to obtain a 30% or greater reduction in iPTH levels from baseline. Results: Baseline mean iPTH levels were 243 pg/mL (ng/L) in the cinacalcet group (n = 27) and 236 pg/mL (ng/L) in the control group (n = 27). At baseline, 28% of subjects were being administered vitamin D sterols and 43% were being administered phosphate binders or calcium supplements. The addition of cinacalcet significantly decreased iPTH concentrations compared with controls during the efficacy-assessment phase: 56% versus 19% of subjects achieved a 30% or greater reduction in iPTH levels (P = 0.006), and mean iPTH levels decreased by 32% in the cinacalcet group, but increased by 6% in the control group (P < 0.001). Mean serum calcium and phosphorus levels remained within normal range throughout the study. Cinacalcet generally was well tolerated; the most frequent adverse events were gastrointestinal. Conclusion: This preliminary study provides evidence that cinacalcet is efficacious for the treatment of SHPT in subjects with CKD not receiving dialysis.

Lien Y-HH, Silva AL, Whittman D. Effects of cinacalcet on bone mineral density in patients with secondary hyperparathyroidism. Nephrology Dialysis Transplantation. Vol. 20(pp 1232-1237), 2005.

We investigated the effects of cinacalcet treatment on bone mineral density (BMD) in patients with SHPT due to CKD. Methods.

Ten patients who were receiving haemodialysis and four patients, who had stage 4 CKD participated and completed the multicentre, randomized, double-blind, placebo-controlled trials evaluating the safety and efficacy of cinacalcet for treating SHPT. The efficacy of cinacalcet was assessed by plasma intact PTH levels. A dual energy X-ray absorptiometry was performed to measure the BMD of total proximal femurs and lumbar spine (L2-L4) before and after 26 weeks of treatment. Results. Cinacalcet reduced iPTH from 912 +/- 296 to 515 +/- 359 pg/ml in haemodialysis patients and from 210 +/- 46 to 56 +/- 51 pg/ml in pre-dialysis patients (means +/- SD; both $P < 0.05$). When data from haemodialysis and pre-dialysis patients were pooled for analysis, cinacalcet treatment increased proximal femur BMD from 0.945 +/- 0.169 to 0.961 +/- 0.174 g/cm^2 ($P < 0.05$), but did not affect lumbar spine BMD. There was a correlation between the change in femur BMD and the change in iPTH during the study period ($R^2 = 0.39$, $P < 0.05$). Conclusions. SHPT is associated with progressive bone loss. Suppression of plasma iPTH with cinacalcet appears to reverse bone loss in the proximal femur, but does not affect BMD of the lumbar spine. A larger study is warranted to confirm that cinacalcet has a beneficial effect on the skeletal system in patients with SHPT.

Harris RZ, Padhi D, Marbury TC, et al.
Pharmacokinetics, pharmacodynamics, and safety of cinacalcet hydrochloride in hemodialysis patients at doses up to 200 mg once daily. American Journal of Kidney Diseases. Vol. 44(6)(pp 1070-1076), 2004.

This study investigated the pharmacokinetics, pharmacodynamics, safety, and tolerability of cinacalcet HCl over a dose range of 25 to 300 mg/d in patients receiving dialysis. Methods: Hemodialysis patients were randomly assigned 4:1 to receive cinacalcet HCl or placebo in this double-blind study. Cinacalcet HCl doses were escalated weekly in 25mg increments from 25 to 300 mg/d. Noncompartmental methods were used to analyze the pharmacokinetic parameters of cinacalcet (the free-base). The effects of cinacalcet concentration on plasma PTH and serum calcium levels were evaluated. Results: Of 23 patients enrolled (17 patients, cinacalcet HCl; 6 patients, placebo), 10 patients (8 patients, cinacalcet HCl; 2 patients, placebo) completed the study. Plasma concentration, median area under the plasma concentration-time curve from time 0 to 24 hours after dosing, and maximal plasma concentration (Cmax) of cinacalcet increased with doses up to 200 mg once daily. Median oral clearance ranged from 222 to 599 L/h, and median time after dosing when Cmax occurred ranged from 2 to 3 hours across all doses. The pharmacokinetics were linear over the 25- to 200mg once-daily dose range, with no substantial increase in exposure at greater than 200 mg. Changes in plasma PTH concentrations correlated inversely with cinacalcet concentration. The concentration-effect relationship was well described by an inhibitory maximal effect model. Cinacalcet HCl was reasonably tolerated, and the incidence of adverse events was similar between groups (76%, cinacalcet; 80%, placebo). Gastrointestinal events were noted at greater doses and may be dose related. Conclusion: Cinacalcet HCl shows a dose-proportional increase in exposure over the range of 25 to 200 mg once daily in patients on hemodialysis therapy, and kinetics were linear up to 200 mg once daily. The incidence of adverse events was similar between groups.

Block GA, Martin KJ, De Francisco ALM, et al.
Cinacalcet for Secondary Hyperparathyroidism in Patients Receiving Hemodialysis. New England Journal of Medicine. Vol. 350(15)(pp 1516-1525), 2004.

We report the results of two identical randomized, double-blind, placebo-controlled trials evaluating the safety and effectiveness of the calcimimetic agent cinacalcet hydrochloride. METHODS: Patients who were receiving hemodialysis and who had inadequately controlled SHPT despite standard treatment were randomly assigned to receive cinacalcet (371 patients) or placebo (370 patients) for 26 weeks. Once-daily doses were increased from 30 mg to 180 mg to achieve intact PTH levels of 250 pg per milliliter or less. The primary

end point was the percentage of patients with values in this range during a 14-week efficacy-assessment phase. RESULTS: Forty-three percent of the cinacalcet group reached the primary end point, as compared with 5 percent of the placebo group (P<0.001). Overall, mean PTH values decreased 43 percent in those receiving cinacalcet but increased 9 percent in the placebo group (P<0.001). The serum calcium-phosphate product declined by 15 percent in the cinacalcet group and remained unchanged in the placebo group (P<0.001). Cinacalcet effectively reduced PTH levels independently of disease severity or changes in vitamin D sterol dose. CONCLUSIONS: Cinacalcet lowers PTH levels and improves calcium-phosphorus homeostasis in patients receiving hemodialysis who have uncontrolled SHPT.

Malluche HH, Monier-Faugere MC, Wang G, et al.

Cinacalcet reduces bone turnover and bone marrow fibrosis in hemodialysis patients with secondary hyperparathyroidism. 41st ERA-EDTA Congress, May 15-18, 2004,Lisbon, Portugal, 2004; abstract MO16, available at www.era-edta.org/congresses.htm

The effects of the calcimimetic cinacalcet on bone turnover, bone marrow fibrosis, serum intact PTH (iPTH), bone-specific alkaline phosphatase (BALP), and N-telopeptide were investigated in a randomized, double-blind, placebo-controlled study in patients on chronic maintenance dialysis. Patients with iPTH levels ≥300 pg/mL on standard therapy were randomly assigned 2:1 to cinacalcet or placebo treatment. Doses were adjusted from 30 to 180 mg/day to achieve a target iPTH ≤250 pg/mL during a 24-week titration phase and a 28-week maintenance phase. Forty-eight patients (32 cinacalcet, 16 placebo) received treatment and 32 patients (19 cinacalcet, 13 placebo) had bone biopsies at baseline and after 1 year of treatment. At baseline, secondary HPT (elevated bone turnover, increased osteoblasts and osteoclasts, marrow fibrosis, and woven bone) was found in 16/19 patients randomized to cinacalcet and 11/13 patients randomized to placebo. Adynamic bone disease (ABD) was found in 1 patient in each group. Treatment with cinacalcet reduced iPTH (-51%), BALP (-18%), and N-telopeptide (-24%). After treatment, improvements in bone turnover parameters were observed in the cinacalcet group as reflected by reductions in activation frequency (-0.51/yr), bone formation rate/bone surface (-1.88 $mm^3/cm^2/yr$), marrow fibrosis (-1.99%), and numbers of osteoblasts (-202/100 mm) and osteoclasts (-64/100 mm). The placebo group showed reduction in activation frequency (-0.12/yr) and osteoclast number (-61/100 mm). At baseline and at end of study, mean values for mineralization parameters (mineralization lag time, osteoid thickness, and osteoid surface) were normal in both treatment groups. At end of study, mixed uremic osteodystrophy occurred in 4/13 patients in the placebo group, compared with 2/19 patients in the cinacalcet group. ABD developed in 3 patients treated with cinacalcet, 2 of whom had sustained oversuppression of PTH (<100 pg/mL). In conclusion, in patients with secondary HPT receiving dialysis, cinacalcet improved control of PTH, which was associated with reductions in bone turnover and bone marrow fibrosis.

Quarles LD, Sherrard DJ, Adler S, et al.

The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. Journal of the American Society of Nephrology. Vol. 14(3)(pp 575-583), 2003.

The current study evaluates the efficacy and safety of AMG 073 when added to conventional treatment of SHPT in ESRD. Seventy-one hemodialysis patients with uncontrolled SHPT, despite standard therapy with calcium, phosphate binders, and active vitamin D sterols, were treated in this 18-wk, dose-titration study with single daily oral doses of AMG 073/ placebo up to 100 mg. Changes in plasma PTH, serum calcium, serum phosphorus, and calcium-phosphate product levels were compared between AMG 073 and placebo groups. Mean PTH decreased by 33% in the AMG 073 patients compared with an increase of 3% in placebo patients (P = 0.001). A significantly greater proportion of AMG 073 patients (44%) had a mean PTH ≤ 250 pg/ml compared with placebo patients (20%; P = 0.029). Also, a significantly greater

proportion of AMG 073 patients (53%) had a decrease in PTH ≥ 30% compared with placebo patients (23%; P = 0.009). calcium-phosphate product levels decreased by 7.9% in AMG 073 patients compared with an increase of 11.3% in placebo patients (P = 0.013). Adverse event rates were low and mostly mild to moderate in severity; however, the incidence of vomiting was higher in AMG 073 patients. In this study, the calcimimetic AMG 073 at doses up to 100 mg for 18 wk provided a safe and effective means to attain significant reductions in PTH and calcium-phosphate product in ESRD patients. AMG 073 represents a novel and promising therapy to improve the management of SHPT.

Lindberg JS, Moe SM, Goodman WG, et al.
The calcimimetic AMG 073 reduces PTH and calcium x phosphorus in secondary hyperparathyroidism. Kidney International. Vol. 63(1)(pp 248-254), 2003.

Seventy-eight hemodialysis patients with SHPT were enrolled into this 18-week, double-blind, randomized, placebo-controlled, dose titration study. Daily oral AMG 073 doses were administered to determine the effect on PTH, serum calcium, phosphorus, and calcium-phosphate product. Results. The mean baseline PTH was similar in patients administered AMG 073 or placebo (632 +/- 280.1 pg/mL vs. 637 +/- 455.9 pg/mL, respectively). PTH decreased by 26.0% in the AMG 073-treated group, compared with an increase of 22.0% in the placebo group (P < 0.001). A greater proportion in the AMG 073 group (38%) had a decrease in PTH ≥30%, compared with the placebo group (8%) (P = 0.001). Decreases in PTH were independent of baseline vitamin D usage. Patients receiving AMG 073 had an 11.9% decrease in calcium-phosphate product compared with a 10.9% increase in the placebo group (P < 0.001). Use of vitamin D sterols, as well as both calcium and noncalcium-containing phosphate binders. were similar between treatment groups. Administration of AMG 073 was safe and well tolerated in this 18-week study. Conclusions. The calcimimetic AMG 073 decreases both PTH and calcium-phosphate product in hemodialysis patients with SHPT.

Goodman WG, Hladik GA, Turner SA, et al.
The calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. Journal of the American Society of Nephrology. Vol. 13(4)(pp 1017-1024), 2002.

Fifty-two hemodialysis patients with SHPT were given single orally administered doses of the calcimimetic agent AMG 073 ranging from 5 to 100 mg, or placebo. Plasma PTH levels decreased 2 h after 25-, 50-, 75-, or 100mg doses, falling by a maximum of 43 +/- 29%, 40 +/- 36%, 54 +/- 28%, or 55 +/- 39%, respectively. Plasma PTH levels decreased in all patients given doses of ≥25 mg but did not change in those who received placebo. In patients treated with daily doses of 25 or 50 mg of AMG 073 for 8 d, plasma PTH levels declined for the first 3 to 4 d and remained below baseline values after 8 d of treatment. Serum calcium concentrations aldecreased by 5 to 10% from pretreatment levels in patients given 50 mg of AMG 073 for 8 d, but values were unchanged in those who received lower doses. Serum phosphorus levels and values for the calcium-phosphate product both decreased after treatment with AMG 073. Thus, 8 d of treatment with AMG 073 effectively lowers plasma PTH levels and improves several disturbances in mineral metabolism that have been associated with soft tissue and vascular calcification and with adverse cardiovascular outcomes in patients with ESRD.

Goodman WG, Frazao JM, Goodkin DA, et al.
A calcimimetic agent lowers plasma parathyroid hormone levels in patients with secondary hyperparathyroidism.
Kidney International. Vol. 58(1)(pp 436-445), 2000.

Twenty-one patients undergoing hemodialysis three times per week with plasma PTH levels between 300 and 1200 pg/mL were randomly assigned to 15 days of treatment with either 100 mg of R-568 (N = 16) or placebo (N = 5). Plasma PTH and blood ionized calcium levels were measured at intervals of up to 24 hours after oral doses on days 1, 2, 3, 5, 8, 11, 12, and 15. Results: Pretreatment PTH levels were 599

+/- 105 (mean +/- SE) and 600 +/- 90 pg/mL in subjects given R-568 or placebo, respectively, and values on the first day of treatment did not change in those given placebo. In contrast, PTH levels fell by 66 +/- 5%, 78 +/- 3%, and 70 +/- 3% at one, two, and four hours, respectively, after initial doses of R-568, remaining below pretreatment values for 24 hours. Blood ionized calcium levels decreased after the first dose of R-568 but did not change in patients given placebo. Despite lower ionized calcium concentrations on both the second and third days of treatment, predose PTH levels were 422 +/- 70 and 443 +/- 105 pg/mL, respectively, in patients given R-568, and values fell each day by more than 50% two hours after drug administration. Predose PTH levels declined progressively over the first nine days of treatment with R-568 and remained below pretreatment levels for the duration of study. Serum total and blood ionized calcium concentrations decreased from pretreatment levels in patients given R-568, whereas values were unchanged in those given placebo. Blood ionized calcium levels fell below 1.0 mmol/L in 7 of 16 patients receiving R-568; five patients withdrew from study after developing symptoms of hypocalcemia, whereas three completed treatment after the dose of R-568 was reduced. Conclusions. The calcimimetic R-568 rapidly and markedly lowers plasma PTH levels in patients with SHPT caused by ESRD.

Other studies

Spiegel DM, Casey L, Bell S, Parker M, Chonchol M.
Achieving targets for bone and mineral metabolism: The impact of cinacalcet HCl in clinical practice. Hemodialysis International. Vol. 10(SUPPL. 2)(pp S24-S27), 2006.

The purpose of this study was to evaluate the effect of the introduction of combination algorithm for managing SHPT (SHPT) on phosphorus, calcium, and biointact PTH. The 61 patients who dialyzed in the facility from January 2004 (baseline) and who remained in the facility as of April 2005 (follow-up) were included in the study. In the baseline period, 37 (61%) of the patients received paricalcitol at some time during the 3-month observation period. In the follow-up period, 19% or 31% of the patients received cinacalcet HCl. Of those not receiving cinacalcet HCl, 67% had PTH at or below target, 17% were felt to be noncompliant with oral meds, 7% had low calcium, and 10% either could not get the medication or were not switched to the combination pathway. Compared with the baseline period, the percent of patients who met the PTH target increased from 19.7% to 37.7%, $p<0.05$. The percent of patients meeting all 4 targets increased from 14.8% to 24.6%, although this did not reach statistical significance. The introduction of cinacalcet HCl into a treatment algorithm for management of SHPT resulted in a significant increase in the percentage of patients achieving the PTH target while maintaining the other mineral metabolism targets.

Velasco N, MacGregor MS, Innes A, et al.
Successful treatment of calciphylaxis with cinacalcet - An alternative to parathyroidectomy? Nephrology Dialysis Transplantation. Vol. 21(7)(pp 1999-2004), 2006.

No abstract available.

Moe SM, Cunningham J, Bommer J, et al.
Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl. Nephrology Dialysis Transplantation. Vol. 20(10)(pp 2186-2193), 2005.

Dialysis patients with SHPT [PTH level ≥300 pg/ml] who were enrolled in one of four phase 2 placebo-controlled studies were eligible to enrol in an open-label extension study in which all patients received cinacalcet. For this extension study, cinacalcet was initiated at 30 mg in all patients and the dose was escalated to a maximum of 180 mg once daily if PTH concentrations were >250 pg/ml. Use of concomitant vitamin D sterols and phosphate binders was not restricted. Results. The analysis of all patients (n = 59) completing 100 weeks of cinacalcet treatment showed long-term control of PTH and calcium-phosphate product. Approximately 55% achieved a PTH concentration ≤300 pg/ml at the week-100

study visit, and ~60% had at least a 30% reduction in PTH from baseline. Serum calcium, phosphorus and the calcium-phosphate product did not increase during the study. Concomitant vitamin D sterol and phosphate binder therapy remained stable. Cinacalcet was safe and generally well tolerated at doses up to 180 mg/day. Conclusions. In this long-term study, cinacalcet effectively sustained reductions in PTH for up to 3 years without increasing concentrations of serum calcium, phosphorus or calcium-phosphate product.

Moe SM, Chertow GM, Coburn JW, et al. Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCl. Kidney International. Vol. 67(2)(pp 760-771), 2005.

The ability of cinacalcet HCl (Sensipar) treatment to improve achievement of target levels of PTH, calcium, phosphorus, and calcium-phosphate product was investigated in subjects on dialysis with secondary HPT. Methods. Data were combined from three placebo-controlled, double-blind, 26-week studies with similar design that randomized 1136 subjects on dialysis to receive traditional therapy plus cinacalcet or placebo. Oral cinacalcet was titrated from 30 to 180 mg/day. Achievement of K/DOQI goals was determined for each treatment group overall and for subgroups defined by baseline intact PTH (iPTH) and Ca x P levels. Results. Cinacalcet-treated subjects were more likely to achieve a mean iPTH ≤300 pg/mL (31.8 pmol/L) than were control subjects on traditional therapy (56% vs. 10%, P <0.001). Cinacalcet-treated subjects were more likely to achieve concentrations of serum calcium within 8.4 to 9.5 mg/dL (2.10-2.37 mmol/L) and serum phosphorus within 3.5 to 5.5 mg/dL (1.13-1.78mmol/L) than were control subjects (49% vs. 24% and 46% vs. 33%, P < 0.001 for each). Cinacalcet alimproved achievement of Ca x P < 55 mg^2/dL^2 (4.44 $mmol^2/L^2$) and concurrent achievement of Ca x P <55 mg^2/dL^2 (4.44 $mmol^2/L^2$) and iPTH ≤300 pg/mL (31.8 pmol/L) (65% vs. 36% and 41% vs. 6%, P < 0.001 for each). Conclusion. In subjects on dialysis with secondary HPT, cinacalcet facilitates achievement of the K/DOQI-recommended targets for PTH, calcium, phosphorus, and calcium-phosphate product.

Use in Children

No papers found.

Predictors of response

No papers found.

Safety

No papers found.

Health economics, resources, risk/benefit

Cunningham J, Danese M, Olson K, et al. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. Kidney International. Vol. 68(4)(pp 1793-1800), 2005.

We undertook a combined analysis of safety data (parathyroidectomy, fracture, hospitalizations, and mortality) from 4 similarly designed randomized, double - blind, placebo-controlled clinical trials enrolling 1184 subjects (697 cinacalcet, 487 control) with ESRD and uncontrolled secondary HPT (intact PTH ≥300 pg/mL). Cinacalcet or placebo was administered to subjects receiving standard care for hyperphosphatemia and secondary HPT (phosphate binders and vitamin D). Relative risks (RR) and 95% CI were calculated using proportional hazards regression with follow-up times from 6 to 12 months. HRQOL data were obtained from the Medical Outcomes Study Short Form-36 (SF-36), and the Cognitive Functioning scale from the Kidney Disease Quality of Life instrument (KDQOL-CF). Results. Randomization to cinacalcet resulted in significant reductions in the risk of parathyroidectomy (RR 0.07, 95% CI 0.01-0.55), fracture (RR 0.46, 95% CI 0.22-0.95), and cardiovascular hospitalization (RR0.61,

95% CI 0.43-0.86) compared with placebo. Changes in HRQOL favored cinacalcet, with significant changes observed for the SF-36 Physical Component Summary score and the specific domains of Bodily Pain and General Health Perception. Conclusion. Combining results from 4 clinical trials, randomization to cinacalcet led to significant reductions in the risk of parathyroidectomy, fracture, and cardiovascular hospitalization, along with improvements in self-reported physical function and diminished pain. These data suggest that, in addition to its effects on PTH and mineral metabolism, cinacalcet had favorable effects on important clinical outcomes.

Phosphate Binders

Efficacy

RCTs - sevelamer

Liu Y-L, Lin H-H, Yu C-C, et al. A comparison of sevelamer hydrochloride with calcium acetate on biomarkers of bone turnover in hemodialysis patients. Renal Failure. Vol. 28(8)(pp 701-707), 2006.

In this prospective, open-label, randomized, active-controlled study, 70 patients (38 men and 32 women) with hyperphosphatemia (serum phosphorus level >6.0 mg/dL) underwent a two-week washout period and were randomly selected to receive sevelamer hydrochloride (n = 37) or calcium acetate (n = 33) for eight weeks. Changes in serum levels of intact PTH, alkaline phosphatase (Alk-P), phosphorus, and calcium were measured and compared. Results. After eight weeks of treatment, calcium acetate lowered iPTH levels significantly more than sevelamer hydrochloride did (-178.0 vs. -69.0 pg/mL, p = 0.0019). Levels of Alk-P were significantly elevated in patients given sevelamer hydrochloride compared with levels in those given calcium acetate treatment (24.09 vs. 7.45 U/L, p = 0.0014). Changes in serum phosphorus levels did not differ between sevelamer hydrochloride (-1.93 mg/dL) and calcium acetate (-2.5 mg/dL) at the end of the study (p = 0.0514). Changes in the calcium and phosphorous product did not significantly differ between the sevelamer-hydrochloride group (-18.06 mg 2 /dL2) and the calcium-acetate group (-19.05 mg 2 /dL2 , p = 0.6764). Fifteen patients (45.5%) treated with calcium acetate had hypercalcemia (serum-adjusted calcium level >10.5 mg/dL); the rate was significantly higher than that of patients treated with sevelamer (five [13.5%] of 37, p = 0.0039). Conclusion. Treatment with sevelamer hydrochloride had the advantage of maintaining stable iPTH levels and elevating Alk-P levels while lowering serum phosphorus levels and calcium-phosphate product.

Fischer D, Cline K, Plone MA, et al. Results of a Randomized Crossover Study Comparing Once-Daily and Thrice-Daily Sevelamer Dosing. American Journal of Kidney Diseases. Vol. 48(3)(pp 437-444), 2006.

Twenty-four patients were enrolled in this study, 21 of whom were randomly assigned to sevelamer administration at their previously prescribed dose, either once daily with the largest meal or thrice daily with meals, with crossover to the other regimen after 4 weeks. Eighteen patients completed both treatment periods. The primary efficacy measure for which the study was powered is comparison of the effect of once-daily versus standard thrice-daily sevelamer dosing on serum phosphorus level control, determined by using equivalence testing. Secondary efficacy measures are the effects of the 2 regimens on serum calcium level corrected for albumin level; calcium-phosphate product; albumin; intact PTH; total, low-density lipoprotein, high-density lipoprotein, and non-high-density lipoprotein cholesterol; and triglyceride levels. Results: Once-daily sevelamer was as effective as thrice-daily dosing of sevelamer in controlling serum phosphorus, calcium, calcium-phosphate product, serum albumin, and serum lipid levels. Bioequivalence was not shown for intact PTH, likely because of high variability. Mean serum phosphorus levels were 4.6 +/- 0.3 mg/dL (1.49 +/- 0.10 mmol/L) during thrice-daily dosing and 5.0 +/- 0.3 mg/dL (1.61 +/- 0.10 mmol/L) during once-daily dosing. The average prescribed dose of sevelamer during both treatment regimens was 6.7 +/- 2.4 g. Routine

laboratory measures were similar in the 2 groups. Both regimens were well-tolerated. Conclusion: Despite concerted patient-directed educational efforts, phosphorus level control in patients with renal failure is suboptimal and contributes to increased mortality risk. Once-daily sevelamer could simplify these regimens and encourage medication compliance, perhaps improving hyperphosphatemia management.

Block GAD,Spiegel M, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int **68**(4): 1815-24, 2005.

One hundred and twenty-nine patients new to hemodialysis were randomized to receive calcium containing phosphate binders or the noncalcium phosphate binder sevelamer hydrochloride. Subjects underwent electron beam computed tomography scanning (EBCT) at entry into the study and again at 6, 12, and 18 months. RESULTS: One hundred and nine patients underwent baseline and at least one additional assessment of coronary calcification. At baseline, 37% of sevelamer treated and 31% of calcium treated patients had no evidence of coronary calcification. No subject with a zero coronary artery calcium score (CACS) at baseline progressed to a CACS >30 over 18 months. Subjects with a CACS > 30 at baseline showed progressive increases in CACS in both treatment arms ($P < 0.05$ for each time point in both groups). Subjects treated with calcium containing phosphate binders showed more rapid and more severe increases in CACS when compared with those receiving sevelamer hydrochloride ($P= 0.056$ at 12 months, $P= 0.01$ at 18 months). CONCLUSION: New hemodialysis patients with no evidence of coronary calcification showed little evidence of disease development over 18 months independent of phosphate binder therapy. However, subjects with evidence of at least mild coronary calcification had significant progression at 6, 12, and 18 months. Use of calcium containing phosphate binders resulted in more rapid progression of coronary calcification than did use of sevelamer hydrochloride.

Iwasaki Y, Takami H, Tani M, et al. Efficacy of combined sevelamer and calcium carbonate therapy for hyperphosphatemia in Japanese hemodialysis patients. Therapeutic Apheresis & Dialysis. Vol. 9(4)(pp 347-351), 2005.

We prospectively evaluated the clinical efficacy of the combination of sevelamer hydrochloride and calcium carbonate ($CaCO_3$) for hyperphosphatemia. The study group comprised 65 HD patients who had been administered $CaCO_3$ (≥1500 mg/ day) for hyperphosphatemia [≥6.0 mg/dL (≥1.94 mmol/L)]. At the beginning of the study the dose of $CaCO_3$ was reduced by 1500 mg/day and the patients divided into two groups according to the dose of additional sevelamer hydrochloride: group A 2250 mg/day; group B 3000 mg/ day. Oral active vitamin D therapy was unchanged. Fourteen patients (21.5%) dropped out because of adverse effects and of the 51 remaining patients 35 (53.8%) suffered from gastrointestinal problems. Serum phosphate concentration decreased significantly [from 7.5 +/- 0.8 mg/ dL (2.42 +/- 0.26 mmol/L) to 6.6 +/- 1.3 mg/dL (2.13 +/- 0.42 mmol/L), $P < 0.01$] in group B only after the 8 weeks of combination therapy. The calcium-phosphate product also decreased in group B only [from 74.4 +/- 13.4 mg2 /dL^2 (5.99 +/- 1.07 $mmol^2/l^2$) to 63.7 +/- 15.8 mg^2 /dL^2 (5.13 +/- 1.27 $mmol^2/l^2$), $P < 0.001$]. The combination of sevelamer hydrochloride and $CaCO_3$ is a suitable regimen for hyperphosphatemia treatment in HD patients because it avoids both the hypercalcemia of $CaCO_3$ and the adverse effects of sevelamer hydrochloride when each is used as single-drug therapy. The ability of sevelamer hydrochloride to decrease the serum phosphate concentration is 2/3 (2250/1500 mg) that of $CaCO_3$.

Koiwa FN, Onoda N, et al. Prospective randomized multicenter trial of sevelamer hydrochloride and calcium carbonate for the treatment of hyperphosphatemia in hemodialysis patients in Japan. Ther Apher Dial **9**(4): 340-6, 2005.

A prospective, randomized open-label trial of sevelamer hydrochloride with or without calcium carbonate ($CaCO_3$) involved 86

hemodialysis patients in Japan. The dosage of CaCO3 was fixed at 3.0 g/day for the 12-week study. After the first 4 weeks all subjects were changed from CaCO3 to sevelamer 3.0 g/day for another 4 weeks, then allocated randomly to three groups for the final 4 weeks: group A, sevelamer 6.0 g/day; group B, sevelamer 3.0 g/day and CaCO3 3.0 g/day; group C, CaCO3 3.0 g/day. The target serum phosphorous concentration (P)=5.5 mg/dL and the corrected calcium concentration (Ca) was 9.0-10.0 mg/dL. Of the 86 patients, 62 finished the study without a change of dosage and their data were analyzed (group A, N=16; group B, N=26; group C, N=20). At week 8 compared with week 4, the concentration of P increased from 5.7+/-1.4 to 6.4+/-1.7 mg/dL in group A, and decreased significantly in groups B and C, and in group B compared with groups A and C; groups A and C had similar concentrations at week 8. The Ca concentration decreased significantly from 9.7+/-1.0 to 9.1+/-0.7 mg/dL after the change to sevelamer. At week 8 Ca was not significantly changed in group A, whereas a significant increase occurred in groups B and C. Side-effects with sevelamer administration occurred in 34 of the 86 patients and 24 dropped out of the study, with a high frequency in group A (13/29; 44.8%). In conclusion, there was an additive effect of sevelamer for the treatment of hyperphosphatemia with CaCO3. The combination therapy was better tolerated and showed higher patient compliance than CaCO3 or sevelamer monotherapy.

Ferramosca E, Burke S, Chasan-Taber S, et al.

Potential antiatherogenic and anti-inflammatory properties of sevelamer in maintenance hemodialysis patients. American Heart Journal. Vol. 149(5)(pp 820-825), 2005.

One hundred eight patients undergoing maintenance hemodialysis were randomized to sevelamer or calcium acetate as treatment for hyperphosphatemia. A coronary artery calcium score, as a measure of plaque burden, was calculated at baseline and 1 year, along with serial measurements of serum lipoproteins, $beta_2$- microglobulin, and high-sensitivity C-reactive protein (hs-CRP). At 1 year, coronary artery calcium score progressed significantly from baseline in calcium acetate-treated subjects ($P < .001$) but not in sevelamer-treated patients ($P = NS$). Total cholesterol ($P < .0001$), low-density lipoprotein cholesterol ($P < .0001$), apolipoprotein B ($P < .0001$), $beta_2$-microglobulin ($P = .018$), and hs-CRP ($P < .002$) decreased, and high-density lipoprotein increased significantly ($P = .036$) from baseline in the sevelamer-treated subjects but not in subjects treated with calcium acetate despite the more frequent use of statins in the latter group (46% vs 22%, $P < .05$). The changes in total and low-density lipoprotein cholesterol, apolipoprotein B, and hs-CRP were significantly different between treatment groups (all $P < .01$). Conclusions: Sevelamer leads to favorable changes in lipids and inflammatory markers with potentially useful antiatherogenic effects in hemodialysis patients

Garg JP, Chasan-Taber S, Blair A, et al.

Effects of sevelamer and calcium-based phosphate binders on uric acid concentrations in patients undergoing hemodialysis: A randomized clinical trial. Arthritis & Rheumatism. Vol. 52(1)(pp 290-295), 2005.

Two hundred subjects undergoing maintenance hemodialysis were randomly assigned to receive either sevelamer or calcium-based phosphorus binders in an international, multicenter, clinical trial. Data on baseline and end-of-study uric acid concentrations were available in 169 subjects (85%); the change in uric acid concentration from baseline to the end of the study was the outcome of interest. Results. Baseline clinical characteristics, including mean uric acid concentrations, were similar in subjects randomly assigned to receive sevelamer and calcium-based phosphate binders. The mean change in uric acid concentration (from baseline to the end of the study) was significantly larger in sevelamer-treated subjects (-0.64 mg/dl versus -0.26 mg/dl; $P = 0.03$). The adjusted mean change in uric acid concentration was more pronounced when the effects of age, sex, diabetes, vintage (time since initiation of dialysis), dialysis dose, and changes in blood urea nitrogen and bicarbonate

concentrations were considered (-0.72 mg/dl versus -0.15 mg/dl; P = 0.001). Twenty-three percent of sevelamer-treated subjects experienced a study-related reduction in the concentration of uric acid equal to -1.5 mg/dl or more, compared with 10% of calcium-treated subjects (P = 0.02). Conclusion. In a randomized clinical trial comparing sevelamer and calcium-based phosphate binders, treatment with sevelamer was associated with a significant reduction in serum uric acid concentrations.

Qunibi WY, Hootkins RE, et al. Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renagel Evaluation (CARE Study). Kidney Int 65(5): 1914-26, 2004.

To determine whether calcium acetate or sevelamer hydrochloride best achieves recently recommended treatment goals of phosphorus </=5.5 mg/dL and calcium-phosphate product </=55 mg(2)/dL(2), we conducted an 8-week randomized, double-blind study in 100 hemodialysis patients. RESULTS: Comparisons of time-averaged concentrations (weeks 1 to 8) demonstrated that calcium acetate recipients had lower serum phosphorus (1.08 mg/dL difference, P= 0.0006), higher serum calcium (0.63 mg/dL difference, P < 0.0001), and lower Ca x P (6.1 mg(2)/dL(2) difference, P= 0.022) than sevelamer recipients. At each week, calcium acetate recipients were 20% to 24% more likely to attain goal phosphorus [odds ratio (OR) 2.37, 95% CI 1.28-4.37, P= 0.0058], and 15% to 20% more likely to attain goal Ca x P (OR 2.16, 95% CI 1.20-3.86, P= 0.0097). Transient hypercalcemia occurred in 8 of 48 (16.7%) calcium acetate recipients, all of whom received concomitant intravenous vitamin D. By regression analysis hypercalcemia was more likely with calcium acetate (OR 6.1, 95% CI 2.8-13.3, P < 0.0001). Week 8 intact PTH levels were not significantly different. Serum bicarbonate levels were significantly lower with sevelamer hydrochloride treatment (P < 0.0001). CONCLUSION: Calcium acetate controls serum phosphorus and calcium-phosphate product more effectively than sevelamer hydrochloride. Cost-benefit analysis indicates that in the absence of hypercalcemia, calcium acetate should remain the treatment of choice for hyperphosphatemia in hemodialysis patients.

Braun J, Asmus H-G, Holzer H, et al. Long-term comparison of a calcium-free phosphate binder and calcium carbonate - Phosphorus metabolism and cardiovascular calcification. Clinical Nephrology. Vol. 62(2)(pp 104-115), 2004.

114 adult hemodialysis patients were randomly assigned to open label sevelamer or CaCO3 for 52 weeks. Study efficacy endpoints included changes in serum phosphorus, calcium, calcium-phosphate product, and lipids. In addition, initial and sequential electron beam computerized tomography scans were performed to assess cardiovascular calcification status and change during follow-up. Safety endpoints were serum biochemistry, blood cell counts and adverse events. Results: Patients receiving sevelamer had a similar reduction in serum phosphorus as patients receiving CaCO3 (sevelamer -0.58 +/- 0.68 mmol/l, CaCO3 -0.52 +/- 0.50 mmol/l; p = 0.62). Reductions in calcium-phosphate product were not significantly different (sevelamer -1.4 +/- 1.7 $mmol^2/1^2$, CaCO3 -0.9 +/- 1.2 $mmol^2/1^2$ p = 0.12). CaCO3 produced significantly more hypercalcemia (> 2.8 mmol/l in 0% sevelamer and 19% CaCO3 patients, p < 0.01) and suppressed intact PTH below 150 pg/ml in the majority of patients. Sevelamer patients experienced significant (p < 0.01) reductions in total (-1.2 +/- 0.9 mmol/1, -24%) and LDL cholesterol (-1.2 +/- 0.9 mmol/1, -30%). CaCO3 patients had significant increases in coronary artery (median +34%, p < 0.01) and aortic calcification (median +32%, p < 0.01) that were not observed in sevelamer-treated patients. Patients on sevelamer required more grams of binder (sevelamer 5.9 g vs. CaCO3 3.9 g) and experienced more dyspepsia than patients on calcium carbonate. Conclusions: Sevelamer is an effective phosphate binder that unlike calcium carbonate is not associated with progressive cardiovascular calcification in hemodialysis patients.

Sadek TH, Mazouz H, et al. Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in

dialysis patients: an open-label, randomized study. Nephrol Dial Transplant 18(3): 582-8, 2003.

We compared for 5 months two strategies for controlling moderate hyperparathyroidism: CaCO(3) alone vs sevelamer in conjunction with measures to increase calcium balance. METHODS: Forty-two patients were randomized: 21 continued their treatment with 4.8 g/day CaCO(3) and 21 were switched to sevelamer (initial dose: 2.4 g/day, increased to 4.4 g/day). Each month, when serum-corrected calcium decreased below 2.30 mmol/l, dialysate calcium was increased or alphacalcidol was given at each dialysis session, according to serum PO(4) levels. The following parameters were monitored: serum Ca, PO(4), bicarbonate and protein, weekly; and serum PTH, 25-OH vitamin D and total, LDL and HDL cholesterol monthly. RESULTS: Except for higher serum phosphate at month 1, lower serum bicarbonate at month 2 and lower LDL cholesterol at month 5 in the sevelamer group, no difference was found between the two groups. Compared with baseline levels, PTH increased and 25-OH vitamin D decreased significantly in both groups, these two parameters being inversely correlated. CONCLUSIONS: Given comparable control of plasma calcium, phosphate and 25-OH vitamin D, PTH control is comparable in both strategies. Sevelamer does not induce greater vitamin D depletion than CaCO(3). The transient decrease of serum bicarbonate after discontinuation of CaCO(3) in the sevelamer group suggests a less optimal prevention of acidosis. The sevelamer-induced decrease in LDL cholesterol gives this drug a potential advantage in cardiovascular prevention.

Chertow GM, Raggi P, McCarthy JT, et al. The effects of sevelamer and calcium acetate on proxies of atherosclerotic and arteriosclerotic vascular disease in hemodialysis patients. American Journal of Nephrology. Vol. 23(5)(pp 307-314), 2003.

To determine whether treatment with calcium acetate was specifically associated with hypercalcemia and progressive vascular calcification, we conducted an analysis restricted to 108 hemodialysis patients randomized to calcium acetate or sevelamer and followed for one year. Results: The reduction in serum phosphorus was roughly equivalent with both agents (calcium acetate -2.5 +/- 1.8 mg/dl vs. sevelamer -2.8 +/- 2.0 mg/dl, p = 0.53). Subjects given calcium acetate were more likely to develop hypercalcemia (defined as an albumin-corrected serum calcium ≥ 10.5 mg/dl) (36 vs. 13%, p = 0.015). Treatment with calcium acetate (mean 4.6 +/- 2.1 g/day - equivalent to 1.2 +/- 0.5 g of elemental calcium) led to a significant increase in EBT-determined calcification of the coronary arteries (mean change 182 +/- 350, median change +20, p = 0.002) and aorta (mean change 181 +/- 855, median change +73, p < 0.0001). These changes were similar in magnitude to those seen with calcium carbonate. There were no significant changes in calcification among sevelamer-treated subjects. Conclusion: Despite purported differences in safety and efficacy relative to calcium carbonate, calcium acetate led to hypercalcemia and progressive vascular calcification in hemodialysis patients.

Chertow GM, Burke SK, et al. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 62(1): 245-52, 2002.

We conducted a randomized clinical trial comparing sevelamer, a non-absorbed polymer, with calcium-based phosphate binders in 200 hemodialysis patients. Study outcomes included the targeted concentrations of serum phosphorus, calcium, and intact PTH, and calcification of the coronary arteries and thoracic aorta using a calcification score derived from electron beam tomography. RESULTS: Sevelamer and calcium provided equivalent control of serum phosphorus (end-of-study values 5.1 +/- 1.2 and 5.1 +/- 1.4 mg/dL, respectively, P = 0.33). Serum calcium concentration was significantly higher in the calcium-treated group (P = 0.002), and hypercalcemia was more common (16% vs. 5% with sevelamer, P = 0.04). More subjects in the calcium group had end-of-study intact PTH below the target of 150 to 300 pg/mL (57% vs. 30%, P = 0.001). At study completion, the median absolute calcium score in the coronary arteries and

aorta increased significantly in the calcium treated subjects but not in the sevelamer-treated subjects (coronary arteries 36.6 vs. 0, P = 0.03 and aorta 75.1 vs. 0, P = 0.01, respectively). The median percent change in coronary artery (25% vs. 6%, P = 0.02) and aortic (28% vs. 5%, P = 0.02) calcium score also was significantly greater with calcium than with sevelamer. CONCLUSIONS: Compared with calcium-based phosphate binders, sevelamer is less likely to cause hypercalcemia, low levels of PTH, and progressive coronary and aortic calcification in hemodialysis patients

Chertow GM, Burke SK, et al. (1997). Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. Am J Kidney Dis 29(1): 66-71, 1997.

We evaluated the efficacy of cross-linked poly[allylamine hydrochloride] (RenaGel; Geltex Pharmaceuticals, Waltham, MA), a nonabsorbable calcium- and aluminum-free phosphate binder, in a randomized, placebo-controlled, double-blind trial of 36 maintenance hemodialysis patients followed over an 8-week period. RenaGel was found to be as effective as calcium carbonate or acetate as a phosphate binder. The reduction in serum phosphorus was significantly greater after 2 weeks of treatment with RenaGel (6.6 +/- 2.1 mg/dL to 5.4 +/- 1.5 mg/dL) compared with placebo (7.0 +/- 2.1 mg/dL to 7.2 +/- 2.4 mg/dL; P = 0.037). There was no significant change in serum calcium concentration in either treatment group. The total serum cholesterol and low-density lipoprotein cholesterol fraction were significantly reduced in RenaGel-treated patients compared with placebo-treated patients (P = 0.013 and P = 0.003, respectively) without a concomitant reduction in high-density lipoprotein cholesterol (P = 0.93). There was no difference among recipients of RenaGel and placebo in terms of adverse events. RenaGel is a safe and effective alternative to oral calcium for the management of hyperphosphatemia in ESRD.

Bleyer AJ, Burke SK, Dillon M, et al. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. American Journal of Kidney Diseases. Vol. 33(4)(pp 694-701), 1999.

This investigation describes the use of a calcium- and aluminum-free phosphate-binding polymer in hemodialysis patients and compares it with a standard calcium-based phosphate binder. An open-label, randomized, crossover study was performed to evaluate the safety and effectiveness of sevelamer hydrochloride in controlling hyperphosphatemia in hemodialysis patients. After a 2-week phosphate binder washout period, stable hemodialysis patients were administered either sevelamer or calcium acetate, and the dosages were titrated upward to achieve improved phosphate control over an 8-week period. After a 2-week washout period, patients crossed over to the alternate agent for 8 weeks. Eighty-four patients from eight centers participated in the study. There was a similar decrease in serum phosphate values over the course of the study with both sevelamer (-2.0 +/- 2.3 mg/dL) and calcium acetate (- 2.1 +/- 1.9 mg/dL). Twenty-two percent of patients developed a serum calcium greater than 11.0 mg/dL while receiving calcium acetate, versus 5% of patients receiving sevelamer (P < 0.01). The incidence of hypercalcemia for sevelamer was not different from the incidence of hypercalcemia during the washout period. Patients treated with sevelamer also sustained a 24% mean decrease in serum low-density lipoprotein cholesterol levels. Sevelamer was effective in controlling hyperphosphatemia without resulting in an increase in the Incidence of hypercalcemia seen with calcium acetate. This agent appears quite effective in the treatment of hyperphosphatemia in hemodialysis patients, and its usage may be advantageous in the treatment of dialysis patients.

Chertow GM, Dillon M, Burke SK, et al. A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium. Clinical Nephrology. Vol. 51(1)(pp 18-26), 1999.

We performed a randomized clinical trial to compare the efficacy of RenaGel alone and RenaGel with calcium, using the serum phosphorus concentration and intact PTH as the principal outcomes of interest. Calcium (900 mg elemental) was provided as a once nightly dose on an empty stomach. 71 patients were randomized and included in the intent-to-treat population; 55 completed the 16-week study period (2 weeks washout, 12 weeks treatment, 2 weeks washout). 49% of subjects were taking vitamin D metabolites. Results: Serum phosphorus and PTH rose significantly when patients stopped their phosphate binders during both washout periods. RenaGel and RenaGel with calcium were equally effective at reducing serum phosphorus (mean change -2.4 mg/dL vs. -2.3 mg/dL). RenaGel with calcium was associated with a small increase in serum calcium (mean change 0.3 mg/dL vs. 0.0 mg/dL in RenaGel group, P = 0.09) that was not statistically significant. During the treatment phase, the reduction in PTH tended to be greater in the RenaGel with calcium group (median change -67.0 vs. -22.5 pg/mL in RenaGel group, P = 0.07). Non-users of vitamin D metabolites treated with RenaGel with calcium experienced a significant decrease in PTH (median change -114.5 vs. -22 pg/mL in RenaGel group, P = 0.006). Adverse events were seen with equal frequency in both groups, being generally mild in intensity, and rarely attributable to the drugs. Conclusion: We conclude that RenaGel and RenaGel with calcium are similarly effective in the treatment of ESRD-related hyperphosphatemia. Provision of supplemental calcium or metabolites of vitamin D with RenaGel may enhance control of hyperparathyroidism.

RCTs - lanthanum

Chiang S-S, Chen J-B, Yang W-C.
Lanthanum carbonate (Fosrenol) efficacy and tolerability in the treatment of hyperphosphatemic patients with end-stage renal disease. Clinical Nephrology. Vol. 63(6)(pp 461-470), 2005.

Following a one- to three-week washout phase and a four-week, open-label lanthanum carbonate dose-titration phase, male and female hemodialysis patients were randomized (1:1) to receive either lanthanum carbonate or placebo for four weeks. The primary efficacy parameter of the study was the control of serum phosphorus levels (≤ 1.8 mmol/l [≤ 5.6 mg/dl]). Secondary endpoints included the profile of serum phosphorus during titration and PTH, calcium, and calcium-phosphate product levels. The safety and tolerability of lanthanum carbonate were assessed by monitoring adverse events throughout the study. Results: Mean serum phosphorus level at the end of washout was 2.5 +/- 0.5 mmol/l (7.7 +/- 1.5 mg/dl; n = 73), and there was no evidence of a difference in levels between the treatment groups pre-randomization. At the end of the study, lanthanum carbonate-treated patients had significantly lower phosphorus levels (1.6 +/- 0.5 mmol/l [5.1 +/- 1.5 mg/dl]; n = 30) than those receiving placebo (2.3 +/- 6.4 mmol/l [7.2 +/- 1.3 mg/dl]; n = 31; p < 0.001). In addition, a significantly higher proportion of patients receiving lanthanum carbonate had controlled serum phosphorus levels (60%) compared with the placebo group (10%; p < 0.001). calcium-phosphate product levels were also significantly lower in the lanthanum carbonate group at the end of randomized treatment (p < 0.001). Lanthanum carbonate was well tolerated; only one serious adverse event was reported, which was unrelated to treatment. Conclusions: Lanthanum carbonate was shown to be an effective and well-tolerated phosphate binder for the treatment of hyperphosphatemia in Chinese patients with ESRD. This finding supports the results of previous US and European studies, which have also shown that lanthanum carbonate treatment effectively controls serum phosphorus levels.

Hutchison AJ, Maes B, Vanwalleghem J, et al.
Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: A 6-month, randomized, comparative trial versus calcium carbonate. Nephron Clinical Practice. Vol. 100(1)(pp c8-c19), 2005.

This study compares lanthanum carbonate with calcium carbonate for control of serum phosphate in hemodialysis patients.

Methods: In this European multicentre study, 800 patients were randomised to receive either lanthanum or calcium carbonate and the dose titrated over 5 weeks to achieve control of serum phosphate. Serum levels of phosphate, calcium and PTH were followed over the following 20 weeks. Results: Around 65% of patients in each group achieved phosphate control, but in the calcium carbonate group this was at the expense of significant hypercalcemia (20.2% of patients vs. 0.4%). Consequently, calcium-phosphate product tended to be better controlled in the lanthanum group. Conclusion: This 6-month study demonstrates that serum phosphate control with lanthanum carbonate (750-3,000 mg/day) is similar to that seen with calcium carbonate (1,500-9,000 mg/day), but with a significantly reduced incidence of hypercalcemia. Lanthanum carbonate is well tolerated and may be more effective in reducing calcium-phosphate product than calcium carbonate.

Al-Baaj F, Speake M, Hutchison AJ. Control of serum phosphate by oral lanthanum carbonate in patients undergoing haemodialysis and continuous ambulatory peritoneal dialysis in a short-term, placebo-controlled study. Nephrology Dialysis Transplantation. Vol. 20(4)(pp 775-782), 2005.

This was a double-blind, placebo-controlled, parallel-group study consisting of three phases: a 2 week washout period; a 4 week, open-label, dose-titration phase; and a 4 week, double-blind, placebo-controlled phase. After washout, patients (n = 59) received lanthanum (375 mg/day), titrated up to a maintenance dose (maximum: 2250 mg) that achieved control of serum phosphate levels between 1.3 and 1.8 mmol/l (4.03-5.58 mg/dl). After titration, patients were randomized to receive their maintenance dose of lanthanum (n = 17) or placebo (n = 19) for 4 weeks. Control of serum phosphate was the primary efficacy assessment. Levels of calcium, PTH, calcium-phosphate product and lanthanum as well as adverse events were evaluated. Results. By the end of titration, 70% of patients had serum phosphate levels ≤1.8 mmol/l. Lanthanum carbonate continued to control serum phosphate levels in the double-blind phase. At the end of the study, 64.7% of lanthanum carbonate-treated patients were controlled compared with 21.4% in the placebo group. Results in patients receiving continuous ambulatory peritoneal dialysis (CAPD) were similar to those seen in the group as a whole. Mean PTH levels (P = 0.41) and calcium-phosphate product (P < 0.001) were both higher in the placebo than the lanthanum carbonate group. Conclusions. Lanthanum carbonate is an effective phosphate binder able to control serum phosphate and calcium-phosphate product.

Finn WF, Joy MS, Hladik G, et al. Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receiving hemodialysis. Clinical Nephrology. Vol. 62(3)(pp 193-201), 2004.

196 patients (≥ 18 years) receiving hemodialysis for at least 6 months entered a 1- to 3-week, single-blind, placebo run-in phase. Of these, 145 patients were randomized to a double-blind phase in which they received placebo or lanthanum carbonate in daily lanthanum doses of 225, 675, 1,350 or 2,250 mg for 6 weeks. Serum levels of phosphorus, calcium and PTH, and adverse events were monitored throughout the study. Results: The intent-to-treat analysis (n = 144) showed significant dose-related reductions in serum phosphorus at lanthanum doses of 675, 1,350 and 2,250 mg. After 6 weeks of treatment, phosphorus levels were significantly lower in the lanthanum groups receiving 1,350 mg/day and 2,250 mg/day, compared with the placebo group (respective changes from randomization: -0.95 +/- 1.39 mg/dl (-0.31 +/- 0.45 mmol/l), -1.13 +/- 2.01 mg/dl (-0.36 +/- 0.65 mmol/l), 0.75 +/- 1.47 mg/dl (0.24 +/- 0.47 mmol/l), p < 0.001). Significant reductions in serum phosphorus, compared with placebo, occurred in the lanthanum 1,350 mg/day group from the second week of treatment and in the 2,250 mg/day group from the first week of treatment. Adverse events were mainly gastrointestinal (e.g. nausea and vomiting). Treatment-related adverse events occurred in 39% of patients treated with lanthanum carbonate and 44% of the placebo group. Conclusion: Lanthanum carbonate is an effective and

well-tolerated agent for the short-term treatment of hyperphosphatemia in patients with ESRD.

Joy MS, Finn WF.
Randomized, double-blind, placebo-controlled, dose-titration, phase III study assessing the efficacy and tolerability of lanthanum carbonate: A new phosphate binder for the treatment of hyperphosphatemia. American Journal of Kidney Diseases. Vol. 42(1 SUPPL. 2)(pp 96-107), 2003.
This 16-week study assessed the control of serum phosphorus with lanthanum carbonate, and its effects on serum calcium, calcium-phosphate product, and PTH. Hemodialysis patients ≥18 years old entered into a 1- to 3-week washout period during which serum phosphorus levels rose to >5.9 mg/dL (1.90 mmol/L). In total, 126 patients were titrated with lanthanum carbonate at doses containing 375, 750, 1,500, 2,250, or 3,000 mg/d elemental lanthanum, given in divided doses with meals over a 6-week period, to achieve serum levels ≤5.9 mg/dL. By the end of dose titration, 11/126 (9%) patients received ≤750 mg/d of lanthanum, 25 (20%) received 1,500 mg/d, 37 (29%) received 2,250 mg/d, and 53 (42%) received 3,000 mg/d. Following titration, patients were randomized to receive either lanthanum carbonate or placebo during a 4-week, double-blind maintenance phase. Results: At the study endpoint, the mean difference in serum phosphorus between the lanthanum carbonate and placebo treatment arms was 1.91 mg/dL (0.62 mmol/L) ($P < 0.0001$). calcium-phosphate product ($P < 0.0001$) and serum PTH levels ($P < 0.01$) were also significantly lower with lanthanum carbonate versus placebo. The incidence of drug-related adverse events was similar between placebo- and lanthanum carbonate-treated patients. Conclusion: Lanthanum carbonate is an effective and well-tolerated agent for the treatment of hyperphosphatemia in patients with ESRD.

D'Haese PC, Spasovski GB, et al. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. Kidney Int Suppl(85): S73-8, 2003.
In this phase III, open-label study, we compared the effects of LC and calcium carbonate (CaCO3) on the evolution of renal osteodystrophy (ROD) in dialysis patients. METHODS: Ninety-eight patients were randomized to LC (N = 49) or CaCO3 (N = 49). Bone biopsies were taken at baseline and after one year of treatment. Acceptable paired biopsies were available for static and dynamic histomorphometry studies in 33 LC and 30 CaCO3 patients. Blood samples were taken at regular intervals for biochemical analysis and adverse events were monitored. RESULTS: LC was well tolerated and serum phosphate levels were well controlled in both treatment groups. The incidence of hypercalcemia was lower in the LC group (6% vs. 49% for CaCO3). At baseline, subtypes of ROD were similarly distributed in both groups, with mixed ROD being most common. At one-year follow-up in the LC group, 5 of 7 patients with baseline low bone turnover (either adynamic bone or osteomalacia), and 4 of 5 patients with baseline hyperparathyroidism, had evolved toward a normalization of their bone turnover. Only one lanthanum-treated patient evolved toward adynamic bone compared with 6 patients in the CaCO3 group. In the LC group, the number of patients having either adynamic bone, osteomalacia, or hyperpara decreased overall from 12 (36%) at baseline to 6 (18%), while in the calcium group, the number of patients with these types of ROD increased from 13 (43%) to 16 (53%). CONCLUSION: LC is a poorly absorbed, well-tolerated, and efficient phosphate binder. LC-treated dialysis patients show almost no evolution toward low bone turnover over one year (unlike CaCO3-treated patients), nor do they experience any aluminum-like effects on bone.

Other studies - sevelamer

Brewster UC, Ciampi MA, Abu-Alfa AK, et al.
Long-term comparison of sevelamer hydrochloride to calcium-containing phosphate binders. Nephrology. Vol. 11(2)(pp 142-146), 2006.
This study compares the long-term efficacy of sevelamer hydrochloride to calcium-

containing binders (CCB). Methods: A retrospective chart review was conducted in 30 patients receiving sevelamer hydrochloride for >1 years and 25 patients receiving CCB. Results: Patients on sevelamer hydrochloride had lower serum bicarbonate concentration than those on CCB, 18.6 +/- 2.7 versus 20.3 +/- 1.8 mmol/L (P = 0.0017). Serum phosphorus concentration was higher in patients on sevelamer hydrochloride compared to CCB 2.10 +/- 0.87 versus 1.74 +/- 0.28 mmol/L (P = 0.0013), as was the Ca-P product 4.97 +/- 0.94 $mmol^2/L^2$ (62.1 +/- 11.8 mg^2/dL^2) versus 3.97 +/- 1.18 $mmol^2/L^2$ (49.7 +/- 14.7 mg^2/dL^2, P = 0.0009). Only 36% of patients on sevelamer hydrochloride compared with 68% on CCB (P = 0.015) met the serum phosphorus goal of ≤1.78 mmol/L. Conclusion: Patients on sevelamer hydrochloride for >1 years compared to those on CCB had a lower serum bicarbonate concentration, a higher serum phosphorus concentration and a higher Ca-P product. Clinicians should balance the increase in calcium load with CCB versus the cost and effectiveness of sevelamer hydrochloride in choosing a phosphate binder for ESRD patients.

Yonova D, Georgiev M, Papazov V, et al.
RenaGel: Treatment of hyperphosphatemia in dialysis patients. Nephrology, Dialysis & Transplantation. Vol. 11(1)(pp 42-44), 2005.

To determine the effectiveness of RenaGel, we performed a 6-month clinical trial in 14 adult patients with ESRD on hemodialysis. Drug-related changes in the concentrations of serum phosphorus, calcium, PTH, some parameters of the coagulation and low- and high-density lipoproteins were the major outcomes of interest. Treatment with RenaGel was associated with a significant change in serum phosphorus and LDL-C. There was no significant overall treatment-related changes in PTH. Coagulation status was not sizably disturbed and no elevation of bleeding episodes was registered. The study proved the effectiveness of sevelamer against hyperphosphatemia - the 'silent killer' of dialysis patients - and a quite positive 'side' effect on lipid profile, and an adequate tolerance of the drug without serious complications.

Izumi M, Shirai K, Ito K, et al.
Is 2.5 mEq/L the optimal calcium concentration of dialysate in the use of sevelamer hydrochloride? A study of the dialysate calcium concentration recommended by K/DOQI guidelines. Therapeutic Apheresis & Dialysis. Vol. 9(1)(pp 24-31), 2005.

We tested the effect of three different dialysate calcium concentrations on calcium-phosphorus metabolism during the use of sevelamer hydrochloride. After a calcium-containing phosphate binder was switched to sevelamer, the serum calcium, phosphorus, and intact PTH levels and the markers of bone turnover were measured in the patients whose dialysate calcium concentrations were 2.5, 2.75, and 3.0 mEq/L. As a result, in the 2.75-mEq/L group, the serum calcium concentrations decreased and the intact PTH level increased significantly. In the 2.5-mEq/L group, transient hypocalcemia occurred and the levels of both bone-alkaline phosphatase and osteocalcin increased. In the 3.0-mEq/L group, the serum calcium concentrations did not change significantly and only bone-alkaline phosphatase increased. If a calcium-containing phosphate binder is completely switched to sevelamer, dialysis using a dialysate calcium concentration below 3.0 mEq/L may result in hypocalcemia and acceleration of bone turnover.

Ando R, Naito S, Inagaki Y, et al.
The influence of dialysate calcium on the therapeutic effects of sevelamer hydrochloride in hemodialysis patients with secondary hyperparathyroidism under treatment of intravenous vitamin D metabolites. Therapeutic Apheresis & Dialysis. Vol. 9(1)(pp 16-23), 2005.

We investigated the influence of dialysate calcium on the therapeutic effect of sevelamer in 40 hemodialysis patients who are under treatment of intravenous vitamin D metabolites for SHPT (VD(+)) and compared the results with those of 41 patients who had not received vitamin D metabolites (VD(-)). Serum phosphorus and calcium-phosphate product showed no significant change by sevelamer in either the VD(+) subgroup of patients receiving hemodialysis with

dialysate calcium of 2.5 mEq/L (DCa2.5) or those receiving hemodialysis with dialysate calcium of 3.0 mEq/L (DCa3.0), while serum phosphorus and calcium-phosphate product decreased in both the VD(-) subgroups. Serum calcium decreased in the DCa2.5 subgroup and did not change in the DCa3.0 subgroup in both the VD(+) and the VD(-) subjects. PTH and alkaline phosphatase increased in the DCa2.5 subgroup and did not change in the Ca 3.0 subgroup in the VD(+) subjects. Serum calcium decreased in both subgroups in the VD(-) subjects. PTH obtained after sevelamer administration in the VD(-) group was within the target range of the K/DOQI guidelines. In conclusion, the concomitant use of sevelamer as a phosphate binder and the dialysate of calcium concentration of 2.5 mEq/L have possibilities for worsening SHPT in patients receiving intravenous vitamin D.

Ogata H, Koiwa F, Shishido K, et al. Combination therapy with sevelamer hydrochloride and calcium carbonate in Japanese patients with long-term hemodialysis: Alternative approach for optimal mineral management. Therapeutic Apheresis & Dialysis. Vol. 9(1)(pp 11-15), 2005.

We evaluated the effects of combination therapy with sevelamer and calcium carbonate (CaCO3) on mineral metabolism in Japanese hemodialysis patients, as an alternative form of P management. A total of 210 hemodialysis patients were enrolled, and were given a small dose of sevelamer (0.75-1.5 g/day) on CaCO3 treatment. Sevelamer dose was gradually increased, while CaCO3 decreased during 24 weeks. Five patients discontinued sevelamer treatment because of severe constipation, anorexia, and parathyroidectomy for severe SHPT. After 24 weeks, the dose of sevelamer was significantly increased to 3.29 g/day (initial dose: 1.47 g/day), while CaCO3 was decreased by 54%. Adjusted serum Ca significantly decreased (9.63 +/- 0.57-9.45 +/- 0.67 mg/dL; P = 0.0012), although serum P increased (5.89 +/- 1.32-6.25 +/- 1.32 mg/dL; P = 0.017). Serum intact PTH (iPTH) significantly increased in patients with a low or normal iPTH level (≤300 pg/mL), while it did not change in patients with SHPT (>300 pg/mL). The results suggest that the therapeutic regimen is more tolerant and reduces Ca load in Japanese hemodialysis patients while avoiding hypocalcemia. In addition, the mitigated Ca overload could improve PTH hyposecretion in patients with adynamic bone disease, which is associated with soft tissue calcification and higher mortality in uremia.

Sturtevant JM, Hawley CM, Reiger K, et al. Efficacy and side-effect profile of sevelamer hydrochloride used in combination with conventional phosphate binders. Nephrology. Vol. 9(6)(pp 406-413), 2004.

Dialysis patients meeting the following inclusion criteria participated in this study: (i) hyperphosphataemia >1.8 mmol/L (5.6 mg/dL); and (ii) an inability to tolerate currently available binders. The trial was conducted in three phases each lasting 3 months: (i) an observation phase (patients continued on their regular phosphate binders); (ii) a titration phase (sevelamer was added at a dose of 403 mg three times daily with meals, titrated to a maximum of 1209 mg three times daily); and (iii) a maintenance phase. Results: Twenty-five patients were recruited into the study. Eighteen patients completed all three trial phases. Mean serum phosphate dropped from 2.11 +/- 0.06 mmol/L (6.6 +/- 0.2 mg/dL) during the observation period to 1.91 +/- 0.01 mmol/L (5.9 +/- 0.003 mg/dL) during the maintenance phase (P = 0.02). calcium-phosphate product fell from 5.49 +/- 0.17 $mmol^2/L^2$ (68.64 +/- 2.11 mg^2 dL^2) to 4.89 +/- 0.27 $mmol^2/L^2$ (61.36 +/- 3.35 mg^2 dL^2) (P = 0.02). There was no significant change in serum calcium or PTH. Total serum cholesterol fell from 3.8 mmol/L (3.4-4.37) 147 mg/dL (131-169) to 3.55 mmol/L (2.97-4.2) 137 mg/dL (115-162) (P = 0.02). Serum low-density lipoprotein cholesterol also fell significantly from 1.67 +/- 0.10 mmol/L (65 +/- 4 mg/dL) to 1.52 +/- 0.11 mmol/L (59 +/- 4 mg/dL) (P = 0.04). The average prescribed dose of sevelamer was 2.4 g/day. Elemental calcium dropped from 3.4 g/day (1.4 to 4.6) to 1.2 g/day (0.6-2.4) (P = 0.04). Seventy-two per cent of patients reported mild flatulence, nausea and indigestion. Three patients discontinued treatment because of adverse effects. Conclusions: Sevelamer in combination with conventional phosphate

binders is effective in lowering serum phosphate and calcium-phosphate product in patients with refractory hyperphosphataemia. Beneficial effects on lipid profile were also observed. Mild gastrointestinal upset is common.

Braun J, Asmus H-G, Holzer H, et al. Long-term comparison of a calcium-free phosphate binder and calcium carbonate - Phosphorus metabolism and cardiovascular calcification. Clinical Nephrology. Vol. 62(2)(pp 104-115), 2004.

114 adult hemodialysis patients were randomly assigned to open label sevelamer or CaCO3 for 52 weeks. Study efficacy endpoints included changes in serum phosphorus, calcium, calcium-phosphate product, and lipids. In addition, initial and sequential electron beam computerized tomography scans were performed to assess cardiovascular calcification status and change during follow-up. Safety endpoints were serum biochemistry, blood cell counts and adverse events. Results: Patients receiving sevelamer had a similar reduction in serum phosphorus as patients receiving CaCO3 (sevelamer -0.58 +/- 0.68 mmol/l, CaCO3 -0.52 +/- 0.50 mmol/l; p = 0.62). Reductions in calcium-phosphate product were not significantly different (sevelamer -1.4 +/- 1.7 $mmol^2/1^2$, CaCO3 -0.9 +/- 1.2 $mmol^2/1^2$; p = 0.12). CaCO3 produced significantly more hypercalcemia (> 2.8 mmol/l in 0% sevelamer and 19% CaCO3 patients, p < 0.01) and suppressed intact PTH below 150 pg/ml in the majority of patients. Sevelamer patients experienced significant (p < 0.01) reductions in total (-1.2 +/- 0.9 mmol/1, -24%) and LDL cholesterol (-1.2 +/- 0.9 mmol/1, -30%). CaCO3 patients had significant increases in coronary artery (median +34%, p < 0.01) and aortic calcification (median +32%, p < 0.01) that were not observed in sevelamer-treated patients. Patients on sevelamer required more grams of binder (sevelamer 5.9 g vs. CaCO3 3.9 g) and experienced more dyspepsia than patients on calcium carbonate. Conclusions: Sevelamer is an effective phosphate binder that unlike calcium carbonate is not associated with progressive cardiovascular calcification in hemodialysis patients.

Shaheen FA, Akeel NM, Badawi LS, et al. Efficacy and safety of sevelamer. Comparison with calcium carbonate in the treatment of hyperphosphatemia in hemodialysis patients. Saudi Medical Journal. Vol. 25(6)(pp 785-791), 2004.

Due to race differences we performed a short-term study on the Saudi hemodialysis patients and compared sevelamer with a standard calcium-based phosphate binder. Methods: An open-label, randomized, cross-over study was performed to evaluate the safety and effectiveness of sevelamer hydrochloride in controlling hyperphosphatemia in hemodialysis patients. After a 2-week phosphate binder washout period, stable hemodialysis patients were given either sevelamer or calcium carbonate, and the dosages were titrated to achieve phosphate control over an 8-week period. After a 2-week washout period, patients crossed over to the alternate agent for 8 weeks. Twenty patients from the Dialysis Unit of King Fahd Hospital, Jeddah, Kingdom of Saudi Arabia, were recruited for the study between March 2003 and June 2003. Results: There was a similar decrease in serum phosphate values over the course of the study with both sevelamer (-3.3 +/- 2.2 mg/dL) and calcium carbonate (-3.9 +/- 2.8 mg/dL). Fifty-two percent of patients developed serum calcium greater than 2.75 mmol/L (11.0 mg/dL) while receiving calcium carbonate versus 26% of patients receiving sevelamer (p<0.05). The incidence of hypercalcemia for sevelamer was not different from the incidence of hypercalcemia during the washout period. Patients treated with sevelamer also sustained a 13% mean decrease in serum cholesterol levels. Conclusion: Sevelamer was effective in controlling hyperphosphatemia without resulting in an increase in the incidence of hypercalcemia seen with calcium carbonate. This agent appears quite effective in the treatment of hyperphosphatemia in hemodialysis patients, and its usage may be advantageous in the treatment of dialysis patients.

Almirall J, Lopez T, Vallve M, et al. Safety and efficacy of sevelamer in the treatment of uncontrolled hyperphosphataemia of

haemodialysis patients. Nephron Clinical Practice. Vol. 97(1)(pp c17-c22), 2004.

We identified 34 patients with a maintained serum phosphorus concentration >6.5 mg/dl and/or toxicity related to standard phosphorus-binding treatment (aluminium or calcium based). Sevelamer was added and titrated up fortnightly to achieve phosphorus control. Previous phosphate binders were decreased, whenever possible. The period of the study was 6 months. Results: Thirteen patients (38%) dropped out because of side effects, mainly related to the gastro-intestinal tract. The efficacy analysis disclosed that the phosphorus concentration decreased from 2.39 +/- 0.48 to 1.84 +/- 0.48 mmol/l ($p < 0.001$). The mean dose of sevelamer was stabilised at 3.4 +/- 1.8 g/day. The amount of calcium- and aluminium-based phosphate binders could be decreased from 5.1 +/- 3.5 to 3.1 +/- 2.7 g/day (38% decrease) and from 2.4 +/- 1.5 to 1.5 +/- 1.7 g/day (36% decrease), respectively. The calcium-phosphate product was significantly decreased from 5.83 +/- 1.19 to 4.36 +/- 1.12 mmol/l^2 ($p < 0.001$). The total cholesterol concentration decreased from 4.34 +/- 0.9 to 3.98 +/- 0.9 mmol/l ($p < 0.01$) and the low-density lipoprotein cholesterol level from 2.61 +/- 0.98 to 2.20 +/- 0.77 mmol/l ($p < 0.03$). Conclusions: Sevelamer is an effective phosphate binder that allows a better serum phosphorus control, while allowing a decrease in the dose of calcium- and aluminium-based phosphate binders in these difficult patients. The drawbacks are the high intolerance rate and the price of the product.

Braun J, Asmus H-G, Holzer H, et al. Long-term comparison of a calcium-free phosphate binder and calcium carbonate - Phosphorus metabolism and cardiovascular calcification. Clinical Nephrology. Vol. 62(2)(pp 104-115), 2004.

114 adult hemodialysis patients were randomly assigned to open label sevelamer or CaCO3 for 52 weeks. Study efficacy endpoints included changes in serum phosphorus, calcium, calcium-phosphate product, and lipids. In addition, initial and sequential electron beam computerized tomography scans were performed to assess cardiovascular calcification status and change during follow-up. Safety endpoints were serum biochemistry, blood cell counts and adverse events. Results: Patients receiving sevelamer had a similar reduction in serum phosphorus as patients receiving CaCO3 (sevelamer -0.58 +/- 0.68 mmol/l, CaCO3 -0.52 +/- 0.50 mmol/l; $p = 0.62$). Reductions in calcium-phosphate product were not significantly different (sevelamer -1.4 +/- 1.7 mmol2 /12 , CaCO3 -0.9 +/- 1.2 mmol2 /12 ; $p = 0.12$). CaCO3 produced significantly more hypercalcemia (> 2.8 mmol/l in 0% sevelamer and 19% CaCO3 patients, $p < 0.01$) and suppressed intact PTH below 150 pg/ml in the majority of patients. Sevelamer patients experienced significant ($p < 0.01$) reductions in total (-1.2 +/- 0.9 mmol/1, -24%) and LDL cholesterol (-1.2 +/- 0.9 mmol/1, -30%). CaCO3 patients had significant increases in coronary artery (median +34%, $p < 0.01$) and aortic calcification (median +32%, $p < 0.01$) that were not observed in sevelamer-treated patients. Patients on sevelamer required more grams of binder (sevelamer 5.9 g vs. CaCO3 3.9 g) and experienced more dyspepsia than patients on calcium carbonate. Conclusions: Sevelamer is an effective phosphate binder that unlike calcium carbonate is not associated with progressive cardiovascular calcification in hemodialysis patients.

Burke SK, Dillon MA, Hemken DE, et al. Meta-analysis of the effect of sevelamer on phosphorus, calcium, PTH, and serum lipids in dialysis patients. Advances in Renal Replacement Therapy. Vol. 10(2)(pp 133-145), 2003.

We conducted a meta-analysis on the effects of sevelamer hydrochloride on parameters of mineral metabolism (serum phosphorous, calcium, calcium-phosphate product, and iPTH) and the lipid profile (total, LDL, HDL, and non-HDL cholesterol, and triglycerides) in dialysis patients. After application of inclusion/exclusion criteria, 17 core studies were statistically analyzed to determine the sevelamer treatment effect on the study parameters as demonstrated by simple, n-weighted, and inverse variance-weighted mean changes. Analysis of inverse variance-weighted mean changes indicated that sevelamer treatment was associated

with a 2.14 mg/dL drop in serum phosphorus (P < .001), no significant overall effect on calcium (0.09 mg/dL, P = .364), significant decline in calcium-phosphate product product (15.91 mg^2/dL^2, P < .001), 35.99 pg/mL reduction in iPTH (P = .026), significant reduction in total cholesterol (30.58 mg/dL, P < .001), 31.38 mg/dL drop in LDL cholesterol (P < .001), significant increase in HDL cholesterol (4.09 mg/dL, P = .008), and a significant reduction in triglycerides (22.04 mg/dL, P < .001). This meta-analysis suggests that sevelamer offers a dual therapeutic benefit in dialysis patients - a population at high risk for cardiovascular disease - by improving phosphorus control and the lipid profile, without altering serum calcium.

McIntyre CW, Patel V, Taylor GS, et al. A prospective study of combination therapy for hyperphosphataemia with calcium-containing phosphate binders and sevelamer in hypercalcaemic haemodialysis patients. Nephrology Dialysis Transplantation. Vol. 17(9)(pp 1643-1648), 2002.

We report on a strategy of partial replacement of calcium with sevelamer for the management of hyperphosphataemia in hypercalcaemic chronic HD patients. Methods. We identified 23 HD patients with serum calcium > 2.6 mmol/1. Dietary phosphate and calcium intake were assessed and baseline serum calcium, phosphate and 1a calcidol and elemental calcium dose recorded. Fifty per cent of this initial calcium dose was exchanged for sevelamer. Vitamin D doses were left unchanged. If serum calcium was still > 2.6 mmol/1 after 4 weeks a further 50% of calcium was exchanged. If serum phosphate was >2 mmol/1 the sevelamer dose was increased by 25%. The patients were followed up for a further 4 weeks. Results. Seven patients complained of gastrointestinal intolerance of sevelamer. Serum calcium fell from a mean value of 2.8 +/- 0.04 (2.64-3.54) mmol/1 to 2.56 +/- 0.03 (2.4-2.9) mmol/1, P < 0.0005. The hypercalcaemic percentage of patients fell from 100 to 26%. Mean serum phosphate was not significantly changed, 1.59 +/- 0.1 (0.57-2.6) mmol/1 to 1.63 +/- 0.11 (0.55-2.68) mmol/1, 17-22% of patients having serum phosphate > 2 mmol/1. Serum intact PTH increased from 166 +/- 47 (12-933) ng/l to 276 +/- 104 (20-1013) ng/1, P=0.02. Mean sevelamer dose was 2.77 +/- 0.36 (0-5.6) g per day. Elemental calcium dose fell from 2.05 +/- 0.23 (0.5-4.5) g to 1.03 +/- 0.1 (0. 5-2.5) g, P < 0. 0001. Conclusion. A regimen based on the combination of sevelamer and calcium is capable of effectively managing hyperphosphataemia, without hypercalcaemia, in the majority of hypercalcaemic HD patients. Such a minimally calcaemic approach might reduce the financial burden of sevelamer therapy, and enable a wider range of patients to be treated.

Gallieni M, Cozzolino M, Carpani P, et al. Sevelamer reduces calcium load and maintains a low calcium-phosphorus ion product in dialysis patients. Journal of Nephrology. Vol. 14(3)(pp 176-183), 2001.

This single-center, open-label, dose titration study assessed the efficacy of sevelamer in a cohort of European hemodialysis patients with different dietary habits, in particular with lower phosphate intake. The aim of the study was to obtain a calcium-phosphate product lower than 60 mg^2/dL^2 in all patients. Methods. Administration of calcium- or aluminum-based phosphate binders was discontinued during a two-week washout period. Nineteen patients whose serum phosphate level at the end of washout was greater than 5.5 mg/dL (1.78 mmol/L) qualified to receive sevelamer for six weeks. Based on the degree of hyperphosphatemia during washout, patients were started on 403 mg sevelamer capsules with a dose schedule different from previous studies. Only one capsule was administered at breakfast, and the rest of the phosphate binder was divided equally at the two main meals. Sevelamer could be increased by two capsules per day every two weeks, if necessary. A second two-week washout period followed. Results. Mean serum phosphorus rose from a baseline of 5.3+/-1.0 to 7.4+/-1.4 mg/dL at the end of washout, then declined to 5.4+/-0.8 mg/dL (p < 0.001) by the end of the six-week treatment period and rebounded significantly to 7.1+/-1.1 mg/dL after the second two-week washout. calcium-phosphate product showed a similar pattern, decreasing

significantly from 64.1+/-14.1 to 46.9+/-7.4 mg^2/dL^2 ($p < 0.001$) after six weeks of sevelamer. A level of less than 50 mg2 /dL2 was reached by 68% of patients, and 95% had less than 60 mg2 /dL2 . The mean dose of sevelamer at the end of treatment was 3.1 +/- 0.6 g per day. As expected, calcium declined from 9.2+/-0.5 to 8.7 mg/dL ($p<0.01$) during the initial washout after stopping calcium-based phosphate binders, but remained stable thereafter. Ionized calcium did not change significantly throughtout the washout and sevelamer treatment. However, interruption of calcium salts led to a 81% reduction of total calcium intake. Conclusions. We confirmed in an European sample of hemodialysis patients that sevelamer can reduce phosphate levels without inducing hypercalcemia. The drug can also be successfully used to reduce mean calcium-phosphate product levels below 50 mg2 /dL2 , closer to normal values. Although similar results can be obtained with other phosphate binders, a concomitant accumulation of aluminum, calcium or magnesium could be detrimental to patients.

Slatopolsky EA, Burke SK, Dillon MA, et al.
RenaGel(TM), a nonabsorbed calcium- and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. Kidney International. Vol. 55(1)(pp 299-307), 1999.

This multicenter, open-label, dose-titration study assessed the safety and efficacy of RenaGelrho, a nonabsorbed calcium-and aluminum-free phosphate binder, in lowering serum phosphorus. Secondary outcomes were its effects on serum intact PTH and serum lipids. Methods. Phosphate binders were discontinued during a two-week washout period. Patients whose serum phosphorus was more than 6.0 mg/dl during washout were eligible for treatment. RenaGel(TM), at starting doses of two, three, or four 440 mg capsules three times per day with meals, was administered to 172 hemodialysis patients for eight weeks. RenaGel(TM) could be increased by one capsule per meal every two weeks as necessary to achieve serum phosphorus control. A second two-week washout period followed. Results. Mean serum phosphorus rose from 6.8 +/- 2.0 mg/dl at pre-washout to 9.1 +/- 2.4 mg/dl at the end of the washout period. It then declined to 6.6 +/- 1.9 mg/dl by the end of the eight- week RenaGel(TM) treatment period ($P < 0.0001$). Serum phosphorus increased to 8.0+/- 2.2 mg/dl at the end of the second washout period. The mean dose at the end of RenaGel(TM) treatment was 5.4 g per day. Eighty-four percent of the patients previously used calcium-based phosphate binders. As expected, calcium declined during the initial washout period when calcium-based phosphate binders were discontinued. Mean serum calcium declined from 9.6 +/- 1.0 mg/dl at pre-washout to 9.1 +/- 0.8 mg/dl after washout. It then increased to 9.4 +/- 0.9 mg/dl by the end of RenaGel(TM) treatment. Median serum iPTH increased during the two-week washout from 208 pg/ml to 316 pg/ml and then declined to 224 pg/ml at the end of the eight-week treatment period ($P < 0.0001$ vs. end of initial washout). After eight weeks of treatment, RenaGel(TM) reduced mean serum total cholesterol from 171.0 +/- 43.1 mg/dl to 145.0 +/- 38.7 mg/dl ($P < 0.0001$) and mean serum low-density lipoprotein cholesterol from 102.0 +/- 34.9 mg/dl to 75.6 +/- 29.4 mg/dl ($P < 0.0001$). High-density lipoprotein cholesterol, triglycerides, and serum albumin did not change. Conclusions. RenaGel(TM), a novel and calcium- plus aluminum-free effective phosphate binder, can control serum phosphorus and reduce the levels of PTH and cholesterol without inducing hypercalcemia or other side effects. Thus, this new phosphate binder may be effective in the treatment of renal osteodystrophy in uremic patients.

Other studies - lanthanum

Hutchison AJ, Maes B, Vanwalleghem J, et al.
Long-term efficacy and tolerability of lanthanum carbonate: Results from a 3-year study. Nephron Clinical Practice. Vol. 102(2)(pp c61-c71), 2006.

Patients who participated in a 6-month, randomized trial comparing lanthanum carbonate with calcium carbonate were eligible for a 24-week, open-label extension. Lanthanum carbonate-treated patients continued taking their established

maintenance dose ('continued-lanthanum group') and calcium carbonate-treated patients switched to lanthanum carbonate, 375-3,000 mg/day ('switch group'). Patients could also enter a further 2-year extension. Efficacy parameters, including serum phosphate, were monitored. Results: Mean serum phosphate was ~1.80 mmol/l throughout the trial. The percentage of patients with controlled serum phosphate (≤1.80 mmol/l) after the 6-month extension was 63.3 and 58.4% in the continued-lanthanum and switch groups, respectively; after the 2-year extension, 54.4% of patients had controlled serum phosphate. After discontinuation of calcium carbonate and initiation of lanthanum carbonate, the hypercalcemia incidence was 2.7%, compared with 20.2% during the double-blind phase. calcium-phosphate product was maintained at an acceptable level. Lanthanum carbonate was well tolerated; adverse events were mild/moderate and mainly gastrointestinal. Conclusions: Lanthanum carbonate maintains effectiveness with continued tolerability for up to 3 years.

Use in Children

Civilibal M, Caliskan S, Adaletli I, et al.
Coronary artery calcifications in children with end-stage renal disease. Pediatric Nephrology. Vol. 21(10)(pp 1426-1433), 2006.

Coronary artery calcification (CAC) is common in adults with ESRD, but little is known about the prevalence and the extent of it in children. We used multidetector spiral computed tomography (MDCT), echocardiography, and carotid and brachial high-resolution ultrasonography to screen for the presence and predisposing factors of CAC in 53 children with ESRD [15 hemodialysis (HD) patients, 24 peritoneal dialysis (PD) patients, and 14 renal transplant (rTx) recipients]. CAC was present in 15% of patients (three HD patients, three PD patients, and two rTx). The mean age of the patients with CAC was 16.4 years (range: 11.0-21.2 years), and their median CAC score was 101.3, ranging from 8.5 to 4,322 according to the Agatston method. The patients with CAC had longer duration of total dialysis (P=0.005), had higher time-integrated serum phosphorus (P<0.001), calcium-phosphorus product (P=0.012), intact PTH (P=0.010), vitamin B_{12} levels (P=0.010), the amount of cumulative calcium-containing oral phosphate binders (OBPs) (P<0.001), and calcitriol intake (P<0.001), and had lower serum hemoglobin level (P=0.014). Interventricular septum systolic thickness (P=0.033) was significantly higher, relative wall thickness (P=0.062) tended to be higher, and flow-mediated endothelium-dependent dilatations (P=0.071) were lower without reaching statistically significant levels in those with CAC. A stepwise logistic regression analysis revealed that serum phosphorus (P=0.018) and the cumulative exposure to calcium-containing OPBs (P=0.016) were the most significant independent predictors in the development of CAC. These results indicate that even adolescents and children with ESRD may have coronary calcifications. We concluded that impaired divalent ion metabolism is the main factor in the formation of CAC in this age group.

McElhiney LF.
Sevelamer suspension in children with end-stage renal disease. International Journal of Pharmaceutical Compound. Vol. 11(1)(pp 20-24), 2007.

Control of hyperphosphatemia is a major clinical challenge in children with ESRD. The best treatment option is a calcium-based phosphate binder, but there is evidence that this treatment protocol causes long-term complications, including vascular calcifications. Sevelamer hydrochloride has been shown to be effective in reducing serum phosphorus levels and the calcium-phosphate product in children on maintenance dialysis and may be key in preventing soft-tissue and vascular calcifications in such patients. Until the U.S. Food and Drug Administration approves the use of sevelamer hydrochloride in children undergoing dialysis, and a liquid dosage form becomes available, compounding pharmacists will need to prepare this unique compound for these patients.

Pieper A-K, Haffner D, Hoppe B, et al.
A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD.

American Journal of Kidney Diseases. Vol. 47(4)(pp 625-635), 2006.

A multicenter, randomized, open-label, crossover study was performed to compare the efficacy and safety of sevelamer, a calcium-free phosphate binder, with calcium acetate in pediatric patients with CKD. Methods: Children (age, 0.9 to 18 years) with CKD undergoing hemodialysis or peritoneal dialysis or with a glomerular filtration rate of 20 or greater and less than 60 mL/min/1.73 m^2 (<0.33 and <1.00 mL/s/1.73 m^2 were randomly assigned to the following treatment scheme: 2 weeks of washout followed by 8 weeks of treatment with either sevelamer or calcium acetate in a crossover fashion. Phosphorus, calcium, and intact PTH in serum were measured every 2 weeks, and phosphate binder dosages were adjusted, if needed. Serum lipid and vitamin concentrations were measured at the beginning and end of each treatment period. The primary end point was the decrease in serum phosphorus levels after 8 weeks of treatment. Results: Forty-four patients were screened. Altogether, data for 18 patients (5 girls) aged 12.4 +/- 4.1 years were used for the crossover analysis. There was no significant difference in serum phosphorus levels at 8 weeks after the start of treatment in both groups. Total cholesterol (-27%) and low-density lipoprotein cholesterol (-34%) levels decreased significantly with sevelamer treatment (P < 0.02 and P < 0.005). An increased incidence of hypercalcemia (P < 0.0005) was observed with calcium acetate treatment, whereas metabolic acidosis was more frequent with sevelamer treatment (P < 0.005). Conclusion: Treatment of children with CKD with sevelamer and calcium acetate provides similar phosphorus level control. The marked decrease in lipid levels and lower rate of hypercalcemia may augment the long-term benefit of sevelamer.

Williams R.
Sevelamer for treating hyperphosphatemia in pediatric CKD patients. Nature Clinical Practice Nephrology. Vol. 2(6)(pp 296), 2006.

No Abstract available.

Salusky IB, Goodman WG, Sahney S, et al.
Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols. Journal of the American Society of Nephrology. Vol. 16(8)(pp 2501-2508), 2005.

The effects of calcium carbonate (CaCO3) and sevelamer were compared in pediatric peritoneal dialysis patients with bone biopsy-proven 2degreesHPT. Twenty-nine patients were randomly assigned to CaCO3 (n = 14) or sevelamer (n = 15), concomitant with either intermittent doses of oral calcitriol or doxercalciferol for 8 mo, when bone biopsies were repeated. Serum phosphorus, calcium, PTH, and alkaline phosphatase were measured monthly. The skeletal lesions of 2degreesHPT improved with both binders, and bone formation rates reached the normal range in approximately 75% of the patients. Overall, serum phosphorus levels were 5.5 +/- 0.1 and 5.6 +/- 0.3 mg/dl (NS) with CaCO3 and sevelamer, respectively. Serum calcium levels and the calcium-phosphate product increased with CaCO3; in contrast, values remained unchanged with sevelamer (9.6 +/- 01 versus 8.9 +/- 0.2 mg/dl; P < 0.001, respectively). Hypercalcemic episodes (>10.2 mg/dl) occurred more frequently with CaCO3 (P < 0.01). Baseline PTH levels were 980 +/- 112 and 975 +/- 174 pg/ml (NS); these values decreased to 369 +/- 92 (P < 0.01) and 562 +/- 164 pg/ml (P < 0.01) in the CaCO3 and the sevelamer groups, respectively (NS between groups). Serum alkaline phosphatase levels also diminished in both groups (P < 0.01). Thus, treatment with either CaCO3 or sevelamer resulted in equivalent control of the biochemical and skeletal lesions of 2degreesHPT. Sevelamer, however, maintained serum calcium concentrations closer to the lower end of the normal physiologic range, thereby increasing the safety of treatment with active vitamin D sterols.

Mahdavi H, Kuizon BD, Gales B, et al.
Sevelamer hydrochloride: An effective phosphate binder in dialyzed children. Pediatric Nephrology. Vol. 18(12)(pp 1260-1264), 2003.

This pilot study was designed to evaluate the efficacy and acceptability of sevelamer hydrochloride as a phosphate binder in pediatric patients treated with dialysis. A 6-month open-label trial of sevelamer hydrochloride (Renagel) was initiated in 17 patients, aged 11.8+/-3.7 years, undergoing hemodialysis (n=3) or peritoneal dialysis (n=14). Following a 2-week washout period of the phosphate binders, serum phosphorus increased from 5.2+/-1.3 mg/dl to 7.5+/-2.2 mg/dl (P<0.0002). After initiation of therapy with sevelamer hydrochloride, serum phosphorus levels decreased to 6.2+/-1.2 mg/dl (P<0.01) during the first 8 weeks and final values were 6.3+/-1.5 mg/dl. Serum calcium concentration decreased during the washout period from 9.4+/-0.9 mg/dl to 8.9+/-1.5 mg/dl (P<0.01); values remained unchanged thereafter. The serum calcium-phosphate product decreased during the first 8 weeks and values did not change subsequently. Serum bicarbonate, PTH, total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol, and triglyceride levels did not change. The initial prescribed dose of sevelamer hydrochloride was 121+/-50 mg/kg (4.5+/-5 g/day) and the final prescribed dose was 163+/-46 mg/kg (6.7+/-2.4 g/day). Sevelamer hydrochloride was well tolerated and without adverse effects related to the drug.

Predictors of response

No papers found.

Safety

Altmann P, Barnett ME, Finn WF.
Cognitive function in Stage 5 chronic kidney disease patients on hemodialysis: No adverse effects of lanthanum carbonate compared with standard phosphate-binder therapy. Kidney International. Vol. 71(3)(pp 252-259), 2007.

Patients with Stage 5 CKD who have hyperphosphatemia require treatment with phosphate binders to lower serum phosphorus levels. Existing binders are effective but may be associated with important safety disadvantages. Lanthanum carbonate is a phosphate binder with demonstrated efficacy, safety, and tolerability in clinical trials. Changes in cognitive function were evaluated over time using the Cognitive Drug Research computerized cognitive assessment system (Simple Reaction Time, Digit Vigilance Task, Choice Reaction Time, Numeric Working Memory, and Delayed Picture Recognition) in 360 hemodialysis patients who were enrolled in a 2-year, multicenter, comparative study of lanthanum carbonate versus standard therapy. A decline in cognitive function from baseline was observed in both groups. The deterioration in cognitive function was similar in both the lanthanum carbonate and standard therapy groups. One parameter - Numeric Working Memory - showed a statistically significant between-group difference in favor of lanthanum carbonate (P=0.02). Given the magnitude of the changes, however, and the differences that were observed at baseline between treatment groups, the clinical significance of this difference is doubtful. This study demonstrates that cognitive function deteriorates in hemodialysis patients over a 2-year time period. Use of lanthanum carbonate as a phosphate binder does not adversely affect cognitive function compared with standard therapy.

De Santo NG, Frangiosa A, Anastasio P, et al.
Sevelamer worsen metabolic acidosis in hemodialysis patients. Journal of Nephrology. Vol. 19(SUPPL. 9)(pp S108-S114), 2006.

Sevelamer hydrochloride, a major phosphate binder for patients on maintenance hemodialysis (MHD) is associated with reduced serum bicarbonate concentration due to hydrochloric acid release in the gut and to the binding of short chain fatty acids in the large intestine. Since metabolic acidosis can be deleterious, a study was devised to compare the time course of serum bicarbonate concentration during treatment with sevelamer hydrochloride or calcium carbonate. Methods: Sixteen well nourished patients on NMD who were in excellent clinical conditions and achieving target levels for blood pressure (BP) and hemoglobin (Hb), while on a protein intake of 1.1g/kg body

weight (bw), were enrolled in the study. After a 2-week washout period, the patients were divided into two groups, each consisting of eight patients, and randomized either to 24 weeks of sevelamer followed by 24 weeks of calcium carbonate (group A) or to 24 weeks of calcium carbonate followed by 24 weeks of sevelamer (group B). Protein intake, n-protein catabolic rate (nPCR), serum concentrations of calcium, phosphate, calcium-phosphate product product, bicarbonate, intact PTH and albumin were monitored. Time course changes in serum bicarbonate concentrations in relation to short and long dialytic intervals (48 vs. 72 hr) were also investigated. Results: Both sevelamer and calcium carbonate effectively controlled serum phosphate and the calcium-phosphate product product. During calcium carbonate treatment plasma phosphate concentrations were significantly below those of patients on sevelamer. Plasma bicarbonate concentration fell within target DOQI values during calcium carbonate administration both in group A and in group B, a goal which was not achieved under sevelamer administration. After a long dialytic interval in patients on sevelamer, serum bicarbonate concentration averaged 17.3 +/- 1.1mEq/L, whereas it averaged 21.1 +/- 0.7mEq/L in patients on calcium carbonate ($p<0.01$). Finally, a 24-week sevelamer administration caused a statistically significant ($p<0.05$) reduction (0.8 g/dL) in serum albumin concentration, without affecting iPTH. Taken together, these results indicate that sevelamer worsens metabolic acidosis, which needs to be corrected.

Katopodis KP, Andrikos EK, Gouva CD, et al.
Sevelamer hydrochloride versus aluminum hydroxide: Effect on serum phosphorus and lipids in CAPD patients. Peritoneal Dialysis International. Vol. 26(3)(pp 320-327), 2006.

The present study was designed to evaluate the efficacy of SH in the control of hyperphosphatemia and its effect, compared to AH, on serum lipid parameters in patients on CAPD. Methods: 30 stable patients on CAPD were included in an open-label, randomized crossover study. After a 2-week phosphorus binder washout period, 15 patients (group I) were administered SH for 8 weeks and in the remaining patients (group II), AH was introduced (phase A). After a new 2-week washout period, patients crossed over to the alternate agent for another 8 weeks (phase B). Results: There were similar reductions in serum phosphorus levels over the course of the study with both agents: by 1.18 +/- 0.07 mg/dL (0.38 +/- 0.03 mmol/L) with SH and by 1.25 +/- 0.15 mg/dL (0.40 +/- 0.05 mmol/L) with AH in phase A (p = NS), and by 1.35 +/- 0.25 mg/dL (0.43 +/- 0.08 mmol/L) with AH and by 1.23 +/- 0.80 mg/dL (0.39 +/- 0.25 mmol/L) with SH in phase B (p = NS). Moreover, SH administration was associated with a 10.5% +/- 9.4% and a 20.1% +/- 6.8% fall in total cholesterol ($p < 0.05$) and low-density lipoprotein cholesterol ($p < 0.001$) in phase A, and 11.9% +/- 7.2% ($p < 0.05$) and 21.5% +/- 2.4% ($p < 0.001$), respectively, in phase B. In both phases of the study, AH administration was not followed by a significant change in serum lipid parameters. Conclusion: Sevelamer hydrochloride is a well-tolerated alternative to calcium- or aluminum-containing phosphorus binder in the control of serum phosphorus in CAPD patients. Furthermore, SH improves the lipid profile in these patients.

Daly JA, Valenzuela Mujica MP.
The safety of phosphate binders. Expert Opinion on Drug Safety. Vol. 5(5)(pp 675-686), 2006.

Disturbances of mineral metabolism occur during the early stages of CKD. As renal function worsens, excess dietary phosphorus accumulates and blood levels increase, that can be clearly seen when the glomerular filtration rate has fallen below 30 ml/min/ 1.73m2 . In patients with ESRD, standard dialysis (three times/week) falls far short of removing adequate amounts of absorbed phosphorus; therefore, hyperphosphataemia is found in the majority of these patients. Hyperphosphataemia has long been associated with progression of SHPT and renal osteodystrophy, it can also lead to soft-tissue and vascular calcification. Recent observational data have associated hyperphosphataemia with increased cardiovascular mortality among dialysis patients. Adequate control of serum phosphorus remains a cornerstone in the

clinical management and, despite the growing amount of available therapeutic options, achievement of NFK/KDOQI targets for mineral metabolism remain poor. Several reasons may explain the failure to adequately treat hyperphosphataemia: poor compliance with diet and phosphate binder prescriptions are common causes. Also, factors related with cost, tolerance, palatability, safety and efficacy are important. In this article, the authors review the advantages and drawbacks of conventional and emerging therapies in phosphorous binding.

Finn WF.
Lanthanum carbonate versus standard therapy for the treatment of hyperphosphatemia: Safety and efficacy in chronic maintenance hemodialysis patients. Clinical Nephrology. Vol. 65(3)(pp 191-202), 2006.

This large-scale study compares the safety of lanthanum with standard therapy (any approved phosphate binder) in patients who were treated for up to 2 years. Efficacy, having previously been demonstrated, was a secondary endpoint. Materials and methods: After washout, patients were randomized to receive lanthanum (n = 682) or their pre-study phosphate binder (n = 677). Over a 6-week period, lanthanum was titrated to a maximum daily dose of 3,000 mg elemental lanthanum (serum phosphorus target levels for titration were ≤ 5.9 mg/dl (1.90 mmol/1)). Safety assessments included adverse events (AEs), full laboratory parameters and blood profiles. Efficacy assessments included serum phosphorus, calcium, calcium-phosphate product and PTH levels. Results: Average treatment exposure was greater in the standard therapy group (501.4 days) than in the lanthanum group (370.3 days) because standard therapy patients who switched or combined treatments were allowed to continue in the study. The most common AEs were gastrointestinal. The incidences of AEs in the lanthanum and treatment exposure-corrected standard therapy groups were nausea, 37 versus 29%; vomiting, 27 versus 22% and diarrhea (24% in each group). Hypercalcemia that was reported as an AE (lanthanum versus treatment exposure-corrected standard therapy) occurred in 4.3% and 8.4% of patients, respectively. There was no indication of liver toxicity, suppression of erythropoiesis or changes in the mini-mental state examination. Over 2 years, phosphorus control was similar in both groups; in the lanthanum group, however, serum calcium was lower and serum PTH levels were maintained in the range recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI). Conclusions: The 2-year tolerability and efficacy of lanthanum are similar to those seen with standard therapy, although lower serum calcium levels and improved PTH levels were observed in the lanthanum group. These results support lanthanum as a viable new option for the management of hyperphosphatemia in ESRD.

Finn WF and Joy MS. A long-term, open-label extension study on the safety of treatment with lanthanum carbonate, a new phosphate binder, in patients receiving hemodialysis. Curr Med Res Opin 21(5): 657-64, 2005.

A 1-year extension study to two randomized controlled studies was conducted to evaluate the long-term safety of lanthanum carbonate in patients who received hemodialysis. RESEARCH DESIGN AND METHODS: Patients from two previous lanthanum carbonate studies were eligible to continue treatment in a 1-year open-label extension. A total of 77 patients (N = 77; 11 from Study 1, 66 from Study 2) were enrolled in this extension. The mean age of patients was 60.9 years (SD +/- 12.5 years); 65% were male and 35% were female. All patients received lanthanum carbonate at the optimal dose for phosphorus control, determined in their previous study. Safety and tolerability were assessed by monitoring adverse events, laboratory parameters, and vital signs. The number of patients who maintained serum phosphorus levels at < or = 5.9 mg/dL (1.9 mmol/L) was recorded, along with serum calcium, calcium-phosphate product, and PTH levels. RESULTS: Lanthanum carbonate was well tolerated and was associated with few treatment-related adverse events. The most commonly reported adverse events were nausea (26.0%), peripheral edema (23.4%), and myalgia (20.8%). No treatment-related

serious adverse events occurred. By Week 4, the mean serum phosphorus level had decreased by approximately 1 mg/dL to 5.7 +/- 2.0 mg/dL (1.84 +/- 0.7 mmol/L). At the end of the study, the mean pre-dialysis serum phosphorus level was 5.7 +/- 1.4 mg/dL (1.84 +/- 0.5 mmol/L); 53% of patients had controlled phosphorus levels. calcium-phosphate product decreased during Week 1 and remained within a clinically acceptable range thereafter. There were no clinically significant changes in serum calcium, or PTH levels. CONCLUSION: Lanthanum carbonate is well tolerated and is effective for the long-term maintenance of serum phosphorus control in patients with ESRD.

Sonikian MA, Pani IT, Iliopoulos AN, et al.
Metabolic acidosis aggravation and hyperkaliemia in hemodialysis patients treated by sevelamer hydrochloride. Renal Failure. Vol. 27(2)(pp 143-147), 2005.

In a retrospective analysis, we evaluated SH impact on metabolic acidosis and serum potassium (K) in hemodialysis (HD) patients. Two groups of stable HD patients were studied. Group A included 17 patients, M/F=15/2, 64 (42-80) years old, dialyzed since 130 (34-253) months, under SH for 24 months. Group B serving as controls was made of 7 patients, M/F=4/3, 67 (48-91) years old, dialyzed since 67 (27-174) months, under CaCO3 and/or Al (OH)3 as phosphate binders also for 24 months. Bicarbonate (BIC), K, Ca, phosphorus (P), Ca-PP, alkaline phosphatase (ALP), and intact PTH were recorded before (MO) and at the end (M24) of 24-month SH or CaCO 3-Al(OH)3 treatment in group A and B patients. In group A, BIC fell from 20.02+/-1.43 to 17.89+/-2.30 mEq/L, P=.002; and K rose from 5.45+/-0.51 to 5.75+/-0.49 mEq/L, P=0.02. In group B, BIC (19.8+/-3.03 to 19.0+/-3.3 mEq/L) and K (5.01+/-0.8 to 4.9+/-1.1 mEq/L) had nonsignificant changes. In group A, iPTH rose from 132.82+/- 124.08 to 326.89+/-283.91 pg/mL, P=.0008; P fell from 5.92+/-1.48 to 4.9+/-1.01, P=.02; and Ca-PP decreased from 52.04+/-9.7 to 45.58+/- 10.42 mg2 /dL2 , P=.04. In group B, changes in iPTH from 240.71 +/-174.7 to 318.57+/- 260.2 pg/mL, P from 4.9+/-0.5 to 4.8+/-1.3 mg/dL, and Ca-PP product from 44.3+/-6.6 to 44+/-11.2 mg^2/dL^2 were nonsignificant. The changes observed in Ca and ALP in both groups were nonsignificant. Correlations in group A between metabolic acidosis (BIC) and SH doses, or iPTH and BIC, Ca, or P changes, were also found to be nonsignificant. Long-term use of SH, effectively controlling serum P levels and Ca-PP values, is associated with acidosis aggravation and hyperkaliemia. Worsening of SHPT, also noted, needs to be confirmed and could be related to Ca/Al salt discontinuation and to metabolic acidosis aggravation itself.

Loghman-Adham M.
Safety of New Phosphate Binders for Chronic Renal Failure. Drug Safety. Vol. 26(15)(pp 1093-1115), 2003.

Phosphate (Pi) retention is a common problem in patients with CKD, particularly in those who have reached ESRD. In addition to causing SHPT and renal osteodystrophy, recent evidence suggests that, in ESRD patients, high serum phosphorus concentration and increased calcium-phosphate product are associated with vascular and cardiac calcifications and increased mortality. Dietary phosphorus restriction and Pi removal by dialysis are not sufficient to restore Pi homeostasis. Reduction of intestinal Pi absorption with the use of Pi binders is currently the primary treatment for Pi retention in patients with ESRD. The use of large doses of calcium-containing Pi binders along with calcitriol administration may contribute to over-suppression of PTH secretion and adynamic bone disease as well as to a high incidence of vascular calcifications. When used in patients with impaired renal function, aluminium salts were found to accumulate in bone and other tissues, resulting in osteomalacia and encephalopathy. Sevelamer, an aluminium- and calcium-free Pi binder can reduce serum phosphorus concentration and is associated with a significantly lower incidence of hypercalcaemia, while maintaining the ability to suppress PTH production. An additional benefit of sevelamer is its ability to lower low density lipoprotein-cholesterol and total cholesterol levels. Sevelamer attenuates the progression of vascular calcifications in haemodialysis patients, which may lead to lower mortality. The use of sevelamer in

non-dialysed patients might aggravate metabolic acidosis, common in these patients. Several other calcium-free Pi binders are in development. Lanthanum carbonate has shown significant promise in clinical trials in ESRD patients. Magnesium salts do not offer a significant advantage over currently available Pi binders. Their use is restricted to patients receiving dialysis since excess magnesium must be removed by dialysis. Iron-based compounds have shown variable efficacy in short-term clinical trials in small numbers of haemodialysis patients. Mixed metal hydroxyl carbonate compounds have shown efficacy in animals but have not been studied in humans. Major safety issues include absorption of the metal component with possible tissue accumulation and toxicity.

Health economics, resources, risk/benefit

White CA, Jaffey J, Magner P.
Cost of applying the K/DOQI guidelines for bone metabolism and disease to a cohort of chronic hemodialysis patients. Kidney International. Vol. 71(4)(pp 312-317), 2007.

Hyperphosphatemia is a common feature of advanced CKD and is treated routinely with oral calcium-based phosphate binders. In 2003, the National Kidney Foundation Kidney Disease Outcomes and Quality Initiative (K/DOQI) published Clinical Practice Guidelines (CPGs) for the treatment of Bone Metabolism and Disease in CKD. These advocate broad usage of expensive non-calcium-based phosphate binders such as sevelamer. This study was designed to determine the cost of implementation of the K/DOQI CPGs as they pertain to phosphate binding in a large Canadian hemodialysis (HD) unit. Laboratory and medication data for all chronic HD patients at the Ottawa Hospital were reviewed (n=416). Patients meeting each of the relevant K/DOQI guidelines were identified. Where guidelines would recommend a switch to non-calcium binders, equivalent sevelamer doses were estimated. The cost of implementing each guideline was then calculated individually and an estimate total cost of implementing all the guidelines was derived. Overall, 53% (222) patients fulfilled at least one criterion for sevelamer use. The yearly cost of implementation of the K/DOQI guidelines at this center was estimated at $ 500 605 (American dollars). Given the significant cost, widespread adoption of the K/DOQI CPGs for Bone Metabolism and Disease should await the publication of compelling data demonstrating significant improved outcomes in patients treated with sevelamer.

Brennan A, Akehurst R, Davis S, et al.
The cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in patients with end-stage renal disease. Value in Health. Vol. 10(1)(pp 32-41), 2007.

To assess the cost-effectiveness of lanthanum carbonate (LC) as a second-line therapy for hyperphosphatemia in ESRD patients not achieving target phosphorus levels. Methods: A cohort of ESRD patients not adequately maintained on calcium carbonate (CaCO3) and three subgroups of patients with baseline phosphorus levels of 5.6 to 6.5 mg/dl, 6.6 to 7.8 mg/dl, and more than 7.9 mg/dl were modeled. The following policy options were considered: continued CaCO3 (Policy 1); LC trial - if successful continue LC, if unsuccessful switch to CaCO3 (Policy 2). The survival benefit of using second-line LC to improve phosphorus control has been extrapolated from the relationship between hyperphosphatemia and mortality. Lifetime UK National Health Service drug and monitoring costs, expected survival, and quality-adjusted life-years (QALYs) were examined (discounting at 3.5% per annum). Results: Policy 2 had a cost-effectiveness ratio (cost/QALY) of 25,033 relative to Policy 1. The results show it is particularly cost-effective to treat patients with phosphorus levels above 6.6 mg/dl. The outcomes did not vary significantly during the one-way sensitivity analysis carried out on important model parameters and assumptions except when the utility value for ESRD was decreased by more than 30%. Conclusions: Applying a cost-effectiveness threshold of 30,000 per QALY, the model shows it is cost-effective to follow current treatment guidelines and treat all patients who are not adequately maintained on CaCO3 (serum phosphorus

above 5.6 mg/dl) with second-line LC. This is particularly the case for patients with serum phosphorus above 6.6 mg/dl. Our estimates are probably conservative as the possible compliance difference in favor of LC and the reduced number of hypercalcemic events with LC relative to CaCO3 was not considered.

White A, Odedina F, Xiao H, et al.
The economic burden of end-stage renal disease with hyperphosphatemia: A study of Florida Medicaid. Disease Management & Health Outcomes. Vol. 14(2)(pp 99-106), 2006.

The aims of this study were to: (i) describe the characteristics of ESRD patients with hyperphosphatemia in terms of demographics, comorbidities, and healthcare utilization; (ii) evaluate the primary cost drivers in the treatment of these patients; and (iii) assess the cost of illness associated with treating ESRD patients with hyperphosphatemia. Methods: This retrospective study extracted data from the Florida Medicaid database. Healthcare costs were assessed from a third-party payor perspective. The patient inclusion criteria were current use of either sevelamer or calcium acetate and continuous eligibility to receive Florida Medicaid services from July 1, 1999 to December 31, 2002 with a run-in period from July 1, 1999 to December 31, 1999 to ensure that patients had been taking either of the two drugs for at least 6 months. The patient exclusion criteria were documented HIV and hemophilia. The specific direct costs included in the study were hospitalization costs, outpatient costs, emergency room costs, and prescription costs (only those for sevelamer and calcium acetate). The price year for the cost analysis was 2002. Results: A total of 10 058 recipients constituted the study sample, of which 54.0% were male and 46.0% were female. African Americans represented the largest racial group (45.6%), followed by Caucasians (28.6%). The most frequent comorbidities were hypertension, anemia, and congestive heart failure. Healthcare was most often utilized through facility visits (78.1%), followed by pharmacy-related services (17.2%) and then medical services (4.7%). Based on medical claims, the ambulance service contributed the most to healthcare utilization (8.7%), followed by recipient home visits (3.3%) and inpatient visits (2.1%). Facility claims utilization was dominated by dialysis center visits (48.5%), followed by general hospital visits (43.3%) and nursing home visits (7.4%). The major cost driver for 2000-2 was dialysis center visits ($US95 million), followed by general hospital visits ($US92 million), and prescription medication ($US11 million). The cost analysis revealed that ESRD patients with hyperphosphatemia within Florida Medicaid imposed an economic burden (including facility, medical, and prescription claims) of $US228 million for the years 2000-2. Conclusions: This is the first study to report the economic impact of ESRD with hyperphosphatemia. Given the high economic burden of this population, efforts should be undertaken to enhance preventative measures for hyperphosphatemia as well as the treatment and recovery of these patients.

Nolan CR.
Strategies for improving long-term survival in patients with ESRD. Journal of the American Society of Nephrology. Vol. 16(11 SUPPL. 2)(pp S120-S127), 2005.

In 2003, more than 320,000 people in the United States were receiving dialysis for ESRD, with predicted increases to 650,000 by 2010 and 2 million by 2030. Mortality from cardiovascular disease (CVD) in patients with ESRD is 10 to 30 times higher than in the general population. The exact mechanism of accelerated CVD in patients with kidney disease is unknown. Treatment costs for ESRD are in excess of $14 billion annually (6.4% of Medicare budget). Strategies to improve long-term outcomes include aggressive risk factor modification, minimization of dialysis complications, and kidney transplantation. Because abnormalities of mineral metabolism contribute to mortality risk, phosphate binder therapy is fundamental. More expensive non-calcium-containing phosphate binders such as sevelamer have been recommended to reduce cardiovascular calcification. However, the lack of outcome data and the $2 to $3 billion annual cost make it difficult to justify widespread utilization of newer binders as first-line therapy. Conversely, kidney transplantation

is known to improve survival in ESRD. Progression of atherosclerosis and CVD in patients with renal failure is largely due to loss of renal function per se, and provision of a functioning kidney through renal transplantation halts the progression of CVD and dramatically reduces mortality. Despite this fact, many patients lose Medicare funding for immunosuppressive therapy 3 yr posttransplantation. To achieve the goal of prevention of cardiovascular mortality in patients with ESRD, it clearly would be more prudent, efficacious, and cost-effective to use Medicare prescription drug dollars to provide full coverage for life-long immunosuppressive drug therapy after renal transplantation.

Huybrechts KF, Caro JJ, Wilson DA, et al. Health and economic consequences of sevelamer use for hyperphosphatemia in patients on hemodialysis. Value in Health. Vol. 8(5)(pp 549-561), 2005.

A model of the predicted long-term consequences of sevelamer compared with calcium-based binders (acetate and carbonate) was developed. Methods: Long-term cardiovascular implications of 1 year of treatment with phosphate binders in patients on hemodialysis are estimated based on the patient's demographics, comorbidities, and physiologic and renal parameters. The initial calcification score and expected changes over 1 year are derived using regression equations developed from the Treat-to-Goal study and translated to cardiovascular disease risk based on equations developed from a long-term cohort study. In this article, the implications of cardiovascular disease for life expectancy and medical costs are accounted for from a US payer perspective. Results: The cardioprotective effect of sevelamer over 1 year is estimated to result in a 12% reduction in cardiovascular events compared with calcium acetate. In a population of 100 patients, the savings of $205,600 accrued due to avoiding nine cardiovascular events with sevelamer, largely offset the increased binder costs, leading to a favorable cost-effectiveness ratio of about $2200 per (discounted) life-year gained. Conclusions: Although both binders provide equivalent phosphate binding capacity, the results indicate that the advantage of 1 year of treatment with sevelamer in attenuating the progression of calcification has important clinical and economic consequences, suggesting that this provides good value for money.

Collins AJ, St Peter WL, Dalleska FW, et al. Hospitalization risks between Renagel phosphate binder treated and non-Renagel treated patients. Clinical Nephrology. Vol. 54(4)(pp 334-341), 2000.

We evaluated 152 sevelamer hydrochloride treated Medicare patients on hemodialysis in a case-controlled study matching 152 randomly selected non-sevelamer hydrochloride treated Medicare patients from the same dialysis facilities and time period. The main outcomes evaluated were the risk of all-cause hospitalization and per-member per-month (PMPM) Medicare expenditures in the follow-up period. Patients and methods: Medicare patients were identified from a total of 195 patients who were included in a long-term safety and efficacy clinical trial evaluating sevelamer hydrochloride [Chertow et al. 1999a]. The average serum calcium-phosphate product as well as lipid profiles improved in the sevelamer hydrochloride treated group during the trial. Sevelamer treated patients were matched with randomly selected Medicare patients for age, gender, race, diabetic status, and geographic location. Comorbid conditions were characterized and sequential Cox regression models were applied with the outcome being risk of first hospitalization in a 17- month follow-up period. Results: Across all four models, the relative risk of hospitalization was 46% to 54% less in the sevelamer hydrochloride treated group, as compared to the case control group (significant at the p-value 0.03 level). Overall, Medicare expenditures for the control patients per-member per-month were US-$4,745, compared to US-$3,368 in the sevelamer hydrochloride treated patients. Conclusion: Sevelamer hydrochloride treated patients had a 50% lower likelihood of hospitalization in the follow-up period after adjustments for the differences in the population. Potential bias may exist between groups because of differences in baseline characteristics that could not be adjusted for within the study design. We feel that to further advance this

area, a randomized clinical trial should be performed.

Brophy DF, Wallace JF, Kennedy DT, et al. Cost-effectiveness of sevelamer versus calcium carbonate plus atorvastatin to reduce LDL in patients with chronic renal insufficiency with dyslipidemia and hyperphosphatemia. Pharmacotherapy. Vol. 20(8 I)(pp 950-957), 2000.

We conducted a cost-effectiveness analysis to compare costs and clinical outcomes of sevelamer versus calcium carbonate plus atorvastatin for treatment of dyslipidemia in patients with chronic renal insufficiency. The model was from the third-party payer perspective. Efficacy and adverse event rates for each regimen were obtained from published clinical trials. Drug costs were based on average wholesale prices; monitoring costs were based on Medicare reimbursement rates. Our model suggests that the combination of calcium carbonate plus atorvastatin is substantially more cost-effective than sevelamer in reducing low-density lipoprotein (LDL) in these patients. One-way sensitivity analyses were performed to assess if 25% and 50% price reductions in sevelamer affected overall cost-effectiveness results. A 50% sevelamer price reduction was less expensive than combination therapy but remained less cost-effective. A two-way sensitivity analysis on the probability that a patient achieves the goal of a 35% LDL reduction resulted in calcium carbonate plus atorvastatin remaining more cost-effective. Further cost-effectiveness studies are necessary to corroborate our data.

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