Medicines Adverse Reactions Committee

Meeting date:	7 December 2017	Agenda item: 3.2.2
Title:	**Modified-release paracetamol: risk of overdose**	
Submitted by:	Medsafe Pharmacovigilance Team	Paper type: For advice

Active constituent	*Medicines*	*Sponsor*
Paracetamol 665 mg	**Panadol Osteo Modified-release tablet** *(TT50-7876)*	GlaxoSmithKline Consumer Healthcare New Zealand Ltd
	Paracetamol Osteo-Tab Modified-release tablet *(TT50-8774)*	AFT Pharmaceuticals Ltd
	Panadol Back + Neck Long Lasting Modified-release tablet *(TT50-7878; not available)*	GlaxoSmithKline Consumer Healthcare New Zealand Ltd
	APO-Osteo Paracetamol 665 mg modified-release tablet *(TT50-9328; not available)*	Apotex NZ Ltd
	APO-Paracetamol XR 665 mg modified-release tablet *(TT50-9329; not available)*	Apotex NZ Ltd
	Osteomol 665 Modified-release tablet *(TT50-9458; not available)*	Pharmbio Pty Ltd
	Paracetamol XR 665 mg Modified-release tablet *(TT50-9327; not available)*	Apotex NZ Ltd

Funding:	No funded products
Previous MARC meetings:	Modified-release paracetamol has not been discussed previously by the MARC. Related topics previously referred to the MARC include: – Use of N-acetylcysteine in the management of paracetamol overdose (155th Meeting, September 2013) – Dextropopoxyphene/paracetamol combination products and the risk of overdose (138th Meeting, June 2019 and 122nd Meeting, June 2005)
International action:	EMA (see Annex 1) On 1 September 2017, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recommended that modified-release paracetamol be removed from the market due to the complexity of managing overdose with these products.
Classification:	Pharmacy-only medicine
Usage data:	Not available
Advice sought:	**The Committee is asked to advise whether:** – Any updates to the data sheets for modified release paracetamol, in particular the overdose section, are required? – The current classification of 'pharmacy only' should be reviewed?

- Any additional communication to healthcare professionals other than MARC's remarks is required?

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1.0 PURPOSE

On 1 September 2017, the PRAC recommended that modified-release paracetamol be removed from the European market due to the complexity of managing overdose with these products.

The purpose of this paper is to:

- review the risks associated with overdose of modified-release paracetamol,
- examine the information currently available on the management of overdose with modified-release paracetamol formulations and consider whether the information currently provided in the data sheet is sufficient and consistent with current Australasian guidelines, and
- consider whether any further regulatory action is required in New Zealand, in light of the recent PRAC recommendation to withdraw modified-release paracetamol from the EU market.

2.0 BACKGROUND

2.1 Concerns raised by Swedish MPA about modified-release paracetamol

A modified-release paracetamol formulation received marketing authorisation in Sweden in 2003 under the brand name Alvedon 665 mg tablet (GSK), where it is available as a prescription-only medicine in pack sizes of up to 100 tablets. The product is fully funded in Sweden by the Dental and Pharmaceutical Benefits Agency. The popularity of the product in Sweden has increased over recent years (particularly since 2010) and it now constitutes nearly 40% of prescriptions of all paracetamol products. With increasing patient exposure, there has been a parallel rise in the number of consultations to the Swedish Poisons Information Centre (Swedish PC) about this product. In 2016, paracetamol accounted for 4391 consultations to the Swedish PC, of which 21% concerned Alvedon 665 mg. [1]

In 2016, the Swedish PC published a retrospective pharmacokinetic and clinical analysis of 53 cases of acute overdose with Alvedon 665 mg modified-release tablets, which had been reported to them between 2009 and 2015.[1] (See 3.1.1 for details of this study). The study concluded:

- In comparison with what would be expected with immediate-release formulations, the exposure profile following an overdose and the subsequent clinical course are unpredictable. Namely, absorption was prolonged and maximal plasma concentrations of paracetamol were observed later than would be expected from overdoses with immediate-release paracetamol formulations. The unpredictability was more apparent with increasing dose.
- The standard assessment and treatment protocol, based on overdose with immediate-release paracetamol formulations, was insufficient in the majority of cases (of overdose with modified-release paracetamol).
- Cases of overdose with Alvedon 665 mg modified-release tablets causing hepatic injuries, despite timely treatment, have been identified.

Based on the safety concerns raised in the Swedish PC study, the MPA took the issue to the European Medicines Agency's PRAC, asking the committee to:

- Assess how to minimise the harm in cases of overdose involving Alvedon 665 mg modified-release tablets, and whether recommendations to manage such cases can be further improved.
- Consider measures to minimise the risk of poisoning with Alvedon 665 mg modified-release tablets.

- Evaluate the benefit/risk balance for all indications pertaining to the Alvedon 665 mg modified-release tablets, where the benefit of prolonged exposure and pain relief is weighted against the increase risk of serious harm following overdose.

Further, the PRAC was asked to make a recommendation on whether the marketing authorisations for modified-release paracetamol products in the EU should be maintained, varied, suspended or revoked. The notification to the PRAC from the MPA is provided in Annex 1.

Comments:

In Sweden, modified-release paracetamol is available only as the prescription medicine Alvedon 665 mg tablet. The popularity of this product has increased significantly since 2010 and now constitutes 40% of paracetamol tablet prescriptions. Approximately 65% of total paracetamol usage is on prescription. The rise in population exposure to modified-release paracetamol has been reflected in an increase in the number of consultations with the Swedish Poisons Centre concerning this product, which in 2016 accounted for 21% of all paracetamol consultations.

In contrast with Sweden, modified-release 665 mg paracetamol tablets are not widely used in New Zealand. Two modified-release 665 mg tablet products are currently available in New Zealand: Panadol Osteo (GSK) and Paracetamol Osteo-Tab (AFT). Although sales information for these products is not available, their use is not expected to be great as neither product is funded by PHARMAC. Modified-release 665 mg paracetamol products are classified as pharmacy only medicines, making them less readily available than immediate-release 500 mg products, which are classified as general sales medicines. (See section 2.3 for more information on modified-release paracetamol products in New Zealand).

Also in contrast with Sweden, enquiries to the New Zealand Poisons Centre regarding modified-release paracetamol products constitute < 1 percent of all paracetamol-related enquiries. (See section 3.4 for more information on paracetamol poisoning in New Zealand).

2.2 PRAC safety review of modified-release paracetamol

On 1 September 2017, the PRAC recommended that modified-release paracetamol be removed from the market due to the complexity of managing overdose with these products. (See Annex 2)

The marketing authorisation holders (MAHs) concerned have the right to request the PRAC to re-examine its recommendations, and several have done so. This re-examination is expected to conclude by 30 November 2017, and the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) is expected to adopt a position by 8 December 2017.

Comments:

In light of the recent PRAC recommendation, Medsafe considers that a review of the safety of modified-release paracetamol products in New Zealand is both timely and prudent.

2.3 Modified-release paracetamol products in New Zealand

2.3.1 Approval status of modified-release paracetamol products in New Zealand

To date, seven modified-release paracetamol products have been granted consent for distribution in New Zealand. The first products to be approved, in 2008, were Panadol Osteo Modified-release 665

mg tablets and Panadol Back + Neck Long Lasting Modified-release 665 mg tablets (both sponsored by GSK Consumer Healthcare NZ). Paracetamol Osteo-Tab Modified-release tablet (AFT Pharmaceuticals Ltd) was subsequently approved in January 2012. Currently only two of the seven approved modified-release products are marketed in New Zealand: Panadol Osteo Modified-release 665 mg tablets and Paracetamol Osteo-Tab Modified-release tablet.

2.3.2 Classification of modified-release paracetamol products in New Zealand

Modified-release paracetamol 665 mg tablets were initially classified as prescription medicines in New Zealand. This classification was consistent with the guidelines for paracetamol-containing products, which at the time specified a 500 mg upper limit for the amount of paracetamol allowed in over-the-counter (OTC) tablets.

On 11 December 2001, the Medicines Classification Committee (MCC) considered a company submission to reclassify modified-release paracetamol 665mg tablets as a pharmacy-only medicine. The MCC recommended that these products remain prescription only due to the potential confusion between modified- and immediate-release products that could result in unintentional overdosing. The MCC considered that professional intervention was necessary to ensure that consumers were made aware of the specific dosing regimen for modified-release paracetamol products. The MCC was also concerned that, following overdose, modified-release paracetamol would continue to be absorbed for a longer period than immediate-release paracetamol. Further details of the MCC's recommendation can be found in the minutes of the 26th MCC Meeting (Section 6.3), available at: http://www.medsafe.govt.nz/profs/class/Minutes/2001-2005/mccMin11Dec01.htm.

In Australia, tablets containing 665 mg of paracetamol had been classified as pharmacy-only (S2) medicines and in 2006, with a view to harmonisation, the Australian National Drug and Poisons Schedule Committee (NDPSC) asked the MCC to review its earlier recommendation. At their meeting on 9 June 2006, the MCC acknowledged that 665 mg tablets had been available in Australia for four years without evidence of significant problems related to overuse or overdose. However, the MCC expressed ongoing concern that emergency rooms might not be aware of slow-release paracetamol products, and of the need to retest patients with equivocal blood paracetamol levels following overdose. The treatment protocol for paracetamol overdose at the time did not specify the management of overdose with slow-release forms.

The Committee agreed that there appeared to be no reason for New Zealand not to harmonise with the Australian classification for these products, but required an assurance from the company that the protocol for the treatment of paracetamol overdose would be revised to include management guidelines following overdose of 665 mg slow-release paracetamol. Further details of this recommendation can be found in the minutes of the 34th MCC Meeting (Section 8.1.4), available at: http://www.medsafe.govt.nz/profs/class/Minutes/2006-2010/mccMin9June06.htm.

The revised classification as 'pharmacy only' was gazetted on 14 September 2006.

Comments:

An application for consent to distribute modified-release paracetamol was not submitted to Medsafe until the classification as pharmacy only medicine had been approved. Consent to distribute Panadol Osteo modified-release tablets and Panadol Back + Neck Long Lasting Modified-release tablets was granted to GSK Healthcare New Zealand Ltd in 2008.

2.4 Difference between immediate- and modified-release paracetamol

2.4.1 Immediate-release paracetamol

Paracetamol is rapidly absorbed from the small intestine. In therapeutic doses, peak serum concentrations occur within 1–2 hours of ingestion for standard tablet or capsule formulations, and within 30 minutes for liquid preparations. Peak serum concentrations after therapeutic doses do not usually exceed 20 mg/L (132 µmol/L).

Distribution is usually within 4 hours of ingestion for standard tablet or capsule preparations, and 2 hours for liquid preparations. The volume of distribution is 0.9 to 1.0 L/kg. Paracetamol crosses the placenta and is excreted in breast milk [2].

Metabolism is predominantly (98%) by the liver. In adults, the major metabolic pathways involve conjugation to inactive glucuronide (42%) and sulphate (52%) metabolites, which are excreted in the urine. The remainder is oxidised in the liver via cytochrome P450 (chiefly 2E1, 1A2 and 3A4), which results in the highly reactive intermediary compound *N*-acetyl-*p*-benzoquinone imine (NAPQI). (Figure 1)

In normal conditions, NAPQI is immediately bound by intracellular glutathione and eliminated in the urine. With increased paracetamol doses, greater production of NAPQI may deplete glutathione stores. When glutathione depletion reaches a critical level (thought to be about 30% of normal stores), NAPQI binds to other proteins, causing damage to the hepatocyte.[3]

After therapeutic doses, the elimination half-life is 1.5–3 hours. Less than 5% is excreted unchanged in the urine.

In infants, sulphate conjugation predominates with a gradual shift towards glucuronide conjugation with increasing age until 12 years, after which glucuronide conjugation predominates.

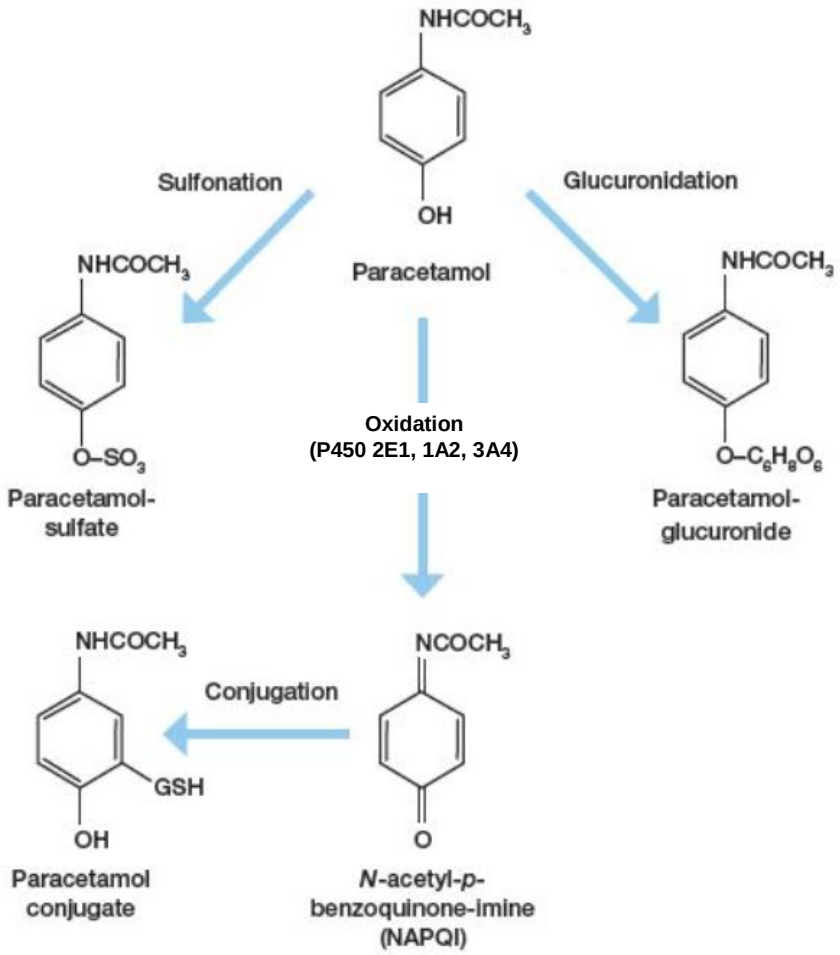


Figure 1. Important routes of paracetamol metabolism in humans to form the various metabolites. Under normal circumstances, 40 to 67 per cent of a given therapeutic dose is eliminated as paracetamol-glucuronide, 20 to 40 per cent as paracetamol-sulfate and up to 5 per cent as unchanged paracetamol. Five to 15 per cent is metabolised to NAPQI, which is conjugated with glutathione to form the paracetamol-glucuronide conjugate. (Modified from Schep *et al* [4])

2.4.2 Modified-release paracetamol

Modified-release paracetamol tablets are currently marketed in New Zealand in a formulation containing 665 mg of paracetamol, of which 69% is slow-release and 31% is immediate-release paracetamol. [3, 5, 6]

The tablets are constructed in two layers: an immediate-release layer and a sustained-release layer. The immediate-release layer of the tablet is absorbed rapidly, similar to standard paracetamol formulations. The sustained-release layer contains a hydroxypropyl methylcellulose (HPMC) polymer, which rapidly hydrates to form a gel layer at the matrix periphery. Paracetamol is then released from the matrix by a combination of diffusion and erosion of the gel layer. With therapeutic dosing, the sustained release formulation allows for the gradual release of paracetamol from the tablet over a period of 8 hours, reducing the frequency of paracetamol dosing to three times per day.[6]

To compare the pharmacokinetics of a modified-release and an immediate-release paracetamol formulation, Tan *et al* used a simulated overdose model in a cross-over study with seven healthy volunteers [5]. The mean paracetamol dose was 73 mg/kg actual body weight. The modified-release formulation produced a lower C_{max} (0.208 mmol/L ± 0.02 *vs* 0.48 mmol/L ± 0.02, $P = 0.0001$) and $AUC_{0-12\,h}$ when compared with the immediate-release formulation, but the T_{max} was significantly

delayed with the modified-release formulation (2.83 h ± 0.26 *vs.* 0.94 h ± 0.17, *P* = 0.0001). Absorption was complete in all subjects by 4 h post ingestion in both study arms. There was no significant difference in the elimination $t_{1/2}$ between the two formulations.

Comments:

The lower C_{max} observed with the modified-release paracetamol formulation was thought to be due to elimination occurring during the absorption phase. Although the maximum concentration may be lower with modified-release formulation, the time to maximum concentration (T_{max}) is delayed due to the ongoing absorption of the medicine.

2.5 Management of paracetamol overdose:

2.5.1 Australasian Guidelines

Paracetamol is a widely-used non-narcotic analgesic and antipyretic medicine. When taken at therapeutic doses, paracetamol is considered the safest of all available analgesic agents, but in overdose it is potentially lethal. [4, 7]

Paracetamol is involved in a large proportion of accidental paediatric exposures and deliberate self-poisoning cases [7, 8]. It is the leading pharmaceutical agent responsible for calls to the Poisons Information Centres in Australia and New Zealand. Paracetamol is the single most common drug taken in overdose leading to hospital presentation and admission, accounting for 22.4% of poisonings presenting to New Zealand public hospitals [8]. Paracetamol poisoning is the most common cause of acute liver failure in the developed world. [3]

The quantity of paracetamol that may be associated with liver injury is shown in Table 1.

Table 1. Paracetamol dosing that may be associated with hepatic injury [3]

	Adults and children over 6 years of age	Children (aged 0–6 years)*
Acute single ingestion	> 200 mg/kg or 10 g (whichever is lower) over a period of less than 8 hours	> 200 mg/kg or more over a period of less than 8 hours
Repeated Supra-therapeutic Ingestion (RSI)	> 200 mg/kg or 10 g (whichever is lower) over a single 24-hour period	> 200 mg/kg over a single 24-hour period
	> 150 mg/kg or 6 g (whichever is lower) per 24-hour period for the preceding 48 hours	> 150 mg/kg per 24-hour period for the preceding 48 hours
	> 100 mg/kg or 4 g (whichever is lower) per 24-hour period, for more than 48 hours in those who also have symptoms indicating possible liver injury e.g. abdominal pain, nausea or vomiting	> 100 mg/kg per 24-hour period for more than 48 hours

* **NOTE:** For obese children the weight used, should be based on an ideal body weight.

2.5.1.1 Acute immediate-release paracetamol overdose with known time of ingestion

The approach to treatment of acute paracetamol poisoning in New Zealand is well described [3]. The sequence and timing of each intervention depends on the time of presentation following paracetamol ingestion (Figure 2) and the results of laboratory investigations to assess the risk of hepatotoxicity [2] (Table 2).

Activated charcoal may limit the absorption of paracetamol in co-operative adults if administered within 2 hours (or 4 hours for larger overdoses).

The serum paracetamol concentration is used to determine the need for treatment with the paracetamol antidote N-acetylcysteine (NAC). A single serum paracetamol level measured within 8 hours of ingestion is sufficient to determine the need for NAC administration. The timed serum paracetamol concentration is plotted on the paracetamol treatment nomogram (Figure 3). If the level sits above the line, treatment with NAC should be started.

For patients who present beyond 8 hours, NAC should be initiated immediately, while awaiting the paracetamol concentration. A serum alanine aminotransferase (ALT) should also be measured to guide the duration of NAC treatment.

Treatment with NAC is administered as a three-stage infusion, as shown in Table 3.

Treatment of acute paracetamol overdose with NAC within 8 hours will prevent serious hepatic injury in almost all patients. Beyond 8-10 hours after ingestion, efficacy decreases with increasing delay to treatment.

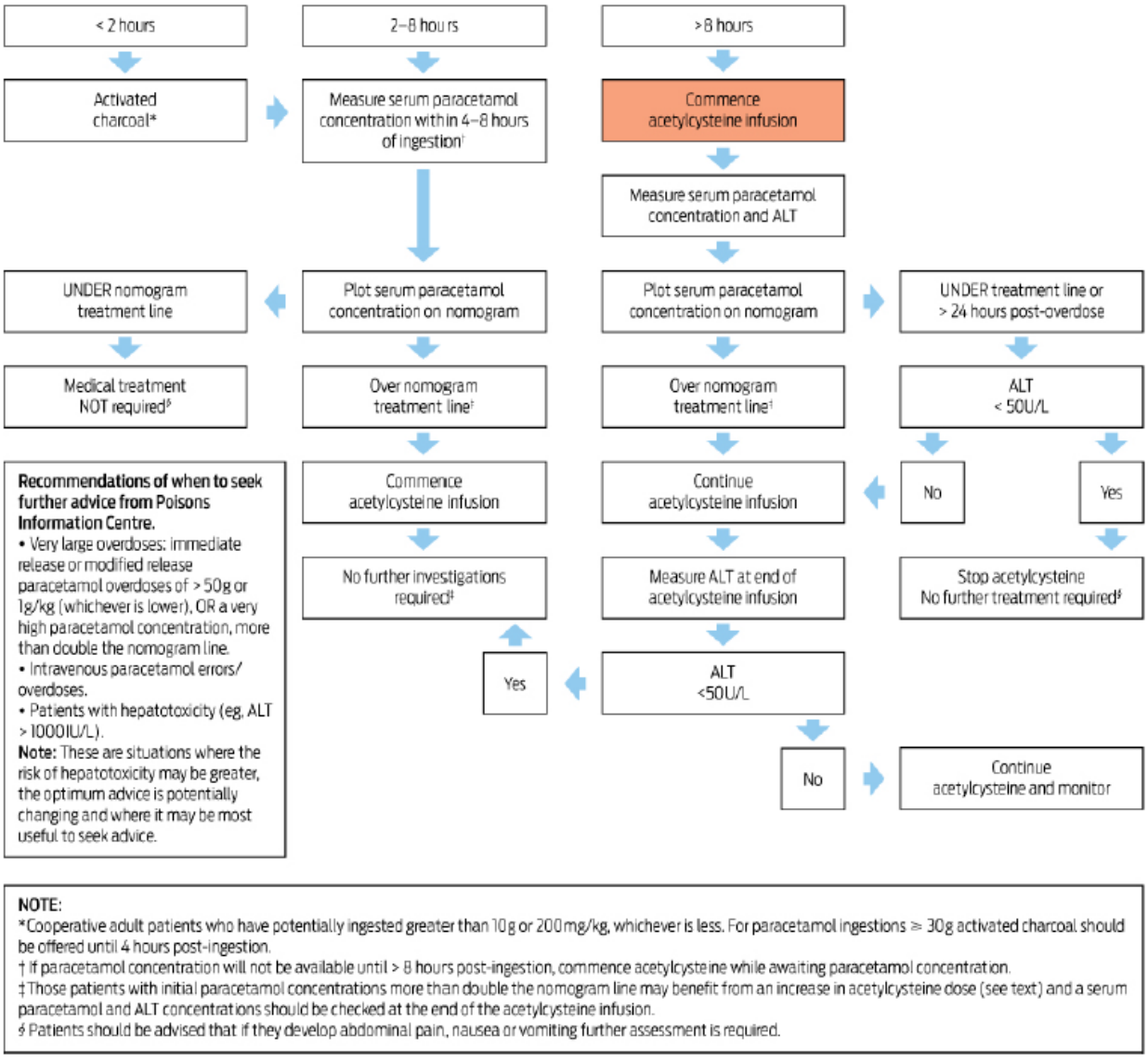


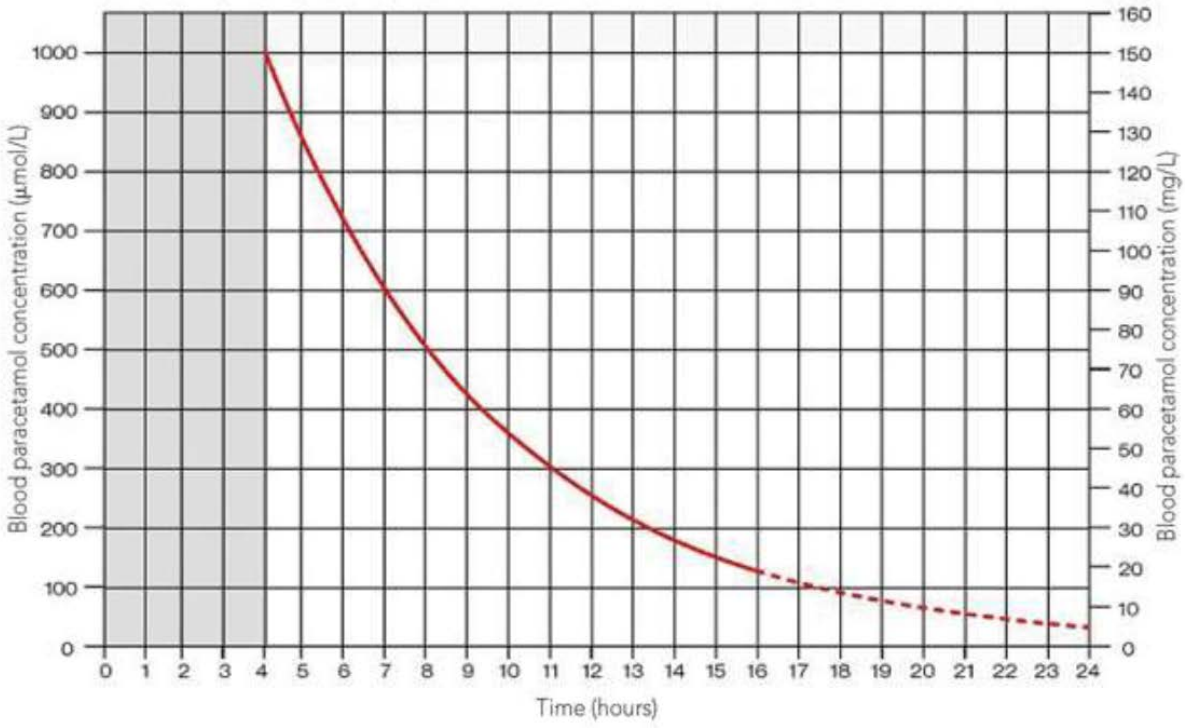
Figure 2. Management flow chart for acute paracetamol exposure with known time of ingestion [3]

Table 2. Recommended investigations according to time from paracetamol ingestion to acetylcysteine treatment [3]

Time (hours) from paracetamol ingestion to acetylcysteine	Investigations on admission	Investigations at the completion of acetylcysteine
Less than 8 hours	Serum paracetamol concentration	Nil*
8–24 hours	Serum paracetamol concentration and ALT	ALT and UEC*
Greater than 24 hours	Serum paracetamol concentration, ALT and INR	ALT, INR and UEC
Patients who have an abnormal ALT	UEC, LFTs, INR, BSL, phosphate and VBG (looking at the pH and lactate).	**Repeat investigations every 12 hours, including:** UEC, LFTs, INR, BSL, phosphate and VBG (looking at the pH and lactate).

ALT = alanine aminotransferase, BSL = blood sugar level, INR = international normalised ratio, UEC = urea, electrolytes, creatinine, VBG = venous blood gas.

* **NOTE:** If symptoms of hepatotoxicity (i.e. nausea, vomiting, abdominal pain or tenderness) then **repeat** ALT. Or if initial concentration more than double the nomogram line, then **repeat** ALT and paracetamol concentration at the completion of acetylcysteine.



Note: Ensure correct units are used when utilising the paracetamol treatment nomogram.

Figure 3. Paracetamol treatment nomogram [3]

Table 3. Three-stage acetylcysteine infusion [3]

Initial Infusion	An initial dose of 150 mg/kg of acetylcysteine diluted in 200 mL of 5% glucose and infused over 60 minutes
Second Infusion	The initial infusion is followed by a continuous infusion of 50 mg/kg of acetylcysteine in 500 mL of 5% glucose over the next 4 hours
Third Infusion	The second infusion is followed by a continuous infusion of 100 mg/kg of acetylcysteine in 1000 mL of 5% glucose over the next 16 hours.*

* **Note**: Patients who have a paracetamol concentration more than double the nomogram line, may benefit from an increase in the dose of acetylcysteine in the 100 mg/kg over 16 hours infusion (third infusion) to 200 mg/kg IV acetylcysteine in 1000 mL of 5% glucose over 16 hours. (see text)

2.5.1.2 Acute modified-release paracetamol overdose with known time of ingestion

Activated charcoal is recommended for use up to 4 hours post-ingestion of modified-release paracetamol. In massive overdoses, absorption may continue for up to 24 hours, so patients may benefit from activated charcoal even beyond 4 hours.

If a toxic dose of more than 200 mg/kg or 10 g (whichever is lower) has been ingested, NAC treatment should be started immediately. Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later. If either concentration is above the nomogram line, the full 21 hour course of NAC should be continued to completion. NAC may be discontinued if serial concentrations, taken 4 hours apart are below the nomogram line and are decreasing.

Serum paracetamol concentrations may also be used to determine the need for NAC when a less than toxic dose of modified-release paracetamol has been ingested. As for the toxic dose, serum concentrations should be taken at 4-8 hours post ingestion and repeated 4 hours later, with NAC infusion initiated accordingly.

The ALT and paracetamol concentration should be repeated near the completion of the NAC infusion: if ALT is increasing (> 50 U/L) or paracetamol concentration is greater than 10 mg/L (66 µmol/L), then NAC should be continued over a further 16 hours (100 mg/kg in 1000ml of 5% dextrose over 16 hours). [3]

Comments:

For patients who present within 8 hours of overdose with a modified-release paracetamol formulation, the guidelines recommend measurement of two paracetamol concentrations: the first should be taken 4-8 hours following ingestion and the second taken 4 hours later. If either concentration is above the treatment line when plotted on the nomogram, treatment with NAC should be commenced. For patients presenting 8-24 hours after ingestion, a paracetamol concentration should be measured immediately and repeated 4 hours later, but NAC treatment should begin immediately, without waiting for the test results.

A biphasic and prolonged pattern of paracetamol absorption is known to occur following overdose with modified-release paracetamol. Such cases emerged in the literature as early as 1996 [9-11], and highlighted that the standard treatment protocol for paracetamol overdose based on the Rumack-Matthew nomogram may not be adequate to prevent liver toxicity following overdose with modified-release paracetamol. This observation lead to the recommendation to repeat the serum paracetamol concentration 4 hours after the initial measurement and to consider an extended administration of NAC. [12]

With very large overdoses of modified-release paracetamol, formation of a pharmacobezoar (clump of tablets) in the gut can further delay the absorption beyond 24 hours due to altered disintegration and dissolution properties of the clumped tablets[1].

The Swedish Poisons Information Centre has recently revised its national guidelines for the management of paracetamol overdose, and now includes specific guidance on overdose with modified-release products. Differences between the Swedish and Australasian Guidelines for the treatment of modified-release paracetamol overdose are discussed below (section 2.5.2).

2.5.1.3 Other paracetamol overdose scenarios

Paracetamol overdose is more difficult to manage when the timing of the ingestion is unknown, the amount of paracetamol ingested is very large (paracetamol concentration at double the nomogram line), or the ingestion has occurred over a prolonged period (as with repeated supratherapeutic ingestion).

Acute paracetamol overdose with unknown time of ingestion

If the time of ingestion is unknown, it is safest to treat the patient as a delayed presentation. The recommendation in this situation is to follow the > 8 hours scenario in Figure 2, i.e. to start NAC.

Large/massive paracetamol ingestion

For large/massive paracetamol ingestions, the optimal treatment is uncertain. One approach proposed for patients with a paracetamol concentration more than double the nomogram line is to double the concentration of the 16 hour infusion (3rd bag) of NAC. Such patients may also benefit from prolonged NAC infusion. The ALT and paracetamol concentration should be measured 2 hours prior to completion of the third infusion. If the ALT is increasing (> 50 U/L) or the paracetamol concentration is > 10mg/L (66 µmol/L), NAC infusion can be continued over a further 16 hours. [3]

Multiple or staggered paracetamol overdose

If the time since the first dose is less than 8 hours, and a paracetamol concentration can be obtained within 8 hours of ingestion, the patient can safety be treated as per the 1-8 hour scenario in Figure 2.

If the time elapsed since the first ingestion is more than 8 hours, the patient should be treated as per the > 8 hours scenario in Figure 2.

The paracetamol concentration should be plotted on the paracetamol treatment nomogram at the earliest time of ingestion.

Repeated supratherapeutic paracetamol ingestion

Hepatotoxicity associated with repeated supratherapeutic doses is considered to be uncommon. Patients should have a paracetamol concentration and ALT measured if they meet the following criteria for supratherapeutic ingestion:

- More than 10 g or 200 mg/kg (whichever is lower) in a single 24 hour period
- More than 6g or 150 mg/kg (whichever is lower) per 24 hours for the preceding 48 hours
- More than 4 g/day or 100 mg/kg (whichever is lower) for more than 48 hours, in those who also have symptoms indicating possible liver injury (e.g. abdominal pain, nausea or vomiting)

The Guidelines indicate that treatment with NAC is not required if the ALT is < 50 U/L and the serum paracetamol concentration is < 20 mg/L (132 µmol/L). (Figure 4)

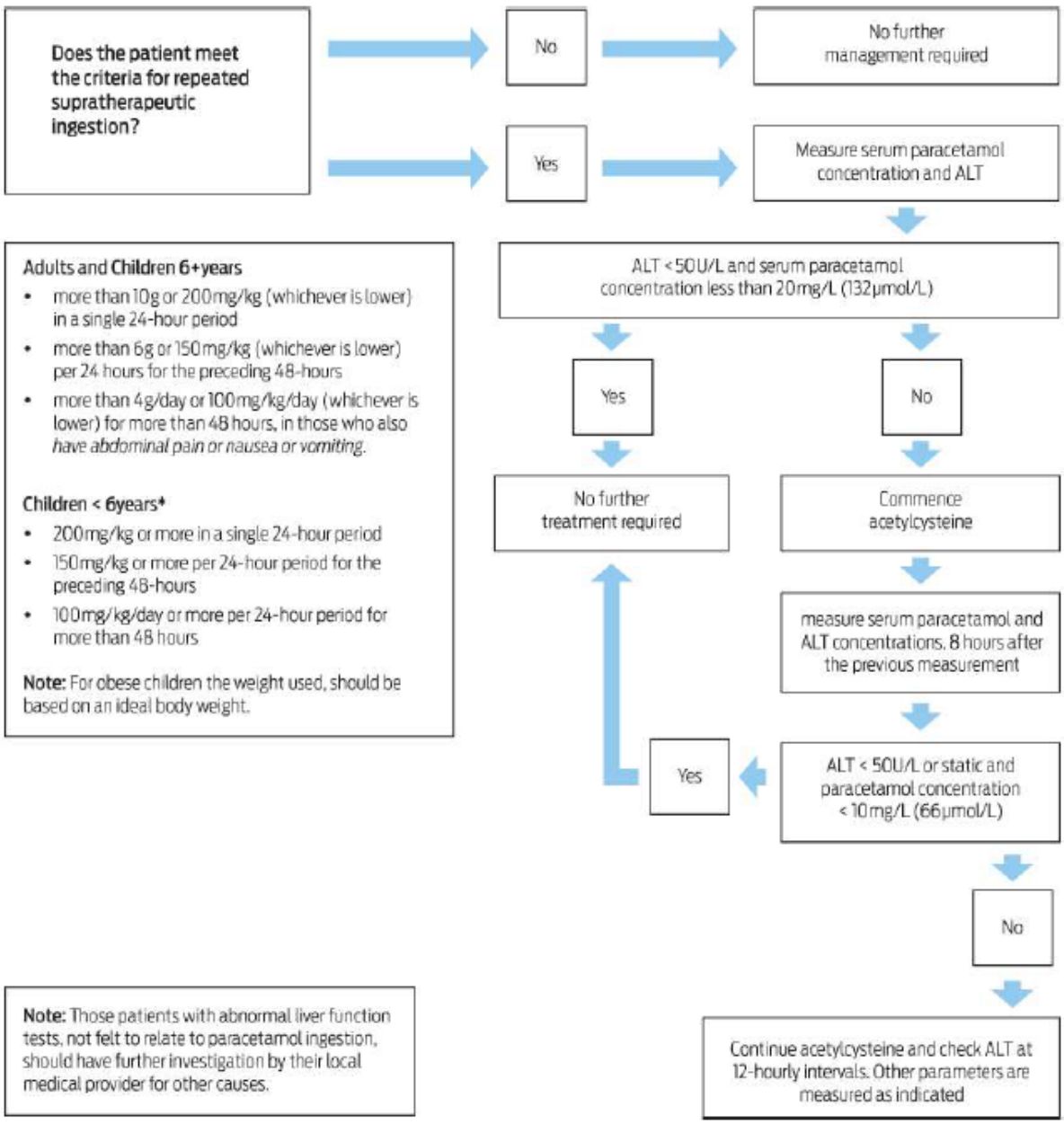


Figure 4. Management flow chart for repeated supratherapeutic paracetamol ingestion [3]

Comments:

The use of N-acetylcysteine (NAC) in paracetamol overdose was discussed at the 155th MARC Meeting, in September 2013. The MARC paper is included as Annex 3 for ease of reference. In September 2012 the MHRA had announced new guidance on the use of intravenous NAC. The purpose of the 2013 Medsafe paper was to review the MHRA guidance, current Australasian poisons centres' advice and compare this advice with the information provided in the data sheets, to determine whether any changes to the data sheets were required.

The Committee recommended that the data sheets for NAC containing medicines should be updated to:

- Include more information on when it is appropriate to use NAC
- Remove the contraindication

- Include weight based dosing tables
- Update the nomogram in line with that recommended by the Australasian guideline
- Change the timing of the first NAC infusion to 60 minutes (1 hour)
- Add additional information on anaphylactoid reactions
- Add additional information on NAC effect on prothrombin time

The current NAC data sheet is include as Annex 4.

2.5.2 Swedish Guidelines

The guidelines for managing paracetamol overdose in Sweden were revised in January 2017 as a result of the study (referred to in sections 2.1 and 3.1.1) undertaken by the Swedish PC. The Swedish guidelines, which are available at www.giftinfo.se and translated below, provide separate advice for overdose with immediate- and modified-release paracetamol tablets.

Investigations:

- **Immediate-release paracetamol:** A serum paracetamol concentration taken at 4 hours after ingestion or, if presenting later, as soon as possible. Repeated sampling is only required when drugs that inhibit gastrointestinal motility (primarily opiates) have been taken concurrently. The repeat sample should be taken 2 hours after the first, and if the serum concentration is increasing then further samples should be taken at 2-hour intervals, as the maximum serum concentration may be delayed for many hours. NAC should be started if the serum paracetamol concentration is at a toxic level (defined below in section 2.4.4.2). No further sampling for serum paracetamol concentration is needed, unless the serum concentration is very high (approximately 3000 µmol/L). In these cases, a serum paracetamol concentration should be measured before the NAC infusion is due to complete; if it remains elevated, the NAC treatment should be prolonged.
- **Modified-release paracetamol:** Serum paracetamol concentrations should be taken at 4, 6, 12 and 18 hours following ingestion, including during NAC treatment. If the patient presents later than 4 hours following ingestion, a sample should be taken immediately and then according to the above schedule. If the serum concentration rises but remains below the toxic concentration, serum paracetamol concentrations should be measured at 2 hour intervals instead. In these cases, the maximum serum concentration can be delayed for many hours. Treatment with NAC should be initiated if any of the samples exceed the threshold for treatment relative to the time of sampling.

In all cases of paracetamol overdose (immediate- or modified-release formulation), the following blood tests should be taken on initial presentation: aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time (PT), full blood count (FBC), serum creatinine and electrolyte status (UEC) and blood sugar level (BSL). For patients who require NAC treatment, the AST, ALT and PT are then measured daily. If liver toxicity is detected, AST, ALT and PT should be measured 2-(3) times per day. If these tests remain normal after 36 hours, no further tests are required.

Treatment:

Gastric lavage is rarely indicated. Activated charcoal can be administered if the patient presents < 2 hours since ingestion and the amount ingested was > 140 mg/kg.

In the case of overdose with modified-release paracetamol, a further dose of activated charcoal may be given after 2-4 hours

If the overdose is suspected to be toxic (adults > 140 mg/kg, children > 175 mg/kg) and serum paracetamol concentration cannot be obtained within 8 hours of ingestion, NAC should be started without waiting for test results.

- **Immediate-release paracetamol:** NAC should be started if the serum paracetamol concentration is > 1000 µmol/L at 4 hours, > 700 µmol/L at 6 hours, 500 µmol/L at 8 hours and 350 µmol/L at 10 hours after overdose. In case of starvation, dehydration, hepatic impairment or treatment with the enzyme-inducing drugs phenobarbital or isoniazid, lower limits apply: 650, 450, 325 and 230 µmol/L, respectively.
- **Modified-release paracetamol:** NAC should be started if serum paracetamol concentration is > 650 µmol/L at 4 hours, > 450 µmol/L at 6 hours, 325 µmol/L at 8 hours or 160 µmol/L at 12 or 18 hours after overdose.

In all cases of suspected toxic overdose, if the patient arrives 24-36 hours after ingestion and has symptoms or if paracetamol is detectable in serum, NAC should be started. If the patient arrives > 36 hours after overdose and has normal liver tests, treatment with NAC is not required.

Comments:

The treatment thresholds specified in the Swedish guidelines for modified-release paracetamol overdose are plotted below against the standard treatment line for immediate-release paracetamol (Figure 5). As can be seen in the figure, the recommended threshold for starting NAC is considerably lower for modified release paracetamol compared to immediate release paracetamol, according to the Swedish guidelines.

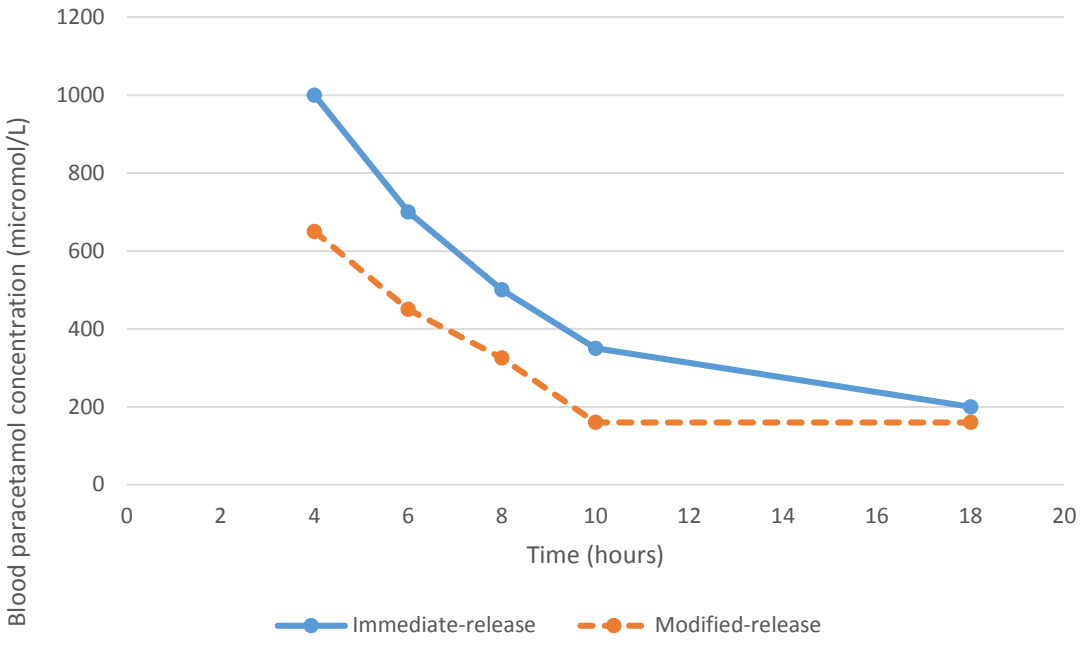


Figure 5. Comparison of NAC treatment thresholds for modified-release (dashed line) and immediate-release (solid line) overdose based on the Swedish guidelines described in section 2.5.2.

NAC dosing:

- **Immediate-release paracetamol:**

- Initially 150 mg/kg in 200-300ml glucose 50 mg/ml or isotonic saline over 15 minutes.
- Then 50 mg/kg in 500 ml glucose 50 mg/ml over 4 hours (12.5 mg/kg/hour)
- Then 6.25 mg/kg/hour over 16 hours or longer (see below) – practically, 75 mg/kg dissolved in 500 ml over 12 hours per bag).

- **Modified-release paracetamol:**
  - Initially 150 mg/kg in 200-300ml glucose 50 mg/ml or isotonic saline over 15 minutes
  - Maintenance treatment with 12.5 mg/kg/h for at least 20 hours (practically, 150 mg/kg dissolved in 500ml over 12 hours per bag)

  Before discontinuing NAC treatment, check that serum paracetamol is not detectable.

Comments:

The 2017 Swedish Guidelines for treatment of modified-release paracetamol overdose are more cautious than the current Australasian Guidelines.

The key differences are:

- More frequent monitoring of the paracetamol concentration over a longer period (measured at 4, 6, 12 and 18 hours after ingestion).
- Lower threshold for initiation of NAC treatment: the nomogram treatment line for modified-release paracetamol starts at 650 µmol/L (100 mg/L) at 4 hours in the Swedish guidelines *c.f.* 1000 µmol/L (150 mg/L) at 4 hours in the standard Rumack-Matthew nomogram. (Figure 5).
- More aggressive treatment with NAC:
  - First bag given over 15 minutes instead of 60 minutes (also applies to overdose with immediate-release formulations)
  - Concentration of third bag doubled to 12.5 mg/kg/h (instead of 6.25 mg/kg/h). Effectively, there are just two phases to the NAC treatment specified in the Swedish guidelines:
    - Initiation: 150 mg/kg over 15 minutes
    - Maintenance: 12.5 mg/kg/h for at least 20 hours.

2.6 Data sheets

2.6.1 New Zealand

Data sheets are available on the Medsafe website for the modified-release paracetamol products Panadol Osteo Modified-release tablet and Panadol Back + Neck Long Lasting Modified-release tablet (both GSK products), although only the former is currently marketed. A data sheet has not been provided by the sponsor Paracetamol Osteo-Tab Modified-release tablet (AFT product). Table 4 shows the overdose information in the New Zealand data sheet for modified-release paracetamol products. The data sheet for Panadol Osteo, which has identical wording to the data sheet for Panadol Back & Neck, is provided in Annex 4.

Table 4. Overdose information in New Zealand data sheet for modified-release paracetamol products.

Product	Overdose information
Panadol Osteo Modified-release tablet (GlaxoSmithKline Consumer Healthcare New Zealand Ltd)	Paracetamol overdose may cause liver failure which can lead to liver transplant or death. Because PANADOL OSTEO is a sustained-release formulation of paracetamol, absorption will be prolonged in overdose. It is recommended that for the management of overdose, where PANADOL OSTEO is suspected, that an additional plasma paracetamol level be obtained 4-6 hours after the initial measurement. If either level is above or close to the treatment line on the paracetamol overdose nomogram, administration of antidote would be indicated. <u>Treatment</u> Immediate medical management is required in the event of an overdose, even if the symptoms of overdose are not present. If an overdose is taken or suspected, contact the Poisons Information Centre immediately for advice (0800 764 766), or the patient should go to the nearest hospital straight away. This should be done even if they feel well because of the risk of delayed, serious liver damage. (See ADVERSE EFFECTS.) Administration of N-acetylcysteine may be required. In cases of overdosage, methods of reducing absorption of ingested drug are important. Activated charcoal may reduce absorption of the medicine if given within one hour after ingestion.
Panadol Back + Neck Long Lasting Modified-release tablet (GlaxoSmithKline Consumer Healthcare New Zealand Ltd)	Paracetamol overdose may cause liver failure. Because PANADOL BACK & NECK LONG LASTING is a sustained-release formulation of paracetamol, absorption will be prolonged in overdose. It is recommended that for the management of overdose, where PANADOL BACK & NECK LONG LASTING is suspected, that an additional plasma paracetamol level be obtained 4-6 hours after the initial measurement. If either level is above or close to the treatment line on the paracetamol overdose nomogram, administration of antidote would be indicated. <u>Treatment</u> Immediate medical management is required in the event of an overdose, even if the symptoms of overdose are not present. If an overdose is taken or suspected, contact the Poisons Information Centre immediately for advice (0800 764 766), or the patient should go to the nearest hospital straight away. This should be done even if they feel well because of the risk of delayed, serious liver damage. (See ADVERSE EFFECTS.) Administration of N-acetylcysteine or methionine may be required.

	In cases of overdosage, methods of reducing absorption of ingested drug are important. Activated charcoal may reduce absorption of the medicine if given within one hour after ingestion.
Paracetamol Osteo-Tab Modified-release tablet (AFT Pharmaceuticals Ltd)	No data sheet available

Comments:

The data sheets for the two GSK modified-release paracetamol products recommend contacting the Poisons Information Centre immediately for advice if an overdose is suspected, or the patient should go to the nearest hospital straight away. The data sheets note that NAC treatment may be required, but the details about when to initiate NAC are not provided (this information is provided in the NAC data sheet, see Annex 5). The use of activated charcoal is also recommended within one hour of ingestion.

The overdose information provided in the data sheets for modified-release paracetamol is limited. More information on when to test paracetamol levels would be useful. The information on when to give activated charcoal is not consistent with the Australasian Guidelines for treatment of paracetamol overdose, and should be revised. The Australasian Guidelines recommend the use of activated charcoal up to two hours post-ingestion, while the datasheet recommends use up to 1 hour post-ingestion. (The Swedish Guidelines state that activated charcoal can be administered if the patient presents < 2 hours since ingestion and the amount ingested was > 140 mg/kg. and in the case of overdose with modified-release paracetamol, a further dose of activated charcoal may be give after 2-4 hours).

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Salmonson *et al*, Clinical Toxicology, 2017 [1]

The standard treatment protocol for paracetamol poisoning may be inadequate following overdose with modified-release formulation: a pharmacokinetic and clinical analysis of 53 cases

The authors performed a retrospective study using data from the Swedish Poisons Information Centre (Swedish PC) and hospital records concerning overdoses of Alvedon 665.

Method

Overdose cases were identified from the Swedish PC database; clinical information was retrieved from hospital medical records, including laboratory data, for the period 2009 to 2015.

Inclusion criteria were: acute ingestion of a reported toxic dose (≥ 10 g or ≥ 140 mg/kg), documented serum paracetamol and standard liver tests in medical records, and a reported time interval between ingestion and the measured laboratory analyses.

Patients with a mixed intake of immediate-release and modified-release paracetamol were excluded, as were patients with evidence of hepatic injury on initial biochemistry.

Relevant demographic and clinical data were recorded and the clinical course of all included patients was followed.

Population PK modelling using MONOLIX was performed to analyse the clinical data. An additional 20 cases with self-poisoning using the IR formulation were included in the modelling in order to provide support for estimating the absorption parameters. A one compartment model with linear elimination was assumed for the disposition of paracetamol. The absorption was modelled as parallel first-order and transit compartment processes, respectively, to reflect the drug release properties of the specific MR formulation. The proportion of the total dose subject to the transit compartment absorption process was estimated for the modified-release formulation. The influence of dose on the mean transit time parameter (Mtt) for this process was also estimated. For the immediate-release cases, absorption was assumed to occur only through the first-order process.

Results

During the study period, there were 1348 consultations concerning the modified-release formulation registered at the Swedish PC, 652 (48%) of which originated from hospitals. Medical records were received for 145 cases, of which 53 met the inclusion criteria.

Median age of the 53 patients meeting the inclusion criteria was 26 years (range 13-68); 74% were female. Median reported dose was 20 g (range 10-166 g). The number of serum paracetamol levels per individual ranged from 1 to 10 (median 3); in total, there were 185 paracetamol levels available for analysis, of which 24 were below the lower limit of quantification (LLOQ). The LLOQ differed between hospitals and was in the range of 1.2-15 mcg/mL (8-100 µmol/L). In 25 cases, coingestion with other drugs was reported, mostly benzodiazepines.

Median age of the cases of OD with immediate-release paracetamol that were included in the PK modelling was 23 years (range 12-67 years); the median reported dose was 10 g (range 5-45 g).

The observed paracetamol concentrations in all 53 cases with modified-release overdoses versus time after the reported ingestion are shown in Figure 6.

Seventeen cases had ingested a dose over 50 grams and are depicted in red in the figure. As can be seen in Figure 6, the exposure profiles become more unpredictable with higher doses in terms of delayed serum peaks and persistently high serum levels.

The population PK-modelling revealed that the absorption was increasingly delayed with increasing doses of modified-release paracetamol. As a result of this delay, double peaks became more evident with increasing doses as seen in Figure 7.

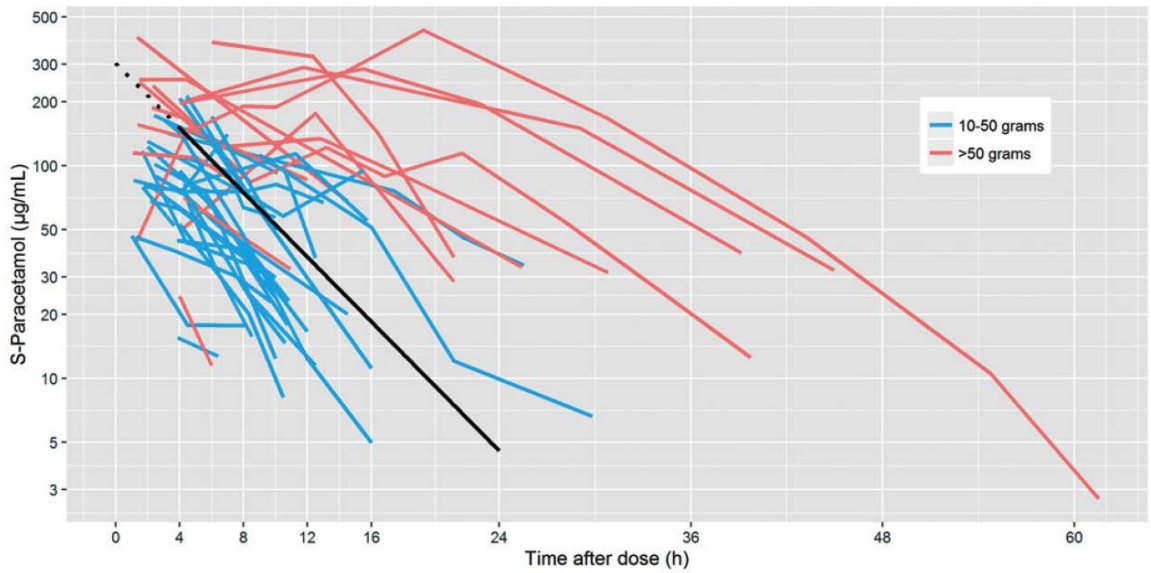


Figure 6. The figure displays the observed serum paracetamol concentration versus time after ingestion in 53 cases with MR overdose in a log-linear scale. Cases with dose range 10–50 g in blue, cases with dose over 50 g in red. The paracetamol treatment nomogram line (150 lg/ml at 4 h) in black as a comparison.

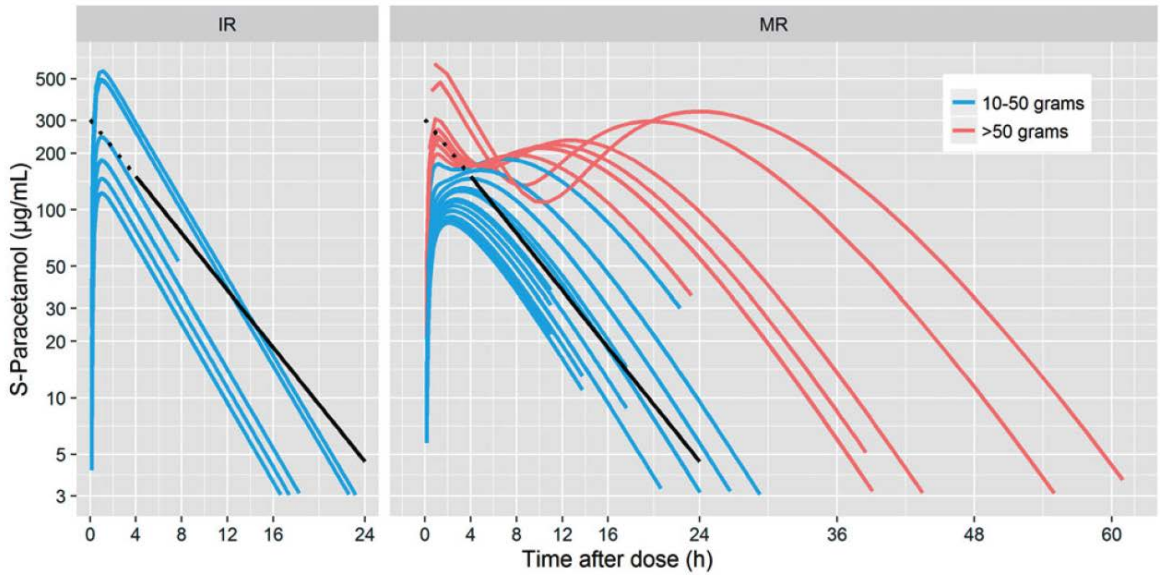


Figure 7. The figure shows the predicted serum paracetamol concentration versus time profile at each reported dose in a log-linear scale. The right panel ("MR") shows the PK profiles following ingestion of paracetamol MR. The left panel ("IR") shows the profiles following ingestion of paracetamol IR. The dose level is colour coded in the same way for MR and IR for purpose of comparison. Blue colour represents low overdose (10–50 g) while red represents high overdose (>50 g). The range of MR doses goes from 10 to 166.25 g. The top IR profile corresponds to a dose of 45 g. The black solid curve represents the paracetamol treatment nomogram (150 lg/mL at 4 h). Back extrapolation of the nomogram line to zero hours is represented with a dotted black curve. The MR PK profile displays a clearly visible biphasic shape at high overdoses and the second peak is shifted to the right with increasing dose**.**

Persistent high serum levels for 24 h or more were observed in 10 patients, the majority (9/10) had a reported dose of 50 g or more. In six of these 10 patients a second peak in the serum concentration was observed 8–19 h after intake, four of them had a reported dose of 50 gram or more.

The phenomenon of 'late nomogram line crossers' was observed in 10 patients, where the initial serum concentration, 4–8 h after reported intake, were below the nomogram but subsequently crossed the line.

In total 81% (43/53) of the patients were treated with NAC, the majority (n=34) within 8 h. Of these 34 patients, 14 received extended duration of infusion (36–144 h), in six cases due to persistently high paracetamol concentration at 21 h (> 45 mcg/ml or 300 micromol/L). Eleven patients had a serum alanine aminotransferase (ALT), above the reference range (ALT >50 IU/L) at 24 h or later. Two of these patients had non-toxic paracetamol concentrations at 4–12 h after intake. Six out of eleven patients developed hepatotoxicity (ALT >1000 IU/L). No signs of mitochondrial paralysis (coma, hypothermia, hyperglycemia) were reported, and no transplantations or fatalities. Seven of the eleven patients with an ALT above the reference range were treated with NAC within 8 h of ingestion, of which three developed hepatotoxicity. A summary of the seven cases are shown in Table 5.

Table 5. Summary of patients treated with N-acetylcysteine (NAC) within 8 h post-ingestion, developing elevated alanine aminotransferase (ALT)

Patient-id age/gender	Parcetamol dose (g)	Initial s-paracetamol (μg/ml)	Second peak s-paracetamol (μg/ml)	NAC[a] start (h) duration (h)	ALT[b] peak (h)	INR[c] peak (h)
A	33.25	117 (1.5 h)	—	2 h	137 (24 h)	1.1 (24 h)
28/F				21 h		
B	66.5	382 (6 h)	321 (12 h)	8 h	62 (24 h)	1.4 (24 h)
37/F				21 h		
C	66.5	246 (2 h)	122 (13 h)	3 h	468 (72 h)	2.2 (48 h)
48/F				72 h		
D[d]	66.5	156 (1 h)	434 (19 h)	1 h	6720 (79 h)	2.0 (79 h)
47/M				144 h		
E	83	237 (2 h)	134 (13 h)	2 h	108 (30 h)	1.2 (30 h)
26/F				21 h		
F[d]	166	201 (4 h)	290 (12 h)	6 h	10980 (74 h)	2.7 (74 h)
68/F				30 h		
G[d]	166	196 (4 h)	285 (10 h)	4 h	4740 (75 h)	3.0 (75 h)
55/M				84 h		

[a]N-Acetylcysteine, NAC, standard treatment protocol: Bolus 150 mg/kg for 15 minutes followed by 50 mg/kg for 4 h and 6.25 mg/kg/h for 16 h or continued.
[b]ALT, alanine aminotransferase (IU/L), reference range <50 IU/L.
[c]INR, international normalized ration, reference range <1.2.
[d]Patients (D,F,G) reaching the definition of paracetamol-induced hepatotoxicity (ALT >1000 IU/L), also shown in Figure 4.

The time course of paracetamol levels and ALT levels versus time after intake in the three cases with ALT >1000 IU/L are shown in Figure 8.

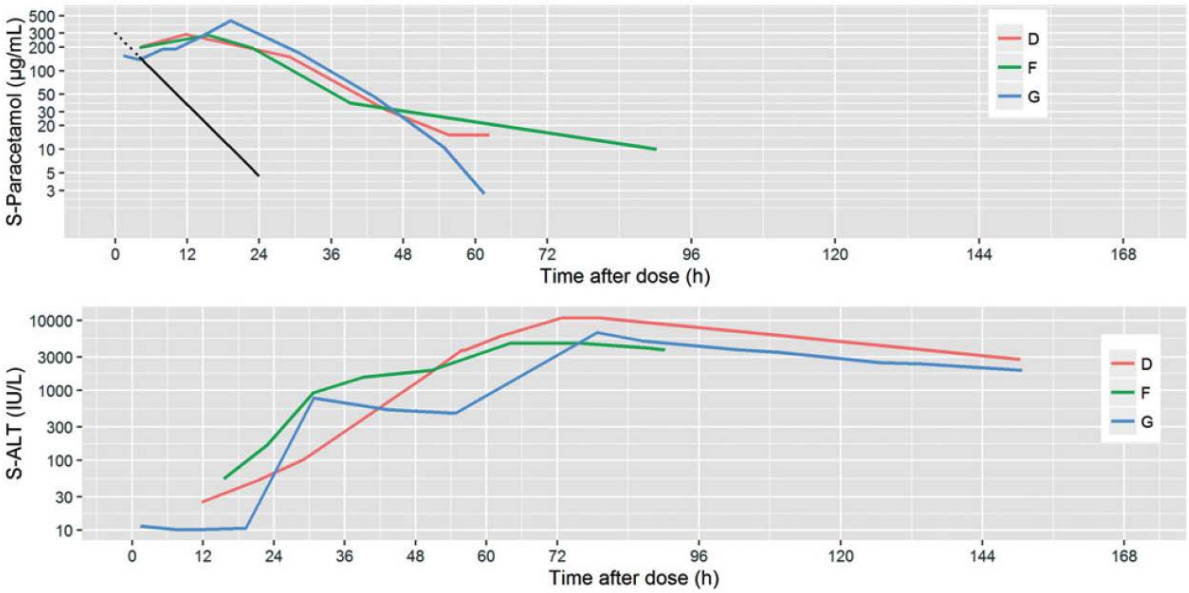


Figure 8. The figure shows the time course of serum paracetamol and alanine aminotransferase (ALT) levels versus time in a log-linear scale, after ingestion of MR overdose in three patients (D, F and G). The paracetamol treatment line (150 mcg/ml at 4 h) is included in the upper panel for comparison. Information about ingested dose, serum peak level and peak ALT for each patient is found in Table 5.

Discussion

The authors state that in this study descriptive and PK analysis along with population PK-modelling revealed a complex, dose-dependent serum paracetamol versus time profile with prolonged absorption exhibiting double peaks. Although the non-linear PK profile also could reflect saturable elimination, this was not supported by modelling.

As a consequence of the prolonged, dose-dependent absorption, some subjects displayed “flip-flop” kinetics during late parts of the concentration-time curve. Hence, the decline did not consistently follow a proportional decline and the estimated half-life was longer than the expected elimination half-life of paracetamol. At high overdoses, a first serum peak of paracetamol corresponding to the IR part was seen within 4 h after ingestion, and thereafter a second delayed peak was noticed due to absorption of the MR part. The delay and magnitude of this second peak correlated to increasing dose.

The PK analysis and PK modelling clearly demonstrates that risk assessment using only one or two serum samples 4–8 h after ingestion can be misleading and may result in inadequate treatment and risk of hepatotoxicity. Repeated measurements of serum paracetamol are warranted even if treatment with NAC is ongoing, as persistently high serum concentrations for more than 24 h and double peaks can develop, especially after ingestion of high doses.

Elevated ALT above the reference range was seen in seven cases, of which three developed hepatotoxicity (ALT >1000 IU/l) despite early (within 8 h post-ingestion) and extended treatment with NAC. This indicates that the standard maintenance dose of NAC (6.25 mg/kg/h) is not enough to prevent development of liver damage in cases with persistently high serum levels.

Repeated and tailored measurements for determination of paracetamol levels and liver enzymes together with tailored administration of NAC will probably be sufficient to avoid serious hepatic damage, if the patient comes to the emergency unit in time. Although, it is currently not possible to recommend a predefined dose of NAC or concentration threshold for paracetamol above which NAC treatment should be systematically initiated.

Limitations

The data was collected retrospectively. Reported ingested dose and time of ingestion may not be accurate. Reporting to the Swedish PC is voluntary, so reporting or selection bias is possible. Extrapolation of results for overdose with Alvedon 665 from this study to other MR formulations should be done with caution as differences in the pharmaceutical formulation may affect the dissolution and PK behaviour of the drug.

Conclusions

The study shows that the serum paracetamol-time profile following overdose with modified-release paracetamol is characterised by prolonged absorption with delayed maximum serum concentrations. Persistent high levels of paracetamol were observed, clearly correlated to increasing doses. The standard treatment protocol, based on experiences with immediate-release paracetamol, was insufficient to prevent development of liver damage especially in the cases with persistent high serum levels.

Comments:

The data published in this paper formed the basis of the referral by the Swedish MPA to the PRAC in June 2016 regarding the benefit-risk profile of Alvedon 665 mg tablets.

The Swedish PC undertook their retrospective study of the pharmacokinetics and clinical outcome of acute overdose of the modified-release formulation after recognising an increasing number of such cases with prolonged, persistently high and unpredictable paracetamol levels. The study aimed to determine whether the recommended assessment and treatment protocol at the time was sufficient to manage overdoses with this formulation.

Following this study, the Swedish PC modified their guidelines for managing paracetamol overdose. The current Swedish guidelines for the treatment of paracetamol overdose, described above in section 2.5.2, came into effect in January 2017.

During the period when the 53 patients were treated, the Swedish guidelines for managing overdose with modified-release paracetamol were similar to the current Australasian guidelines. It should be noted that of the 53 patients included in the study, 6 developed hepatotoxicity (ALT > 1000 IU/L); however, no patients developed signs of mitochondrial paralysis (coma, hypothermia, hyperglycaemia), no patients required liver transplant, and there were no fatalities.

The revised (2017) Swedish PC Guidelines for managing acute overdose with modified-release paracetamol are more cautious than the current Australasian Guidelines.

3.1.2 Fountain *et al*, NZMJ, 2014 [7]

Awareness, acceptability and application of paracetamol overdose management guidelines in a New Zealand emergency department

The aim of this study was to measure emergency physicians' awareness, acceptance, access to and application of the Australasian Paracetamol Overdose Guidelines.

Method

The authors undertook a retrospective record review of 100 consecutive presentations of paracetamol overdose to the Dunedin Hospital Emergency Department from 1 Dec 2011 to 31 Dec 2012 (13 months). Key analyses were: comparison of the management of each case to that

recommended by the Australasian Guidelines, analysis of access to both an online poisons information resource and the New Zealand National Poisons Centre, survey of clinical staff opinion of the Guidelines, and comparison of actual and recommended management costs for laboratory tests and service delivery.

Data collected included: patient demographics; paracetamol dose and timing; co-ingested substances; investigations undertaken, their timing and results; antidote administration, dose and timing; periods and location of management; and disposition.

To assess cost of care, commercial charges for biochemical investigations were obtained from the hospital laboratory services provider – Southern Community Laboratories; and pharmaceutical prices were obtained from the Pharmaceutical Management Agency (PHARMAC) Section H Schedule for hospital pharmaceuticals.

Daily bed cost was identified using the WHO-CHOICE unit cost estimates for service delivery – a WHO estimate of the 'hotel' component of a hospital bed-day (i.e. the cost of personnel, capital and food but excluding drugs and investigations).

To gauge clinician's self-assessed awareness, opinion and use of the Guidelines, a survey tool was developed, and conducted within the Dunedin ED during the period 24 May 2013 to 16 July 2013.

When assessing investigations, it was recognised that further tests were reasonable beyond those indicated in the Guidelines due to coingestants and/or comorbidities. A medical toxicologist reviewed all cases and identified investigations that were indicated for the compound(s) involved.

Records of logins and poisons information monographs accessed on the TOXINZ database were analysed, and National Poisons Centre telephone records reviewed, to identify Dunedin Hospital utilisation of these resources.

Results

During the study period, 36229 patient encounters were recorded, of which 555 (1.53%) were entered into the Emergency Department Information System as 'poisoned' or 'suffering overdose'. The 100 paracetamol encounters studied represented 18% of overdose presentations and 0.28% of all ED presentations. Of the study patients, 82% patients intended self-harm/suicide, 15% were unintentional overdoses (i.e. therapeutic misadventure or paediatric exploratory ingestion), and intent was unknown in 3%. Age ranged from 11 months to 72 years, with a median age of 19 years.

All ingestions involved standard immediate-release formulations, including 5 patients (aged 11 months to 3 years) who ingested liquid formulations.

Twenty-seven percent of patients were managed by consultants, 58% by registrars; house officers accounted for the remaining 15%. There was no statistically significant difference in the characteristics of the patients seen by these doctor groups.

Thirty-nine (39%) of these 100 paracetamol encounters had co-ingested a median of 1.77 compounds (range 1 to 5); 38 (97.4%) of whom intended self-harm. Of the 69 co-ingested substances, the most common classes were: NSAIDs, 23 (33.33%); opioids, 10 (14.49%); and, ethanol, 8 (11.59%).

The response rate to the clinicians' survey was 92.9% (26 of 28), comprising: eight (30.8%) consultants, 11 (42.3%) registrars, and seven (26.9%) house officers. Seventeen (65%) responders were aware of the Guidelines, 16 (94%) of whom viewed them as best practice (one individual was unsure).

While not all responders were aware of the Guidelines *per se*, 96.2% considered they either directly applied the Guidelines in 90% or more of patients seen, or referred to sources based on the Guidelines "often" or "always" when treating patients.

Sources utilised were reported as: Poisons Information Centre 3.8%, text book 3.8%, original journal article 3.8%, poster 23.0%, ED protocol 23.0%, internet poisons information database 77.0% (more than one source allowed in the response).

Review of National Poisons Centre records for the study period identified that Dunedin Hospital staff viewed 2,903 poisons information monographs, 363 (17.3%) relating to paracetamol; and rang the National Poisons Centre on three occasions regarding paracetamol overdose.

Two patients had no biochemical investigation, and in one otherwise investigated case no paracetamol level was assessed. A total of 1,085 blood analyses were undertaken: 829 (75.85%) in the ED and 256 (24.15%) on the ward. The mean number of investigations of untreated patients was 7.33, while a mean 16.83 investigations were conducted in those receiving the antidote NAC.

Total cost of investigations was $10,153; a median cost per patient of $95 (range $0 to $270), and a mean cost $59.32 per patient greater than recommended. Registrars and house officers spent twice the cost of investigations compared to their consultants.

The mean cost of care was calculated at $686.89 per case.

Discussion

Despite wide dissemination by a variety of media, a high level of awareness, and a high level of self-reported access to the Australasian Paracetamol Overdose Guidelines, the group of physicians studied did not manage the majority of their patients strictly according to the Guidelines.

The major source of variation from the Guidelines was the ordering of biochemical analyses beyond those recommended, with an associated increased cost of care.

Conclusions

Despite accessibility via multiple media forms and a high level of self-assessed use and regard for the Australasian Paracetamol Overdose Guidelines, clinicians routinely deviated from these recommendations when treating patients.

Biochemical analyses in excess of those advised comprised the most notable variance, and carried a significant opportunity cost. Novel approaches to improve adherence to clinical practice guidelines need to be considered to better support front-line clinical staff.

Comments:

This study was performed prior to the 2015 update of the Australasian Guidelines.

Although none of the cases concerned modified-release paracetamol, this study provides valuable information on 'real-life' application of clinical guidelines for the management of paracetamol overdose in New Zealand.

The study indicates that even with well-known and well-regarded guidelines, clinicians (particularly junior clinicians) prefer to rely on the certainty of laboratory tests to assure them that their particular patient is responding to treatment as anticipated.

This study cannot be extrapolated to the management of modified-release paracetamol as overdose with this type of product is relatively rare, the guidelines are new, and the management is inherently more complex than for immediate-release formulations. However, based on these results, it could be expected that clinicians may be even more inclined to perform additional tests given the uncertainty of the paracetamol absorption pattern associated with modified-release products, and the lack of consistency with treatment guidelines for these products. The current guidelines recommend just two paracetamol levels 4 hour apart; it is likely that clinicians may wish to follow these levels more closely, if for no other reason than 'peace of mind'.

3.1.3 Freeman *et al*, NZMJ, 2015 [8]

Care versus convenience: Examining paracetamol overdose in New Zealand and harm reduction strategies through sale and supply

In this paper, the authors reviewed the literature on effective strategies to reduce paracetamol overdose rates through supply reduction strategies.

Methods

Literature on effective strategies to reduce overdose rates was found through article databases Google Scholar, Scopus and general searches of a wide range of databases using the University of Otago library aggregator. Key word combinations of 'paracetamol', 'overdose', 'self harm', 'suicide', 'acetaminophen', 'quantity', 'restriction' and 'supply reduction' were used for these searches. Articles were selected if they described supply reduction strategies with the aim of reducing paracetamol overdose rates.

Results

There is a large body of evidence that both supports and questions the use of strategies that reduce access to large quantities of paracetamol. Many of these studies concern the effect of the legislative changes introduced to the UK in 1998. This legislation limited the maximum quantity of paracetamol available for purchase in pharmacies to 32 tablets of 500 mg strength (16 g in total), and in all other outlets to 16 tablets of 500 mg strength (8 g in total).

Although several studies have found there were no changes to paracetamol-related suicides or referrals to transplant units in Scotland, some studies found strong indications of the legislation's effectiveness across the UK, with evaluations reporting a 20% reduction in paracetamol-related overdoses, a 22% reduction in deaths and a 30% reduction in liver unit admissions.

These findings have been challenged. A 2007 study by Morgan *et al* observed similar trends for deaths relating to anti-depressants, paracetamol compounds and aspirin. A weakness of this study is that aspirin was not a suitable control comparison, as it was subject to similar restrictions to paracetamol under the UK legislation. However, Morgan's findings raise doubt as to whether reductions in paracetamol-related deaths can be attributed to the UK's legislation change, or may be related to an overall trend in all poisoning-related deaths.

To further investigate the effectiveness of the UK legislation, Hawton *et al* (2013), conducted an analysis of paracetamol-related deaths and liver transplant registrations, adjusting for potentially confounding trends in all drug poisoning and suicide-related deaths. The analysis observed a 43% reduction in paracetamol-related death and a 61% reduction in paracetamol-related registrations for liver transplants, after adjusting for non-paracetamol poisonings. In addition, both Morgan and Hawton found a significant downward step-change for paracetamol-related deaths immediately after the legislations commencement in 1998, which was not observed by other forms of poisoning.

The variation in results may be best explained by a wide variation in legislative compliance amongst retailers, with many individuals who overdosed on paracetamol after 1998, reporting to have purchased quantities in excess of the legislative restrictions.

Discussion

New Zealand does not restrict the amount of paracetamol that can be purchased in pharmacies, and has a set limit of 10 g per packet for all other outlet types, with no limit on the number of packets that may be purchased. This is comparably less secure than the United Kingdom, where steps have been taken to restrict paracetamol sales to a maximum of 16 g per transaction in pharmacies, and 8 g per transaction for all other outlets.

Comments:

There is some evidence from the UK that tighter restrictions on paracetamol availability can have a positive effect in reducing the rates of suicide. Although the UK data concerns immediate-release paracetamol, it does suggest that making the paracetamol more difficult to obtain has a beneficial effect in terms of harm reduction.

If the Committee considers that there is an increased risk of harm with modified release paracetamol, consideration should be given to the classification of these products. Reclassification of modified-release paracetamol to a Pharmacist Only (Restricted) medicine would mean that consumers would be able to benefit from the advice of a pharmacist before use.

3.2 Company reports

3.2.1 GSK Healthcare New Zealand Ltd

3.2.2 AFT

[redacted]

3.3 CARM data

The New Zealand Pharmacovigilance Centre has identified one case of overdose in which modified-release paracetamol is possibly implicated.

- **08286**: 74 y F reported to have hepatic enzymes increased [redacted] after starting *Panadol Osteo* (a modified-release 665 mg tablet). The daily dose was reported to be [redacted]

Comments:

The daily dose reported in this case [redacted]

3.4 Poisons Centre data

For the period 1 January 2008 to 8 October 2017, the National Poisons Information Centre received 13594 calls concerning paracetamol-containing products, of which 31 (0.22 %) concerned modified-release paracetamol products. Table 6 shows the categories of calls to the Poisons Centre for all paracetamol-containing products and for modified-release paracetamol products. Of note, the most common reason for calls concerning modified-release paracetamol was 'therapeutic error', which comprised 77.4% of calls for these products, compared to only 22.2% for paracetamol-containing products overall.

Table 6. National Poisons Information Centre: reason for call

Reason	All paracetamol		Modified-release paracetamol	
	n	%	n	%
Child Exploratory	5492	40.4	3	9.7
Therapeutic Error	3014	22.2	24	77.4
Intentional	2458	18.1	2	6.5
Unintentional	2394	17.6	2	6.5
Unknown	189	1.4		
Abuse	47	0.3		
Total	**13594**	100	**31**	100

Comments:

Although the number of calls to the National Poisons Information Centre concerning modified-release paracetamol is low compared to the overall number of calls for paracetamol, it is interesting that over three-quarters of these calls were for 'therapeutic error' (i.e. incorrect dosage), compared to just over one-fifth of the calls for paracetamol overall.

This data indicates that patients may benefit from intervention by a pharmacist in the sales of these medicines. This benefit would be achieved by reclassification to restricted medicines.

4.0 DISCUSSION AND CONCLUSIONS

International regulatory action

The EMA's PRAC recently recommended that modified-release paracetamol products be removed from the European market. This recommendation is currently being re-reviewed at the request of the MAHs .

The PRAC review was instigated by a referral from the Swedish MPA in June 2016 after concerns were raised in a study published by the Swedish Poisons Information Centre. The study reported on 53 cases of acute overdose with Alvedon 665 mg modified-release tablets during the period 2009 to 2015. The study noted that the exposure profile and subsequent clinical course following overdose with this product was unpredictable, the standard assessment and treatment protocol based on immediate-release paracetamol formulations was insufficient in the majority of these cases, and hepatic injury occurred in some cases despite timely treatment. However, no liver transplants or deaths were noted as outcomes.

It should be noted that Medsafe is looking into this issue as a result of overseas regulatory action; there has been no suggestion of a clinical concern regarding modified-release paracetamol products in New Zealand.

Situation in Sweden different to New Zealand

Sweden has experienced an upsurge in the use of modified-release paracetamol over recent years. Alvedon 665 mg is a prescription-only medicine in Sweden. Following intensive product promotion, it now accounts for 40 percent of all paracetamol prescriptions in Sweden. Furthermore, under the Swedish pharmaceutical funding model, funded prescription medicines are free of charge to the consumer once they have met the annual threshold for out-of-pocket expenditure on prescription items.

Two brands of modified-release paracetamol are currently available on the shelves in New Zealand pharmacies, although neither product is actively being promoted here by the product sponsors. Neither product is funded by PHARMAC.

These differences in the classification, marketing and funding of modified-release paracetamol in Sweden, compared to New Zealand, mean that the availability of these products as an agent for overdose (intentional or inadvertent) is considerably higher in Sweden than is currently the case in New Zealand.

NZ Poisons Centre data indicates that the number of cases of overdose with modified-release paracetamol in New Zealand is low compared to immediate-release paracetamol.

Medicine Classification

The current classification as a Pharmacy Only medicine means that any pharmacy salesperson may conduct the sale; consultation with a pharmacist, including advice on appropriate dosing, is not required at the time of sale.

Given that modified-release paracetamol is not widely used in New Zealand, consumers may not yet be aware of the difference in dosing recommendations between modified-release and immediate-release paracetamol products. Evidence that a lack of awareness may lead to inadvertent overdose comes from the New Zealand Poisons Information Centre. Although the number of calls to the Poisons Centre concerning modified-release paracetamol products is just a fraction of all calls concerning paracetamol (31/13594, 0.22%), the majority (24/31, 77.4%) were for therapeutic error. By comparison, less than a quarter (3014/13594, 22.2%) of the calls regarding immediate-release paracetamol preparations were for therapeutic error.

Advice on the correct dosing by a pharmacist at the point-of-sale may help to reduce inadvertent supratherapeutic doses with modified-release paracetamol 665 mg tablets. Furthermore, introducing a healthcare provider step in the process of obtaining modified-release paracetamol may help to reduce the likelihood that this product is purchased with the intention to overdose (less chance of an impulse purchase, and increased differential in the relative availability of immediate-release products).

Management of overdose with modified-release paracetamol

Sweden has developed a more conservative protocol for management of paracetamol overdose, including modified-release products, which involves more frequent testing and a lower threshold for treatment with NAC following overdose with modified-release paracetamol. Review of the clinical guidelines for management of paracetamol overdose in New Zealand is outside the scope of this paper.

Given the relatively low number of cases of overdose with modified-release paracetamol in New Zealand (as per the NZ Poisons Centre data) compared to immediate-release paracetamol, data on the effectiveness of the current Australasian guidelines is also likely to be limited.

The study by Fountain *et al* indicated that the treatment guidelines for paracetamol overdose are not always strictly adhered to, with a tendency for doctors to request additional serum paracetamol and liver function tests even in the more 'routine' cases of immediate-release paracetamol overdose. Nevertheless, in light of the unpredictable pattern of absorption of modified-release paracetamol when taken in overdose, consideration should be given to incorporating advice to monitor paracetamol levels more frequently and for a longer period than is currently recommend in these cases, in line with the Swedish 2017 guidelines for paracetamol overdose.

Data sheet

The information provided in the New Zealand data sheet for modified-release paracetamol concerning the use of activated charcoal should be revised. The Australasian Guidelines recommend the use of activated charcoal up to two hours post-ingestion, while the datasheet recommends use up to 1 hour post-ingestion. (The Swedish Guidelines state that activated charcoal can be administered if the patient presents < 2 hours since ingestion and the amount ingested was > 140 mg/kg. and in the case of overdose with modified-release paracetamol, a further dose of activated charcoal may be give after 2-4 hours).

Consideration should be given as to whether the New Zealand data sheet for modified release paracetamol products should also include information on when to test paracetamol levels in relation to the time of ingestion, and indicate when NAC should be given.

Options available to reduce the potential risk of overdose with modified-release paracetamol

1. **Up-scheduling modified-release paracetamol 665 mg formulations to Pharmacist-Only (i.e. restricted)***:* This option would introduce a 'healthcare professional step' in the process of obtaining these products, providing an opportunity for the pharmacist to discuss the appropriate use and recommended dose of the medicine with the consumer at the point of sale.

2. **Communication to healthcare professionals** (e.g. Prescriber Update article) reminding them of the difference in dose frequency with modified-release paracetamol, so that their sales staff can be advised accordingly.
3. **Revision of data sheet advice on the treatment of overdose:** include information on when to test paracetamol levels in relation to the time of ingestion, and indicate when NAC should be given.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- Any updates to the data sheets for modified release paracetamol, in particular the overdose section, are required?
- The current classification of 'pharmacy only' should be reviewed?
- Any additional communication to healthcare professionals other than MARC's remarks is required?

6.0 ANNEXES

1. Notification to the PRAC of a Referral under Article 31 of Directive 2001/83/EC. Medical Products Agency, Sweden. 30 June 2016
2. PRAC recommends modified-release paracetamol be removed from market. EMA/562720/2017 Corr1. 01 September 2017
3. Use of N-acetyl cysteine (NAC) in the management of paracetamol overdose. MARC Paper Sept 2013 http://www.medsafe.govt.nz/profs/adverse/Minutes155.htm#3.2.3
4. Panadol Osteo data sheet (Jan 2016)
5. DBL Acetylcysteine data sheet (Apr 2017)

7.0 REFERENCES

1. Salmonson, H., G. Sjoberg, and J. Brogren, *The standard treatment protocol for paracetamol poisoning may be inadequate following overdose with modified-release formulation: a pharmacokinetic and clinical analysis of 53 cases.* Clin Toxicol (Phila), 2017: p. 1-6.
2. *TOXINZ Poisons Information: Acetaminophen*. [cited 2017 24 Oct]; Available from: www.toxinz.com.
3. Chiew, A.L., *et al*., *Consusnus statement: Guidelines for the management of paracetamol poisoning in Australia and New Zealand - explanation and elaboration.* Med J Aust, 2015. **203**.
4. Schep, L. and R. Slaughter *Paracetamol toxicity, overdose and associated treatment: An update*. New Zealand Doctor Online, 2017.
5. Tan, C. and A. Graudins, *Comparative pharmacokinetics of Panadol Extend and immediate-release paracetamol in a simulated overdose model.* Emerg Med Australas, 2006. **18**(4): p. 398-403.

6. GlaxoSmithKline Consumer Healthcare. *New Zealand Data Sheet: Panadol Osteo (paracetamol 665 mg tablets). (15 January 2016)*. 2016; Available from: http://www.medsafe.govt.nz/profs/Datasheet/p/panadolOsteocaplets.pdf.

7. Fountain, J.S., *et al*., *Awareness, acceptability and application of paracetamol overdose management guidelines in a New Zealand emergency department.* N Z Med J, 2014. **127**(1402): p. 20-9.

8. Freeman, N. and P. Quigley, *Care versus convenience: Examining paracetamol overdose in New Zealand and harm reduction strategies through sale and supply.* N Z Med J, 2015. **128**(1424): p. 28-34.

9. Bizovi, K.E., *et al*., *Late increase in acetaminophen concentration after overdose of Tylenol Extended Relief.* Ann Emerg Med, 1996. **28**(5): p. 549-51.

10. Cetaruk, E.W., *et al*., *Extended-release acetaminophen overdose.* JAMA, 1996. **275**(9): p. 686.

11. Vassallo, S., A.N. Khan, and M.A. Howland, *Use of the Rumack-Matthew nomogram in cases of extended-release acetaminophen toxicity.* Ann Intern Med, 1996. **125**(11): p. 940.

12. Graudins, A., A. Chiew, and B. Chan, *Overdose with modified-release paracetamol results in delayed and prolonged absorption of paracetamol.* Internal medicine journal, 2010. **40**(1): p. 72-76.

13. Wong, A. and A. Graudins, *Risk prediction of hepatotoxicity in paracetamol poisoning.* Clin Toxicol (Phila), 2017. **55**(8): p. 879-892.

14. Doyon, S. and W. Klein-Schwartz, *Hepatotoxicity Despite Early Administration of Intravenous N-Acetylcysteine for Acute Acetaminophen Overdose.* Academic Emergency Medicine, 2009. **16**(1): p. 34-39.