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TOXICOLOGY

The comparative pharmacokinetics of modified-release and immediate-release paracetamol in a simulated overdose model

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Abstract

Background: Panadol Extend (PEx) is an over-the-counter, modified-release formulation of paracetamol. Each 665 mg tablet contains 69% slow-release and 31% immediate-release paracetamol. In simulated human overdose, PEx exhibits lower and later peak serum concentrations and a lower area-under-the-curve (AUC) than comparable doses of immediate-release paracetamol (APAP-IR). The lower AUC might result from incomplete absorption of paracetamol or simultaneous metabolism with absorption.

Objective: Do differences in pharmacokinetics (PK) between PEx and APAP-IR result from incomplete absorption or simultaneous absorption and metabolism of paracetamol?

Methods: Cross-over study of 80 mg/kg of PEx or APAP-IR in nine volunteers. Serial plasma paracetamol, glucuronide, sulphate and cysteine metabolite estimates performed over 24 h. Peak plasma concentration (Cmax), $AUC_{(0-\infty)}$, time to peak concentration (Tmax) and elimination half-life ($t_{1/2}$) were compared.

Results: PEx exhibited significantly lower paracetamol Cmax (252.33 μmol/L *vs* 565.56 μmol/L, $P = 0.0421$), $AUC_{(0-\infty)}$ (2133 μmol/h/L *vs* 2637 μmol/h/L, $P = 0.0004$) and delayed Tmax (2.889 h *vs* 1.389 h, $P = 0.0189$) than APAP-IR. Sulphate metabolite PK parameters for both preparations, PEx *vs* APAP-IR, showed similar $AUC_{(0-\infty)}$ (1369 μmol/h/L *vs* 1089 μmol/h/L), Tmax (3.889 h *vs* 4.444 h), Cmax (95.889 μmol/L *vs* 95.889 μmol/L) and $t_{1/2}$ (3.895 h *vs* 3.810 h). Glucuronide metabolite concentrations revealed that PEx produced a lower Cmax (257.44 μmol/L *vs* 335.22 μmol/L, $P = 0.0239$) than APAP-IR. All other pharmacokinetic parameters were similar. Cysteine metabolite was not detected.

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Conclusion: There were minor differences between the PK parameters of the two major paracetamol metabolites of these two preparations in simulated overdose. The variability in paracetamol AUC seen between the two preparations in moderate overdose might be explained by concurrent metabolism of paracetamol during slower absorption with PEx.

Key words: *metabolites, modified-release, overdose, paracetamol, pharmacokinetics.*

Introduction

Paracetamol is the most commonly used over the counter analgesic agent worldwide and the commonest drug leading to hospital presentations and admissions following deliberate self-poisoning and accidental overdose.[1] Panadol Extend (GlaxoSmithKline, Ermington, NSW, Australia), a modified-release formulation of paracetamol has been available in Australia since 2001. The same modified-release paracetamol formulation is also marketed in Australia under three other names: Panadol Osteo, Panadol Back + Neck Long Lasting (GlaxoSmithKline, Ermington, NSW, Australia) and Duatrol SR (Menley & James, Boronia, Vic, Australia). The formulation contains 665 mg of paracetamol of which 69% is slow-release and 31% immediate-release paracetamol (APAP-IR) in a bilayer tablet.[2] Panadol Extend is marketed as providing pain relief for up to 8 h, thus reducing dosing frequency of paracetamol from 4 to 3 times a day. In 2005, Panadol Osteo and Duatrol SR were listed on the Pharmaceutical Benefits Scheme for the treatment of osteoarthritis. Panadol Back + Neck Long Lasting was recently released and has now replaced Panadol Extend.

The decision to treat an acute, single paracetamol overdose with N-acetylcysteine is based on a serum paracetamol level taken 4–15 h after ingestion. This level is plotted on the Rumack-Matthews paracetamol toxicity nomogram, if the paracetamol serum level is above the treatment line then N-acetylcysteine is administered.[3] The efficacy and safety of using the Rumack-Matthew nomogram to risk stratify patients with paracetamol poisoning has been demonstrated in a study of more than 11 000 patients.[4] This nomogram was derived from serum concentration data collected from patients who overdosed with APAP-IR and it is uncertain whether it can be used to predict the potential for hepatotoxicity with modified-release paracetamol.[5] In 2008, an Australasian consensus guideline for the management of paracetamol poisoning was released. This included recommendations for the management of overdose with modified-release paracetamol.[6] However, there are limited data on the pharmacokinetics of Panadol Extend in overdose. A previous pharmacokinetic study by Tan and Graudins used healthy volunteers given a simulated moderate overdose (mean dose, 73 mg/kg).[7] Panadol Extend produced a lower peak concentration, lower area under the curve and delayed time to peak concentration (Tmax) when compared with APAP-IR. It was hypothesized that the differences between the two formulations might be due to either incomplete absorption of Panadol Extend or simultaneous metabolism, and absorption due to the slowed absorption phase of Panadol Extend. The aim of the current study is to assess whether the previously observed differences in pharmacokinetics between Panadol Extend and APAP-IR in moderate overdose resulted from incomplete absorption or simultaneous absorption and metabolism in a simulated overdose model using healthy human volunteers. It was hypothesized that if the fall in paracetamol AUC with Panadol Extend is because of incomplete absorption this would result in a marked reduction in sulphate and glucuronide metabolite recovery compared with the immediate-release formulation.

Methods

Study design

This was a prospective, non-blinded, randomized, cross over trial involving nine healthy volunteers. All subjects gave informed consent before entry into the study. The study was approved by the Human Research and Ethics Committee Northern Network, South East Sydney Illawarra Area Health Service and the The University of New South Wales Ethics Secretariat.

Setting and population

The study method followed that of the previous study by Tan and Graudins.[7] The subjects consisted of eight men and one woman. The exclusion criteria of the study were pregnancy, pre-existing liver disease, chronic alcohol consumption greater than 20 g per day, any chronic illness, use of any regular medication, body weight more than 100 kg, use of paracetamol products in the 7 days

before participation in the study, and any abnormality in liver function tests performed 1 week before the study and 3 days after the first arm of the study.

Study protocol

All subjects had liver function tests performed in the week before the commencement of the study. Pregnancy was excluded in women using a plasma beta-Human Chorionic Gonadotrophin assay. On the day of the study, subjects were fasted from midnight and weighed and randomized to receive either Panadol Extend (GlaxoSmithKline, Ermington, NSW, Australia) or APAP-IR (Panadol 500 mg: tablets, GlaxoSmith-Kline). Paracetamol products were purchased through the Prince of Wales Hospital, Randwick, Australia pharmacy. An intravenous cannula was inserted into a forearm vein for multiple blood collections. Subjects received a dose of 80 mg/kg of paracetamol preparation as close as possible in whole tablets. Subjects remained fasted for 2 h after administration of the paracetamol product. At time zero, patients were randomized to take one of the paracetamol formulations and blood was collected at time zero and paracetamol product administered. Blood samples were then collected at 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 10, 12 h post-ingestion in all subjects. Six subjects also had samples taken at 16 and 24 h as analysis of the first three subjects, detected significant amounts of paracetamol metabolite present at 12 h post-ingestion. Liver function tests were performed 3 days after each study arm. The other formulation of paracetamol was ingested in the subsequent arm after at least a 1 week wash-out period. All blood samples were stored for later batch analysis by South Eastern Area Laboratory Services at Prince of Wales Hospital.

Sample analysis

Analysis of samples was performed using High Performance Liquid Chromatography (HPLC). Plasma samples were assayed for the presence of paracetamol, glucuronide metabolite, sulphate metabolite and cysteine metabolite. Paracetamol and metabolites were isolated following protein precipitation with acetonitrile. The resulting precipitate was centrifuged and the supernatant evaporated to dryness. Following reconstitution paracetamol and metabolites were assayed by HPLC with ultraviolet (UV) detection. The HPLC system consisted of a Shimadzu LC-10AT pump, a SIL-10AD auto-injector and a SPD-10A UV-Vis detector set at a wavelength of 245 nm. A mobile phase consisting of 100 mM phosphate buffer pH 3.2 with 1.5% isopropanol was circulated through a Synergi Hydro-RP 4 µ C18 reverse phase column a flow rate of 1.0 mL/min (Phenomenex Corporation, Lane Cove West, NSW, Australia). A stock standard was prepared containing equivalent concentrations of paracetamol, paracetamol glucuronide and paracetamol sulphate (4 mM) (Sigma Chemicals, St Louis, MO, USA). A separate stock standard solution was prepared for paracetamol cysteine metabolite (Sigma Chemicals). Appropriate dilutions were performed to prepare calibration standards of the analytes to concentrations of 25 and 500 µM of 400 µL aliquots in paracetamol-free plasma.

Quality control samples were prepared by spiking paracetamol-free plasma to levels of 20 and 300 µM. The internal standard was 1 mM 3-acetamidophenol. Samples were de-proteinated by the addition of 1.2 mL cold acetonitrile (–20°C). The de-proteinated samples were centrifuged for 10 min at 13 000 r.p.m. One millilitre of supernatant was evaporated on a MiVac concentrator for 45 min at 55°C. The evaporation was reconstituted with 500 µL of mobile phase. The samples were again centrifuged for 10 min at 13 000 r.p.m. and 200 µL transferred to HPLC injection vials. A total of 30 µL was injected for HPLC analysis. The threshold for detection of paracetamol and its metabolites was 1 µmol/L. The interday and intraday %CV (coefficient of variation) of the assay for paracetamol and its metabolites are shown in Table 1.

Data analysis

The pharmacokinetic parameters for each subject were determined for both Panadol Extend and APAP-IR. These included peak plasma concentration (Cmax), Tmax, terminal phase half-life ($t_{1/2}$) and area under the time concentration curve (AUC) to infinity hours ($AUC_{(0-\infty)}$) for paracetamol and metabolites. These parameters were calculated using EQUIV Test/PK Test Statistical Software (Statistical Solutions Ltd, Farmer's Cross, Cork, Ireland). AUC to infinity was calculated using the linear trapezoidal rule up to the last sampling point above the limit of quantitation, plus extrapolation to infinity. Mean (±SEM) time concentration curves were plotted. Data were compared between groups using the two-tailed paired Student's *t*-test for normally distributed data using Graph Pad InStat Version 3b for Macintosh (GraphPad Software, San Diego, CA, USA). Statistical significance was defined as a P-value < 0.05.

Table 1. Interday and intraday %CV of the paracetamol and metabolite assay

	Paracetamol	Glucuronide metabolite	Sulphate metabolite
Between run precision			
Interday			
Low value (μmol/L)	24	25	23
%CV	4.5	8.3	6.7
High value (μmol/L)	366	377	317
%CV	3.0	5.8	5.2
Within run precision			
Intraday			
Low value (μmol/L)	25	22	20
%CV	0.6	2.6	1.3
High value (μmol/L)	327	292	217
%CV	1.5	1.4	2.4

CV, coefficient of variation.

Table 2. Demographic characteristics of subjects in the study of Panadol Extend pharmacokinetics in moderate overdose expressed as the mean (range)

Age (years)	34 (27–46)
Body weight (kg)	73.11 (62–84)
Actual paracetamol dose	
Panadol Extend (mg/kg)	78.78 (75–81)
APAP-IR (mg/kg)	79 (77–83)

APAP-IR, immediate-release paracetamol.

Results

Eight male and one female subject completed both arms of the study. No subjects developed abnormal liver function tests, defined as any value outside the normal reference range. Demographic data for the subjects in the present study are summarized in Table 2.

The mean Panadol Extend and APAP-IR doses ingested were 78.78 mg/kg and 79 mg/kg, respectively. Side effects only occurred with APAP-IR and included light headedness and nausea, lasting 30 to 60 min post-ingestion in six subjects.

The calculated pharmacokinetic parameters for Panadol Extend and APAP-IR are summarized in Table 3. Paracetamol kinetic parameters were comparable to those reported by Tan and Graudins.[7] Paracetamol Cmax for Panadol Extend was significantly reduced compared with APAP-IR (252.33 μmol/L *vs* 565.56 μmol/L, $P = 0.0421$). Paracetamol Tmax was delayed for Panadol Extend (2.889 h *vs* 1.389 h, $P = 0.0189$). Paracetamol $AUC_{(0-\infty)}$ for Panadol Extend was reduced when compared to APAP-IR (2133 μmol/h/L *vs* 2637 μmol/h/L, $P = 0.0004$). When the mean values of the serum paracetamol concentrations of both formulations are graphed (Fig. 1), Panadol Extend yields a flatter and more plateau shaped curve in the first 4 h, after this the two curves resemble one another. Terminal phase paracetamol half-life ($t_{1/2}$) was comparable between the two formulations (2.837 h *vs* 2.601 h).

Comparison of paracetamol glucuronide metabolite pharmacokinetic parameters showed that mean Cmax was moderately reduced for Panadol Extend (257.44 μmol/L *vs* 335.22 μmol/L, $P = 0.0239$). There were no significant differences between Tmax or $AUC_{(0-\infty)}$ of glucuronide metabolites (Table 3). The $t_{1/2}$ estimations of the glucuronide metabolite were similar between the two preparations (3.950 h *vs* 3.536 h) When mean serum concentrations of the glucuronide metabolite are plotted graphically (Fig. 2), in the Panadol Extend group, there is a lower Cmax. Eight hours post-ingestion the glucuronide metabolite concentrations are marginally higher in the Panadol Extend arm with the 12 h glucuronide concentration for Panadol Extend group being significantly higher than that for APAP-IR (114 μmoll/L *vs* 91 μmol/L, $P = 0.0003$). This later rise in glucuronide concentrations might contribute to the similar AUC between the two groups.

Comparison of paracetamol sulphate metabolite pharmacokinetics for Panadol Extend and APAP-IR showed no significant difference in Cmax, Tmax or $AUC_{(0-\infty)}$ (Table 3). When comparing the $t_{1/2}$ of the two preparations they are comparable (3.895 h *vs* 3.810 h). Results are represented graphically in Figure 3.

In all of the serum samples tested, for paracetamol and its glucuronide and sulphate metabolites, none of

Table 3. Comparative pharmacokinetics for Panadol Extend and immediate-release paracetamol (Panadol), Glucuronide metabolite and Sulphate metabolite for Panadol Extend and expressed as mean (±SEM)

Parameter	Panadol	Panadol Extend	*P*-value
Cmax (μmol/L)	565.56 ± 140.75	252.33 ± 17.346	0.0421
Tmax (h)	1.389 ± 0.4042	2.889 ± 0.3514	0.0189
$T_{1/2}$ (h)	2.601 ± 0.08584	2.837 ± 0.4381	NS
$AUC_{(0-\infty)}$ (μmol/h/L)	2637 ± 189	2133 ± 137	0.0004
	IR paracetamol glucuronide metabolite	Panadol Extend glucuronide metabolite	*P*-value
Cmax (μmol/L)	335.22 ± 22.135	257.44 ± 21.959	0.0239
Tmax (h)	3.556 ± 0.1757	4.222 ± 0.2222	NS
$T_{1/2}$ (h)	3.536 ± 0.1553	3.950 ± 0.2590	NS
$AUC_{(0-\infty)}$ (μmol/h/L)	3059 ± 206	3034 ± 269	NS
	IR paracetamol sulphate metabolite	Panadol Extend Sulphate metabolite	*P*-value
Cmax (μmol/L)	95.889 ± 8.845	95.889 ± 8.558	NS
Tmax (h)	4.444 ± 0.2940	3.889 ± 0.3514	NS
$T_{1/2}$ (h)	3.810 ± 0.1582	3.895 ± 0.2634	NS
$AUC_{(0-\infty)}$ (μmol/h/L)	1089 ± 118	1369 ± 229	NS

$AUC_{(0-\infty)}$, area under the time concentration curve to infinity hours; Cmax, peak plasma concentration; IR, immediate-release; NS, not significant; $T_{1/2}$, terminal phase half-life; Tmax, time to peak concentration.

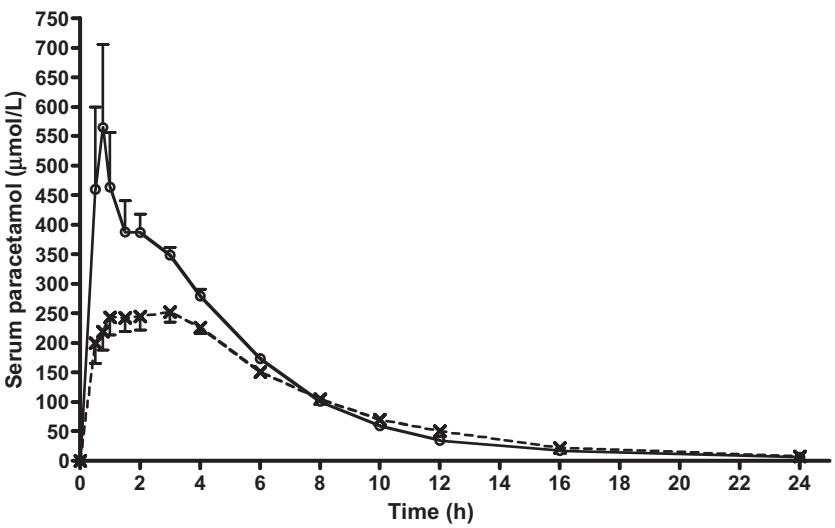

Figure 1. Graph of mean serum paracetamol concentrations following simulated overdose with Panadol Extend and immediate-release (IR) paracetamol. (–o–) IR paracetamol; (-×-) Panadol Extend.

the concentrations fell below the limit of quantitation, for the assay used. No evidence of the cysteine metabolite was detected in either arm of the study suggesting that serum concentrations were below the threshold for detection. We were unable to source a mercapturate metabolite standard to assay this metabolite for the study.

Discussion

As with the previous pharmacokinetic study by Tan and Graudins,[7] the present study found a significant difference in the pharmacokinetic profile of Panadol Extend in simulated moderate overdose compared to APAP-IR. Despite comparable ingested doses, Panadol

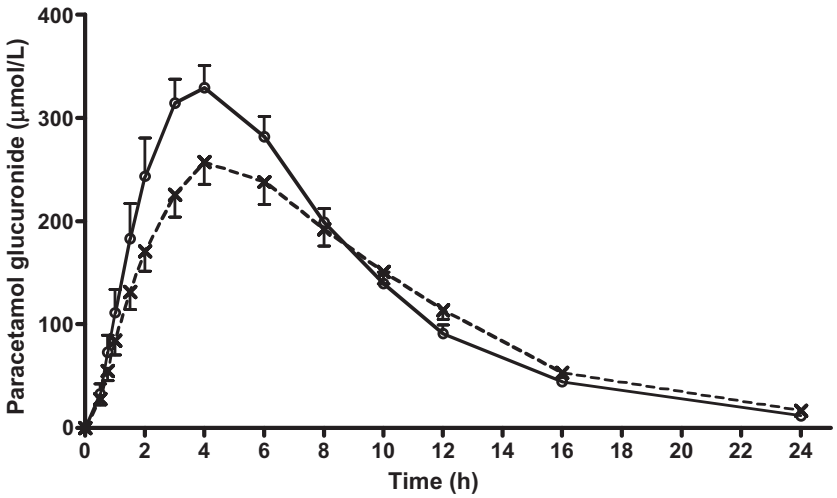

Figure 2. Graph of mean (±SEM) serum paracetamol glucuronide metabolites following simulated overdose with Panadol Extend and immediate-release (IR) paracetamol. (—○—) IR paracetamol glucuronide; (- ×-) Panadol Extend glucuronide.

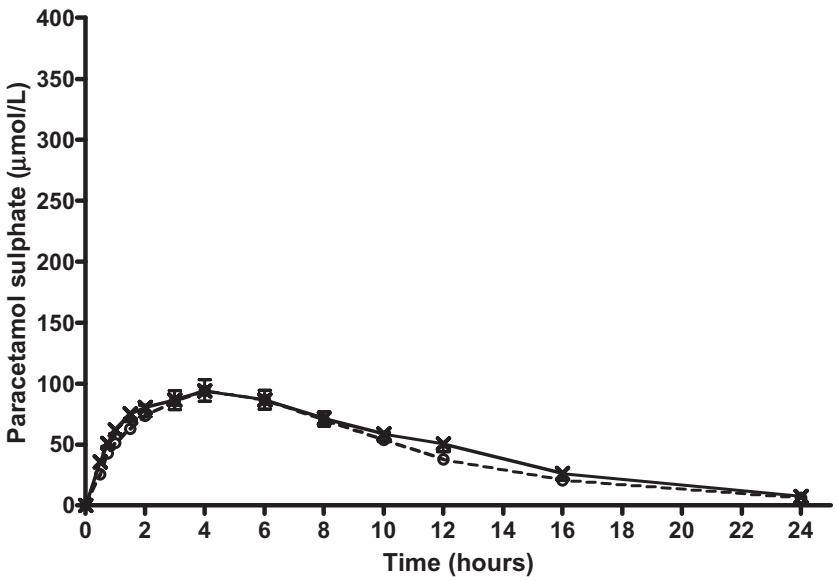

Figure 3. Graph of mean serum paracetamol sulphate metabolite following simulated overdose with Panadol Extend and immediate-release (IR) paracetamol. There was no significant difference in sulphate metabolite concentrations between the two groups. (-○-) IR paracetamol sulphate; (—×—) Panadol Extend glucuronide sulphate.

Extend had a reduced Cmax and $AUC_{(0-\infty)}$ when compared to APAP-IR and a delayed time to maximum concentration. In this current study we assessed the pharmacokinetics of the two conjugation metabolites of paracetamol in moderate paracetamol overdose in an attempt to explain the significant differences in paracetamol AUC seen with the differing formulations. AUC to infinity for the two metabolites was used as a surrogate marker for metabolite recovery. If the fall in paracetamol $AUC_{(0-\infty)}$ with Panadol Extend was the result of incomplete absorption of paracetamol we hypothesized this would manifest as a significant reduction in sulphate and glucuronide metabolite recovery. The present study found there was no significant difference in

$AUC_{(0-\infty)}$ for both assayed metabolites, hence similar metabolite recovery. There are a few explanations for this result, it most likely represents simultaneous metabolism of paracetamol in the Panadol Extend formulation during its absorption phase. However, incomplete absorption cannot be completely ruled out. Equal metabolite recovery might represent saturation of both the sulphation and glucuronidation pathways. Without measuring total urine metabolite recovery a definite conclusion regarding paracetamol absorption cannot be reached. Another possibility to explain our results is a mixed mechanism of incomplete absorption and slowed absorption with concomitant hepatic first-pass metabolism.

The sulphate conjugation pathway is the first to become saturated in adults at therapeutic doses and in overdose.[8] This pathway might have reached saturation point rapidly in our subjects, after ingestion of both formulations, hence the similar pharmacokinetic profiles. Yet it is unlikely this occurred in the glucuronide conjugation pathway. Glucuronide conjugation is the major route of paracetamol metabolism accounting for about 60% of metabolism at a therapeutic dose. There is no decrease in this fraction after overdosage and glucuronide conjugation probably only becomes saturated in large overdoses.[9] Comparison of pharmacokinetic parameters of the glucuronide metabolite showed no significant difference in $AUC_{(0-\infty)}$ and Tmax between the two formulations. However, in the Panadol Extend arm there was a moderate but significant lower Cmax. A possible explanation for this is that because of the delayed absorption of Panadol Extend a lower peak glucuronide metabolite concentration resulted from the presence of reduced quantity of substrate for metabolism when peak concentrations were observed. The $AUC_{(0-\infty)}$ remains comparable between the two formulations because of the presence of higher glucuronide metabolite concentrations in the Panadol Extend arm from 10 to 24 h post-ingestion. Hence, given the similarities in major metabolite AUC in the two arms of the study, it is more likely that the difference in AUC for paracetamol between the two formulations is the result of slowed absorption with concomitant metabolism of paracetamol with Panadol Extend in moderate overdose.

Interestingly, when comparable therapeutic doses of these two formulations are ingested, there are no differences in AUC,[10] suggesting that this observation might be a reflection of the dose ingested and the rate of absorption of paracetamol from the modified-release matrix following ingestion of supra-therapeutic doses. Similar observations of reduced paracetamol AUC have been reported when comparable doses of paracetamol in moderate overdose have been administered to volunteers with the addition of oxycodone.[11] Opioid-induced slowing of gut motility might play a role in delayed absorption of paracetamol in overdose, resulting in a similar phenomenon of paracetamol metabolism occurring simultaneously during a slowed absorptive phase.[11]

The first published case of an acute overdose with Panadol Extend was reported by Roberts and Buckley.[12] A 25-year-old woman ingested 1185 mg/kg of Panadol Extend. The patient presented more than 12 h post-ingestion and her observed peak paracetamol concentration was at 20 h post-ingestion. Serum paracetamol levels remained elevated for 48 h post-overdose. The patient received prolonged treatment with intravenous N-acetylcysteine infusion and made a full recovery. Graudins *et al.* also report a case series of patients presenting following overdose with Panadol Extend presenting early to hospital with doses ranging from 8 to 24 g. In these patients serum paracetamol concentrations were observed to plateau in the first 8 to 10 h post-ingestion, and exhibited prolonged absorption for up to 16 h post-ingestion.[13] Although the doses were larger in these clinical cases of self-poisoning, the presence of delayed peak paracetamol concentrations is consistent with the findings in our volunteer study. Finally, massive ingestion (>70 g) of this modified-release formulation might be associated with biphasic and prolonged paracetamol absorption and require prolonged administration of N-acetylcysteine to prevent delayed development of hepatotoxicity.[14]

Limitations

For safety reasons subjects ingested 80 mg/kg of paracetamol formulation, this is approximately 50% of the toxic dose. Extrapolation of results from the present study, to larger overdoses, is only possible if paracetamol has linear pharmacokinetics. The pharmacokinetics of sustained-release paracetamol are more than likely altered further in larger overdoses as evidenced by the few case report observations of overdose with this formulation. However, our model of delayed peak paracetamol concentrations reflects the observations of Roberts and Buckley and Graudins *et al.* where peak paracetamol concentrations were delayed even further in the clinical overdoses.[12,13,14] In acute clinical overdose, glucuronidation and sulphation pathways become saturated with a resultant increase in metabolite production along the cytochrome P450 pathways. This might alter

the ratios of the metabolites measured when compared to therapeutic dosing with increases in P450 metabolite production. We did not assay paracetamol mercapturate concentrations as we were unable to find a ready supply of this conjugate to use as a standard for assay. The cysteine metabolite was not detectable in either arm of our study because of its low concentrations. This metabolite is likely to be detectable following higher ingested doses of paracetamol. As a result, we cannot comment on whether microsomal metabolism varied between the two formulations.

Twenty-four hour urine collection for paracetamol parent and metabolite recovery would have been a more accurate method for estimating paracetamol absorption and metabolite production. We did not undertake this in our study for both logistic and cost reasons.

In the present study, subjects were fasted. In clinical overdose, patients normally co-ingest food, alcohol and other medications. This might alter the absorption kinetics of Panadol Extend further and result in further delays in absorption of the paracetamol. As the dose ingested by volunteers was subtoxic with respect to acute paracetamol toxicity, we cannot make any inferences as to the applicability of the paracetamol treatment nomogram in acute overdose with Panadol Extend.

Conclusions

In this simulated model of moderate overdose of Panadol Extend, comparative reductions in Cmax and AUC_{24h} are likely to be related to concomitant hepatic first-pass metabolism and slowed absorption of paracetamol with the modified-release formulation, rather than incomplete absorption of paracetamol from the GI (gastrointestinal) tract. This is evidenced by the presence of comparable AUC of major paracetamol metabolites between the two preparations used in the study. There might be implications as to toxic dosing thresholds with modified-release formulations of paracetamol.

Using the data in the present study, we are unable to make any recommendations on the applicability of the paracetamol treatment nomogram in clinical overdose with Panadol Extend. Delayed peak serum levels in the present study reflect the observations made in the few cases of clinical overdose with this product. Because Panadol Extend results in slowed absorption and delayed peak serum concentrations of paracetamol, using one paracetamol concentration plotted on the toxicity nomogram might not predict potential hepatotoxicity reliably.

Competing interests

Andis Graudins is a Section Editor, Toxicology, for Emergency Medicine Australasia.

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