An initiative of NSW clinical pharmacologists and pharmacists funded by the NSW Department of Health

PARACETAMOL USE

A Position Statement of the

NSW Therapeutic Advisory Group Inc.

December 2008

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Paracetamol Use

A position statement of the New South Wales Therapeutic Advisory Group Inc.

The policy directive PD 2006_004 'Paracetamol Use' is under review by NSW Health. This position statement has been developed by NSW Therapeutic Advisory Group Inc. (NSW TAG) with funding from a grant provided by NSW Health and is intended to inform the revision of that policy directive.

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SUMMARY – PARACETAMOL USE

To be read in conjunction with full position statement

Paracetamol is an effective analgesic and antipyretic and is well tolerated

In children and adults paracetamol is indicated as first line therapy for

- mild to moderate pain
- symptoms of fever, when temperature is above 38.5 ˚C (per axilla)

In acute overdose, paracetamol can lead to severe and sometimes fatal hepatotoxicity.

In children

- short term use of paracetamol in standard recommended doses is well tolerated
- multiple, excessive (supratherapeutic) doses of paracetamol or, occasionally, multiple doses within the recommended dose range, given with therapeutic intent, may lead to hepatotoxicity in sick children

In adults

- chronic use of paracetamol in standard recommended doses is very well tolerated
- multiple, supratherapeutic doses with therapeutic intent have occasionally been associated with severe liver toxicity

Factors that may potentially increase risk of paracetamol toxicity

Infants and children

- febrile illness
- younger age
- prolonged fasting, vomiting or dehydration
- chronic under nutrition
- hepatic impairment

Adults

- prolonged fasting or dehydration
- chronic under nutrition
- chronic, excessive alcohol use
- severe hepatic impairment

The presence of risk factors does not contraindicate treatment with paracetamol but indicates additional considerations for the management of patients with paracetamol.

The extensive availability of a wide range of paracetamol containing products contributes to the potential for inadvertent supratherapeutic dosing with paracetamol.

Key prescribing guidelines for paracetamol in hospitals:

- take a full history and assess for potential risk factors for toxicity prior to initiation of paracetamol treatment
- only prescribe paracetamol when non-pharmacological intervention is insufficient

- only use paracetamol for appropriate indications
- identify if and when any products containing paracetamol have been ingested, both prescribed and over-the-counter (OTC)
- use the appropriate dose of paracetamol
- use 'ideal weight' for dose calculation in obese children
- prescribe only one paracetamol preparation at any one time
- prescribe the paracetamol preparation in one section of the medication chart only
- include the generic term 'paracetamol' (or 'contains paracetamol') on prescriptions for brand products
- prescribe liquid paracetamol in milligrams(mg) or grams(g)
- include the brand name 'Perfalgan®' on prescriptions for intravenous paracetamol
- do not use paracetamol and NSAIDs (e.g. ibuprofen) in combination or as an alternating regimen in children with fever
- include the following on all prescriptions for paracetamol
    1. Name and age of patient
    2. Weight for children, frail elderly patients and low weight adults
    3. Indication for paracetamol use
    4. Dose of paracetamol (total dose in mg)
       For children, frail elderly patients and adults < 50kg with eating disorders or chronic disease, qualify dose in mg/kg/dose
    5. Dose frequency
    6. Route of administration
    7. Maximum daily dose (maximum number of doses/day)
       For children, frail elderly patients and adults < 50kg with eating disorders or chronic disease, express this as total daily dose in mg and mg/kg/day
    8. Maximum duration of therapy

Monitoring and administration of paracetamol in hospitals:

- consult medication chart prior to giving each dose of paracetamol
- sign medication chart after giving each dose of paracetamol
- regularly review pain/fever and the need for ongoing management with paracetamol
- recognise and treat any suspected cases of paracetamol hepatotoxicity without delay
- prescribe and record self administration of paracetamol
- educate staff regarding the number of paracetamol containing products on the market (Appendix 2)
- reduce the number of paracetamol containing preparations available in the hospital

Advice for patients:

- ensure patients, parents and carers receive detailed information (preferably in written as well as verbal form) regarding their, or their child's, medication on discharge
- ensure recipients of paracetamol understand the need to avoid paracetamol containing OTC preparations

1. INTRODUCTION

This position statement provides guidance about the judicious, effective and safe use of paracetamol within the National Strategy for the Quality Use of Medicines (QUM) framework (1).

The recommendations in this position statement are intended to promote best practice in the hospital environment and support clinical decision making. There will be circumstances where the specific recommendations may not produce the best patient outcome. Departure from the recommendations is a consideration for the treating physician

The recommendations are intended for use by health professionals in hospitals and the community setting. However, paracetamol use is frequently initiated by consumers or their parents and carers. Therefore, the recommendations and principles included here should be promoted by health professionals to the community.

The position statement was written following review of the most recent published literature. Consultation with a clinical advisory committee, health practitioners in NSW public hospitals and other relevant advisory groups was sought at all stages of preparation (Appendix 1).

Purpose

The purpose of this document is to:

- emphasise the safety of paracetamol when used appropriately
- advise the appropriate indications for the use of paracetamol
- alert prescribers, nurses, residential care centre staff and pharmacists, to the possible risk factors for hepatotoxicity with paracetamol
- advise the current recommended dose of paracetamol for adults and children for different indications and routes of administration
- provide advice to inform the development of inpatient protocols for paracetamol use
- highlight the range of paracetamol containing preparations available and increase awareness of the potential for inadvertent paracetamol overdose when using more than one preparation
- assist health professionals to inform consumers and their carers about safe and appropriate paracetamol use

2. **INDICATIONS FOR PARACETAMOL USE**

Consideration of the use of non-pharmacological intervention is recommended prior to initiating treatment with paracetamol.

For *adults and children*, paracetamol is an effective analgesic and antipyretic agent and may be used as first line therapy for:

- mild to moderate pain
- symptoms of fever, when temperature is above 38.5 ˚C (per axilla) (symptoms may include: irritability, lethargy and loss of appetite)

Paracetamol is NOT recommended for use

- in asymptomatic adults or children with fever
- in gastroenteritis without fever
- as a sedative

Temperature can vary depending on site and method of measurement. Consistent use of the same method is recommended throughout patient management (i.e. axillary, tympanic, rectal).

There is controversy over the necessity to treat fever associated with acute infection (2). Mild fever itself is not harmful. Indeed, it is considered the body's natural defence mechanism in the immunological response to infection. Treating fever with antipyretics has the potential to prolong a viral illness (3, 4, 5). It is important also to note that antipyretic use does not prevent febrile convulsions (6, 7) and the evidence for the benefits of treatment on symptoms such as mood, feeding, activity and comfort is weak (2, 8).

Paracetamol given to treat symptomatic fever may make the patient feel more comfortable but it will not treat the underlying illness and may not completely normalise temperature. In addition, the response of fever to antipyretics is not related to the severity of the underlying illness and any reassurance provided by temperature reduction is unwarranted.

In children, febrile illness may be a risk factor for hepatotoxicity with paracetamol (9), although selection bias is a confounding issue given fever is an indication for paracetamol therapy. Animal studies indicate fever influences the metabolism of paracetamol and detoxification of the toxic intermediate metabolite (10). Unwell children receiving multiple doses of paracetamol appear to have a smaller margin of safety for paracetamol compared with those receiving occasional, intermittent administration (Section 4). Some factors, such as dehydration, also increase risk of toxicity with other antipyretic agents e.g. ibuprofen.

Routine use of paracetamol at the time of vaccination is unnecessary (11). If high fever develops post-immunisation then paracetamol may be used according to the recommended dose in Table1.

Adults: The need for antipyretic therapy with paracetamol in adults is questionable and probably unnecessary unless paracetamol is also required for analgesia.

3. SAFETY OF PARACETAMOL

Paracetamol is used extensively worldwide and has a well established safety profile when used appropriately.

In acute overdose, paracetamol can lead to severe and sometimes fatal hepatotoxicity.

In certain circumstances patients may be at increased risk of toxicity with paracetamol. This may vary depending on age, indication for use and any existing conditions. These should be carefully reviewed prior to initiating paracetamol therapy (see Section 4).

Children

Short term use of paracetamol in standard recommended doses is well tolerated in children.

In general, the margin of safety for repeated dosing within the recommended range is wide. However, published cases or case series indicate that hepatotoxicity can undoubtedly occur in sick children who receive multiple, supratherapeutic doses of paracetamol (12, 13, 14, 15, 16). In some cases, multiple doses within the recommended dose range given with therapeutic intent may be toxic (17).

Adults

Chronic use of paracetamol in standard recommended doses, e.g. in the treatment of osteoarthritis, is well tolerated by adults.

An increased susceptibility to multiple, supratherapeutic doses with therapeutic intent is less clear in adults, but severe liver toxicity and death have occasionally been reported and may be due to the dose ingested with possible confounders such as viral infection, glutathione depletion or enzyme induction (18).

4. POSSIBLE INFLUENCES ON HEPATOTOXICITY WITH PARACETAMOL

A full medical history, including medication history, should be obtained from the patient, or their representative, before prescribing paracetamol. The principal aims are to identify factors potentially increasing risk of paracetamol toxicity and if paracetamol has been recently ingested.

a) Factors that may potentially increase risk of paracetamol toxicity

A number of risk factors may alter the metabolism of paracetamol, increasing production of the toxic metabolite (NAPQI) or decreasing the detoxification of this metabolite by depleting glutathione (9). There is considerable ongoing discussion in the literature regarding the extent to which these risk factors may influence paracetamol metabolism. Studies reporting hepatotoxicity with standard doses of paracetamol are often retrospective and actual doses received are difficult to establish. Patients and parents may over or under estimate the ingested dose depending on circumstances (19, 20, 21).

In addition, some individuals may be particularly sensitive to paracetamol. However, it remains possible that a profile of risk factors may predispose an individual to toxicity with paracetamol given with therapeutic intent.

The presence of risk factors does not contraindicate treatment with paracetamol but indicates additional considerations for the management of patients with paracetamol.

The factors that may increase the risk of hepatotoxicity with paracetamol use include:

For *infants and children (8, 9, 12, 14, 16, 22, 23, 24):*

- febrile illness
- younger age
- prolonged fasting, vomiting or dehydration
- chronic under nutrition
- hepatic impairment

In small numbers of sensitive children a combination of some of these factors appears to increase susceptibility to hepatotoxicity with paracetamol. A **risk profile** for development of hepatotoxicity with paracetamol has been identified as *'sustained administration of high doses of paracetamol (>90mg/kg/day) [supratherapeutic] to a sick child who is younger than 2 years for more than one day'* (9).

This risk profile should be considered when prescribing paracetamol and the dose should be adjusted accordingly (Section 5a; Table 1).

In obese children, obesity itself is not a 'risk factor'. However, paracetamol does not enter fatty tissue well and overestimation of standard doses of paracetamol using actual weight may represent a relative overdose potentially leading to hepatotoxicity with paracetamol (Section 5e).

In addition, the following factors contribute to the risk profile in children (22):

- prior paracetamol intake (e.g. in OTC cough/cold preparations)
- use of adult rather than paediatric formulations or use of paediatric formulations designed for an older age group e.g. siblings

The early identification of children at risk is critical to reduce the incidence of hepatotoxicity with paracetamol (12). In patients receiving cumulative multiple doses of paracetamol the time to presentation and delays in treatment with N-acetylcysteine are a major contributing factor to outcome (25, 26, 27).

For *adults*:

- prolonged fasting or dehydration
- chronic under nutrition
- chronic, excessive alcohol use (see Section 6)
- severe hepatic impairment

These risk factors are largely theoretical. The evidence is limited to case reports or at best case series and thus the risks are probably overstated because of publication bias. For short term therapy patients with these conditions receiving standard doses of paracetamol are not at risk (28). However, individual case reports suggest a dose reduction for paracetamol where these factors are present (Section 5a; Table 1) (29).

For the elderly:

Risk factors are the same as for younger adults. However, whilst conjugation of the paracetamol metabolite is similar in young and old, fit patients, it may be reduced in old, frail patients (30, 31). Hepatic glutathione is reduced in old age (32) and may be further reduced in the presence of frailty and malnutrition.

Adult doses of paracetamol are recommended for elderly, fit patients. A dose reduction is recommended in elderly, frail patients (Section 5a; Table 1) (29).

b) Extensive availability of paracetamol containing preparations

The availability of a wide range of paracetamol containing products contributes to the potential for inadvertent supratherapeutic dosing with paracetamol.

A comprehensive medication history should include prescription drugs and all over-the-counter (OTC) products, including those currently taken and those carried for potential use. In history taking it is important to note:

- Patients may carry OTC, paracetamol containing products without disclosing these because they are familiar and their significance is overlooked.
- Patients may ingest combination cold and flu preparations without realising they contain paracetamol.
- Patients may not realise the relevance of OTC medications to those prescribed in hospital.

An extensive array of paracetamol containing preparations is currently available in NSW. These are listed in Appendix 2.

5. USE OF PARACETAMOL

a) Recommended dose

The appropriate dose of paracetamol depends on the patient's age, weight, general medical condition, indication for use, route of administration and possible risk factors for hepatotoxicity (Table 1, 33).

TABLE 1. RECOMMENDED DOSE FOR PARACETAMOL		
ADULTS AND CHILDREN OVER 12 YEARS		
Oral	0.5 – 1 g every 4 to 6 hours up to a maximum of 4 g in 24 hours.	• For chronic pain, review as necessary. • For acute pain and symptomatic fever > 38.5 ºC, review at 48 hours • Consider lowering dose in those with risk factors for hepatotoxicity (Section 4)
Rectal	0.5 – 1 g every 6 hours up to a maximum of 4 g in 24 hours **(Section 5b)**	• Only use when oral dosing not possible. Substitute oral paracetamol at the earliest opportunity. • Do not cut suppositories. Calculate dose to nearest suppository strength. • Do not use in immunocompromised or those with coagulopathy • Review at 48 hours • Consider lowering dose in those with risk factors for hepatotoxicity (Section 4)
Intravenous infusion	1 g every 4 to 6 hours up to a maximum of 4 g in 24 hours **(Section 5c)**	• Perfalgan® (IV paracetamol) may be used for acute, short term treatment of mild to moderate pain when oral or rectal dosing is not possible. Oral or rectal paracetamol should be substituted at the earliest opportunity. • Review at 24 hours. • Do not use if paracetamol was administered in any form (including loading dose) in preceding 6 hours. • After IV administration of paracetamol, a 6 hour dosing interval is required before further administration of paracetamol by any other route. • Perfalgan® (IV paracetamol) is NOT recommended for the treatment of fever. • Consider lowering dose in those with risk factors for hepatotoxicity (Section 4)
These dosages are generally well tolerated. However, hepatotoxicity can arise in adult patients with extremely low body weight or if other risk factors are present (Section 4a). For frail, older patients and adults less than 50 kg with eating disorders or chronic disease paracetamol dose should be adjusted for weight, 15 mg/kg/dose every 4 to 6 hours up to four times daily. Refer to specialist centres for administration of stat or loading doses of paracetamol. Any paracetamol given in the 24 hours preceding a stat dose must be included in the total 24 hour calculation. Dosing subsequent to the stat dose must include the stat dose in the total 24 hour calculation.		
NEONATES AND INFANTS LESS THAN 3 MONTHS		
Babies < 3months and neonates require careful medical review and treatment with paracetamol requires specialist management. The pharmacokinetics of paracetamol in neonates will be influenced by weight, gestational age and a number of other factors (34).		

INFANTS AND CHILDREN 3 MONTHS TO 11 YEARS		
For analgesia		
Oral	15 mg/kg/dose* 4 to 6 hourly, up to a maximum of 60 – 90 mg/kg/day. Never exceed 4 g in 24 hours.	• The lower maximum (60 mg/kg/day) is recommended for children with risk factors for hepatotoxicity (Section 4), younger infants (e.g. < 6 months) and children treated in a community setting. • Review at 48 hours. Consider reducing dose if continued treatment necessary.
Rectal	20 mg/kg/dose* 6 hourly, up to a maximum of 90 mg/kg/day. Never exceed 4 g in 24 hours. **(Section 5b)**	• Consider lowering dose in children with risk factors for hepatotoxicity (section 4), younger infants (e.g. < 6 months) and children treated in a community setting. • Only use when oral dosing not possible. Substitute oral paracetamol at the earliest opportunity. • Do not cut suppositories. Calculate dose to nearest suppository strength. • Do not use in immunocompromised child or those with coagulopathy. • Review at 48 hours. Consider reducing dose if continued treatment necessary.
Intravenous infusion	15 mg/kg/dose* every 6 hours up to a maximum of 60 mg/kg/day. Never exceed 1 g per dose and 4 g in 24 hours. **(Section 5c)**	• Perfalgan® (IV paracetamol) may be used for acute, short term treatment of mild to moderate pain when oral or rectal dosing is not possible. Oral or rectal paracetamol should be substituted at the earliest opportunity. Review at 24 hours. • Consider lowering dose in children with risk factors for hepatotoxicity (Section 4) • Only use in children < 6 months and/or < 5 kg with specialist review. • Do not use if paracetamol was administered in any form (including loading dose) in preceding 6 hours. • After IV administration of paracetamol, a 6 hour dosing interval is required before further administration of paracetamol by any other route.
For symptomatic fever > 38.5 ˚C		
Oral or rectal	15 mg/kg/dose* every 6 hours up to 60 mg/kg/day. Never exceed 4 g in 24 hours.	• If pain and fever are both present, the lower dose recommended for fever should be used. Review at 48 hours. • Perfalgan® (IV paracetamol) is NOT recommended for the treatment of fever.
***Recommended dose is based on 'ideal weight' relative to age and height of child (Section 5e).** Refer to specialist centres for administration of stat/ loading doses of paracetamol. Any paracetamol given in the 24 hours preceding a stat dose must be included in the total 24 hour calculation. Dosing subsequent to the stat dose must include the stat dose in the total 24 hour calculation.		

b) Rectal paracetamol

Oral paracetamol is recommended wherever possible. Rectal paracetamol is effective. A recent study has shown rectal and intravenous paracetamol provide equally effective analgesia with pain relief maintained for longer with rectal dosing (35). However, absorption of paracetamol given rectally is erratic and the time taken to achieve maximum concentration is not predictable (36, 37). The bioavailability for rectal paracetamol compared with oral forms is approximately 78% (38). Therefore, oral dosing should be resumed as soon as possible.

Due to the difference in absorption between rectal and oral routes of administration the route must be clearly specified on the prescription. A prescription written for both oral and rectal administration is NOT acceptable.

Suppositories must not be divided or broken to achieve smaller doses and suppositories are NOT recommended for use in the immunocompromised or those with coagulopathy.

c) IV paracetamol

Perfalgan® [intravenous (IV) paracetamol] may be used for the acute, short term treatment of mild to moderate pain when administration of paracetamol via the oral or rectal route is not possible (39, 40). IV paracetamol is NOT recommended for the treatment of fever. Use of IV paracetamol is preferably managed by senior clinicians in anaesthesia, intensive care and pain management. Administration of IV paracetamol in children < 6 months and/or < 5 kg is not recommended for routine use but may be appropriate in individual patients following specialist review.

Enteral (oral [preferred] or rectal) paracetamol should be substituted for IV paracetamol as soon as clinically appropriate. When IV paracetamol is replaced by enteral paracetamol, the maximum dose for the 24 hour period from the start of IV administration is 60 mg/kg/day (maximum 4 g/day). After IV dosing allow a period of 6 hours to elapse before administering the next dose of paracetamol via any route. Do not use IV paracetamol if paracetamol was administered, in any form (including a loading dose) in the preceding 6 hours.

IV paracetamol is administered as an infusion. The additional volume of fluid is important to consider in fluid restricted patients.

d) Use of paracetamol with NSAIDs

Paracetamol may be used for the treatment of mild to moderate pain alone, or in combination with NSAIDs, including ibuprofen (41).

Paracetamol is recommended as first line therapy for the treatment of symptomatic fever > 38.5 ˚C. The use of paracetamol and NSAIDs (e.g. ibuprofen) in combination or as an alternating regimen is not recommended in children with fever (8, 41, 42).

- Although a few studies evaluating combined or alternating regimens exist (43, 44), there is no good evidence that using paracetamol and NSAIDs together has improved efficacy in relieving important clinical symptoms associated with fever versus each used individually (22, 41)

- The physiological effects of a combination of ibuprofen and paracetamol may potentiate the risk of toxicity of each drug (45), although the clinical safety outcomes of this practice have not been well evaluated

- Some potential risk factors for paracetamol toxicity, e.g. dehydration, also increase the risk of toxicity with NSAIDs

- Dose regimens with the combination cause confusion and increase the incidence of adverse effects due to dosing errors (2, 8, 22, 46)

e) Estimating 'ideal weight' for dose calculation purposes

Recommended doses apply only to patients of normal or average build where their actual weight is a reasonable estimate of their lean body weight**.** In every case the adult maximum dose of 4 g daily should not be exceeded.

Children

For obese children, calculation of paracetamol dose using actual bodyweight may lead to a relative overdose. The recommended dose in an obese child is based on lean body weight (47) relative to the age and height of the child. The 'ideal weight' for dose calculation purposes for a child may be approximated using growth charts which are widely available in health care facilities and can be accessed at (http://www.cdc.gov/growthcharts/).

- If age and height are known, a height growth chart will indicate the percentile at which to read the weight from a weight growth chart.
- If only age is known, reading from the 50th percentile on a weight growth chart is a practical and expedient method for weight estimation.

For underweight, malnourished or inactive children recommended dose is based on actual bodyweight whilst taking into consideration general nutritional status and precautions as discussed under risk factors in section 4a.

Adults

Adults weighing 50 kg or more: recommended adult dose (Table 1)

Adults weighing less than 50 kg with no accompanying risk factors: recommended adult dose (Table 1)

For frail, older people and adults less than 50 kg with eating disorders or chronic disease, adjust dose for weight: 15 mg/kg/dose every 4 to 6 hours up to four times daily. If dosing for longer than 48 hours, monitoring of liver function tests, including International Normalized Ratio (INR), is recommended.

f) Pain and pain management assessment and review

- *Children and adults* receiving oral or rectal paracetamol for acute pain or symptomatic, high fever: Review regularly and no later than 48 hours after commencement of paracetamol and at least 24-hourly thereafter.

- *Adults* receiving paracetamol for chronic pain: Review as necessary

- *Children and adults* receiving IV paracetamol: Review regularly and no later than 24 hours after commencement of paracetamol

Routine assessment of pain will result in improved patient management. Regular review of patients receiving analgesia or other forms of pain management before and after each dose ensures treatment is judicious and effective. A validated and age appropriate pain assessment tool together with other indicators of pain (e.g. behaviour) will accurately assess pain. The same methods should be used to reassess pain after intervention.

If analgesia is required, regular maintenance therapy is indicated. Prescribing on an 'as required' basis is rarely necessary, unless pain is truly intermittent. Frequent review of maintenance therapy is more appropriate.

Paracetamol prescriptions require regular review by the prescriber to ensure at each pain assessment the treatment continues to be appropriate for the needs of the patient bearing in mind the potential for hepatotoxicity.

6. DRUG INTERACTIONS:

A number of drugs have the potential to interact with paracetamol. When used in recommended, therapeutic doses the clinical significance of these interactions is minimal, and with the exception of warfarin, not enough to alter the course of treatment.

Anticonvulsants

Anticonvulsants that induce hepatic microsomal enzymes, including phenytoin, barbiturates and carbamazepine have a theoretical potential to increase paracetamol-induced liver toxicity. However, when paracetamol is used within recommended doses, there is no evidence for an increase in hepatotoxicity with concomitant anticonvulsant use (48).

Isoniazid

Isoniazid and paracetamol used concurrently may result in increased risk of hepatotoxicity when larger than recommended doses of paracetamol are taken (49). Within the recommended dosage regimen there is no evidence for increased risk.

Warfarin

Anticoagulation with warfarin is slightly potentiated by the chronic ingestion of paracetamol (50, 51, 52). Nevertheless, paracetamol is still the preferred treatment in patients taking warfarin who require mild to moderate analgesia. The warfarin dose

should be reduced, if necessary, according to INR values in patients likely to require chronic therapy with paracetamol for more than 2 weeks.

Alcohol

It has been widely stated that chronic, excessive consumption of alcohol may increase the risk of paracetamol induced hepatotoxicity after paracetamol overdose (53). Whilst prospective studies have failed to find liver injury at therapeutic doses (54, 55), case reports of liver injury in alcoholic patients receiving standard doses of paracetamol have been published (19). It has been suggested this apparent anomaly is due to higher than standard doses of paracetamol ingested either intentionally or as a result of memory loss. Also, the time to treatment with N-acetylcysteine may be delayed in chronic alcoholics (53). In summary, evidence is insufficient to support any alleged major toxic interaction (56).

Short term use of therapeutic doses of paracetamol (for 3 days) in chronic alcoholics appears safe (28).

Acute alcohol intake does not influence the course of paracetamol toxicity, as measured by liver function tests, after paracetamol overdose (57), and may even offer a protective effect in chronic alcoholics who co-ingest alcohol with paracetamol (53).

7. PARACETAMOL TREATMENT PROTOCOLS

a) Hospital inpatient protocols

Paracetamol was the third most frequently reported single medication (2.7%), associated with medication incidents in NSW hospitals over a one year period from 2005 to 2006 (58). To reduce potential for adverse events the following information should be included on all prescriptions for paracetamol:

- Name and age of patient.
- Weight for children, frail elderly patients and adults < 50kg with eating disorders or chronic disease.
- Indication for paracetamol use (e.g. pain/symptomatic high fever)
- Dose of paracetamol (total dose in mg)
  For children, frail elderly patients and adults < 50kg with eating disorders or chronic disease, qualify dose in mg/kg/dose
- Dose frequency
- Route of administration (specify single route i.e. oral or rectal, NOT both)
- Maximum daily dose (maximum number of doses/day)

For children, frail elderly patients and adults < 50kg with eating disorders or chronic disease, this should be expressed as total daily dose in mg and mg/kg/day

- Maximum duration of therapy

Dose must be appropriate for the indication, risk factors, route of administration, age and 'ideal weight' (Section 5).

Route of administration

Hospitals should consider using only one concentration of liquid paracetamol. Each dose of paracetamol should be expressed in milligrams (mg) or grams (g) per dose to avoid confusion with differing concentrations. The form of paracetamol, i.e. oral liquid, must be stated.

There is potential for inadvertent administration of oral formulations via the IV route. Prescriptions for IV paracetamol should be written as 'IV paracetamol' and 'Perfalgan®' to emphasise route of administration and intended formulation.

Avoiding the use of multiple paracetamol containing preparations

Inadvertent overdose by taking two or more paracetamol containing preparations is an occasional cause of liver injury (18, 59). Hospital personnel should be educated about the availability of multiple paracetamol containing preparations in the community (Appendix 2). Drug and Therapeutics Committees should limit the number of preparations available for initiation of treatment in the hospital.

Prescription of only one paracetamol preparation at any one time will help to avoid higher than intended dosing. Wherever possible, paracetamol should be written in only one section of the medication chart. Prescribing in both the regular and 'prn' areas of the chart may potentially lead to overdose. If paracetamol is intentionally written in two sections of the chart, connecting the two entries with a comment will increase clarity.

Ideally, prescriptions should use generic product names. Where a brand name is used on the prescription, the generic term 'paracetamol' or 'contains paracetamol' should be written adjacent to the brand name.

Nursing protocols

Protocols for nurse initiated medication should incorporate guidelines on the use of paracetamol to allow nursing staff to make informed decisions about when to give and not give paracetamol.

Nursing staff must consult the medication chart PRIOR to administration of paracetamol and ensure that paracetamol is not administered before the next dose is due, particularly following patient request. Signing the chart at each dose administration is mandatory.

Paracetamol for self-administration in hospital must be ordered by a prescriber on a medication chart. Each dose of paracetamol taken must be recorded and the importance of following the prescribed dose regimen emphasised to the patient.

b) Medical discharge and transfer summaries

Hospital staff are reminded of the need to expeditiously and accurately complete transfer and discharge summaries.

Rigorous recording of paracetamol doses administered peri-operatively and post-operatively in theatre and recovery is essential. Wherever possible, all prescriptions should be written on a single medication chart that accompanies the patient in all areas of the hospital. Continuing therapy must take into account paracetamol already received, including medication taken prior to admission.

At the time of discharge, specific information regarding paracetamol administration should be provided to patients and their parents or carers, including:

- indication for the use of paracetamol
- strength of the paracetamol preparation dispensed or recommended
- dose in milligrams (**and** millilitres for liquid preparations with appropriate strength indicated)
- route of administration
- frequency of administration
- maximum daily dose
- maximum duration of use. This is particularly important to emphasise in the case of children since some may be at risk of toxicity with chronic dosing.

It is also important for the patient to understand their discharge medication contains paracetamol and that many over-the-counter products recommended for cold, cough, headache etc. also contain paracetamol and should not be taken concurrently.

c) Community education

Most cases of hepatotoxicity with paracetamol occur outside hospital. Factors contributing to paracetamol overdose and toxicity in the wider community include:

- incorrect interpretation of dosing instructions
- lack of understanding regarding potential toxicity
- use of more than one paracetamol containing preparation
- substitution of adult for paediatric preparations in children either due to a lack of availability of the paediatric preparation or on the assumption that it will be more effective (15)
- use of excessive dosing because desired effect has not been achieved

It is important to relay clear information to consumers regarding appropriate paracetamol administration:

- Adults receiving chronic paracetamol treatment can be reassured of the safety profile of paracetamol provided it is taken under medical advice and the maximum daily dose is not exceeded.

- Parents and carers can more easily understand the guidance within an educational setting when they are not immediately worried about a sick child.

Provision of written information e.g. Parent and carer brochure from Sydney Children's Hospital (60) on safe and appropriate use of paracetamol is suitable.

8. PARACETAMOL HEPATOTOXICITY DUE TO ACUTE OVERDOSE

If advice is required for the management of acute poisoning with paracetamol contact the Poisons Information Centre on 131126.

In acute overdose, adults are more susceptible than children to hepatic toxicity with paracetamol. It has been shown that in adults, sulfation (one of the metabolic pathways for paracetamol) declines from around 10 to 12 years of age. This leads to more paracetamol being metabolised by the cytochrome p450 system with resultant higher concentrations of the potentially toxic metabolite, NAPQI (61). More recent studies support the view that, in children, their relatively larger liver mass compared to total body mass ratio allows them to metabolise more drug per kg of body weight than an adult, thereby conferring greater tolerance to acute paracetamol poisoning (62).

The management of acute overdose with paracetamol is well documented in a recently published consensus statement from clinical toxicologists in Australasia which includes the current paracetamol treatment nomogram for Australasia (63). It is important for clinicians to promptly identify patients at risk of developing hepatotoxicity with paracetamol poisoning. The prognosis for recovery is good with early recognition and treatment.

If clinicians have any doubt about the diagnosis of hepatotoxicity or interpretation of hepatic transaminase levels and INR results, they must seek prompt toxicology advice from the Poisons Information Centre on 131126.

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NSW TAG also acknowledges the contribution of expert groups including the following:

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NSW TAG also acknowledges contribution from the following individuals:

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APPENDIX 2 - COMMONLY AVAILABLE PARACETAMOL CONTAINING PREPARATIONS IN NSW

An extensive range of paracetamol containing preparations is available in NSW. The analgesic/antipyretic market is frequently changing with the introduction of new products and re-branding of existing products. In addition, travelling Australians, visitors and residents from overseas may possess a host of other paracetamol containing preparations from across the world. Hence, this list of products does not describe every paracetamol containing preparation a patient may use, but does highlight the importance of history taking, nursing protocols and community education to avoid inadvertent paracetamol overdose.

Products containing paracetamol alone include:

Oral, solid dose forms

Chemists' Own Paracetamol 500mg Tablets
Chemists' Own Paracetamol Capseals
Children's Panadol Chewable Tablets (GlaxoSmithKline Consumer)
Dymadon Tablets (Johnson & Johnson)
Dymadon Capsule Shaped Tablets (Johnson & Johnson)
Dymadon P Tablets (Johnson & Johnson)
Febridol Clear Effervescent Soluble Tablets (Genepharm)
Febridol Tablets (Genepharm)
Gold Cross Paracetamol Tablets (Biotech)
Herron Paracetamol Capseals (Herron)
Herron Paracetamol Tablets (Herron)
Herron Paracetamol Tabsules (Herron)
Lemsip Max Powder (Reckitt Benckiser)
Lemsip Original Lemon Powder (Reckitt Benckiser)
Panadol Caplets (GlaxoSmithKline Consumer)
Panadol Cold & Flu Sachets
Panadol Gel Caps (GlaxoSmithKline Consumer)
Panadol Mini Caps Tablets (GlaxoSmithKline Consumer)
Panadol Rapid Tablets (GlaxoSmithKline Consumer)
Panadol Rapid Soluble Tablets (GlaxoSmithKline Consumer)
Panadol Tablets (GlaxoSmithKline Consumer)
Panamax Tablets (sanofi-aventis)
Paracetamol 7+ Years Soluble Tablets (GlaxoSmithKline Consumer)
Paracetamol Soluble Tablets (Cipla GenPharm)
Parahexal Tablets (Hexal)
Paralgin Tablets (Fawns & McAllan)
Parmol Tablets (Arrow)

Controlled release formulations:

Duatrol SR Modified Release Tablets (Menley & James)
Panadol Extend Tablets(GlaxoSmithKline Consumer)
Panadol Osteo Modified Release Tablets (GlaxoSmithKline Consumer)

Oral, liquid dose forms

Benylin Sore Throat (Johnson & Johnson)
Chemists' Own Children's Paracetamol Suspension 1-5
Chemists' Own Children's Paracetamol Suspension 5-12
Chemists' Own Paracetamol Pain & Fever Drops
Children's Panadol 1 Month - 2 Years Colourfree Baby Drops (GlaxoSmithKline Consumer)
Children's Panadol 1 Month - 2 Years Colourfree Easy Dose Baby Drops (GlaxoSmithKline Consumer)
Children's Panadol 1 Month - 2 Years Original Easy Dose Baby Drops (GlaxoSmithKline Consumer)
Children's Panadol 1 - 5 Years Elixir (GlaxoSmithKline Consumer)
Children's Panadol 1 - 5 Years Colourfree Suspension (GlaxoSmithKline Consumer)
Children's Panadol 5 - 12 Years Elixir (GlaxoSmithKline Consumer)
Children's Panadol 5 – 12 Years Colourfree Suspension (GlaxoSmithKline Consumer)
Dymadon Drops 2 Months to 2 Years (Johnson & Johnson)
Dymadon Suspension 1 to 4 Years (Johnson & Johnson)
Dymadon Suspension 1 to 4 Years (Colour Free) (Johnson & Johnson)
Dymadon Suspension 5 Years Plus (Johnson & Johnson)
Dymadon Suspension 5 Years Plus (Colour Free) (Johnson & Johnson)
Febridol Infant Drops (Genepharm)
Panamax Elixir (sanofi-aventis)
Panamax 240 Elixir (sanofi-aventis)

Suppositories

Children's Panadol 6 Months - 5 Years Suppositories (GlaxoSmithKline Consumer)
Children's Panadol 5 - 12 Years Suppositories (GlaxoSmithKline Consumer)
Panadol Children 10 -12 Years + Adult Suppositories (GlaxoSmithKline Consumer)

Intravenous injection

Perfalgan (Bristol Myers Squibb)

Combination products containing paracetamol include:

Oral, solid dose forms

Paracetamol with codeine phosphate

Chemist's Own Dolaforte Tablets
Chemists' Own Pain Tablets
Chemists' Own Pain Tabsules
Codalgin Tablets (Fawns & McAllan)
Codalgin Forte Tablets (Fawns & McAllan)
Codapane Tablets (Alphapharm)
Codapane Forte Tablets (Alphapharm)
Codral Pain Relief Tablets (Johnson & Johnson)
Comfarol Forte (sanofi-aventis)
Dymadon Co Tablets (Johnson & Johnson)

Dymadon Forte (GlaxoSmithKline Consumer)
Mersyndol Daystrength Caplets (Aventis Pharma)
Panadeine Caplets (GlaxoSmithKline Consumer)
Panadeine-15 Caplets (GlaxoSmithKline Consumer)
Panadeine Forte Tablets (sanofi-aventis)
Panadeine Rapid Soluble Tablets (GlaxoSmithKline Consumer)
Panadeine Tablets (GlaxoSmithKline Consumer)
Panamax Co Tablets (sanofi-aventis)
Prodeine 15 Tablets (sanofi-aventis)
Prodeine Forte Tablets (Dakota)

Paracetamol with dextropropoxyphene

Capadex Capsules (Fawns & McAllan)
Di-Gesic Tablets (Aspen Pharmacare)
Paradex Tablets (Aspen Pharmacare)

Paracetamol with codeine phosphate and doxylamine succinate

Chemists' Own Dolased Analgesic-Calmative Tablets
Chemists' Own Dolased Day/Night Pain Relief Tablets
Codalgin Plus Tablets (Sigma)
Fiorinal Tablets (Novartis Consumer)
Fiorinal Capsules (Novartis Consumer)
Fiorinal - Dental Capsules (Novartis Consumer)
Mersyndol Caplets (sanofi-aventis)
Mersyndol Tablets (sanofi-aventis)
Mersyndol Forte Tablets (sanofi-aventis)
Panalgesic Capsules (sanofi-aventis)

Paracetamol in combination with other actives

Anagraine (Aspen Pharmacare)
Anagraine S3 (Aspen Pharmacare)
Chemist's Own Cold & Flu Day/Night Tablets
Chemist's Own Cold & Flu Relief Tablets
Chemist's Own Coldeze Tablets
Chemist's Own Hayfever Sinus Relief Tablets
Chemist's Own Sinus-Pain Relief Tablets
Codral Cold and Flu Tablets (Johnson & Johnson)
Codral Nightime Tablets (Johnson & Johnson)
Codral PE Day & Night Tablets (Johnson & Johnson)
Codral Cold & Flu +Cough Capsules (Johnson & Johnson)
Demazin Cold & Flu Tablets (Schering-Plough)
Demazin Cough, Cold & Flu Tablets (Schering-Plough)
Demazin Day & Night Cold & Flu Tablets (Schering-Plough)
Dimetapp Cold, Cough and Flu Day & Night Liquid Capsules (Wyeth Consumer Healthcare)
Lemsip Pharmacy Flu Strength Daytime (Reckitt Benckiser)
Lemsip Pharmacy Flu Strength Nightime (Reckitt Benckiser)
Logicin Flu Strength Day & Night Tablets (Sigma)

Norgesic Tablets (iNova)
Panadol Allergy Sinus Tablets (GlaxoSmithKline Consumer)
Panadol Cold & Flu Tablets (GlaxoSmithKline Consumer)
Panadol Sinus Tablets (GlaxoSmithKline Consumer)
Panadol Sinus Day/Night Tablets (GlaxoSmithKline Consumer)
Parke Davis Day and Night Original Cold & Flu & Cough Capsules (Johnson & Johnson)
Sinutab Sinus & Pain Relief Tablets (Johnson & Johnson)
Sinutab Sinus, Allergy & Pain Relief Tablets (Johnson & Johnson)
Sudafed Sinus + Allergy & Pain Relief Tablets (Johnson & Johnson)
Sudafed Sinus Day + Night Relief Tablets (Johnson & Johnson)
Sudafed Sinus + Pain Relief Tablets (Johnson & Johnson)
Sudafed PE Sinus + Allergy & Pain Relief Tablets (Johnson & Johnson)
Sudafed PE Sinus + Pain Relief Tablets (Johnson & Johnson)
Sudafed PE Sinus Day + Night Tablets (Johnson & Johnson)

Oral, liquid dose forms

Children's Panadol Cold Relief Elixir (GlaxoSmithKline Consumer)
Painstop Day-Time Pain Reliever Syrup (Paedpharm)
Painstop Night-Time Pain Reliever Syrup (Paedpharm)
Pharma-col Junior Suspension (Johnson & Johnson)

Every effort has been made to ensure these products are accurately described. However, NSW TAG are not responsible for any errors, inaccuracies or currency of information.