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INTRAVENOUS PARACETAMOL USE: AN OVERVIEW

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ABSTRACT

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. Many of the accidental overdoses appear to be related to confusion between mg and mL doses

KEY WORD- *paediatric medication , contributing factors , product information .*

INTRODUCTION :

A generic product, Paramat®, has been approved for marketing in Australia.[1-15] 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]

BACKGROUND TO ADULT ISSUES

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

The product information for Perfalgan was further updated in 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.[15-29] 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.

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]

2.2.2 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]

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.

SUGGESTIONS

• 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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