THE PAEDIATRIC SOCIETY OF NEW ZEALAND

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Dear Vicki,

Paracetamol – Dangerous when not used correctly
Update September 2019

On behalf of the Pharmacists and Therapeutics SIG of the Paediatric Society NZ, I would like to comment on the recent prescriber update 40(3): 46-47 September 2019 titled 'Paracetamol – Dangerous when not used correctly'. This update follows recommendations from BPAC [1] and recommends using 'actual body weight, not ideal body weight'.

There appear to be two schools of thought on this issue and we would like to raise an awareness of the concerns many have with the message to use actual weight in children who are obese.

The majority of hospitals in New Zealand use an adjusted weight for children who are obese, for the dosing of paracetamol as well as other medicines eg opioids. This is due to the risk of accumulated effects with regular dosing. We are not concerned with one-off doses of paracetamol based on actual weight but it is the regular dosing of these large doses that are of concern.

Pharmacokinetics of paracetamol are well reported in BPAC [1] with metabolism via glucuronidation, sulphation as well as CYP2E1 pathways. There is only one study looking at the pharmacokinetics of paracetamol in children who are obese with non-alcoholic fatty liver disease. This identified 'significantly higher concentrations of the paracetamol glucuronide metabolite in the plasma and urine of children with non-alcoholic fatty liver disease which suggests that hepatic glucuronyl transferease activity is upregulated in the presence of hepatic fat'.[2]

This is supported by several adult studies. Van Rongen at al found that although adults with obesity had lower concentrations of paracetamol after an IV dose, they also had higher concentrations of hepatotoxic CYP2E1-mediated paracetamol metabolites, cysteine and mercapturate, putting them at higher risk of toxicity. These data were from data collected from individuals, modelling and statistical analysis.[3]

So although it can be argued that higher doses based on actual weight are needed in children who are obese due to a larger VD, there is also a real risk because of increased CYP2E1 activity leading to overproduction of hepatotoxic paracetamol metabolites namely cysteine and mercapturate.[3]

We need a balance between appropriate dose and preventing toxicity. Many NZ inpatient settings utilise an adjusted dose for paracetamol as described by Ross et al [4], with a co-factor of 0.4 to address these concerns. A medicines information bulletin produced by UK Medicines Information pharmacists also supports using either lean or adjusted weight (correction factor of 0.4) for dosing paracetamol in children who are obese.[5]

For underweight children or malnourished children the recommendation is to use a longer dosing period or smaller dose of eg 10mg/kg due to reduction in glutathione levels.[1]
In the same way, we believe regular dosing of paracetamol in obese children should also be adjusted (by weight) due to the concern around upregulation of CYP2E1 activity. Although we understand the information BPAC and NZFc have based their recommendations on, we feel that the message of using actual weight for dosing paracetamol could have very real problems when administering regular dosing for obese children.
Another concern we have is the lack of funded and appropriate measuring devices. We know from documented errors that wrong measuring devices are used in the home environment. If appropriate measuring syringes were funded by Pharmac, this would reduce the need for other devices to be used.
A strong safety message from Medsafe regarding paracetamol should be a priority: 'Use paracetamol in the recommended dose and recommended frequency for the shortest time necessary'. This has been highlighted in the article by Rajanayagam[6].
We would like Medsafe to consider further wording around this issue in their update so that a safe message is available for all children as well as children who are obese and are requiring more than just a single dose of paracetamol.

Yours sincerely,

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Chairperson
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