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TOXICOLOGY

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Comparative pharmacokinetics of Panadol Extend and immediate-release paracetamol in a simulated overdose model

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Abstract

Background: Panadol Extend is a modified-release paracetamol formulation in which each 665 mg tablet contains 69% slow-release and 31% immediate-release paracetamol. There are no data on Panadol Extend pharmacokinetics in overdose. It is unknown whether the paracetamol treatment nomogram can be used to make decisions regarding the toxicity of this product in overdose.

Objective: To compare the pharmacokinetics of Panadol Extend and immediate-release paracetamol (APAP-IR) in simulated overdose model in healthy volunteers.

Methods: Cross-over study using a dose of 90 mg/kg ideal body weight of Panadol Extend or APAP-IR in seven healthy volunteers. Serum paracetamol concentrations were measured over 12 h. Maximal paracetamol concentration (Cmax), time to Cmax (Tmax), area under the curve (AUC) and elimination half-life ($t_{1/2}$) were compared.

Results: Mean paracetamol dose was 73 mg/kg actual body weight. Panadol Extend produced lower Cmax (0.208 mmol/L ± 0.02 *vs* 0.48 mmol/L ± 0.02, $P = 0.0001$) and $AUC_{0–12\,h}$ when compared with APAP-IR. Tmax was delayed with Panadol Extend (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. Elimination $t_{1/2}$ was 1.69 ± 0.09 h for APAP-IR and 1.65 ± 0.13 h for Panadol Extend (not significant).

Conclusions: Reductions in Panadol Extend Cmax and $AUC_{0–12\,h}$ might be related to elimination occurring during the absorption phase. In this model of Panadol Extend moderate overdose, Tmax was significantly delayed. In larger overdoses, time to peak paracetamol levels might be further delayed, because of continuing absorption from the formulation. Therefore, the paracetamol treatment nomogram might not reliably predict hepatotoxicity from Panadol Extend if paracetamol levels are measured too early.

Key words: *extended-release*, *overdose*, *paracetamol*, *pharmacokinetics*, *volunteer study*.

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Introduction

Paracetamol is probably the most widely used non-narcotic analgesic agent available. It is also one of the most common pharmaceutical agents involved in deliberate self-poisoning. If consumed excessively, it can produce acute hepatic injury characterized by centrilobular hepatic necrosis. Paracetamol is the second most common pharmaceutical agent used for deliberate self-harm at our institution and represents up to 15–20% of the poisoning presentations in the ED across the country.[1] Paracetamol is available as an over-the-counter medication in Australia and is easily purchased from grocery and convenience stores. The decision to treat patients following an acute, single paracetamol overdose is based upon whether a serum paracetamol concentration taken 4–15 h post ingestion indicates the potential for hepatic injury and death when plotted on the Rumack–Matthews paracetamol toxicity nomogram.[2,3] The paracetamol toxicity nomogram was derived from serum concentration data collected from patients who were poisoned with immediate-release paracetamol (APAP-IR).[4]

On 15 June 2001, Panadol Extend (GlaxoSmithKline, Sydney, NSW, Australia) was released onto the Australian market. This is a novel modified release formulation of paracetamol formulated as a bi-layer tablet containing 665 mg of paracetamol, with one layer containing immediate-release paracetamol (31%) and the second layer containing sustained-release paracetamol (69%). The recommended dosage is two 665 mg tablets (1.33 g) three times daily with a maximum daily dose of six tablets (3.99 g). Panadol Extend has a pharmacokinetic profile resulting in plasma paracetamol concentrations adequate for analgesic relief for up to 8 h. In 2005, this formulation was placed on the Pharmaceutical Benefits Scheme as an authority medication for the treatment of pain and fever in palliative care patients and for the relief of persistent pain for osteoarthritis. It is marketed under two other product names for these indications: Panadol Osteo (GlaxoSmithKline, Australia) and Duatrol SR (Menley and James, Boronia, Vic., Australia). Currently, there is no information regarding the pharmacokinetics of Panadol Extend in overdose. Additionally, the validity of paracetamol treatment nomogram in the risk assessment of acute overdose with Panadol Extend is unknown.

Study objective

To compare the pharmacokinetics of Panadol Extend and immediate-release paracetamol (APAP-IR) in simulated overdose model.

Methods

Study design

This was a prospective, non-blinded, cross-over trial involving 10 healthy volunteers. The study was approved by the South East Sydney Area Health Services Human Research Ethics Committee and the University of New South Wales Ethics Secretariat. Written informed consent was obtained from all subjects.

Setting and population

The subjects consisted of eight male and two female adult volunteers. The Clinical and Experimental Toxicology Unit, Department of Emergency Medicine, Prince of Wales Hospital conducted the study between May and August 2004. The exclusion criteria included the presence of any pre-existing liver disease, chronic alcohol consumption (>20 g per day), use of P450 enzyme inducing medications, any chronic medical illness, ideal body weight more than 100 kg, pregnancy, use of paracetamol-containing products in the 7 days prior to participation in the study and the presence of any abnormality on the screening liver function test performed in the week prior to participation of the study.

Study protocol

All subjects had screening liver function test performed prior to the study and female subjects had a serum pregnancy test performed. Subjects were fasted from midnight the day preceding the study. At 07.00 hours, an i.v. cannula was inserted in the forearm vein for multiple blood collection. Subjects were weighed and randomized to receive either Panadol Extend (GlaxoSmithKline, Australia) or APAP-IR (Panadol 500 mg caplets; GlaxoSmithKline, Australia). Paracetamol products were donated by the Consumer Healthcare Division of GSK Australia. Dosing was calculated using ideal body weight,[5] in a dose as close as possible to 90 mg/kg in whole tablets, swallowed with up to 250 mL water. The other formulation of paracetamol was ingested in the subsequent arm of the study after a 1 week wash

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out period. Blood samples were collected at time 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 h for serum paracetamol measurement. The 4 h paracetamol assay was analysed immediately. In the unlikely event of a raised serum paracetamol concentration above the 1320 μmol/L nomogram line at 4 h post ingestion, subjects would be treated with *N*-acetylcysteine. All other blood samples were stored for later batch analysis by South Eastern Area Laboratory Services at Prince of Wales Hospital using Beckman Coulter Synchron LXi 72 (Fullerton, CA, USA). The threshold for paracetamol detection is 15 μmol/L. Subjects were allowed to eat *ad libitum* 2 h post ingestion of paracetamol. Repeat liver function testing was performed 3 days after each study arm.

Data analysis

The pharmacokinetic parameters for each subject were determined for both Panadol Extend and APAP-IR. These included peak plasma concentrations (Cmax), time to peak concentrations (Tmax), elimination half-life ($t_{1/2}$) and area under the time–concentration curve (AUC) to 12 h and infinity. Time concentration curves were plotted using Graph Pad Prism (Graph Pad Software, San Diego, CA, USA) and the mean and standard error of the mean values were calculated for each variable. The AUC to 12 h and infinity and the elimination half-life constant (ke) were calculated using MINIM pharmacokinetic software (RD Purves, University of Otago, Dunedin, Otago, New Zealand). Statistical significance was Defined as a P-value < 0.05. Data were compared between groups using the unpaired student t-test for normally distributed data and the Mann–Whitney test for data not passing the test for normality with Graph Pad Instat (Graph Pad Software).

Results

Three potential volunteers had mildly raised alanine aminotransferase levels during the screening phase and were not enrolled in the study. They were referred to their general practitioner for follow up.

Eight male subjects completed both arms of the study. The two female subjects were excluded from data analysis. One female subject elected to withdraw from the study after participating in the first arm. One of the serum paracetamol levels for the other female subject was lost and her data were also not included in the analysis. No patients developed evidence of hepatotoxicity, as defined by a serum alanine aminotransferase or aspartate aminotransferase greater than 1000 IU/L, following either arm of the study. Demographic data for the volunteers included in the study are summarized in Table 1.

Mean actual Panadol Extend and APAP-IR doses ingested were 74.56 mg/kg ± 2.99 and 73.13 mg/kg ± 2.81, respectively ($P = 0.7323$). The Cmax of Panadol Extend was significantly reduced compared with APAP-IR (0.208 mmol/L *vs* 0.48 mmol/L, $P < 0.0001$); Tmax was delayed for Panadol Extend (2.825 h *vs* 0.94 h, $P = 0.0001$). The Panadol Extend AUC to 12 h and infinity were reduced by 30% despite comparable paracetamol doses (Table 2). Absorption was complete by 4 h post ingestion in all subjects. When mean Panadol Extend and APAP-IR serum paracetamol concentrations are graphically represented, Panadol Extend yielded a flatter, more plateau-shaped curve in the first 4 h. The two curves closely resembled one another from 4 to 12 h (Fig. 1). The elimination half-life was comparable for both products 1.65 h (Panadol Extend) versus 1.69 h (APAP-IR). Pharmacokinetic data are summarized in Table 2. Side effects are summarized in Table 3.

Discussion

The present study demonstrated a significant difference in the pharmacokinetic profile of Panadol Extend in simulated overdose when compared with immediate-release paracetamol. Of note, Tmax was delayed and Cmax was less than half of that of APAP-IR.

Table 1. Demographic characteristics of eight male patients included in the study of Panadol Extend pharmacokinetics in moderate overdose (mean ± standard error of the mean)

Age	32.2 (22–43 years)		
Body weight (kg)	Actual	Ideal	*P*-value
	88.1 ± 4.6	74.3 ± 1.5	$P = 0.02$
Actual paracetamol dose (mg/kg)	Panadol Extend	Immediate-release paracetamol	
	74.5 ± 2.9	73.1 ± 2.8	NS

NS, not significant.

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Table 2. Comparative pharmacokinetics parameters for Panadol Extend and immediate-release paracetamol expressed as mean ± standard error of the mean

Parameter	APAP-IR	Panadol Extend	*P*-value
Cmax (mmol/L)	0.484 ± 0.02	0.208 ± 0.02	<0.0001
Tmax (h)	0.937 ± 0.17	2.825 ± 0.26	0.0001
$t_{1/2}$ (h)	1.690 ± 0.09	1.650 ± 0.13	NS
AUC (mmol/h/L)	1.598 ± 0.54	1.144 ± 0.11	0.0024

APAP-IR, immediate-release paracetamol; AUC, area under the time–concentration curve; Cmax, maximal paracetamol concentration; NS, not significant; Tmax, time to Cmax.

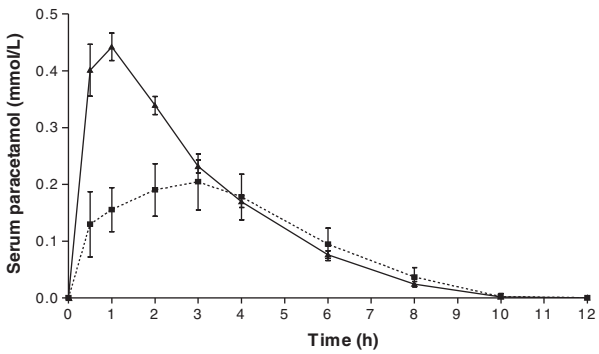

Figure 1. Comparison of mean serum paracetamol concentrations for subjects ingesting (- -■- -) Panadol Extend and (–▲–) immediate-release paracetamol. Error bars show standard error of means.

Additionally, AUC was significantly reduced. This degree of reduction in AUC was not expected. We theorize at least two possible mechanisms for these results. First, incomplete release of paracetamol from the tablet matrix leading to incomplete absorption might have occurred. If this were the case, serum paracetamol concentrations would more than likely have been detectable for a longer period than the 8–10 h seen in the present study. Second, the reduced AUC might be explained by the metabolism of paracetamol during the absorption phase. In the fasted state, therapeutic doses of immediate-release paracetamol are normally absorbed within 30–60 min of ingestion. The elimination half-life of paracetamol is commonly between 1 and 2 h and the amount of paracetamol metabolized during the absorption phase is small. In the present study, Panadol Extend ingestion resulted in a 3 h delay to maximum concentration. Consequently, paracetamol metabolism might have occurred simultaneously with absorption explaining the observed reductions in AUC.[6,7,8]

Table 3. Summary of side-effects seen in the present study

Side-effects	No. complaints	
	APAP-ER	APAP-IR
Dizziness	1	2
Lethargic/tiredness	1	1
Facial flushing	2	
Nausea	2	

APAP-ER, extended-release paracetamol; APAP-IR, immediate-release paracetamol.

Similar reductions in AUC have been observed in other simulated overdose studies of extended-release paracetamol. Douglas *et al.* reported a statistically non-significant reduction in AUC of 12% in subjects ingesting comparable doses of immediate-release paracetamol and Tylenol-ER (a different formulation of sustained-release 650 mg paracetamol marketed in the USA with 50% immediate and 50% extended-release paracetamol).[9] Additionally, Sivilotti *et al.* reported a 27% reduction in AUC in volunteers ingesting 5 g of paracetamol with large doses of oxycodone (0.5 mg/kg) when compared with paracetamol alone.[10] In both instances paracetamol absorption was delayed and AUC reduced when compared with immediate-release paracetamol alone.

The mechanisms for the development of acute toxicity after the ingestion of a significant overdose of immediate-release paracetamol are well defined. Initially, the major pathways of paracetamol metabolism, glucuronidation and sulphation are rapidly saturated.[11] This results in a shunting of paracetamol metabolism to the microsomal pathway (predominantly CYP2E1 and CYP3A4) where production of the intermediary toxic metabolite *N*-acetyl parabenzoquinoneimine (NAPQI) occurs. NAPQI is normally conjugated with hepatic glutathione and excreted as non-toxic mercapturate metabolites.[12] In overdose, NAPQI concentrations increase rapidly in the liver and hepatic glutathione stores are depleted. Hepatotoxicity results from NAPQI accumulation in the liver.[4] When absorption is delayed, as in the case of overdose with Panadol Extend or paracetamol with large doses of oral opiates, there is slower delivery of paracetamol to the liver. This might result in an increased threshold in the time taken to reach saturation point for glucuronidation and sulphation metabolic pathways when compared with similar doses of immediate-release paracetamol. As a result, more paracetamol might be metabolized to non-toxic adjuncts before these pathways are saturated. We theorize that, the slowed paracetamol absorption seen with Panadol

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Extend in simulated moderate overdose might also result in a moderate increase in the toxic threshold following larger overdoses with this formulation. As a result, the potential for hepatotoxicity might occur at a higher ingested dose than with immediate-release paracetamol.[13] Reductions in hepatotoxicity have been observed in cases where paracetamol absorption is delayed because of concomitant ingestion of pharmaceutical agents delaying gastrointestinal motility.[13–15] A similar phenomenon might occur with potentially toxic overdoses of sustained-release paracetamol.

It is difficult to make any inferences regarding the use of the paracetamol toxicity nomogram with Panadol Extend from the present study. The doses ingested do not reflect the amount of paracetamol that might be ingested in cases of deliberate self-poisoning. Currently, it is unknown whether the primary determinant for hepatotoxicity is the peak paracetamol concentration or AUC. If the peak concentration is the determinant for hepatotoxicity in paracetamol poisoning, comparable doses of extended-release preparations might be less toxic than with similar doses of immediate-release paracetamol. Similarly, if AUC is the determinant for hepatotoxicity, sustained-release paracetamol might also have a reduced risk. With a sufficiently large enough overdose of Panadol Extend serum paracetamol concentrations might cross the nomogram line later than seen with immediate-release paracetamol. Hence, the recommendation to measure a second serum paracetamol concentration 3–4 h after the first, as recommended in the USA with Tylenol-ER overdose, might also be valid for this product.

Limitations

We used a paracetamol ingestion dose of 90 mg/kg according to ideal body weight. There was a mean difference in body weight of 13 kg between real and ideal body weight. The mean actual paracetamol dose administered in each arm of the study was approximately 73 mg/kg, which is 50% of the minimum adult toxic dose following acute overdose with immediate-release paracetamol. The dose of Panadol Extend ingested in the present study might not reflect the pharmacokinetics of this product when ingested at larger, potentially hepatotoxic doses. The subjects in the present study were fasted. In clinical overdose there are normally co-ingestants such as alcohol or food, which might alter the pharmacokinetics profile of a drug. It has been previously noted that co-ingestion of certain drugs, such as opiate analgesics, might delay absorption of immediate-release paracetamol and present difficulties in the use of the treatment nomogram.[13,16–19]

In the present study, absorption appeared to be complete by 12 h in all subjects but the limit of detection for the paracetamol assay used in the present study was 15 μmol/L. Consequently, there might have been low concentrations of paracetamol in the blood that were not detected in our subjects as they were below the limit of detection for the assay. However, this amount is unlikely to have influenced the AUC to any significant degree as seen by the AUC^{∞} to infinity calculations.

Conclusions

Ingestion of Panadol Extend resulted in lower Cmax and prolonged Tmax when compared with immediate-release paracetamol in this overdose model. AUC for Panadol Extend was significantly less, suggesting that elimination and absorption might occur simultaneously. The significance of the reduction in AUC following clinical overdose with paracetamol is currently unknown and it is not possible to extrapolate these data to larger overdoses of Panadol Extend.

In view of the delayed time to maximum paracetamol concentration seen in the present study, it is likely that a single serum paracetamol estimation 4 h post ingestion cannot be relied upon to predict the potential for hepatotoxicity using the paracetamol treatment nomogram following Panadol Extend overdose. If a potentially hepatotoxic dose of Panadol Extend (>150 mg/kg) has been consumed, *N*-acetylcysteine should be commenced and serum paracetamol concentrations should be compared with the toxicity nomogram at 4 and 8 h post ingestion. Any delay in the administration of *N*-acetylcysteine more than 8 h from the time of a significant paracetamol overdose might result in an increased incidence of hepatotoxicity.[2] Physicians should also be aware of the three product names for this formulation of paracetamol (Panadol Extend, Panadol Osteo and Duatrol SR) and attempt to elicit the brand name of any paracetamol product that has been taken in overdose. Finally, a clinical toxicologist should be consulted through the National Poisons Information Service or local referral networks in any case where the management of paracetamol poisoning is unclear.

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Competing interests

None declared.

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