Medicines Adverse Reactions Committee

Meeting date	**12 March 2020**	Agenda item	
Title	**Dosing of paracetamol in obese children**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent **Medicines** **Sponsors** See link: https://www.medsafe.govt.nz/regulatory/DbSearch.asp			
Funding	Pharmacare paracetamol oral liquid 120 mg/5ml and 250 mg/5ml, tablets 500 mg. Gacet suppositories 125 mg, 250 mg and 500 mg.		
Previous MARC meetings	Dosing of paracetamol in obese children has not been discussed previously.		
Prescriber Update	Vol 40 No 3 September 2019 "Paracetamol – Dangerous when not used correctly"		
Advice sought	**The Committee is asked to advise whether:** – The evidence supports the need to update paracetamol data sheets and/or label statements with dose adjustments for overweight and/or obese children. – This topic requires further communication other than MARC's Remarks in *Prescriber Update*.		

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1.0 PURPOSE

Medsafe published an article about paracetamol in the September 2019 issue of *Prescriber Update*. The title of the article was "Paracetamol – dangerous when not used correctly (1), and it covered aspects of prescribing, dispensing and advice for caregivers based on medication errors. Under the title "Calculate the correct does" the article stated the following:

- Use weight-based dosing.
- Use actual body weight, not ideal body weight.
- Never exceed the recommended adult dose.

The reference for this part of the article was the paracetamol dosing regimen in the New Zealand Formulary for Children (2) and their reference to Bpac (3).

Since the article was published, Medsafe has been contacted twice by health professionals (one letter and one submission (Annexe 1)) who do not agree with this recommendation. The main critical points are:

- The implication is to use the same recommendation for dosing to very obese children.
- There was no scientific reference to the recommendation.
- The recommendation counteracts current practice in NZ where, according to the writers, the dosing is adjusted to obese children especially for regular treatment, because of the risk of accumulated toxic effects.

They suggest that the recommendations should include an adjustment (by weight) for regular dosing of paracetamol to obese children due to the concern around upregulation of CYP2E1.

No specific information on dosing of paracetamol in obese children is currently included in the data sheets or in the label requirements for OTC paracetamol products for children. Therefore, Medsafe is seeking advice from the MARC on whether the data sheets and information relating to OTC paracetamol for children needs to be updated and if any further actions are required.

2.0 BACKGROUND

2.1 Aspects on paracetamol dosing

Paracetamol is widely used in pediatrics for its analgesic and antipyretic properties. Note that paracetamol is called acetaminophen in the US.

The chosen dose and dosing frequency of a medicine aims to provide enough active ingredient to acquire the desired effect while the risk of adverse effects is minimised. Paracetamol has a relatively low degree of adverse effects both in occasional use and use over some days, providing the dose is not too high. High doses of paracetamol may result in severe liver toxicity.

According to the American data base UptoDate, hepatotoxicity in pediatric patients is most commonly associated with supratherapeutic dosing, more frequent administration than recommended, or use of multiple paracetamol-containing products; however, hepatotoxicity has been rarely reported with recommended dosages (4).

In order to discuss dosing of paracetamol in obese children, it is important to consider the pharmacokinetics of paracetamol in general and specifically in children. Available information on these aspects are summarised below as well as information regarding plasma concentration in relation to effect.

2.1.1 Pharmacokinetics of paracetamol

Absorption

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract, primarily in the small intestine. Food intake delays paracetamol absorption. Oral administration is subject to first pass metabolism. In a comparison between intravenous paracetamol and oral paracetamol, plasma concentrations were significantly higher and obtained earlier, compared to oral administration. However, after the first hour and up to 24 hours the plasma concentrations remained similar.

Distribution

Paracetamol is distributed into most body tissues. Binding to plasma proteins is minimal at therapeutic concentrations but increases with increasing doses. The volume of distribution, V_d is 65 L (approx. 0.8 L/kg) (5).

Metabolism

Paracetamol is extensively metabolized in the liver by different metabolic pathways. The main pathways are glucuronidation (around 55 %, by uridine diphosphate [UDP] glucuronosyltransferases [UGTs]) and sulfation (around 30 %, by sulfotransferase). Volume of distribution of paracetamol glucuronide and paracetamol sulphate are both approximately 0.3 L/kg (6). Only 2–5 % of paracetamol is excreted unchanged.

Approximately 5–10 %of paracetamol is metabolized by cytochrome P450 (CYP), primarily by the CYP2E1 enzyme, to the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). At therapeutic doses, NAPQI is immediately inactivated by conjugation with glutathione to a neutral metabolite and excreted as cysteine and mercapturate metabolites in urine.

At toxic doses glutathione conjugation becomes insufficient to meet the metabolic demand causing an increase in NAPQI concentrations, which, if left untreated, can cause hepatic cell necrosis.

Paracetamol is metabolised differently by infants and children compared to adults, the sulphate conjugate being predominant.

Excretion

Paracetamol is excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unmodified paracetamol with 85% to 90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life (for patients over 12 years of age) varies from one to three hours. The mean plasma half-life is about 2.3 hours. Total body clearance is 18 L/h (4, 7, 8).

Comments: Volume of distribution (V_d) describes how much of the drug is distributed to tissues from the blood. If V_d is less than 4 L the drug is thought to be in the plasma only, if V_d is 4-7 L it is thought to be distributed throughout the blood (to plasma and red blood cells) and if V_d is larger than 42 L the drug is thought to be distributed to all tissues in the body and especially fatty tissue.

2.1.2 Pharmacokinetics of paracetamol in children

Children are not small adults but different, also regarding pharmacokinetics of paracetamol. A review article was published in 2014 describing pharmacogenomics of paracetamol in pediatric populations (9). One part of the review concerned paracetamol pharmacokinetics in children, mostly referring to a study on intravenous paracetamol by Zuppa in 2011 (10).

This Phase 1 study included 75 individuals (3 neonates, 25 infants, 25 children, and 22 adolescents) and was assessing the safety and pharmacokinetics of repeated doses of intravenous paracetamol over 48 hours.

Methods

Neonates (full-term to 28 days) received either 12.5 mg/kg every 6 hours or 15 mg/kg every 8 hours. Infants (29 days to <2 years), children (2 to <12 years) and adolescents (≥12 years) received either 12.5 mg/kg every 4 hours or 15 mg/kg every 6 hours. The maximum single dose could not exceed the lesser of 12.5 or 15 mg/kg or 1000 mg, and the maximum daily dose could not exceed the lesser of 75 mg/kg or 4000 mg.

Both noncompartmental and population nonlinear mixed-effects modelling approaches were used. Urinary metabolite data were analysed, and safety and tolerability were assessed. Pharmacokinetic parameters of paracetamol were estimated using a two-compartment disposition model with weight allometrically expressed on clearances and central and peripheral volumes of distribution.

Results

A total of 5 infants, 8 children, and 6 adolescents did not complete the 48-hour study period.
The clearance (L/hr) of paracetamol increased from 2.02 L/hr at 1 month of age to 4.09 L/hr at 1 year of age to 14.27 L/hr at 16 years of age, while the central volume of distribution remained constant at 0.23 L/kg for all ages. Although the number of neonates (n=3) was small, the median AUC values were 60% to 90% higher than those observed in children and adolescents indicating a variability in the elimination of APAP (paracetamol) in the pediatric population, especially between neonates and older children.

APAP metabolism and excretion include Phase I (oxidation) and Phase II metabolism pathways (glucuronidation, sulfation, and glutathione conjugation). In this study, paracetamol glucuronidation or sulfation represented the primary pathways of paracetamol elimination, with sulfation predominating in younger age strata. The APAP sulfation seem to be more constant among all ages while glucuronidation of APAP increased in older children and during maturation to adolescence, making the proportion change. In addition, total urinary recovery also varied with age.

The figure below shows proportions of paracetamol metabolites in different age-groups.

The data base Up to Date, lists elimination half-lives for children in different age groups compared to adults (4):

- Neonates: 7 hours (range: 4 to 10 hours)
- Infants: ~4 hours (range: 1 to 7 hours)
- Children: 3 hours (range: 2 to 5 hours)
- Adolescents: ~3 hours (range: 2 to 4 hours)
- Adults: ~2 hours (range: 2 to 3 hours); may be slightly prolonged in severe renal insufficiency (CrCl<30 mL/minute): 2 to 5.3 hours.

According to the data sheet for paracetamol infusion, the plasma half-life for neonates is longer than in infant's i.e. around 3.5 hours. The pharmacokinetic parameters of paracetamol observed in infants and children are similar to those observed in adults, except for the plasma half-life that is slightly shorter (1.5 to 2 h) than in adults (8).

Comment: In children the sulfation metabolism is relatively constant for different age-groups while the glucuronidation increases when the child gets older making it predominant in older children. The half-lives of paracetamol differ depending on reference but seem to be different from adult half-life of the medicine, especially longer for the youngest.

2.1.3 Is plasma concentration correlated to effect?

A correlation between paracetamol plasma concentration and pain response was shown by Anderson in 1996 in a prospective, randomized, double-blind study of 100 children (ages 3-15 years) who underwent an elective tonsillectomy with or without adenoidectomy (11).

Group A consisted of 50 children who received 40 mg/kg oral paracetamol 40 minutes prior to the surgery. Group B (also 50 children) received paracetamol suppositories 40 mg/kg after anaesthetic induction.

Children given oral paracetamol had a higher mean paracetamol concentration approximately 1 hour after dosing compared with rectal dosing (22.7 vs. 7.6 mg/L). The authors noted that variable and erratic rectal absorption accounted for this significant difference. The use of rescue morphine was higher in the rectal (23 of 50) vs. the oral (10 of 50) group ($p<0.001$) group.

Group A children had lower median pain scores than Group B (median, 25^{th}-75^{th} centile:5,4-6;7,5-8, P=0.018). Children with acetaminophen concentrations higher than 10 mg/L had superior analgesic response compared with those with values below this concentration ($p<0.05$). For example, at 10 mg/L, 25% (16 of 62) of children failed to achieve adequate analgesia, whereas at 20 mg/L, only 6% failed to do so.

In 1999 the same authors (Anderson et al) published a prospective, randomized, double-blind study including 120 children (ages 2-15 years) who underwent an outpatient tonsillectomy with or without adenoidectomy (12). A pharmacokinetic model was used to describe the concentration-effect relationship using individual serum concentrations of paracetamol and pain scoring with the scale 0-10.

Twenty of the children received 40 mg/kg oral paracetamol (as an oral elixir) 30-60 minutes prior to the surgery, and 100 got the same dose as rectal paracetamol at induction of anaesthesia. The patients who got the oral dose also received one intraoperative rectal dose of 20 mg /kg 2 hours later.

Use of rescue morphine was higher in the rectal group
Effect-compartment concentrations of 10-20 mg/l, which has been proposed to reduce fever, were associated with pain scores of 3.6-2.8. The authors believe that at target concentration of 10 mg/mL will provide satisfactory analgesia for 50% of children undergoing surgery similar to tonsillectomy.

In a publication by Gibb and the same Anderson in 2008, they state that the interpretation of analgesic and antipyretic responses documented after paracetamol administration is confused because response is not directly related to concentration in the blood, but rather to an effect compartment. The effect compartment does not have real measurable concentrations, but concentrations equate approximately to those observed in the cerebrospinal fluid.

A time delay exists before the medicine reaches the effect compartment, reported to be ~1 h for paracetamol. Paediatric analgesic studies are limited because they have only explored postoperative pain after tonsillectomy or day-stay surgery while other pain types and pain confounders have not been investigated. Target effect compartment concentrations 10 mg/L for pain do not seem unreasonable on the basis of current literature. (13). Therapeutic serum concentrations range from 10 to 20 mg/L according to the database UpToDate.

Comment: A correlation has been shown between paracetamol serum concentration, concentration in the effect compartment and analgesic effect in children after tonsillectomy. It may not be exactly the same values if another type of pain is treated. However, a serum concentration between 10 and 20 mg/L seem to be considered as a therapeutic range. The same range has been suggested to produce antipyretic effect.

Note that in the original Anderson publication from 1996, the units for plasma concentration of paracetamol is mmol/L. A formula to convert this to mg/L is (12):

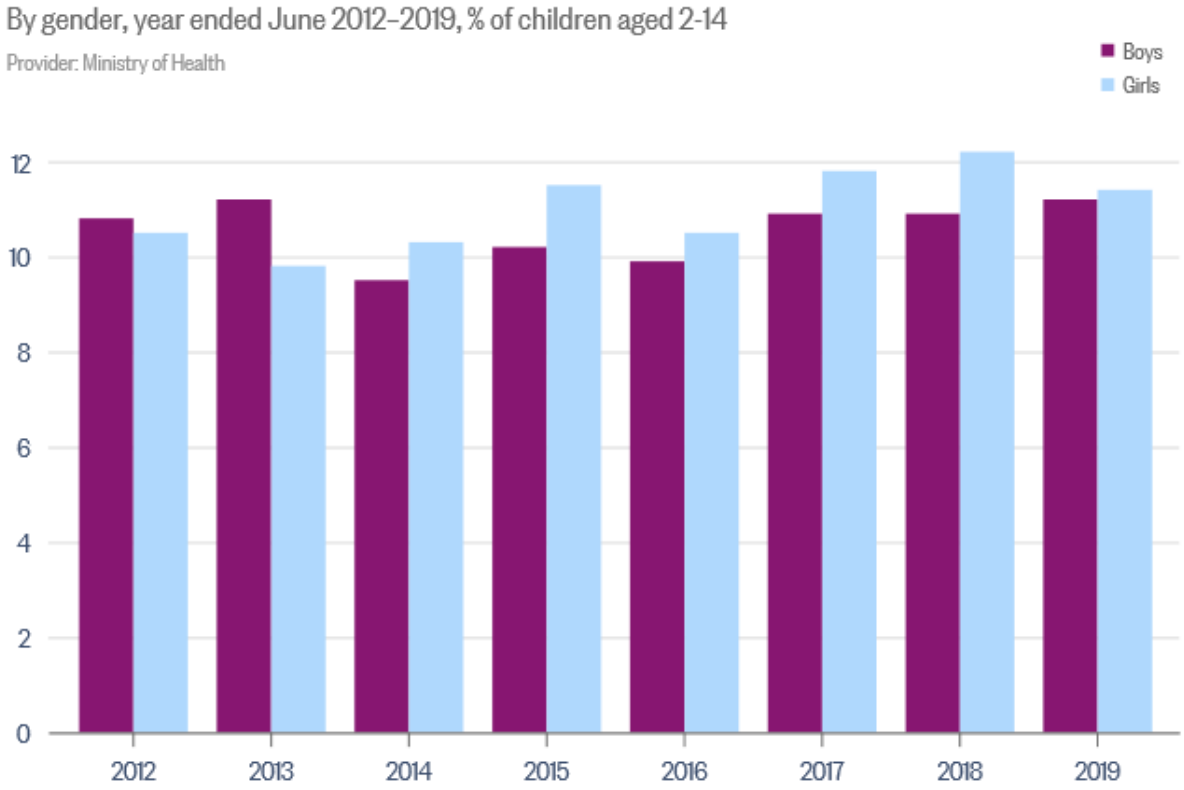
Amount mmol/L x 1000 x 0.15 = Amount mg/L

2.2 Obesity and children

2.2.1 Epidemiology

The figure below shows the number of New Zealand children who are classed as obese, numbers provided by the Ministry of Health.

Figure 2. Percentage of New Zealand children classed as obese (14).



2.2.2 Terminology

The terms overweight and obese have no standardised definitions that pertain to children. For clinical use and for population surveys and screening, the measures used to assess body fatness includes skinfold thickness, waist circumference, waist-to-hip ratio and body mass index. Body mass index (BMI), defined as weight/height^2 is the most commonly used tool for monitoring obesity.

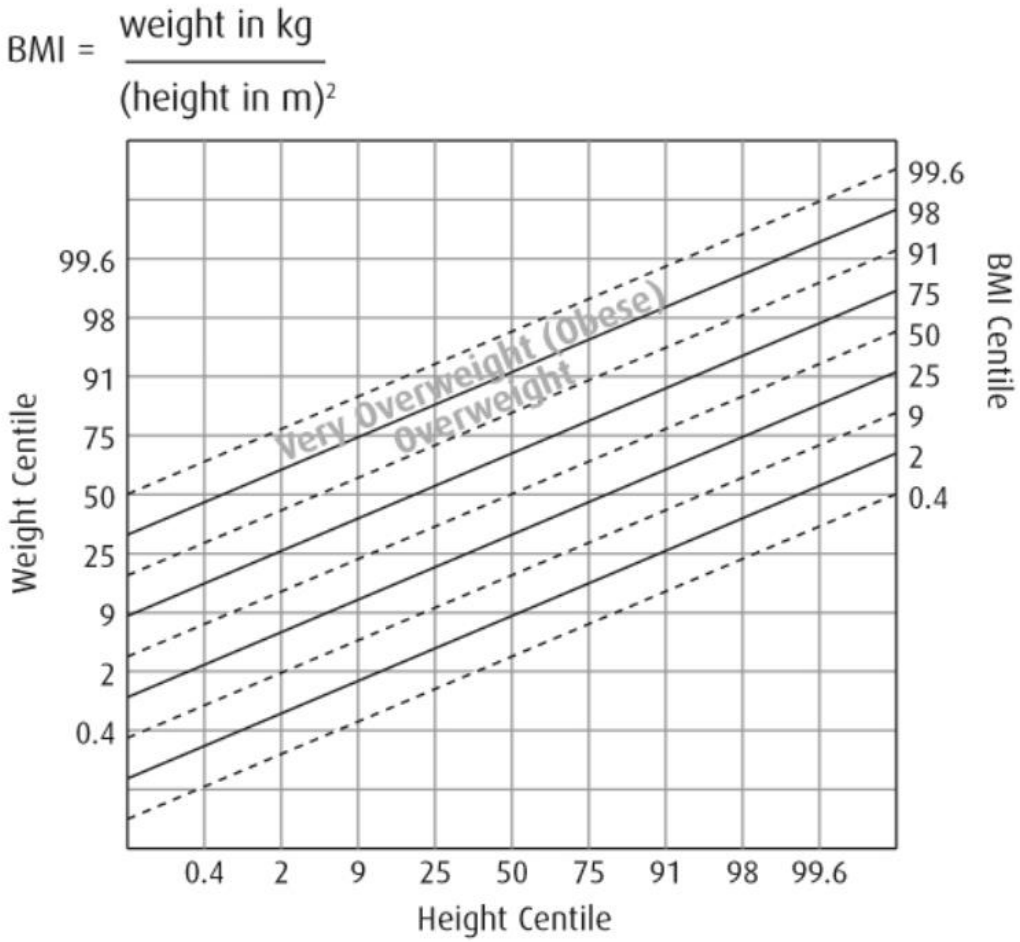
To assess whether a child is obese, BMI is typically plotted on a BMI-for-age reference chart which has percentile lines marked on it to indicate the percentage of children in a reference standard (nonobese) population whose BMI is at or below a given level at each age. Whether or not a child is labelled as being overweight or obese depends on the reference standard used and the percentiles chosen as cut-offs. There is no universal agreement on BMI cut-off points for defining obesity in children and cut-offs differ between countries (15).

For example, the US define overweight as a BMI at or above the 85th percentile and below the 95th percentile for children and teens of the same age and sex. Obesity is defined as a BMI at or above the 95th percentile for children and teens of the same age and sex, using CDC (Centers for disease control and prevention) Growth Charts (16).

CDC recommends that health care providers use the WHO growth standards to monitor growth for infants and children ages 0 to 2 years of age and the CDC growth charts for children age 2 years and older.

The Well Child Tamariki Ora programme is free to all New Zealand families for children up to 5 years of age. The growth charts used in the programme do not include a 95th percentile line, instead using 91st and 98th percentile lines, see figure 3 below. The chart, which is suitable for use with New Zealand children up to age 5, combines World Health Organization (WHO) standards with United Kingdom preterm and birth data (17).

Figure 3. Weight charts used in NZ for children up to 5 years of age.



The use of BMI has some limitations, for example as it does not take account of where on the body the fat is deposited. A high BMI may be due to high muscle mass in an athletic child. It has also been debated if different BMI cut-off points should be used to define obesity in different ethnic groups (15).

Other terminology used for description of weight (18, 19):

Total body weight (TBW): Actual weight

Ideal body weight (IBW): Historically considered to be the "healthy" weight and defined according to its association with lowest mortality. For adults, IBW is derived from life insurance tables or from the Devine estimation. For children, it is more complicated and there is no standard method for

	determining IBW. The McLaren method, which uses the 50th percentile for height, is often used.
Lean body weight (LBW):	Difference between TBW and fat mass. Lean body weight reflects the weight of all 'non-fat' body components, including muscle and vascular organs such as the liver and kidneys.
Adjusted BW (ABW, AdjBW):	Calculating doses based on adjusted body weight is mainly used for aminoglycoside antibiotics. It was developed to account for adipose tissue, which does not affect drug clearance. A correction factor of 0.4 is used to estimate adjusted body weight: ABW=IBW+(0.4 x (TBW-IBW), however this is used for adult patients (19).

There are multiple different formulas used to estimate other weights than TBW. A study compared 6 different ways to calculate IBW for children to the reference Mc Lauren method. The majority of methods used to calculate IBW in pediatric patients lead to statistically different results when compared with the McLaren method. For certain methods, these differences became pronounced at high and low height percentiles and in older age groups (20).

Comments: The uncertainty regarding how to measure overweight and obesity, which numbers to use to define overweight and obesity and the multiple formulas that can be used to calculate weight (other than TBW) is confusing. In the letter sent to Medsafe, the concerns regarded very obese children, which again does not have a clear definition. Given that there is already a high risk for medication errors when children are treated with paracetamol, this confusion may add to the risk.

It is sometimes hard to know what weight is referred to in recommendations and guidelines when they state "weight". It is assumed that "weight" means actual body weight, unless another weight, for example ideal body weight, is stated.

2.2.3 Pharmacokinetics in obese children

The volume of distribution and clearance, both pharmacokinetic determinants of drug dosing, may be altered in obese children. Partly, this is due to changes in physiology and body composition, with a relatively higher increase in fat (60%) compared to lean tissue (40%) per kg of TBW, as well as lean mass being more hydrated, which is attributed to increased extracellular water.

In addition, alterations in drug binding proteins, cardiac output, organ blood flows, and tissue perfusion may influence the pharmacokinetics. There is very limited data on the influence of obesity on hepatic metabolism in children (21).

A literature review article from 2010 by Kendrick describes general pharmacokinetics in obese children (mean age 11±2 years). The authors state that there is a limited understanding of pharmacokinetics in obese children and therefore it is difficult to generalize. However, some aspects are pointed out:

- drug absorption is unlikely to be affected by obesity
- Vd, as expressed per kg of TBW, is likely higher for lipophilic drugs and lower for hydrophilic drugs in obese children.
- no validated equation exists for estimating GFR in obese children; however, the serum creatinine concentration is higher in obese children than normal-weight children (19).

Another literature review by the same authors in 2015 reviewed pharmacokinetics and pharmacodynamics in over- weight and obese children and provided recommendations, where possible, for dosing of a variety of medicines to obese children, although paracetamol was not included (22).

The table shows some examples of included medicines from both studies by Kendrick.

Table 1. Recommended Dosing Weight for Selected Drugs in Children and Adults.

Medicine	Obese adult	Obese child	Comment
Aminoglycosides	ABW= IBW + 0.4 (TBW - IBW)	May use TBW or ABW*	Monitor serum concentrations
Vancomycin	TBW	TBW*	Monitor serum concentrations
Carbamazepine	IBW	IBW*	
Opioids	IBW	IBW*	No studies in children were found. Intermittent doses may be preferred. Monitor clinically.

*Extrapolated from adults

2.3 Data sheets

Below are example extracts from product information or data sheets in NZ and international product information describing dosing of paracetamol to children.

2.3.1 New Zealand

Label statements database

"Dosage (every four to six hours with no more than four doses in 24 hours):

Table 2. Dosing of paracetamol to children (Label statements database), Medsafe.

Age	Average body weight (kg)	Single dose (mg)
1 - 3 months	4 - 6	60 - 90
3 - 6 months	6 - 8	90 - 120
6 - 12 months	8 - 10	120 - 150
1 - 2 years	10 - 12	150 - 180
2 - 3 years	12 - 14	180 - 210
3 - 4 years	14 - 16	210 - 240
4 - 5 years	16 - 18	240 - 270
5 - 6 years	18 - 20	270 - 300
6 - 7 years	20 - 22	300 - 330
7 - 8 years	22 - 25	330 - 375
8 - 9 years	25 - 28	375 - 420
9 - 10 years	28 - 32	420 - 480
10 - 11 years	32 - 36	480 - 540
11 - 12 years	36 - 41	540 - 615
> 12 years	500 to 1000mg. Dosage should not exceed 4g in 24 hours.	

"Wider age ranges (e.g. 1-3 years) may be used on product labelling where appropriate. A medicine label may include only a subset of the age groups - for example, dosing for ages 6-12 years only. Doses must still be consistent with the above table".

Medsafe is currently consulting on proposed changes to current warning and advisory statements for paracetamol (for example to keep to the recommended dose and not take paracetamol for more than 48 hours unless advised by a doctor). The dosing is based on actual weight and there are no specific recommendations for dosing to overweight or obese children, either in the current or the proposed text.

- In the current text:

If you know that your child's weight is less than the weight corresponding to the age in the table, choose the dose for their weight.

- The proposal says:

Use the dose for your child's weight. Only use the dose for age if you do not know your child's weight.

In the consultation Medsafe proposed altering the dosing table to a fixed dose per weight range that would achieve 10-15mg/kg for the weight range.

Web site Pamol Suspension 250 mg/5ml (23)

The paracetamol products used by young children do not have data sheets. The dosing of Pamol is used as an example. Pamol suspension is available as infant drops for babies from 3 to 12 months, and mixtures for children aged 1-12 years. All Pamol suspensions contain 250 mg/5ml paracetamol

The dosing of Pamol is calculated according to the weight of the child, and a syringe is provided to measure the dose, see table:

Table 3. Recommended dose of Pamol, NZ, for children under 12 years calculated according to the child's weight.

Child's weight (kg)	Pamol® dose
5kg or less	Check with your healthcare professional
6kg	1.8mL
7kg	2.1mL
8kg	2.4mL
9kg	2.7mL
10kg	3mL
15kg	4.5mL
20kg	6mL
25kg	7.5mL
30kg	9mL
35kg	10.5mL
40kg	12mL

*Doses can be given every 4-6 hours when required, with no more than 4 doses in 24 hours (or as advised by your healthcare professional).

There are no specific recommendations for dosing to overweight or obese children.

Data sheet Panadol tablets 500 mg (updated August 2017) (7)

Adults and children aged 12 years and over: 1 to 2 tablets every four to six hours as required. Maximum of 8 tablets in 24 hours. Maximum daily dose: 4000 mg.

Do not use for more than a few days at a time in adults without medical advice.

Children 7 to 12 years: ½ to 1 tablet every four to six hours as required. Maximum of 4 tablets in 24 hours.

Should not be used for more than 48 hours for children 7 – 17 except on medical advice.

There are no specific recommendations for dosing to overweight or obese children.

Data sheet Paracetamol 10mg/ml solution for injection (updated Sept 2018) (8)

Section 4.2 Dose and method of administration:

The prescribed dose must be based on the patient's weight.

Dosing recommendations are presented in the table below.

Table 4. Dosing recommendations for paracetamol 10 mg/ml solution for injection, NZ.

Patient Weight	Paracetamol dose (10 mg/mL) per administration	Minimum interval between each administration	Maximum daily dose #
> 50 kg	1 g (i.e. one 100 mL vial) Up to 4 times per day	4 hours *	≤ 4 g Must not exceed 4 g in 24 hours
> 33 kg and ≤ 50 kg	15 mg/kg (i.e. 1.5 mL solution per kg) Up to 4 times per day	4 hours *	≤ 60 mg/kg, without exceeding 3 g Must not exceed 3 g in 24 hours
> 10 kg and ≤ 33 kg	15 mg/kg (i.e. 1.5 mL solution per kg) Up to 4 times per day	6 hours	≤ 60 mg/kg, without exceeding 2 g Must not exceed 2 g in 24 hours
≤ 10 kg **	7.5 mg/kg (i.e. 0.75 mL solution per kg) The volume must not exceed 7.5 mL per dose Up to 4 times per day	6 hours	≤ 30 mg/kg Must not exceed 30 mg/kg in 24 hours

* The minimum interval between each administration must be 4 hours in patients without hepatic or renal impairment. However, in patients with renal and/or hepatic impairment the minimum interval between doses must not be less than 6 hours.

The maximum daily dose takes into account all medicines containing paracetamol or propacetamol.

** No safety and efficacy data are available for premature neonates. There is limited data on the use of PARACETAMOL-AFT in neonates and infants <6 months of age.

There are no special recommendations on dosing in overweight or obese children.

2.3.2 Sweden

Product information Alvedon (updated August 2019) (24)

Oral solution 24 mg/ml and suppositories 60 mg, 125 mg, 250 mg, 500 mg, 1 g: from 3 months (5 kg) to 12 years (40 kg). Dispersable tablets 250 mg and 500 mg: from 1 year of age (10 kg) to 12 years (40 kg).

Dosing for all administration forms: 10-15 mg/kg bodyweight every 4-6 hours, max 4 times per 24 h. Max dose per 24 h: 60 mg/kg bodyweight. Contact doctor if high fever, infection or other symptoms persist after 48 h of treatment. Dosing examples are shown in table 4 and 5.

Table 4. Dosing recommendations for paracetamol oral solution 24 mg/ml, Sweden.

Body weight	Age (approximately)	Dosing, oral solution 24 mg/ml	Max dose per 24 h
5-7 kg	3-6 months	2.5 ml x 4	240 mg
7-10 kg	6 months to 1 year	3.5 ml x 4	336 mg
10-15 kg	1-2 years	5 ml x 4	480 mg
15-20 kg	3-5 years	7.5 ml x 4	720 mg
20-25 kg	5-7 years	10 ml x 4	960 mg
25-30 kg	7-9 years	12.5 ml x 4	1 200 mg
30-40 kg	9-12 years	15 ml x 4	1 440 mg
40 kg	12 years	20 ml x 4	1920 mg

Table 5. Dosing recommendations for paracetamol suppositories, Sweden.

Body weight	Age (approximately)	Dosing
Suppositories 60 mg		
5-10 kg	3 months-1 year	1 suppository every 4-6 hours, max 4 times per 24 h
Suppositories 125 mg		
10-15 kg	1-3 years	1 suppository every 4-6 h, max 4 times/24 h
Suppositories 250 mg		
15-25 kg	3-7 years	1 suppository every 4-6 h, max 4 times/24 h
25-40 kg	7-12 years	1-2 suppositories every 4-6 h, max 4 times/24 h
Suppositories 500 mg		
>40 kg	>12 years	1-2 suppositories every 4-6 h, max 4 times/24h

There are no specific recommendations for dosing to overweight or obese children in the product information.

Comment: Local guidelines for treatment of children in hospital, for example from Karolinska University Hospital, use actual body weight for calculation of the dose and there are no specific recommendations for dosing to overweight or obese children. (25).

2.3.3 Australia

According to the TGA website, the optimal dose for children 1 month to 12 years is 15 mg/kg, which can be given every 4 – 6 hours as required, with no more than 4 doses in 24 h. There are no specific recommendations for dosing to overweight or obese children (26). The label statements in Australia are the same as in the current NZ label statements.

The myDr web site recommends a different dosing:

The usual dose of paracetamol for children is **10-15 mg per kilogram** of weight. This dose can be taken once every 4 to 6 hours, up to 4 times in 24 hours if needed. The packaging may give an estimate of doses based on age and weight.

No child should take a total of more than 60 mg per kilogram of their body weight in a day. Caution is needed to never exceed the adult dose of paracetamol (4000 mg/day), which can happen if weight-based dosing is applied to children weighing over 65 kg (27).

Web site Panadol GSK (28)

Baby drops for children 1 month to 1 year 100 mg/ml, suspension 24 mg/ml for children 1-5 years, elixir or suspension 48 mg/ml for children 5-12 years, chewable tablets 120 mg for children 3+ years and 250 mg for 7+ years and suppositories 125 mg for children 6 months to 5 years and 250 mg for 5 to 12-year olds.

For example, dosing of oral solution 24 mg/ml:

The recommended dose for Children's Panadol in children under 12 years is 15 milligrams of paracetamol for every 1 kg body weight. Match the child's weight to the chart below. If the weight is not known, then match the age of the child.

If your child weighs less than 10kg (or is under 1 year of age) or more than 20 kg, please consult your doctor about adjusting the dosage amount.

Table 7. Dosing recommendations for paracetamol oral solution 24 mg/ml, Australia.

Suspension 24 mg/ml	Average weight	Dose
1 – 2 years	10 – 12 kg	6 – 8 ml
2 – 3 years	12 – 14 kg	8 – 9 ml
3 – 4 years	14 – 16 kg	9 – 10 ml
4 – 5 years	16 – 18 kg	10 – 11 ml

Do not give more than 4 doses in one day or within any 24-hour period. Do not use for more than 48 hours at a time except on medical advice.

2.3.4 UK

MHRA introduced new dosing recommendations for pediatric paracetamol liquids in 2014 (29). The new recommendations for liquid paracetamol products for children have quite narrow age bands with a single dosing option per band. MHRA explains on their web site that although dosing for children on a mg/kg bodyweight is standard practice in hospitals, this is not always practical for parents to manage at home. Dosing recommendations are shown in table 8.

Table 8. Dosing recommendations for paracetamol suspension 120 mg/5ml and paracetamol 250 mg/5ml, UK.

- For paracetamol infant suspension (120 mg/5 mL):

Age: 2–3 months	Dose
1. Post-vaccination fever	2.5 mL If necessary, after 4–6 hours, give a second 2.5 mL dose

2. Other causes of pain and fever if your baby weighs over 4 kg and was born after 37 weeks

Do not give to babies less than 2 months of age. Do not give more than 2 doses. Leave at least 4 hours between doses. If further doses are needed, talk to your doctor or pharmacist

Child's age	How much	How often (in 24 hours)
3–6 months	2.5 mL	4 times
6–24 months	5 mL	4 times
2–4 years	7.5 mL	4 times
4–6 years	10 mL	4 times

Do not give more than 4 doses in any 24-hour period. Leave at least 4 hours between doses. Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist

- For paracetamol six plus suspension (250 mg/5 mL):

Child's age	How much	How often (in 24 hours)
6–8 years	5 mL	4 times
8–10 years	7.5 mL	4 times
10–12 years	10 mL	4 times

Do not give more than 4 doses in any 24-hour period. Leave at least 4 hours between doses. Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist. Do not give to children under the age of 6 years

Dose for children age 12–16 years: 10–15 mL up to 4 times a day.

Dose for adults and children over 16 years: 10–20 mL up to 4 times a day.

Alvedon suppositories 60 mg, 125 mg, 250 mg Intrapharm Laboratories Ltd (Updated July 2019)

Dosing example:
Children 6 to 12 years (250 mg suppositories) (30)
The dosage should be based on age and weight i.e.
6 years (20 Kg) - 250mg (1 suppository)
12 years (40 Kg) - 500mg (2 suppositories)

These doses may be repeated up to a maximum of 4 times in 24 hours. The dose should not be repeated more frequently than every 4 hours. The recommended dose should not be exceeded. Higher doses do not produce any increase in analgesic effect.

There are no specific recommendations for dosing to overweight or obese children in the product information or in the dosing recommendations.

Comments: The dosing recommendations are based on weight or both weight and age. They all include maximum daily doses. Data sheets and product information do not include specific dosing for obese or overweight children. The two web sites from Australia mention children of high weight without giving other advise than to not exceed adult dose/contact doctor. Local guidelines may differ from what is described above, see section 3.1.3.

2.4 NZ Guidelines for treatment of children with paracetamol

2.4.1 New Zealand formulary for children

The figure below shows recommended dosing of paracetamol to children (2).

Figure 4: Recommended dosing of paracetamol to children, New Zealand formulary for children.

Pain; pyrexia with discomfort

Oral

Neonate 28–32 weeks corrected gestational age 20 mg/kg as a single dose, then 10–15 mg/kg every 8–12 hours as necessary; maximum 30 mg/kg per day

Neonate over 32 weeks corrected gestational age 20 mg/kg as a single dose, then 10–15 mg/kg every 6–8 hours as necessary; maximum 60 mg/kg per day

Child 1 month–18 years 15 mg/kg per dose (maximum 1 g) every four hours; maximum 75 mg/kg per day (without exceeding 4 g) for 48 hours, maximum of 60 mg/kg per day (without exceeding 4 g) thereafter

Note A loading dose of 30 mg/kg (maximum 1.5 g) may be given provided there has been no paracetamol given within the preceding 12 hours.

Rectal

Child 1 month–18 years 15–20 mg/kg per dose (maximum 1 g) every four hours; maximum 75 mg/kg per day (without exceeding 4 g) for 48 hours, maximum of 60 mg/kg per day (without exceeding 4 g) thereafter

Note A loading dose of 30 mg/kg (maximum 1.5 g) may be given provided there has been no paracetamol given within the preceding 12 hours.

Intravenous infusion over 15 minutes

Preterm neonate over 32 weeks corrected gestational age 7.5 mg/kg every 8 hours

Neonate 10 mg/kg every 4–6 hours; maximum 30 mg/kg daily

Child under 10 kg 10 mg/kg every 4–6 hours; maximum 30 mg/kg daily

Child 10–33 kg 15 mg/kg every 4–6 hours; maximum 60 mg/kg daily, without exceeding 2 g

Child 33–50 kg 15 mg/kg every 4–6 hours; maximum 60 mg/kg daily, without exceeding 3 g

Child over 50 kg 1 g every 4–6 hours; maximum 4 g daily (see also cautions)

The formulary refers to the recommendations by BPAC on dosing of paracetamol to children in primary care for more information, see section 2.4.3. In the BPAC recommendations, calculation of doses is based on actual body weight.

2.4.2 Starship Children's Hospital, Auckland

The figure below shows analgesic guidelines for use of paracetamol from Starship children's hospital in Auckland.

Figure 5: Pediatric analgesia guidelines for paracetamol, Starship Hospital

Paediatric Analgesia Guidelines

As with all drugs, modification of the recommended dosage must be considered in the presence of organ dysfunction. All analgesics (except slow release preparations) may be given on a PRN basis but strong consideration should be given to prescribing pain relief on a regular basis, especially when initiating therapy. The following information is intended for your guidance and use with **in-patients only.** Please consult a senior colleague, a member of the Department of Anaesthesia or Paediatric Pain Service if you are unsure about your prescription.

Drug	Suggested Dosing Regimens	Preparations	Considerations
Paracetamol -Oral	**Less than 32 weeks - See Newborn Services Guidelines** **Preterm 32 - 38 weeks** 10mg/kg - 8 hourly (Max 40mg/kg/24hrs) **Neonates and infants over 38 weeks and up to 3 months** 10mg/kg - 6 hourly (Max 60mg/kg/24hrs) **Infants and children over 3 months** 20mg/kg - 6 hourly or QID - inpatient use only for a limited time Discharge dose - 15mg/kg/QID -Max 90mg/kg/24hrs -Do not exceed 4 grams/24 hours	Oral suspension: 120mg/5mL, 250mg/5mL Tablets: 500mg	-Jaundice -Hepatic impairment -Renal impairment -Hepatotoxicity with doses exceeding 150mg/kg/24hrs For paracetamol dosing in overweight and obese children consider using ideal body weight for age to dose.
Paracetamol -Rectal	-Dosing as above -Chart suppositories as whole doses (do not cut suppositories)	Suppositories: 25mg, 50mg, 125mg, 250mg, 500mg	
Paracetamol -Intravenous	**See Newborn Services paracetamol guidelines if neonate less than 32 weeks** **Neonates and infants over 32 weeks and less than10kg** 7.5mg/kg - 6 hourly (Max 30mg/kg/day) **Infants and children greater than 10kg** 15mg/kg - 6 hourly Max 60mg/kg/day up to 4 grams/24 hours -Refer to Guardrails for infusion information	500mg/50mL 1000mg/100mL	Only for use in patients that are strictly NBM for medical reason. Dose must not exceed the dosing regimens outlined (max 15mg/kg/6hrly >10kg) **Prescribing must be IV ONLY (not IV/PO)**

Previous guidelines (published 2017) referred to Bpac for dosing of paracetamol to overweight and obese children: "Paracetamol dosing for children in primary care" from 2018. This guideline states that the paracetamol dose should be calculated based on the child's actual body weight, without exceeding the adult dose.

However, the guidelines were changed on 14 February 2020. The new guidelines have been changed regarding dosing in overweight and obese children to:

"For dosing in overweight and obese children consider using ideal body weight for age to dose".

For children in pediatric intensive care who have not received paracetamol, an oral/rectal loading dose of 30-40 mg/kg (max 2g) can be considered.

Comments: The guidelines were changed on 14 February 2020 regarding dosing in overweight and obese children. The recommendation is to *consider* using IBW, which is rather vague. It is also stated that the very high dose of 20mg/kg can be given for a limited period of time but is unclear how that long that is.

No references or explanations to the change are given and no advice for how to calculate ideal body weight. Also, the guideline does not specify that the loading doses are above the approved doses

2.4.3 BPAC Paracetamol dosing for children in primary care

Bpac published recommendations for dosing of paracetamol to children in primary care in February

2018 (3).

Maximum recommended oral dose of paracetamol for children aged 1 month to 18 years:

15 mg/kg every 4–6 hours to a maximum of 1 gram per dose, and no more than 4 doses in a 24-hour period.

BPAC explains the reasons for calculating the dose per kg actual body weight.

- Due to the wide range of body weights across children of different ages, and because the overall rate of paracetamol metabolism per kilogram of body weight does not vary with age, paracetamol is dosed in milligrams per kilogram of body weight, rather than by age.
- Paracetamol is dosed in milligrams per kilogram of actual body weight, without exceeding the adult dose.
- The same milligram per kilogram of body weight method for paracetamol dose calculation is recommended for obese children. However, caution is needed to never exceed the adult dose. There is little evidence supporting the use of weight adjustments in paediatric paracetamol dosing (unless the child is malnourished) and accumulating evidence suggests that methods other than actual weight-based dosing may result in sub-therapeutic treatment".

BPAC also warns of medicine errors being of greatest concern when prescribing paracetamol, for example by exceeding recommended doses, too frequent dosing or prolonged dosing.

2.4.4 Health Navigator

The recommendations from Health Navigator were last updated in august 2019 (31). How to calculate the correct dose of paracetamol:

- Use weight-based dosing.
- Use actual body weight, not ideal body weight.
- Never exceed the recommended adult dose.

They provide a calculator tool and two tables show calculated doses for different weights. They also refer to the article in Prescriber Update.

Table 9. Calculated doses of paracetamol suspension after actual body weight.

Paracetamol dosing chart		
Wait at least 4 hours between doses. Do not give more than 4 doses in 24 hours.		
Child's weight	**120mg/5mL**	**250mg/5mL**
Less than 5 kg	Ask your doctor	Ask your doctor
6.5 kg	4 mL	2 mL
8 kg	5 mL	2.5 mL
10 kg	6 mL	3 mL
15 kg	9 mL	4.5 mL
20 kg	12 mL	6 mL
25 kg	15mL	7.5 mL
30 kg	18 mL	9 mL
35 kg	21 mL	10 mL
40 kg	25 mL	12 mL
45 kg	28 mL	14 mL
50 kg	30 mL	15 mL

Table 10. Calculated doses of paracetamol suspension after actual body weight.

Child's weight	Tablet (500 mg)
35 to 50 kg	1 tablet
50 to 65 kg	1 to 2 tablets
65 kg or more	2 tablets
Maximum: for children weighing more than 65 kg, do not give more than 2 tablets per dose.	

Comments: The national or local guidelines have all recommended calculating the dose of paracetamol using the actual body weight of the child, also for overweight or obese children, the maximum daily dose not to be exceeded. However, Starship Hospital changed their guidelines this month to recommend that dosing according to ideal body weight should be considered.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Pharmacokinetics of paracetamol in obese subjects

A literature search identified a few publications describing possible effects of obesity on paracetamol pharmacokinetics, which are summarised below. The studies are small, and the patients are treated with a single dose or limited doses. Note that the individuals included in some articles are adults or adolescents.

3.1.1.1 Barshop NJ et al Acetaminophen Pharmacokinetics in children with non-alcoholic fatty liver disease 2011 (32)

The objectives of the study were to evaluate UDP-glucuronyltransferase (UGT) activity and the pharmacokinetics of a single oral dose of paracetamol in children with non-alcoholic fatty liver disease (NAFLD). Obesity is highly associated with NAFLD.

Method

Twelve boys, 10–17 years old, with NAFLD and 12 age and gender matched controls without NAFLD were included. Mean BMI was 34 ± 10.95 kg/m^2 in the NAFLD group as compared to 26.22 ± 6.14 kg/m^2 in the control group which was a significant difference. Following administration of a single oral dose of paracetamol (5mg/kg, maximum 325mg), paracetamol and its glucuronide metabolite (APAP-G) were measured in plasma, urine, and sputum at various intervals up to 24 hours.

The boys also received simultaneous administration of a single oral dose of dextromethorphan 0.3 mg/kg (up to 15 mg) and 8 oz Diet Coke for the simultaneous measurement of the activity of multiple drug-metabolizing enzymes (CYP2D6, CYP1A2, CYP3A4, and UGT). The use of such cocktails has been validated in several studies according to the authors.

The activity of UGT was estimated by the plasma ratio of APAP-G to APAP at 4 hours. The area under the concentration/time curves from 0 to 4 hours was calculated. The clearance of APAP was calculated by dividing the initial APAP dose by the area under the concentration/time curve for each patient and expressed per kilogram of body weight.

Results

Linear regression showed a significant linear relation between saliva and plasma concentrations of paracetamol at 4 hours. No significant differences in APAP pharmacokinetic parameters measured in saliva (clearance, half-life, area under the curve, and peak APAP concentration) were observed between the two groups.

The children in the NAFLD-group had significantly higher concentrations of APAP-G in serum (p=.0071) compared with the control group. There was also a statistically significant increase in the ratio of APAP-G to APAP (P=0.0277) in the children with NAFLD.

The children with NAFLD had significantly higher concentrations of APAP-G in urine (p=.0210) between 4 and 24 hours compared to the control group.

The authors discuss that the altered metabolism of APAP regarding APAP-G in children with NAFLD does not appear to affect its rate of elimination, which suggest that a similar dosage schedule should apply for children with NAFLD as for normal children.

The safety of APAP in children with NAFLD is more difficult to assess because of limited data, for example regarding CYP2E1-mediated oxidation of paracetamol (see section YY) which this study does

not include. More research is necessary to determine whether children with NAFLD are at an increased risk for APAP-induced hepatic injury.

The study shows a significant increase in the formation of APAP-G in children with fatty liver disease, which is likely due to UGT upregulation. Although this may represent an overall increase in APAP metabolism, the authors consider it far more likely a reflection of decreased activity in other metabolic pathways not measured in the present study. This hypothesis is supported by the normal pharmacokinetic parameters, in the face of elevated APAP-G formation.

Comments:
A lower dose of paracetamol than recommended dose (5 mg/kg) was used in this study which may have had an impact on the results.

In a systematic review by Harskamp-van Ginkel MW from 2015 (33), the objective was to describe the current evidence of the effect of obesity on drug disposition in children. Relevant data was found for only 21 medicines in 20 studies, and this was the only study on paracetamol that met the inclusion criteria.

According to a publication by Aubert et al 2011 (34), higher hepatic CYP2E1 expression and activity have been frequently observed in the context of obesity and NAFLD. CYP2E1 is responsible for producing the toxic paracetamol metabolite.

3.1.1.2 Lee WH et al The Effects of Obesity on Acetaminophen Pharmacokinetics 1981 (35)

The study examined the absorption and disposition of orally administered paracetamol in adult morbidly obese patients as compared to subjects of normal weight, and possible changes in disposition as the patients underwent weight reduction through dietary modification.

Method

Four morbidly obese patients hospitalised for the purpose of weight reduction through dietary modification were compared with three males of normal weight. None of the patients was in any phase of acute or rapid weight loss.

The subjects received two 325 mg paracetamol tablets after an overnight fast. Blood samples were collected and measured using a high-pressure liquid chromatographic method up to 12 hours after medicine ingestion. Each obese patient was restudied after an average of 14 kg weight loss.

Results

The overall disposition of paracetamol was not affected by a weight loss of 8 to 30 kg; elimination half-life, time to reach the peak, and peak plasma concentration varied within each subject but not in a systematic way.

The half-life was the same in the obese patients (2.6 +/- 0.85 hours) and normal subjects (2.6 +/- 0.12 hours). However, maximum plasma concentrations were reached at a significantly later time and were significantly lower in the obese patients as compared to the control group.

The area under the plasma concentration-time curve for the obese patients when normalized to ideal body weight was more consistent with the normal subjects than when normalized to total body weight.

The authors discuss that it would appear that obesity does not affect the extent to which paracetamol is absorbed or its rate of elimination, however, obese patients may have a slower absorption rate. Administration of a normal dose of acetaminophen to an obese patient should yield plasma levels in the same range as persons of normal weight and in theory have the same effect. They consider that the dose of paracetamol should be based on ideal, not total body weight in the obese patient (as total weight may exceed 200% of the ideal weight in this patient group) to avoid toxic or lethal effects when using the 10 – 20 mg/kg dosing recommendation.

Comment: Very few adult individuals were included in this study, and they only received 1-3 doses of paracetamol. The authors consider that the same effect should be expected even if the maximum plasma concentration is lower and later, but the effect was not measured in the study.

3.1.1.3 Hakim et al Acetaminophen pharmacokinetics in severely obese adolescents and young adults 2019 (36)

In bariatric surgery, paracetamol is given as an adjunct to opioids during the surgical procedure and in the perioperative period, and the maximum dose of paracetamol is 1000 mg every 6 hours.

The objective of this prospective study was to investigate paracetamol serum concentrations following one single dose of 1000 mg intravenous paracetamol in severely obese adolescents following sleeve gastrectomy. Pharmacokinetic analysis of time-concentration profiles included assessment of size descriptors for obese adolescents in order to predict a dose that might achieve a target concentration of 10 mg/L at steady state.

Method

Adolescents, 14-20 years of age, with a body mass index (BMI) ≥95th percentile for age and sex or BMI ≥40 $kg \cdot m^{-2}$, were administered intravenous paracetamol (1000 mg) following completion of the surgical procedure. Venous blood was drawn for paracetamol assay at eight time points, starting 15 minutes after completion of the infusion and up to 12 hours afterward. Time-concentration data profiles were analyzed using nonlinear mixed effects models. Parameter estimates were scaled to a 70-kg person using allometry. Normal fat mass was used to assess the impact of obesity on pharmacokinetic parameters.

Results

Eleven female patients were included, age 17 SD 2 years with a weight of 125 SD 19 kg and a mean BMI of 46 SD 5 kg/m^2. The plasma paracetamol serum concentration was 17 (SD 4) µg/mL at 10-20 minutes after completion of the infusion and 5 (SD 6) µg/mL at 80-100 minutes.

Figure 6 shows a simulation of serum and effect site time-concentration profiles for a 50 kg adolescent and a 125 kg adolescent respectively, given 1000 mg paracetamol intravenously. A dose 0f 2 250 mg is required in the obese adolescent to achieve similar concentration to the non-obese adolescent. An effect site equilibrium half time of 0.7 h was assumed.

A two-compartment model, used to investigate pharmacokinetics, estimated paracetamol population pharmacokinetic parameters standardised to a 70 kg person as: clearance 10.6 (CV 72%) L·h·70 kg^{-1} , intercompartment clearance 37.3 (CV 63%) L·h·70 kg^{-1} , central volume of distribution 20.4 (CV 46%) L·70 kg^{-1} , and peripheral volume of distribution 16.8 (CV 42%) L·70 kg^{-1} . The authors note that the clearance of 10.6 L·h·70 kg^{-1} is at the lower end of that described by others for adults and children (10-21 L·70 kg^{-1} and that clearance scales with total body weight (TBW) in a non-linear relationship.

The authors state that TBW is a better parameter for estimation of paracetamol clearance than lean body mass and should be used to estimate dose.

They discuss that CYP2E1 activity may be increased in obese patients, but there is also commonly an increased glucuronide clearance and so less substrate is available for CYP2E1 metabolism.
There are concerns regarding hepatotoxicity, especially following chronic dosing. The influence of obesity, if any, on paracetamol toxicity is unknown and this lack of understanding restricts dosing, rather than pharmacokinetic knowledge.

Comments: This is a study on intravenous use of paracetamol, and it does not measure safety or toxicity of paracetamol. It included adolescents and your adults and not children. It is not stated how the effect of paracetamol is correlated to the serum concentration of the drug.

Even if the authors consider it better to estimate the dose using TBW to achieve enough effect site concentration, they also note that dosing per kg may result in a relative overdose in obese patients as clearance has a non-linear relationship with weight. Although, presumably for these people a per kg dose would have exceeded the adult dose.

3.1.1.4 Von Rongen et al Morbidly Obese Patients Exhibit Increased CYP2E1-Mediated Oxidation of Acetaminophen 2016 (37)

The authors cite a publication by Abernethy in 1982 (38) stating that the volume of distribution and the total clearance of paracetamol are increased in obese subjects compared to non-obese subjects. Because of this, obese patients may need higher loading and maintenance doses of paracetamol.

However, there are also safety concerns. The minor pathway of paracetamol metabolism through cytochrome P450 (CYP) 2E1 is held responsible for paracetamol hepatotoxicity. In obese patients, CYP2E1 activity has been reported to be induced, thereby potentially worsening the safety profile of paracetamol.

The aim of this study was to determine the pharmacokinetics of paracetamol and its metabolites (glucuronide, sulphate, cysteine and mercapturate) in morbidly obese and non-obese patients.

Methods

Twenty morbidly obese adult patients (with a median TBW of 140.1 kg (106–193.1 kg) and BMI of 45.1 kg/m2 (40–55.2 kg/m^2) and eight non-obese patients (with a TBW of 69.4 kg (53.4–91.7) and BMI of 21.8 kg/m^2 (19.4–27.4) received one dose of 2 g intravenous paracetamol. Blood samples were regularly collected for 8 hours after the infusion and one last time after 24 hours. After 8 h the standard postoperative pain protocol was initiated (1 g IV paracetamol every 6 h).

Paracetamol and its metabolites were measured using high-performance liquid chromatography–electrospray ionization–tandem mass spectrometry. Population pharmacokinetic modelling was performed using NONMEM.

The final population pharmacokinetic model was used to simulate concentration–time curves upon a 2 g intravenous infusion (administration time 20 min) in four typical patients from the data set, i.e. a non-obese patient weighing 60.1 kg (LBW 41.2 kg) and three morbidly obese patients weighing 106, 134 and 193 kg (LBWs 51.3, 65.8 and 96.2 kg, respectively).

Results

In the morbidly obese patients, the median area under the plasma concentration–time curve from 0 to 8 h (AUC0–8h) of paracetamol was significantly smaller (P = 0.009), while the AUC0–8h ratios of the glucuronide, sulphate and cysteine metabolites to paracetamol were significantly higher (P = 0.043, 0.004 and 0.010, respectively) compared to the non-obese patients.

In the model, paracetamol CYP2E1-mediated clearance (cysteine and mercapturate) increased with LBW (population mean (relative standard error) 0.0185 L/min (15 %), P\0.01)). Moreover, formation of the cysteine and mercapturate metabolites accelerated with increasing LBW (P<0.001). Glucuronidation clearance (0.219 L/min (5 %)) and sulfation clearance (0.0646 L/min (6 %)) also increased with LBW (P<0.001).

The authors conclude that obesity leads to lower paracetamol concentrations and earlier and higher peak concentrations of paracetamol cysteine and mercapturate. While a higher dose may be anticipated to achieve adequate paracetamol concentrations, the increased CYP2E1-mediated pathway may preclude this dose adjustment.

Note that the concentration is stated in µmol/L. Using the same calculation as in section 2.1.3, a plasma concentration of 250 µmol/L (maximum plasma level of paracetamol in the patient with TBW 60.1 kg) equals 42 mg/L and a plasma concentration of 125 µmol/L (maximum plasma level in the patient with TBW 193 kg) equals 18.75 mg/L.

Comments: A comment to this article by Reith was published in 2018 (6), stating that the conclusions in the study are based on artefact due to the methods used for data collection, modelling and simulation. His reasons were:

- The urinary excretion of paracetamol and the metabolites were not measured. The V_d for the metabolites were therefore inestimable.

- As the metabolites are more polar than paracetamol, with obesity, V_d of paracetamol would be expected to remain unchanged relative to body weight, but V_d of the metabolites would be expected to decrease relative to body weight. Hence, the conclusion that metabolic clearance increases with obesity is physiologically implausible, whereas decreasing V_d of the metabolites, relative to TBW, is plausible.

- The findings with regard to cytochrome P450(CYP)2E1 metabolism are also based on artefact because of the model used for simulation being inappropriate. There is no evidence here that CYP2E1-mediated metabolism is increased in obesity.

Author's reply to the comment was published in 2018 (39). According to them, the study demonstrated that the observed AUCmetabolite/AUCparacetamol ratios were not caused only by changes in V_d relative to body weight in obese versus non-obese patients but a product of multiple parameters, including clearances.

They note that their model predicts a slightly decreasing fraction of paracetamol being metabolized through the CYP2E1 pathway. Even if the CYP2E1 metabolism is increased, the other metabolic pathways are increased to a greater extent. Therefore, the same dose of acetaminophen would not necessarily be more toxic to obese than to non-obese patients. What they argue is that the

paracetamol dose leading to the same concentrations in obese and non-obese patients will be more toxic to the obese patients because they need a higher dose to reach therapeutic concentrations.

3.1.2 Dosage practice in children with overweight or obesity

3.1.2.1 Gade et al Inconsistencies in dosage practice in children with overweight or obesity: A retrospective cohort study 2018 (21)

This Danish retrospective cohort study aimed to investigate dosage strategies in children with overweight or obesity in a clinical treatment facility (obesity clinic) and in particular, whether dosing guidelines were available, and metrics of body size applied.

Data were collected from 2007 to 2015 and 200 overweight/obese children 3-18 years were included if they had at least one drug prescription. Indication for treatment, drug dose, dosage interval, duration of treatment, age of child at prescription time, weight and height were collected.

For evaluating dosage strategies, the following data were registered: dosage by total body weight (TBW), fixed dose by age (years), use of adjusted weight measures (eg LBW, BSA, IBW, ABW) or dose estimation by other strategies. The table below shows how metrics of body size was calculated.

Overall, 455 prescriptions were registered during the hospitalisation. Of these, 34 were for paracetamol, which was the second most commonly prescribed medicine. It is unknown how long the treatment times were. There were no specific guidelines for dosing strategies for obese/overweight children on the clinic.

In 15 cases, paracetamol was dosed by TBW in accordance with a normal weight child dosing regimen and in 9 cases dose-capping was registered when dose exceeded the recommended maximum adult

dose and in 3 cases dose prescribed exceeded the dose calculated by TBW. In one case, the recommended maximum adult dose was exceeded. The authors conclude that there is a balance between prescribing a high enough dose of paracetamol to obtain analgesic effect but not too high dose for safety reasons, and this balance is currently unknown.

3.1.2.2 Wiese MD, Sluggett JK, Wilson CJ et al Perceived and actual paracetamol dosing in overweight and obese children 2012 (40)

This Australian study had 2 stages. The objective of the first stage was to determine what dose of paracetamol a group of carers and pharmacists would administer to an overweight or obese child, and for the second stage it was to observe the paracetamol doses administered to children that presented to the emergency department of a paediatric tertiary referral hospital.

Methods
Seventy-three caregivers or pharmacists were asked to consider three different scenarios, each of which involved a febrile 8-year-old boy of 3 different weights and state the dose of medicine they would recommend (for pharmacists) or administer (for caregivers) in each situation.

For stage 2, age, gender, weight and paracetamol dose were prospectively collected from the medication charts of children aged 2–18 years who were administered paracetamol at the emergency department.

Results
Carers and pharmacists recommended similar paracetamol doses for children who were the normal weight for their age, but as body weight increased, there was an increasing array of responses. In the scenario with the heaviest weight, pharmacists recommended a twofold variation in dose. Twenty-six% of caregivers did not provide a response to this scenario.

The doses administered to the 86 children that presented to the emergency department of the hospital were based on total body weight.

The authors refer to the risk of hepatotoxicity but also to 3 other studies showing that approximately half of the children who were administered paracetamol by their carer prior to presentation to an emergency department recently received a dose of paracetamol <10 mg/kg, and over half of carers reported that they would not have presented to the emergency department if the fever had subsided at home.

The authors conclude that there is substantial confusion amongst carers and pharmacists about the most appropriate dose. In the emergency department setting, overweight and obese children did not have any empirical dose reduction according to the amount they were above IBW - whether or not this is appropriate practice is unclear, but it does highlight the need to develop guidelines for dosing for these children.

3.1.3 Considerations or position papers on medicine dosing to overweight or obese children

3.1.3.1 Matson KL, Horton ER et al on behalf of the Advocacy Committee for the Pediatric Pharmacy Advocacy Group, 2017 Medication Dosage in Overweight and Obese Children (41)

This American position paper describes how individuals with obesity may have alterations in metabolism and elimination of medicines (not specifically paracetamol):

- generally, a larger volume of distribution for lipophilic medications
- conversely, the Vd of hydrophilic medications may be increased or decreased due to increased lean body mass, blood volume, and decrease percentage of total body water
- it has been hypothesised hepatic clearance may be decreased secondary to fatty infiltrates of the liver
- It has been noted that kidney size increases with elevations in total body weight (TBW), with may result in an increased glomerular filtration rate

The authors recommend that weight-based dosing should be used in patients ages < 18 years who are < 40 kg. Weight-based dosing should also be used in patients ≥ 40 kg, unless the recommended adult dose for the specific indication is exceeded. Clinicians should consider using pharmacokinetic analysis for adjusting medications in overweight/obese children, however limited data are available in this patient population.

3.1.3.2 NSW Therapeutic Advisory Group, Australia

Paracetamol use - A position statement by the NSW Therapeutic Advisory group, 2008 (42)
The recommendations in this position statement are intended to promote best practice in the hospital environment and support clinical decision making. 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 in the document should be promoted by health professionals to the community.

According to the document, 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. In some cases, multiple doses within the recommended dose range given with therapeutic intent may be toxic.

In obese children, obesity itself is not considered to be a 'risk factor' for hepatotoxicity. 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.

For infants and children 3 month to 11 year of age, the recommended doses of paracetamol for analgesia are:

- Oral: 15 mg/kg/dose every 6 hours up to a maximum of 60-90 mg/kg/day based on 'ideal weight'. Ways to estimating 'ideal weight' for dose calculation purposes are provided:
- Rectal: 20 mg/kg/dose every 6 hours up to a maximum of 90 mg/kg/day
- Intravenous: 15 mg/kg/dose every 6 hours up to a maximum of 60 mg/kg/day

For symptomatic fever:

- Oral: 15 mg/kg/dose (every 6 hours up to a maximum of 60 mg/kg/day

A dose of 1 g, or a total dose of 4g in 24 hours shall never be exceeded. All recommended doses are based on 'ideal weight' relative to age and height of child. There is no note to use ideal weight when calculating doses for adults and children over 12 years. However, the dose should be adjusted for frail patients and patients weighting less than 50 kg.

The document provides an instruction for estimating ideal body 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 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.

- 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".

There are no references behind the recommendations for dosing to obese children.

Addendum to the position paper by the NSW Therapeutic Advisory group, 2012 (43)
An addendum concerning intravenous use of paracetamol was published in 2012 stating that for children, the dose should generally be calculated using the patient's current, accurate weight. However, dosing for overweight or obese children should be based on ideal body weight not total body weight.

Comments:
No references are given to support the recommendations for dosing to obese children.
The statement that paracetamol does not enter fat tissue well is surprising considering its volume of distribution (65 L).

3.1.3.3 UK Medicines Information Pharmacists (44) 2018. How should medicines be dosed in children who are obese? (44)

This Q&A document was prepared by UKMI with input from the Neonatal and Paediatric Pharmacists Group (NPPG) for NHS healthcare professionals.

There is a lack of pharmacokinetic studies on individual drugs in obese children as well as clear guidelines for determining whether drug dose adjustments are necessary.

The authors refer to a study illustrating another problem, suggesting that the majority of paediatric prescribers do not calculate BMI to determine whether a child is obese when prescribing medication. Height is not routinely measured at the point of admission to hospital which makes it impossible to determine a child's BMI centile to identify if they are obese (45).

The description of pharmacokinetics in pediatric obesity is generally in line with section 2.2.3 of this report with the addition that the impact of obesity on drug metabolism differs greatly, depending on the metabolic pathway involved. The activity of CYP3A4, is reduced in obese patients while expression of CYP2E1 has been reported to be increased.

They refer to a publication by Brill 2012 (46) summarising clinical studies that reported clearance values of drugs in obese and non-obese patients. Clearance of drugs primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT), glomerular filtration and/or tubular-mediated mechanisms, xanthine oxidase, N-acetyltransferase or CYP2E1 appeared higher in obese versus non-obese patients. However, data from obese children was very limited.

Dosage recommendations for a range of drugs commonly used in children is given, although with the comment that more evidence is needed before definite recommendations can be made. For paracetamol they recommend the dosing scalar "LBM or AdjBW (correction factor 0.4) up to adult max", although commenting that only limited information is available. The same algorithm is referred to in the letter to Medsafe, with the reference to a decision support tool (47).

There are different methods to calculate IBW and AdjBW, what they recommend is shown below:

1. The equation for BMI can be used in reverse to determine IBW:

   IBW = BMI50 x height (m2)

   where BMI50 represents the 50th centile of a BMI chart.

2. To calculate AdjBW, the IBW of the child is used in addition to a specified cofactor, which is a fraction of the excess weight gain between IBW and TBW. The following example uses an AdjBW cofactor of 0.4:

   AdjBW = IBW + 0.4 x (TBW – IBW)

   Example:

   A 7-year-old girl who weighs 30kg and is 1.2m tall has an IBW of 22.5kg (calculated using the BMI Method)

   IBW using BMI method = 22.5kg

   AdjBW = IBW + 0.4 x (TBW – IBW)

   AdjBW = 22.5kg + 0.4 x (30kg - 22.5kg) = 25.5kg

Comment: A variety of methods can be found on how to calculate different types of weights. Not all are suitable for children. Even when a choice of method has been made, the example above illustrates that there are many steps to follow to do the actual calculation, with a risk of errors being made. Note also that the recommendation on paracetamol dosing from the UK comes from a table with recommendations for many medicines, with the comment that there is limited information available.

Considering how many children are obese and how much paracetamol is used globally, there is surprisingly few publications and guidelines addressing dosing of paracetamol in overweight and obese children as being a problem, and ways to overcome such a problem.

3.2 Company report

3.2.1 GlaxoSmithKline (NZ) Ltd

[redacted]

[redacted]

3.3 Coroner case, Australia

In 2002, a 13-year-old boy died in Australia after being administered 31 grams of paracetamol over 14 days in two hospitals, while convalescing from a hip operation.

Following the operation, he was treated with Panadol and Panadeine Forte. After four days, his condition worsened, and paracetamol was given to relieve his spiking temperature and nausea. He was transferred to another hospital and eventually died of end-stage liver failure on March 29, 2000.

The death was referred to the coroner, and an article was published in a newspaper. The article discusses actions to prevent the potential for liver failure in children, such as:

- sell paracetamol only from pharmacies

- stronger warnings on packets of the drug, recommending patients be reviewed after 48 hours' treatment
- an alert be sent to doctors advising of problems that could spring from administering patients with paracetamol who are "not within normal parameters"

A gastroenterologist was interviewed, stating that the patient received a large dosage of paracetamol but might also have been more susceptible to the drug because, at 106 kilograms, he might have been prone to fatty liver.

Comment: The patient received a daily dose of 2.2 g paracetamol which equals 21 mg/kg/day if the dose is calculated using TBW. This is well under the maximum daily dose of 60 mg/kg/day.

The height of the patient is not known but if the CDC growth chart for 2 to 20 year-old males is used to estimate the IBW with the McLauren method, it is 46 kg (using the 50th percentile weight for age line). The dose he received then equals 48 mg/kg/day which is also under the recommended maximum daily dose.

The treatment was continued over 2 weeks. There is no information on if the therapy was reviewed during this time. As he was in hospital, there is a risk that he did not get enough nutrition and was malnourished. Children who are in a poor nutritional state are more susceptible to paracetamol toxicity due to a reduction in the levels of the detoxifying glutathione enzyme

3.4 CARM data

No cases of liver failure affecting overweight or obese children (under 17 years of age) have been reported to CARM.

3.5 ADIS Insight

A search in ADIS insight identified 112 safety reports for paracetamol and liver disorders in neonates and up to 18-year olds. Some reports included several cases and others included 1 case report. Many reports involved multiple medicines.

No case was found where obesity or overweight was mentioned as a factor. However, the weight of the patient is typically not reported.

3.6 National Poisons Center

Medsafe asked the National Poisons Center (NPC) for cases of paracetamol overdose in children when the child was obese and received a report on paracetamol exposures in children aged 0-4.

The data source was calls to the NZ National Poisons Centre (NPC) from 11 August 2016 to 31 December 2019 (41 months). This time frame corresponds to the use period of the current NPC medical record database.

Selection criteria was at least one paracetamol-containing product involved in exposure to a child aged 0-4 years. Reference weights used were based on MOH growth charts using the 91$_{st}$ percentile line of weight for gender and age.

For the purposes of analysis all patients within an age group were compared to the reference weight at the start of the next full year of life (i.e. for those aged 1 to just under 2 years, the reference weight for a 2 year old at the 91$_{st}$ percentile line was used).* This allowed the analysis to detect any 1 year old (whether they be 1 year 0 months 0 days, or 1 year 11 months 29 days) who exceeded the

91st percentile reference weight of a 2 year old. Using this approach age groups from under 1 up to 4 years could be analysed as MOH growth charts do not exceed age 5 years.

NPC was able to compare patients with a stated weight to the MOH 91st percentile reference value for age and gender in 86.7% of cases recorded. Note that all weights documented are as reported to NPC over the phone.

(NPC records patient ages in whole years or by date of birth. This approach taken will likely under-report the actual number of children who exceeded the 91st percentile weight for age at the time of the call to NPC).

Results

Table 12 shows how many females with paracetamol had a weight over reference value.

Table 12. Number of females with paracetamol exposure.

- Female patients:

FEMALES with paracetamol exposure

Age group	Reference weight used; MOH 91st percentile	Total number of patients	Number of patients able to compare*	Number of patients over reference	% of patients over reference	Highest weight recorded	Median kg above reference
Under 1	1-yo: 10.6 kg	211	190	8	4.2%	16 kg	1.5 kg
1	2-yo: 13.6 kg	431	382	31	8.1%	19 kg	0.4 kg
2	3-yo: 16.5 kg	434	399	28	7.0%	36.6 kg**	1.5 kg
3	4-yo: 19.5 kg	225	200	18	9.0%	26 kg	0.5 kg
4	5-yo: 22.4 kg	102	94	3	3.2%	30 kg	3.8 kg
Unknown child	*N/A*	23		*N/A*	*N/A*	*N/A*	*N/A*
Total	*N/A*	1,426	1,265	88	7.0%		

*Age, weight, gender information available **Confirmed with nurse*

Figure 8. Deviation from the 91st percentile weight for females.

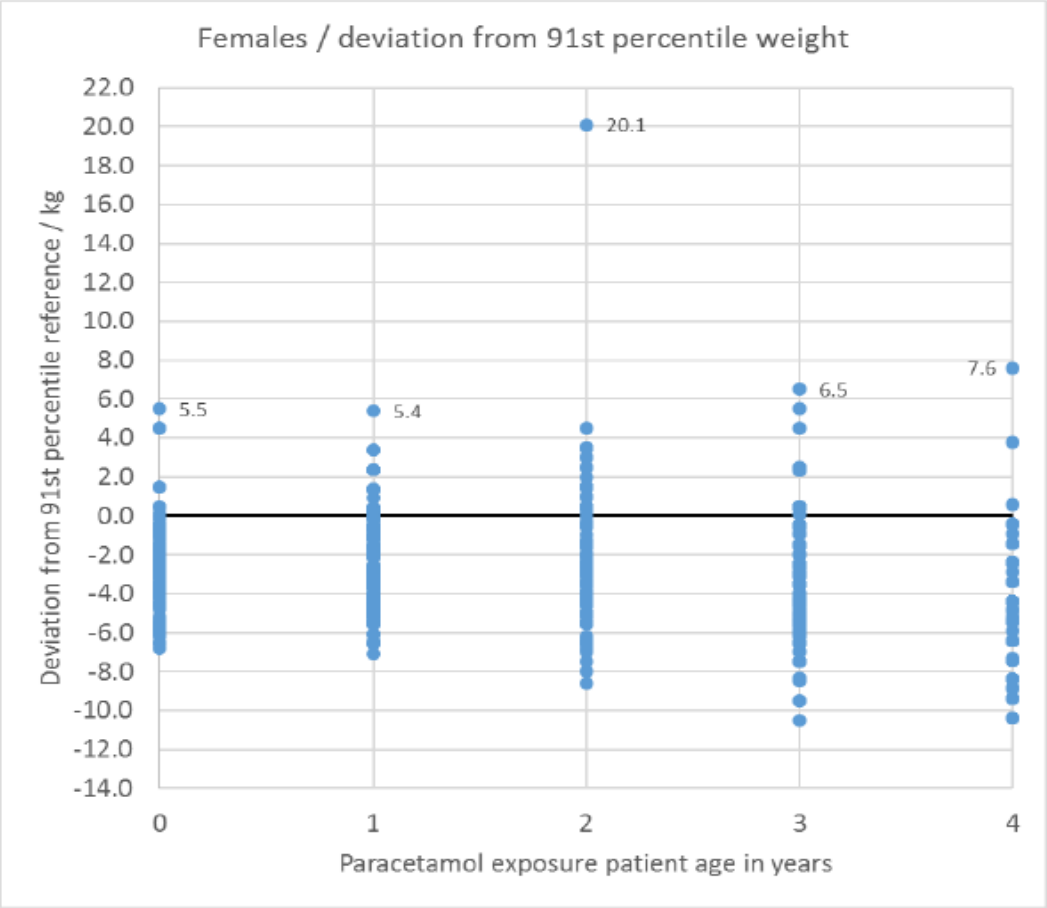


Table 13 shows how many males with paracetamol had a weight over reference value.

Table 13. Number of males with paracetamol exposure.

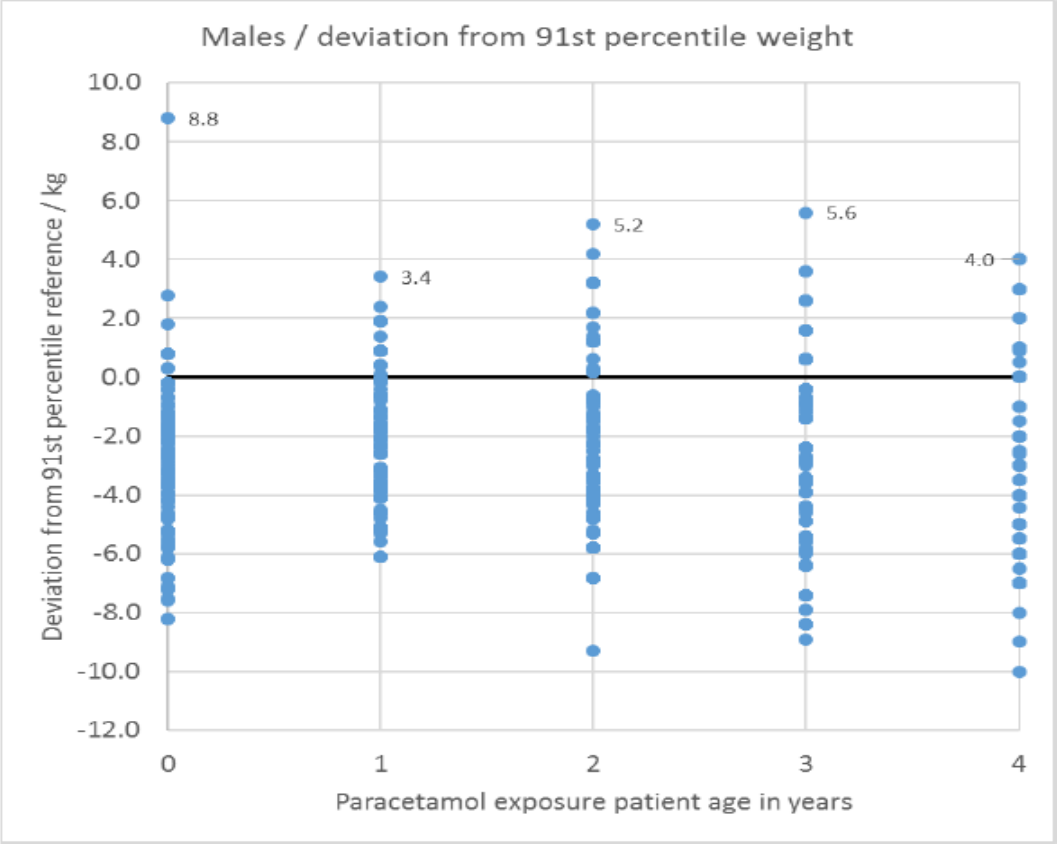
- Male patients:

MALES with paracetamol exposure

Age group	Reference weight used; MOH 91st percentile	Total number of patients	Number of patients able to compare*	Number of patients over reference	% of patients over reference	Highest weight recorded	Median kg over reference
Under 1	1-yo: 11.2 kg	271	231	12	5.2%	20 kg	0.8 kg
1	2-yo: 14.1 kg	445	396	39	9.8%	17.5 kg	0.9 kg
2	3-yo: 16.8 kg	454	419	53	12.6%	22 kg	1.2 kg
3	4-yo: 19.4 kg	344	316	40	12.7%	25 kg	0.6 kg
4	5-yo: 22.0 kg	133	124	13	10.5%	26 kg	2.0 kg
Unknown child	*N/A*	26	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
Total	*N/A*	1,673	1,486	157	10.6%		

*Age, weight, gender information available

Figure 9. Deviation from the 91st percentile weight for males.



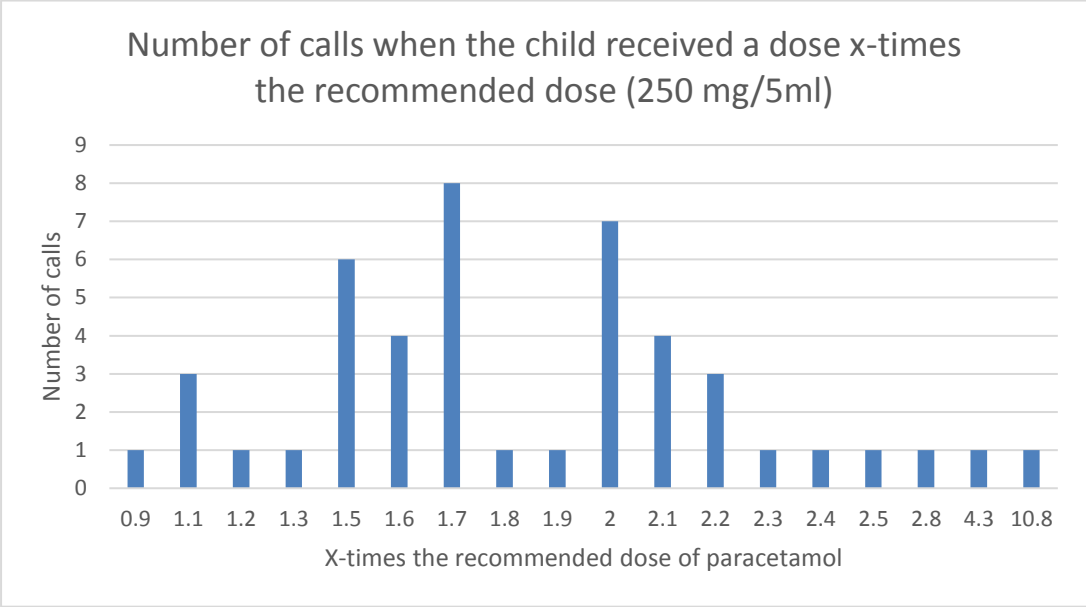
There was a total of 245 calls that that were above the weight threshold that was used in the analysis. For 65 of these the reason for exposure was therapeutic errors and the rest were recorded is child exploratory behaviour. The latter means a child above the weight threshold who was exposed to paracetamol in an unsupervised manner, e.g. found by caregivers with a bottle of paracetamol.

For most of the 65 cases the paracetamol amount is known. That amount of paracetamol was compared to the dose that would have been recommended for the child (10-15 mg/kg actual body weight).

In 51 cases the product used was paracetamol 250 mg/5ml. The children had been exposed to between 1.1 and 16 times the recommended dose (mostly between 2 and 4.5 times using the recommended dose of 10 mg/kg and between 1.5-2.5 times with the recommended dose of 15 mg/kg).

The figure below illustrates the number of calls that regarded a child who had received a dose of paracetamol 250 mg/ml that was x times the recommended 15 mg/kg dose. Note that the x-axis is not continuous.

Figure 9. Amount of calls regarding a dose of paracetamol 250 mg/5ml that was x times the recommended 15 mg/kg dose.



In 8 cases the product used was paracetamol 120 mg/5ml. The children had been exposed to between 0.5 and 4 times the recommended dose (mostly about 2 times with the recommended dose 10 mg/kg and about 1.5 times with the recommended dose 15 mg/kg). There was one case when a one-year old child had received a dose lower than recommended.

***Comment*:** Among all children ages 0-4 years with paracetamol exposures reported to NPC during the period, 7% of the girls and 10.6% of the boys exceeded the 91st percentile weight for age, based on stated weight during the call which is lower than the MOH published demographics.

In some of the cases when the reason was therapeutic error, the doses of paracetamol that the children had received were much higher than recommended doses, including one dose of 3000 mg. In other cases, the dose was not much over the 15 mg/kg recommended dose.

With very few exceptions however, the doses in these cases were higher than recommended doses even if TBW is used for calculation of the dose.

The outcome of the cases is not known.

See Attachment 2 for the full report.

4.0 INTERNATIONAL INFORMATION

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.0 DISCUSSION AND CONCLUSIONS

Paracetamol is an effective medicine for pain and fever and frequently used for children. The approved doses are calculated according to the patient's weight and/or age, with a maximal dose which can be given in 24 h.

Adverse effects are generally few. The risk of hepatotoxicity is the major problem in paracetamol treatment. The main reason for hepatotoxicity is overdose of paracetamol.

Concerns have been expressed regarding dosing in overweight and especially in obese children. Should the dose be calculated using the child's actual weight (TBW) or should the weight be adjusted in the calculation? Is there a safety risk to use TBW?

According to the authors of the letter and the submission to Medsafe, using actual body weight for calculating doses for obese children counters accepted practice in New Zealand and Australia which has been in place for many years. The basis is a first do no harm approach when there is a lack of data.

If the dose is calculated using TBW the concern is that the risk of hepatotoxicity may increase. On the other hand – if the dose is calculated using IBW there is a risk that the dose is too low to be effective.

How much of the paracetamol dose is metabolised to the toxic metabolite, and the fate of this metabolite, depends on the pharmacokinetics of paracetamol. The pharmacokinetics differs between adults/children/obese children.

There is a limited understanding of pharmacokinetics in obese children. Obese children are often excluded from clinical trials. V_d for paracetamol is likely higher for lipophilic drugs and lower for hydrophilic drugs in obese children.

The few publications found concerning paracetamol pharmacokinetics in obese children or adults showed and discussed:

- Same elimination rate of paracetamol for children with NAFLD compared to controls, but formation of the glutatione metabolite was increased. This may mean an increase in other

metabolites too, for example the toxic metabolite, or it may be a reflection of decreased activity in other metabolic pathways which were not measured.

- Maximum plasma concentrations were reached at a significantly later time and were significantly lower in obese adult patients as compared to a control group. The area under the plasma concentration-time curve for the obese patients was more consistent with that in the normal subjects when normalized to IBW compared to if TBW was used.
- In a simulation, a dose of 2 250 mg was required in an obese adolescent to achieve similar concentration as a non-obese adolescent given 1 000 mg paracetamol. Dose is better predicted using total body mass with allometric scaling.
- Lower paracetamol concentrations but increased CYP2E1-mediated clearance (cysteine and mercapturate metabolites) and accelerated formation of the cysteine and mecapturate metabolites were found in obese adults. Glucuronidation and sulfation clearance also increased with LBW. (The result has been debated).

There is no clear guidance from any of the studies on whether a different dose from the current recommendation of paracetamol would be safer and still efficacious for an obese or overweight child. Some studies include adult patients and not children. In most studies, only one or a few doses are given. There seems to be a clearer understanding of how obesity affects the plasma-concentration of paracetamol (although not necessarily the effect) than the influence of obesity, if any, on paracetamol toxicity.

Most paracetamol products used for children in NZ and the international products covered in this report, do not have data sheets or equivalent information. In the product information that has been found, the calculation of the dose is according to weight (or weight and age) with a maximum daily dose, and there is no specific information on dosing to obese children . This is the approved dosing in New Zealand.

In the New Zealand Formulary and other guidelines for use in primary care in NZ, the dose is calculated per kg actual weight, including for overweight and obese children, up to the maximum adult dose in a 24-hour period. According to recently changed guidelines from Starship Hospital however, using IBW should be considered for calculating dose to overweight or obese children. It was noted that there was no recommendation on how to calculate this.

Internationally, local guidelines have been found, mostly from Australia, where IBW (or other adjusted weight) is recommended for calculating dose to overweight or obese children. [redacted]

Product information and guidelines all emphasise to never give higher dose than the maximum recommended daily dose for the patient's weight (or weight and age) (first days in hospital may be an exception).

Among children ages 0-4 years with paracetamol exposures reported to the NZ National Poison Centre between August 2016 and December 2019, at least 7% of the girls and 10.6% of the boys exceeded the 91st percentile weight for age, based on stated weight during the call. With very few exceptions, the doses given to those children were higher than recommended doses even if TBW is used for calculation of the dose.

Since the BPAC article recommending use of TBW for paracetamol dosing CARM have not received any reports indicating that this recommendation has resulted in harm. Similarly, the NPC data appears to be mainly indicative of dose error and child exploratory use.

Hepatotoxicity from paracetamol is often caused by medication errors associated with prescribing, dispensing and communication to caregivers. Adjustments in dosing may increase the confusion, especially as adjusted doses can be calculated in different ways.

The approved dosing does not specify adjustments to overweight or obese children. The purpose of this paper is to consider if there is there enough evidence to support a change in data sheets and on label statements for dosing in obese children.

6.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The evidence supports the need to update paracetamol data sheets and/or label statements with dose adjustments for overweight and/or obese children.
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

7.0 ANNEXES

1. Submission from the Paediatric Society of New Zealand.
2. Report from the National Poisons Centre.

8.0 REFERENCES

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