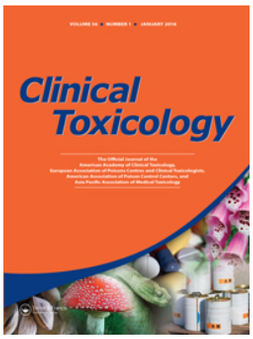

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: Heléne Salmonson, Gunilla Sjöberg & Jacob Brogren (2018) The standard treatment protocol for paracetamol poisoning may be inadequate following overdose with modified release formulation: a pharmacokinetic and clinical analysis of 53 cases, Clinical Toxicology, 56:1, 63-68, DOI: 10.1080/15563650.2017.1339887

To link to this article: https://doi.org/10.1080/15563650.2017.1339887

Published online: 23 Jun 2017.

CLINICAL TOXICOLOGY, 2018
VOL. 56, NO. 1, 63–68
https://doi.org/10.1080/15563650.2017.1339887

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POISON CENTRE RESEARCH

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

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ABSTRACT

Objective: The use of the standard procedure for managing overdoses with immediate release (IR) paracetamol is questionable when applied to overdoses with modified release (MR) formulations. This study describes the pharmacokinetics of paracetamol and the clinical outcomes following overdoses with a MR formulation.

Methods: Medical records including laboratory analyses concerning overdoses of MR paracetamol from 2009 to 2015 were collected retrospectively. Inclusion criteria were ingestion of a toxic dose, known time of intake and documented measurements of serum paracetamol and liver function tests. Graphical analysis, descriptive statistics and population pharmacokinetic modelling were used to describe data.

Results: Fifty-three cases were identified. Median age was 26 years (range 13–68), median dose was 20 g (range 10–166) and 74% were females. The pharmacokinetic analysis showed a complex, dose dependent serum *versus* time profile with prolonged absorption and delayed serum peak concentrations with increasing dose. Ten patients had persistently high serum levels for 24 h or more, six of them had a second peak 8–19 h after ingestion. Seven of 34 patients receiving *N*-acetylcysteine (NAC) within 8 h had alanine aminotransferase (ALT) above reference range. Three of them developed hepatotoxicity (ALT >1000 IU/l).

Discussion and conclusions: The pharmacokinetic and clinical analysis showed that the standard treatment protocol, including risk assessment and NAC regimen, used for IR paracetamol poisoning not appear suitable for MR formulation. Individual and tailored treatment may be valuable but further studies are warranted to determine optimal regimen of overdoses with MR formulation.

ARTICLE HISTORY
Received 22 February 2017
Revised 31 May 2017
Accepted 31 May 2017
Published online 22 June 2017

KEYWORDS
Paracetamol; modified release; pharmacokinetic; overdose; acetylcysteine; hepatic injury

Introduction

Paracetamol is one of the most commonly utilized medicinal products worldwide and also one of the most common substances involved in deliberate self-poisoning in the United States and Europe, including Sweden [1,2]. A modified release (MR) formulation of paracetamol is currently authorized in Sweden, under the brand name of Alvedon 665 mg (GlaxoSmithKline), and has been available since 2003. It comes in pack sizes up to 100 tablets and is sold only on prescription. In recent years there has been a large increase in patient exposure to this MR product in Sweden and today the formulation constitute nearly 40% of the prescriptions of all comparable paracetamol products [3]. As shown in Figure 1, the patient exposure is paralleled by an increasing number of consultations to the Swedish Poisons Information Centre (Swedish PC). The Swedish PC is a nation-wide, 24/7 phone service to clinicians and the public, covering 10 million inhabitants. In 2016, paracetamol accounted for 4391 consultations to the PC and 21% of them applied to Alvedon 665. The MR formulation is currently available under different brand names in several countries in Europe and in the Australasia region. It is intended to provide prolonged pain relief compared to immediate release (IR) formulations [4]. Alvedon 665 has a bilayer delivery system, containing 665 mg of paracetamol of which 31% is intended for IR and 69% for MR. The IR portion of the tablet is absorbed rapidly similar to standard paracetamol formulations. The latter modified formulation includes a HPMC-polymer (hydroxypropyl methylcellulose) which hydrates in the gut forming a gel layer around the matrix. Paracetamol is then released by a combination of diffusion from and erosion of the gel layer [4]. Little is known about the absorption of this formulation in overdose. In one published study with simulated overdose of 75 mg/kg, the time to serum peak of paracetamol was noted to increase from 1 to 3.5 h when compared with IR paracetamol [5]. The recommended management of overdose with MR paracetamol is generally based on a standard protocol for managing IR paracetamol overdoses, which is well known and has been used in that setting for decades [6]. In case of acute overdose a serum concentration of paracetamol is measured within 4–24 h post-ingestion to stratify the risk

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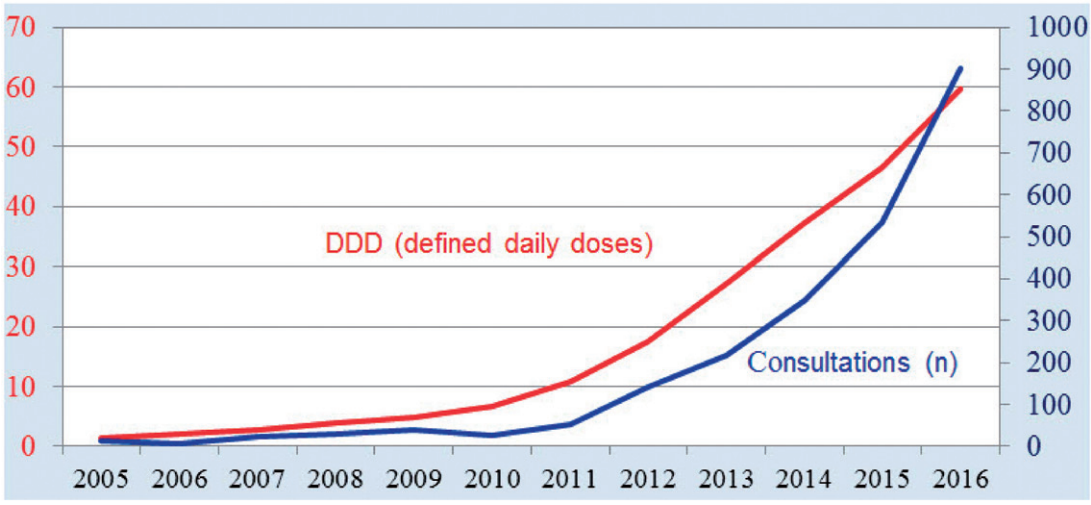

Figure 1. Increasing sales number of MR paracetamol in Sweden (DDD in million) related to the number of consultations with the Swedish Poisons Information Centre.

of hepatotoxicity and whether administration of *N*-Acetylcysteine (NAC) intravenously is indicated. The treatment nomogram used for the risk assessment in Sweden is based on the Rumack–Matthew nomogram [7,8]. The treatment line begins at 4 h and ends at 24 h post-ingestion [7]. In patients with a known time of ingestion of the acute overdose, treatment with NAC is recommended if the measured serum concentration falls on or above the treatment nomogram line extended downward from a serum concentration of 150 μg/ml (or 1000 μmol/l) at 4 h after the time of ingestion [6,9,10]. In Sweden, the traditional three bag infusion protocol is used, i.e. a bolus dose of 150 mg/kg NAC over 15 min, followed by 50 mg/kg over 4 h and 100 mg/kg over 16 h. In overdose with MR paracetamol prolonged absorption have been reported and cases with "late nomogram crossers" i.e. patients with an initial "non-toxic" paracetamol concentration, below the treatment nomogram line, then subsequently crosses the treatment line [11–15]. In response to this, adaptions of national guidelines have been provided, which includes one serum paracetamol level at 4 h post-ingestion (as for IR formulations) and one additional measurement 4 h later. If either level is above the nomogram treatment line NAC should be commenced or continued. In addition, serum paracetamol concentration and serum alanine aminotransferase (ALT) are recommended to be measured before completion of NAC infusion, and the treatment to be continued if the ALT level is increasing (greater than 50 IU/l) or the paracetamol concentration is greater than 10 μg/ml (66 μmol/l) [16,17]. An increasing number of acute overdoses of the MR formulation in Sweden with prolonged, persistently high and unpredictable paracetamol levels were identified by the Swedish PC. This indicated that the recommended assessment and treatment regimen might not be enough for managing overdoses with this formulation. As this could be linked to differences in the exposure profile between the IR- and MR-formulations the pharmacokinetics (PK) and clinical outcome following acute overdoses of the MR product were investigated retrospectively.

Methods

This was a retrospective study using data from the Swedish PC and hospital records concerning overdoses of Alvedon 665. Overdose cases were identified from the Swedish PC database and clinical information was retrieved from hospital medical records, including laboratory data, for the period 2009 to 2015. The 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 analysis. Patients with mixed intake of IR and MR paracetamol overdoses were not included, neither patients with initially biochemical evidence of hepatic injury. Pertinent demographic and clinical data were recorded in a study protocol and the clinical courses of all included patients were followed. Population PK-modelling was employed as it is a suitable method for analysing routine clinical data [18]. The modelling was carried out using MONOLIX® (version 4.4.0, Lixoft, Orsay, France. www.lixoft.com). Data management, graphical analyses and descriptive statistics were performed in R (RStudio version 1.0.136; R version 3.2.3), Microsoft Excel (version 14.0.7177.5000) and MONOLIX®. The goodness-of-fit and stability of the final model was evaluated by examination of predictive checks (VPC, NPC), residual plots (NPDE vs time and predicted value), parameter precision, condition number and convergence of the SAEM algorithm [19]. The assumptions made in the model were assessed by comparing the Akaike information criterion value to that of models with less complexity, a procedure technically similar to traditional hypothesis testing. 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

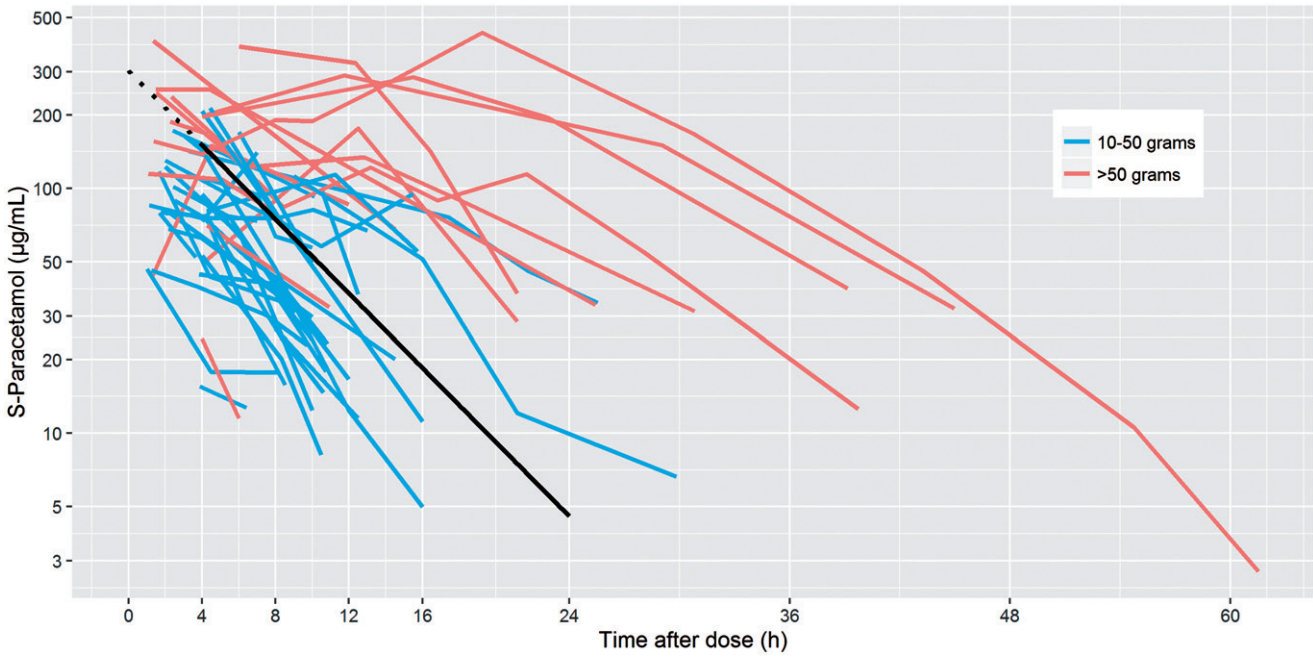

Figure 2. The figure displays the observed serum paracetamol concentration versus time after ingestion in 53 cases with MR overdose in a log-linear scale. Cases with dose range 10–50 g in blue, cases with dose over 50 g in red. The paracetamol treatment nomogram line (150 µg/ml at 4 h) in black as a comparison.

specific MR formulation. The proportion of the total dose subject to the transit compartment absorption process was estimated for the MR formulation. Further, the influence of dose on the mean transit time parameter (Mtt) for this process was estimated. For the IR cases, absorption was assumed to occur only through the first-order process. The typical value of apparent volume of distribution (Vd) and the typical value for the first order absorption rate constant (ka) was fixed to 65 L and 3 h^{-1}, respectively, in order to facilitate estimation of the parameters of the transit compartment absorption model. Serum paracetamol values that were below the lower limit of quantification (LLOQ) were still used in the modelling, using a method where the likelihood of the concentration being < LLOQ is estimated [20].

Results

During the study period 1348 consultations concerning the MR formulation were registered at the Swedish PC, 652 (48%) of them from hospitals, all in Sweden. In total 145 medical records were received and 53 of these cases collected from 29 different hospital met the inclusion criteria. The median age of the patients was 26 years (range 13–68) and 74% were females. The median reported dose was 20 gram (range 10–166). The number of paracetamol concentrations per individual ranged from 1 ($n = 2$) to 10 with a median of 3. There were in total 185 paracetamol concentrations available of which 24 were below the LLOQ. The LLOQ differed between hospitals and was in the range 1.2–15 µg/mL (8–100 µmol/L). In 25 cases, co-ingestion with other drugs was reported, mostly benzodiazepines. Median age of the 20 cases with overdose of IR paracetamol included in the PK-modelling was 23 years (range 12–67) and the median reported dose was 10 gram (range 5–45). The observed paracetamol concentrations in all 53 cases with MR overdoses *versus* time after the reported ingestion are shown in Figure 2. Seventeen cases had ingested a dose over 50 grams and are depicted in red colour in the figure. As seen in Figure 2, 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 paracetamol MR. Further; as a result of this delay double peaks became more evident with increasing doses as seen in Figure 3. 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 µg/ml or 300 µmol/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, neither transplantations nor 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 1. 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 4.

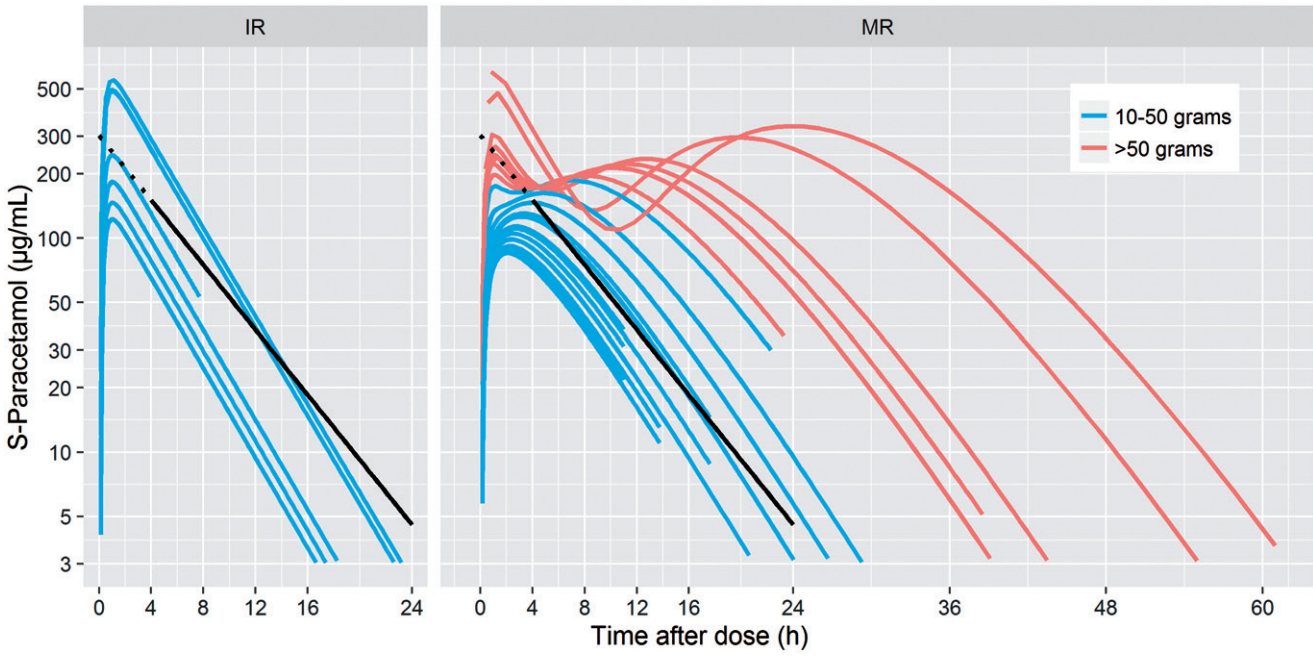

Figure 3. The figure shows the predicted serum paracetamol concentration versus time profile at each reported dose in a log-linear scale. The right panel ("MR") shows the PK profiles following ingestion of paracetamol MR. The left panel ("IR") shows the profiles following ingestion of paracetamol IR. The dose level is color coded in the same way for MR and IR for purpose of comparison. Blue color 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 µg/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.

Table 1. 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.

In two of the patients (D and G) prolonged courses of NAC was given (84–144 h) and in case D the treatment was even restarted with a second full course after 24 h. In case F, one full course was given, then the maintenance dose was restarted after a break of 9 h and given for further 9 h (in totally 30 h treatment).

Discussion

We report 53 cases of overdose of a MR paracetamol formulation from which serial serum concentrations and liver function tests were obtained. Case reports and smaller case series have been published previously, although with fewer serum concentrations and less serious overdoses [11–15,21–25]. In our 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 modeling. A model with Michaelis-Menten elimination (AIC = 3074.35) did not fit the data as good as the model with linear clearance (AIC = 2789.16). 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

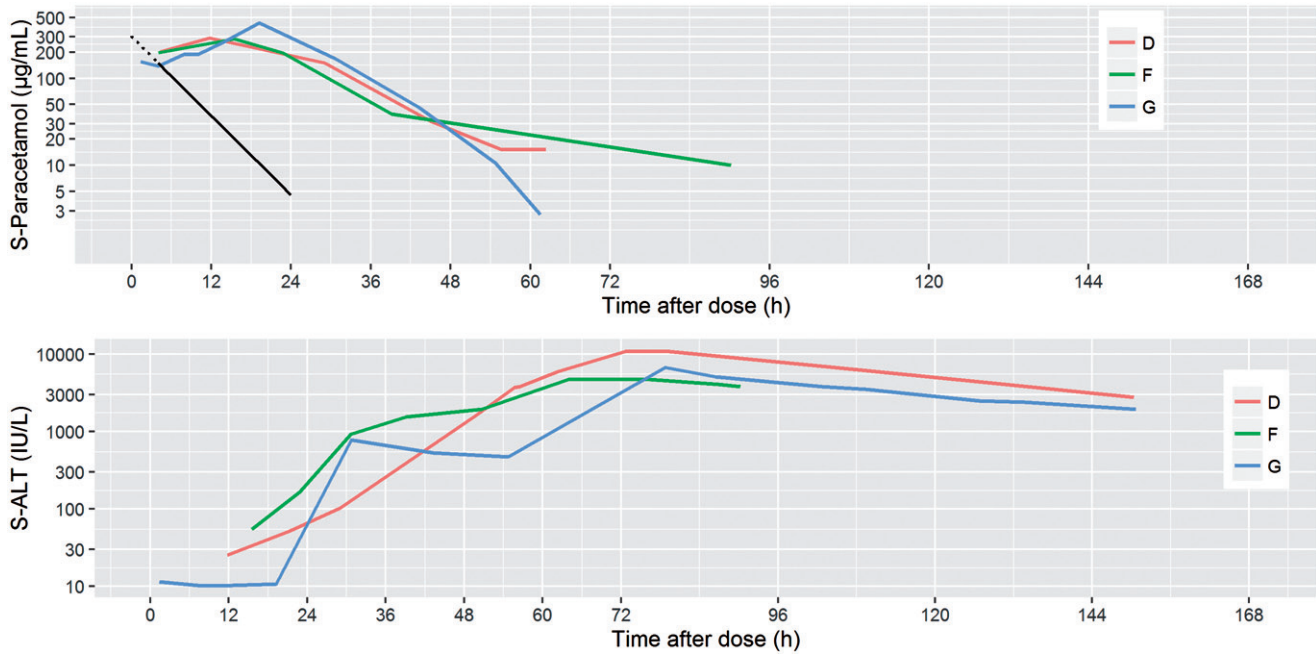

Figure 4. The figure shows the time course of serum paracetamol and alanine aminotransferase (ALT) levels versus time in a log-linear scale, after ingestion of MR overdose in three patients (D, F and G). The paracetamol treatment line (150 µg/ml at 4 h) is included in the upper panel for comparison. Information about ingested dose, serum peak level and peak ALT for each patient is found in Table 1.

consistently follow a proportional decline and the estimated half-life was longer than 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 a thereafter a second delayed peak were noticed due to absorption of the MR part. The delay and magnitude of this second peak correlated to increasing dose. In our study the majority of cases with prolonged and high paracetamol concentrations for more than 24 h had a reported dose of 50 g or more. Other factors that can contribute to delayed absorption and double peaks are delayed disintegration and dissolution profile of the tablets, and possible pharmacobezoar formation in the gut [11,26,27]. In a recent in vitro-study, 30 tablets of either IR or MR formulations of paracetamol (500 mg) were incubated in simulated gastric fluid for 48 h. The IR tablets were dissolved within 30 minutes while the MR tablets had formed a compact bezoar at 4 h, still visible after 48 h. Concomitant with the bezoar formation, a prolonged drug release were observed; after 8 and 48 h, respectively, only 19 and 55% of the paracetamol content in the tablets were released [28]. Another contributory factor, independent of the paracetamol formulations, which can affect and prolong the absorption of paracetamol is co-ingestion of drugs that impair gastrointestinal motility, such as opioids [29]. However, no connection between co-ingestion of other drugs and the erratic exposure profile could be seen in the study. 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 is 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 were 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) not is 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

An inherent limitation of the study is related to the retrospectively collection of data from the Swedish PC and hospital case records. Reported ingested dose, time for ingestion and measurements of serum concentrations might be incorrect in the medical records. Reporting to poison centre is voluntary, so there is a possible reporting or selection bias. Although, extrapolation of results from this study to other MR formulations should be done with cautions as differences in the pharmaceutical formulation may affect the dissolution and PK behaviour.

Conclusions

Overdoses with MR paracetamol increases in Sweden and has turned out to be a challenge for the health care system,

compared with known IR overdoses. The purpose of this study was to gather PK and clinical data to facilitate the management of such overdoses. The study shows that the serum paracetamol-time profile following overdose with paracetamol MR is characterised by prolonged absorption with delayed maximum serum concentrations. Persistent high levels of paracetamol were observed, clearly correlated to increasing doses. This is in line with previously published case reports. The standard treatment protocol, based on experiences with IR paracetamol, was insufficient to prevent development of liver damage especially in the cases with persistent high serum levels. Further studies are required to better determine the optimal and pragmatic management for potential poisoning involving MR formulations.

Disclosure statement

No potential conflict of interest was reported by the authors.

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