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INTRAVENOUS PARACETAMOL USE

Addendum to the 2008 'Paracetamol Use' Position Statement of the NSW Therapeutic Advisory Group Inc. [1]

20 December 2012

This document has been prepared in response to recent changes to the Product Information for intravenous (IV) paracetamol (Perfalgan®) and aims to provide guidance on the appropriate and safe use of IV paracetamol in paediatric and adult patients. It is presented in two sections:

- *Paediatric issues: Background & recommendations*
- *Adult issues: Background & recommendations*

These recommendations have been developed by the NSW Therapeutic Advisory Group (TAG) Editorial Committee, following its usual processes [2]. This has included review of published research evidence; unpublished data (e.g. from drug regulatory bodies and pharmaceutical industry sources); review of up-to-date paediatric prescribing information sources (e.g., BNF for Children and other published guidelines); and input from a multi-disciplinary group of health professionals with paediatric and adult expertise in clinical pharmacology and therapeutics, toxicology, health technology assessment and medicines evaluation, clinical pharmacy, clinical medicine and nursing. (See acknowledgements for details.)

This addendum should be read in conjunction with:

(a) *NSW TAG's 2008 "Paracetamol Use" position statement [1], which is cross referenced in relevant places as indicated*

<http://www.ciap.health.nsw.gov.au/nswtag/documents/publications/position-statements/paracetamol-use-dec-2008.pdf>

(b) *NSW Health's Policy Directive PD2009_009 Paracetamol Use.*

http://www0.health.nsw.gov.au/policies/pd/2009/PD2009_009.html

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1.1 BACKGROUND TO PAEDIATRIC ISSUES

In September 2009, changes were made to the approved Australian product information for intravenous (IV) paracetamol [Perfalgan[®]], halving the recommended dose in term neonates, infants, toddlers and children weighing less than 10 kg, from 15 mg/kg/dose to 7.5 mg/kg/dose (not exceeding 4 administrations per day).[3] This lower dose had been the registered dose in the UK and the rest of Europe since the product was first licensed there in 2001/2002.

NSW Therapeutic Advisory Group (TAG)'s communication with the Therapeutic Goods Administration (TGA) indicated that the sponsor, Bristol Myer Squibb Australia Pty Ltd (BMS), requested the dose reduction in the context of toxicity occurring in vulnerable populations.[4] These changes were initiated by BMS's UK counterpart due to safety concerns and not on the basis of new pharmacokinetic data.[5] **The majority of reported cases of toxicity and safety concerns in infants < 10 kg have been due to administration of inadvertent 10-fold overdoses of IV paracetamol.**[6] In 2010, the UK Medicines Healthcare Products Regulatory Agency (MHRA) noted that 23 cases of IV paracetamol overdose had been reported in infants < 1 year worldwide, one of which was fatal; 19 of these cases occurred in the European Union, including 7 in the UK in which a 10-fold error was generally reported.[6] By the end of October 2010 over 200 cases of inadvertent overdose of IV paracetamol had been reported to the National Reporting and Learning System (NRLS) of the UK's National Health Service.[7] There have also been multiple recent literature reports of 10-fold overdoses with IV paracetamol in young infants.[8–11]

There have been no reports of toxicity with IV paracetamol administered at therapeutic doses in low risk infants in recent published literature [12], or any reports to the TGA since the introduction of IV paracetamol in Australia.[13]

The strength of Perfalgan[®] (10 mg/mL) and the existence of two different vial sizes (1000 mg/100 mL and 500 mg/50 mL) are identified as major contributing factors to reported paediatric medication errors with the intravenous formulation, especially 10-fold dosing errors.[9,14] Many of the accidental overdoses appear to be related to confusion between mg and mL doses; for example, the dose would be calculated in mg (150 mg) and the IV Perfalgan[®] administered in the same number of mL (150 mL instead of 15 mL of the 10 mg/mL solution) resulting in a 10-fold overdose.

A generic product, Paramat[®], has been approved for marketing in Australia.[15] The newer generic product Paramat[®], paracetamol 1000 mg/100 mL injection solution, from Actavis Pty Ltd is only available in a 100 mL vial size.

Other contributing factors in reported cases of inadvertent overdose include concomitant administration of oral paracetamol (including that in combination products such as Panadeine[®] and Panadeine Forte[®]), calculation errors including dose calculation error due to incorrect weight, and non-adherence to recommended doses.[16–17]

1.2 RECOMMENDATIONS FOR PAEDIATRICS

1.2.1 General

- *IV paracetamol should be considered a high risk medicine when administered to infants and young children.*
- IV paracetamol should only be used for *acute, short-term treatment of mild to moderate pain* when oral or rectal dosing is not possible.[1: page 10]
 - IV paracetamol should be replaced by enteral paracetamol at the earliest opportunity [1: page 10]; oral administration is preferred since rectal absorption can be delayed or erratic.[1: page 12]
- *Use of paracetamol should always be preceded by a comprehensive risk assessment and reviewed every 24 hours.* This includes particular caution in considering paracetamol use in infants < 6 months.

Risk factors for hepatotoxicity include:

- febrile illness
- younger age
- prolonged fasting
- vomiting or dehydration
- chronic undernutrition
- severe hepatic impairment [18] [1: pages 7–10]

- General principles for safe paediatric prescribing and safe paracetamol prescribing apply.[18–19]

1.2.2 Dose

- Although the TGA approved dose for infants < 10 kg is now 7.5 mg/kg/dose 4–6 hourly (max 30 mg/kg/day), pharmacokinetic data [20–21] and recent published clinical evidence [22] support the use of 15 mg/kg/dose (max 60 mg/kg/day).
- The 2011–2012 edition of the British National Formulary for Children has recommended increasing the dose of IV paracetamol for infants, from 7.5 mg/kg/dose to 15 mg/kg/dose every 4–6 hours.[23] This change was agreed by their expert advisers and Paediatric Formulary Committee in November 2010.[24]
- In view of the above, and the lack of any evidence of toxicity occurring in low risk infants receiving recommended doses of IV paracetamol, *NSW TAG does not recommend any changes to the original dose recommendations for infants contained in its 2008 position statement.*

The recommended dose of IV paracetamol for infants >3 months of age remains **15 mg/kg/dose** every 6 hours up to a maximum of **60 mg/kg/day** (never exceeding 1 g per dose and 4 g in 24 hours).[1: page 11]

- This dose of paracetamol is now “off-label” but falls within the category of “routine off-label use justified”, and meets appropriateness criteria as specified in the NSW Health Policy Directive PD2008_037 on Evaluation of Medicines for Use in Public Hospitals.[25]

1.2.3 Additional safety measures to prevent accidental overdoses

- When prescribing or administering IV paracetamol, clinicians should *first check that no other formulations of paracetamol are concurrently prescribed or administered*, and that the safe maximum daily dose of paracetamol (from *all* sources including combination products such as Panadeine[®] and Panadeine Forte[®]) is not exceeded.
- In the “drug name” section of the medication chart the prescriber should write “**Paracetamol IV**” and should additionally specify the brand name in brackets after this, e.g., (“Perfalgan”) or (“Paramat”) to avoid confusion with other paracetamol formulations.
- The *dose should be calculated using the patient’s current, accurate weight and independently double-checked at the time of prescribing AND at each administration*. (Use of a calculator is highly recommended.)

Dosing for **overweight** or **obese** children should be based on **ideal** body weight *not* total body weight.[1: page 13; 18,26]

For obese children, calculation of paracetamol dose using actual bodyweight may lead to a relative overdose. The ‘ideal weight’ for dose calculation purposes for a child may be approximated using growth charts which are widely available in health care facilities or, if local charts are not available, alternatives 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.

- The dose should be prescribed in *milligrams (mg)* AND *millilitres (mL)* to maximise the clarity of the intended dose: for example, for a 10 kg infant, “150 mg Paracetamol IV (15 mL Perfalgan or Paramat)”. When specifying the dose in mL, it is important to clearly indicate the IV route in the order to avoid confusion with oral liquid formulations.
- Paracetamol orders should only have one route specified (i.e., orders should NOT be written as IV/PO/PR as this is not appropriate and is unsafe).
- The IV paracetamol *vial* should not be hung as an infusion in neonates, infants and children weighing less than 33 kg. **The volume containing the required dose should be drawn up with a syringe** (for infants weighing < 10 kg use a 5 mL or 10 mL syringe), diluted in 0.9% sodium chloride or 5% glucose solution and administered as an infusion.[16]

- Clinicians should take special precautions to ensure that *oral* paracetamol liquid is not administered by the *IV* route inadvertently. Special oral dispensers should be used for oral paracetamol administration.[27]
- In cases where an accidental overdose of IV paracetamol has been administered, a toxicologist should be consulted for appropriate management advice. The most recent Australian guidelines for the management of paracetamol overdoses now provide an updated treatment nomogram, recommended investigations and N-acetylcysteine dosing regimens.[28]

1.2.4 System issues and implementation

- Hospitals are strongly encouraged to evaluate how current practices align with these recommendations and to initiate appropriate educational and other strategies to address any areas of suboptimal practice identified.
 - Use of an effective, evidence-based implementation model [19] is recommended.
- Hospitals are encouraged to consider limiting IV paracetamol prescribing and availability to specified prescribers and wards.
 - All such prescribers and nursing staff should be appropriately educated in safe paediatric prescribing principles and in the appropriate and safe use of IV paracetamol in children. See references 18–19 for available educational resources for safe paediatric prescribing.

2.1 BACKGROUND TO ADULT ISSUES

2.1.1 Dose for underweight adults or frail older people less than 50 kg

The product information for Perfalgan® was further updated in April 2012 to describe dosing in small adults [3]:

- For patients weighing 50 kg or more, the total **daily** dose of paracetamol should not exceed 4 g
- For patients weighing ≤ 50 kg and > 33 kg, the dose is **60 mg/kg/day** (not exceeding 3 g)
- For patients weighing ≤ 33 kg and > 10 kg, the dose is **60 mg/kg/day** (not exceeding 2 g)

These weight adjusted doses are based on pharmacokinetic principles since there is a lack of data on efficacy or safety from studies in smaller adults. Mitchell et al did not observe any hepatotoxicity in robust or frail inpatients ≥ 70 years given a maximum of 3 g or 4 g paracetamol per day; weight was not a specific consideration.[29] There are animal data to suggest old age may be protective against paracetamol hepatotoxicity although it may increase susceptibility to nephrotoxicity.[30] The maximum doses are conservative especially for adults with an ideal body weight at the upper end of the weight categories.

2.1.2 Use in stroke

In the 2008 NSW TAG Position Statement, paracetamol was recommended for use in acute pain and symptomatic fever > 38.5 °C.[1] In patients with acute stroke, increased body temperature can be centrally driven or a result of concurrent infection, and is associated with poorer clinical outcomes.[31,32] Administration of paracetamol for temperature reduction when body temperature is > 37.5 °C has become standard of care in many settings.[32–34] National and international stroke guidelines give mixed advice, with Australia and Canada recommending investigation of increasing body temperature and use of antipyretic medications, the UK allowing their use and the US and Europe finding the evidence for effectiveness of antipyretic use inconclusive but acknowledging the practice.[32,35–38]

Small trials have investigated the use of paracetamol for temperature reduction in stroke patients and shown modest effect.[39–43] Dippel et al have shown that, compared to placebo, paracetamol 1000 mg given 6 times daily reduced the body temperature of acute stroke patients by an average of 0.26 °C within 4 hours of the first dose and the effect lasted for the remaining treatment period of 20 hours.[44] Sulter deemed acetaminophen (1000 mg 4 hourly per rectum) "insufficient for reducing an elevated body temperature to a state of normothermia".[42]

In a large randomised controlled clinical trial [n=1696] Middleton et al showed a 15.7% difference in mortality or functional dependency at 90 days, irrespective of stroke severity, when acute stroke patients were given a 'bundled' intervention to manage fever (defined as temperature ≥ 37.5 °C), hyperglycaemia and swallowing dysfunction for the first 72 hours after admission.[33] This included 4 hourly temperature measurements and treatment of temperatures of 37.5 °C or over with intravenous, rectal or oral paracetamol.

The PAIS-2 trial is underway to determine if temperature reduction with paracetamol has an effect on neurological outcome after stroke [45] but at this stage there is no clearly established evidence for the clinical benefits of temperature reduction alone.[38,46] Furthermore, it is worth noting that prophylactic temperature reduction may potentially mask signs of an underlying infection.[46]

2.2 RECOMMENDATIONS FOR ADULTS

2.2.1 General

- Paracetamol orders should only have one route specified (i.e., orders should NOT be written as IV/PO/PR as this is not appropriate and is unsafe).
- IV paracetamol should be replaced by enteral paracetamol at the earliest opportunity [1: page 10]; oral administration is preferred since rectal absorption can be delayed or erratic.[1: page 12]
- When prescribing or administering IV paracetamol, clinicians should *first check that no other formulations of paracetamol are concurrently prescribed or administered*, and that the safe maximum daily dose of paracetamol (from *all* sources including combination products such as Panadeine[®] and Panadeine Forte[®]) is not exceeded.
- In the “drug name” section of the medication chart the prescriber should write **“Paracetamol IV”** and should additionally specify the brand name in brackets after this, e.g., (“Perfalgan”) or (“Paramat”) to avoid confusion with other paracetamol formulations.

2.2.2 Dose for underweight adults or frail older people less than 50 kg

- *NSW TAG does not recommend any changes to the original dose recommendations contained in its 2008 position statement i.e., 15 mg/kg/dose every 4–6 hours up to four times daily (60 mg/kg/day) for frail, older patients and adults < 50 kg.*[1: page 10]
- Dosing should be based on actual body weight.
- Risk factors for hepatotoxicity that need to be considered for these patients include:

- prolonged fasting [1: pages 8]
- reduced intake that might occur prior to hospital admission for an acute illness [1: pages 8]
- severe hepatic impairment [1: pages 8]
 - In patients with **chronic** or **compensated** active hepatic disease, the maximum daily dose should not exceed 3 g/day
 - The product information notes that hepatic failure or **decompensated** active liver disease should be regarded as a contraindication to paracetamol use. (The degree of hepatic failure that is of concern has not been defined in the product information)

- If still receiving IV paracetamol at 48 hours and, if after clinical review, a decision to continue IV paracetamol is made then monitoring of liver enzymes (ALT, AST) and International Normalised Ratio (INR), is recommended. [1: page 13]

2.2.3 Use in stroke

- NSW TAG recognises that paracetamol is used for temperatures ≥ 37.5 °C in otherwise asymptomatic patients with acute stroke.[33] This practice appears to be based on limited evidence of benefit (in terms of impact on stroke outcomes) and may need to be reviewed as additional evidence becomes available.
- Patients who develop a fever should have appropriate clinical evaluation to promptly assess and treat any concurrent infection.[32]
- NSW TAG notes that the NSW Agency for Clinical Innovation (ACI) is currently developing comprehensive guidance for stroke management. Practitioners are encouraged to refer to this when available.

2.2.4 System issues and implementation

- Hospitals are strongly encouraged to evaluate how current practices align with these recommendations and to initiate appropriate educational and other strategies to address any areas of suboptimal practice identified.
 - Use of an effective, evidence-based implementation model [19] is recommended.
- Hospitals are encouraged to consider limiting IV paracetamol prescribing and availability to specified prescribers and wards.
 - All such prescribers and nursing staff should be appropriately educated in the appropriate and safe use of IV paracetamol.

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