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PHARMACOKINETICS AND DISPOSITION

Paracetamol for intravenous use in medium- and intensive care patients: pharmacokinetics and tolerance

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Abstract
Purpose We studied the pharmacokinetics of paracetamol and determine the incidence of hypotension after intravenous administration in medium- (MCU) and intensive care (ICU) patients.
Methods All patients on the ICU/MCU starting with paracetamol i.v. were included, yielding 38 patients. Blood samples were collected at predetermined time points to determine paracetamol serum concentration. The number of patients with a clinically relevant reduction in systolic blood pressure (SBP) and the number of patients that needed intervention to regain an acceptable blood pressure level were assessed.
Results Overall, pharmacokinetic data were roughly comparable with earlier publications, but differences were noted in the subgroup ICU patients. Also, there was a trend to a larger peak serum concentration ($p=0.052$) and a significantly smaller volume of distribution ($p=0.033$) in MCU patients compared with ICU patients. Twenty-two percent (22%) and 33% of patients had a clinically relevant reduction in systolic blood pressure (SBP) 15 and 30 min after start of paracetamol infusion, respectively. In six patients (16%), an intervention was needed to correct blood pressure. Overall, SBP was significantly reduced at T=15 min and 30 min postinfusion ($p<0.003$ at both time points) when compared with SBP at the start of paracetamol infusion.
Conclusions Further research on differences in paracetamol pharmacokinetics between ICU and MCU patients is warranted, as these differences might result in differences in efficacy. Furthermore, administration of paracetamol i.v. as potential cause of hypotension in the critically ill patient must not be overlooked.

Keywords Paracetamol · Pharmacokinetics · Safety · Critically ill patients

The study was performed at the Albert Schweitzer Hospital, Dordrecht, The Netherlands.

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Introduction

Paracetamol is a frequently used drug on the Intensive Care (ICU) and Medium-Care (MCU) units. It is used both as an analgesic and an antipyretic to reduce oxygen consumption. Paracetamol is, when used in therapeutic dosages, generally well tolerated. However, in overdosage, it can cause severe hepatic necrosis [1, 2]. In the ICU/MCU, paracetamol is mostly administered as a rectal formulation. As the patient has to be turned to administer paracetamol rectally, for the nursing staff at these wards, it is not the most practical way of drug administration. In addition, diarrhea or rectal surgery limits the use of suppositories. Another issue in

this patient category is the unpredictable enteric absorption, which also argues for the use of an i.v. formulation of paracetamol.

Recently, Perfalgan™, a parenteral formulation of paracetamol, became available in The Netherlands [3]. Only a limited amount of pharmacokinetic and pharmacodynamic studies have been performed with this formulation [4–6]. A study in a small group of healthy male volunteers showed a mean peak serum concentration (C_{max}), observed at the end of a 15-min i.v. infusion of 1 g paracetamol (Perfalgan), of 29.9 mg/L (range 17.1–49.3 mg/L) and a mean area under the plasma concentration-time curve (AUC_{inf}) from time zero to infinity of 57.6 mg*h/L [4]. Peak serum concentrations of 10–20 mg/L are considered to be the therapeutic antipyretic range [7]. Serum paracetamol concentrations providing analgesia are unknown but are assumed to be higher than the antipyretic serum concentrations [7]. In children undergoing a tonsillectomy, paracetamol was administered in a dose of 40 mg/kg both orally and rectally [8]. Paracetamol serum concentrations > 20 mg/L yielded insufficient painkilling effects in 15% of children [8]. In contrast, Hahn showed that an i.v. dose of only 5 mg/kg paracetamol (administered as propacetamol), by which an initial serum concentration of 14 mg/L was reached, yielded sufficient analgesia [9]. A study by Beck et al. demonstrated a C_{max} of only 10.4 mg/L and 17.2 mg/L after rectal administration of paracetamol at 20 mg/kg and 40 mg/kg, respectively [10]. Furthermore, another study compared the bioavailability of paracetamol after oral and i.v. (propacetamol) administration [11]. Oral administration of paracetamol as part of multimodal pain management immediately postoperatively resulted in a huge and unpredictable variation in plasma concentration compared with the i.v. administration [11]. Predictability of serum concentrations, quick achievement of C_{max} after administration, and a higher C_{max} (with probably larger therapeutic effect [12, 13]) compared with oral [9] or rectal [6] administration) could argue for use of the parenteral formulation of paracetamol. In addition, ease of administration of drugs in the ICU/MCU, particularly with drugs that need to be administered several times a day, is a factor worth considering.

Perfalgan was introduced in the ICU/MCU of the Albert Schweitzer Hospital (Dordrecht, The Netherlands) mid-2005. In our clinical experience, we noted that approximately 25% of patients showed an episode of hypotension shortly after administration of paracetamol i.v. and that an estimated 8% of the patients needed an intervention to regain an acceptable blood pressure level. This adverse event is described in the product information of Perfalgan, but only with an incidence of 0.01–0.1% [3]. At this time, pharmacokinetic data of Perfalgan in clinical patients, particularly ICU and MCU patients, is limited. We therefore wanted to study the pharmacokinetics of paracetamol after i.v. administration in ICU/MCU patients. In addition, we wanted to determine the incidence of infusion-related hypotension in this patient population.

Methods

Patients and data collection

All adult patients admitted to the ICU or MCU were eligible provided they had an arterial catheter and were to start paracetamol 1 g i.v. four times daily. Only patients or their representatives who gave written informed consent were included in this study. Approval was obtained from the Institutional Review Board. Contraindications for paracetamol administration [3] were considered for every patient and were as follows:

- Hypersensitive for paracetamol, propacetamol hydrochloride, or one of the additives of the infusion solution and/or
- Severe hepatocellular insufficiency (which is left to the discretion of the responsible intensivist)

The following patient characteristics were collected at baseline: age, gender, height/weight, type of admission on ICU or MCU, clinical chemistry parameters (liver, kidney, lactate), activated partial thromboplastin time (APTT), prothrombin time (PT), indication for paracetamol, Acute Physiology And Chronic Health Evaluation (APACHE) II score on the day paracetamol was studied, and body temperature. SBP and diastolic blood pressure (DBP) were recorded at time point (T)=0 min (just before start of paracetamol infusion), T=15 min (end of paracetamol infusion), and T=30 min. SBP and DBP were measured using an arterial line. A reduction of at least 10 mmHg in SBP at T=15 min and T=30 min was considered clinically relevant. Interventions to correct hypotension were recorded until 60 min after the end of paracetamol infusion (T=75 min). During this 60 min period, syringe changes, fluid boluses, administration of other drugs, change of infusion rate of current drugs, and changes in ventilator settings were reduced to a minimum. If, in case of urgent handling, one of the above-mentioned actions had to be executed (for instance, due to paracetamol-induced hypotension), it was written down.

Study drug and blood samples

Perfalgan 10 mg/ml, infusion solution (Bristol-Myers Squibb B.V., Woerden, The Netherlands) was administered in a dose of 1 g four times daily by means of a 15-min infusion of 100 ml=1,000 mg ready-to-use solution [3].

Start of the infusion was T=0. Blood samples were drawn at the following time points: T=0 (just before paracetamol infusion), 15, 30, 45, 60, 120, 180, 240, and 359 min (= just before next paracetamol administration). The exact time of sampling was noted down.

Bioanalysis

Blood samples were obtained at specified time points, centrifuged (4,000 rpm, 5 min), and serum was separated. Serum samples were stored at −20°C until analysis. Concentration of paracetamol in the serum sample was proven to be stable during at least 2 months after withdrawal (data on file). Concentrations of paracetamol in serum were quantitatively determined with fluorescent polarization immunoassay (Cobas Integra 400, Roche Diagnostics, West Sussex, UK). Within-run variation and total variation for low as well as high concentrations (9.9 mg/L, 32.9 mg/L, and 97.4 mg/L) were within a range of 0.7–5.8% and 4.4–7.5%, respectively. Lower limit of detection of the analysis was 0.2 mg/L.

Pharmacokinetic analysis

Pharmacokinetic parameters were derived by noncompartmental analysis with WinNonlin, version 4.1 (WinNonlin 4.1, Pharsight, USA). The highest observed serum concentration was defined as C_{max}. The terminal log-linear period (log C versus t) was defined by the last data points ($n \geq 3$). The absolute value of the slope ($\beta/\ln 10$) was calculated by least squares linear regression analysis. The elimination half-life ($t_{1/2}$) was calculated using the equation $t_{1/2}=\ln 2/\beta$. The area under the serum concentration time curve (AUC) was obtained using the log-linear trapezoidal rule from 0 to the last data point and then extrapolated to infinity (AUC_{inf}). Clearance (CL) was calculated by dividing the dose by the corresponding AUC_{inf}. The volume of distribution (V_d) was calculated by dividing CL by β.

Statistics

SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. Results of pharmacokinetic parameters are expressed as median and interquartile range (IQR). Pharmacokinetic parameters (C_{max}, AUC_{inf}, CL, V_d, and $t_{1/2}$) were compared using the Mann–Whitney U test. SBP at T=15 and T=30 min was compared with that at T=0 min with the Wilcoxon signed-rank test. Relationships between the occurrence of a relevant reduction in SBP at T=30 min and possible risk factors were tested by univariate analysis with logistic regression. Factors considered were baseline characteristics including gender, age, APACHE II, admittance to ICU/MCU, lactate, and SBP at baseline. For these analyses, a p value of ≤ 0.05 was considered statistically significant.

Results

Patient characteristics

Patients were included from December 2006 until April 2007. During this period, data of 38 patients was collected. Table 1 presents the baseline characteristics of these patients.

The patient population was predominantly male (71%) and had a median age of 68 years. Most patients were hemodynamically stable postoperative patients and stayed on the MCU for observation after surgery (68%). The indication of paracetamol in the included patients was, consequently, predominantly pain (Table 1).

Pharmacokinetic analysis

Figure 1 shows the serum paracetamol concentration versus time data for individual study participants. The data set consisted of 28 full pharmacokinetic curves (nine samples per patient). From the ten other patients, five to eight samples were available. Table 2 presents the pharmacokinetic data of all included patients and for the different groups, i.e., patients admitted to the MCU and ICU. The median peak serum concentration (C_{max}) was 25.92 mg/L (IQR 21.05–33.61 mg/L) and ranged from 8.32 to 59.92 mg/L (Table 2). The other pharmacokinetic parameters (AUC_{inf}, CL, V_d, and $t_{1/2}$) showed, in accordance with the C_{max}, a large variation (Table 2).

Statistical analysis showed a trend to a larger C_{max} ($p=0.052$) and a significantly smaller V_d ($p=0.033$) in MCU patients when compared with ICU patients. Although not statistically different ($p>0.05$), CL and AUC_{inf} of paracetamol in MCU patients were 47% lower and 100% higher, respectively, when compared with ICU patients.

Hypotension

Table 3 presents data on observed blood pressure (diastolic and systolic) at the different time points. Blood pressure could be assessed from 36 of the 38 patients at both time points. At T=15 and 30 min, eight (22%) and 12 (33%) of the 36 patients had a reduction in SBP of at least 10 mmHg when compared with baseline (T=0), respectively. Six of eight patients that showed a relevant reduction in SBP at T=15 min had a persistently low SBP at T=30 min (both compared with T=0). In three of the eight patients, there was a further decay in SBP at T=30 min compared with T=15 min. In patients with a clinical relevant reduction in

Table 1 Baseline patient characteristics

Parameter	Number (%)	Median	Interquartile range
APACHE II		12.5	10–16
Gender M/F	27/11 (71/29)		
Age (years)		68	60–74
Height (cm)		173	167–180
Weight (kg)		78	70–88
ICU/MCU	12/26 (32/68)		
Type of admission			
Surgical	33 (87)		
Gastrointestinal bleeding	2 (5)		
Meningitis	2 (5)		
CPR	1 (3)		
Indication paracetamol			
Fever	2 (5)		
Pain	32 (84)		
Both	4 (11)		
Temperature (°C)		36.8	36.1–37.3
Hematology			
APTT (s)		35	28–43
PT (s)		12	11–13
Clinical chemistry parameters			
Creatinine (μmol/L)		89	78–131
Urea (mmol/L)		6	4–10
Albumin (g/L)		26	21–32
Bilirubin (μmol/L)		15	11–18
GGT (E/L)		20	16–51
AF (E/L)		69	47–87
ASAT (E/L)		32	21–61
ALAT (E/L)		21	16–38
LD (E/L)		357	301–608
Lactate (mmol/L)		1.3	0.7–2.0

AF alkaline phosphatase, *ALAT* alanine aminotransferase, *APTT* activated partial thromboplastin time, *ASAT* aspartate aminotransferase, *CPR* cardiopulmonary resuscitation, *F* female, *GGT* gamma-glutamyltransferase, *ICU* Intensive care unit, *LD* lactate dehydrogenase, *M* male, *MCU* Medium care unit, *PT* prothrombin time

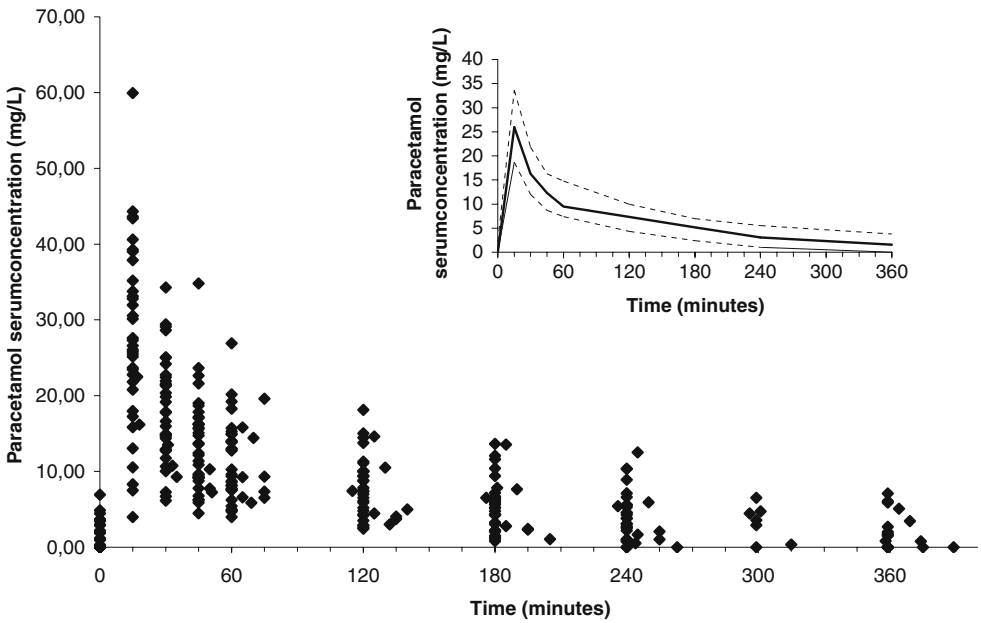

Fig. 1 Concentration-time data of paracetamol. ♦ Individual paracetamol serum concentration. Insert: *Solid line* represents the median value of the paracetamol serum concentration at the different time points in the study population. *Dashed lines* represent first and third quartiles of paracetamol serum concentration

Table 2 Pharmacokinetic data

Median [IQR] (min-max)

	All patients $N=38$	MCU $N=26$	ICU $N=12$	p value*
C_{max} (mg/L)	25.92 [21.05–33.61] (8.32–59.92)	26.97 [23.51–37.21]	20.35 [16.13–28.69]	0.052
AUC_{inf} (mg/L*h)	42.28 [21.36–49.93] (13.19–123.64)	47.99 [31.60–69.89]	24.64 [18.56–54.54]	0.129
CL (L/h)	23.65 [15.71–40.54] (7.49–67.04)	20.84 [14.34–31.65]	39.78 [18.43–53.87]	0.137
V_d (L)	52.01 [44.41–74.36] (15.44–152.11)	50.88 [42.11–61.61]	71.09 [54.20–86.32]	0.033
$T_{1/2}$ (h)	1.63 [1.07–2.30] (0.35–4.73)	1.63 [1.13–2.29]	1.76 [0.92–2.32]	0.963

AUC$_{inf}$ area under the serum concentration versus time curve extrapolated to infinity, *CL* clearance, *C$_{max}$* maximum serum concentration, *ICU* intensive care unit, *IQR* interquartile range, *MCU* medium care unit, *t$_{1/2}$* elimination half-life, *t$_{max}$* time to C_{max}, *V$_d$* volume of distribution

*Mann–Whitney *U* test

SBP, SBP dropped with 6.5–31% ($n=8$) and 6.5–44% ($n=12$) at T=15 and T=30 min, respectively, when compared with baseline.

Two patients with a clinically relevant reduction in SBP were admitted to the ICU; all other patients were admitted to the MCU. Overall, SBP was significantly reduced ($p<0.05$) at T=15 min and 30 min when compared with SBP at the start of the paracetamol infusion (Table 3). The logistic regression analysis did not identify any possible risk factors for a relevant reduction in SBP. Figure 2 shows the APACHE II scores for patients with and without a clinically relevant reduction in SBP.

Six patients (16%) needed an intervention to regain blood pressure control. Three had a clinically relevant reduction in SBP at T=15 or 30 min. Increase of noradrenaline infusion occurred in four patients (11%) and a fluid bolus (gelatin) was given in five patients (13%). Two patients were extremely restless and/or experienced diaphoresis at time point 15 min; both had a clinical reduction in SBP at the defined time points (one at T=15 and one at T=30 min), but no intervention was performed during the following time period (until 60 min after end of paracetamol infusion).

Discussion

Here we describe the pharmacokinetics of paracetamol after i.v. administration in a population of patients admitted to the MCU and ICU. In this observational study, paracetamol was administered as a ready-to-use solution (Perfalgan). In a study by Flouvat et al., the pharmacokinetics of paracetamol was compared with propacetamol, an injectable prodrug of paracetamol requiring reconstitution [4]. The pharmacokinetic parameters in that study were roughly comparable with the parameters of the patients in our study. A difference, however, was observed between the $t_{1/2}$ found in healthy volunteers compared with patients in our study: 2.72 h versus 1.63 h, respectively. A smaller V_d in our population probably accounts for this difference. In addition, AUC_{inf} and CL were lower and higher, respectively, in our study when compared to the data of Flouvat et al. [4].

We also studied whether there was a difference in the pharmacokinetic parameters of patients admitted to the ICU and MCU. ICU patients showed a trend to a smaller C_{max} and a significantly higher V_d when compared with MCU patients. Our hypothesis is that ICU

Table 3 Blood pressure

	Time point (min)			
	T=0	T=15	T=30	p value
Median BP systolic [IQR]	127 [110–145]	120 [103–139]	114 [101–130]	0.0026* 0.0002**
Median BP diastolic [IQR]	64 [55–70]	60 [52–67]	61 [50–66]	

BP blood pressure, *IQR* interquartile range

*BP systolic T=15 versus T=0, Wilcoxon signed rank test

**BP systolic T=30 versus T=0, Wilcoxon signed rank test

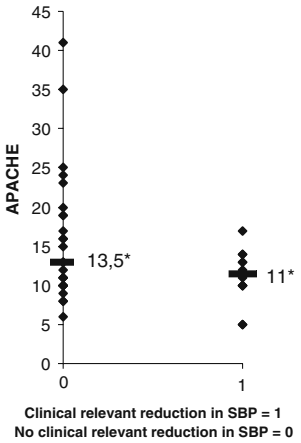

Fig. 2 Acute Physiology And Chronic Health Evaluation (APACHE) II scores in patients with and without a clinically relevant reduction in systolic blood pressure (SBP). *Median value

patients were more severely ill and as a result had a larger extracellular volume because of capillary leakage. A posthoc analysis confirmed this hypothesis: Patients on the ICU had a higher body temperature, APACHE II score, serum urea, LD and lactate at baseline than patients on the MCU (APACHE II, temperature and biochemistry parameters were tested with Mann–Whitney *U* test, see Table 1).

Our ICU patients had a 32% lower C_{max} and a 122% higher CL (and consequently a lower AUC_{inf}) than the healthy volunteers in the study of Flouvat et al. [4]. This was, however, an observational study. Thus, these results must be confirmed in a controlled study with a calculated sample size. Also, whether the observed differences in pharmacokinetics resulted in differences in pharmacodynamic effect cannot be said. Neither pain nor body temperature was monitored in the context of the study.

Furthermore, we found a significant reduction in SBP 15 and 30 min after start of paracetamol infusion when compared with SBP at baseline. In addition, a clinical relevant reduction in SBP (at least 10 mmHg) was seen in 22% and 33% of included patients at 15 and 30 min, respectively. The incidence of hypotension is thus higher than described in the product information for Perfalgan [3]. Moreover, 16% of the included patients needed an increase in noradrenaline infusion or a fluid bolus to regain an acceptable blood pressure. A prospective study in critically ill patients showed 27 events of hypotension in 14 patients after administration of propacetamol. Mean arterial pressure (MAP) dropped significantly in these patients, requiring active intervention (initiation or increase of noradrenaline or a fluid bolus) in 33% of the events [14]. Three other reports of paracetamol-induced hypotension in ICU patients were found in the literature [15–17]. Boyle and colleagues [16] found a significant reduction in MAP within 15 min of oral paracetamol administration, which persisted for 90 min. Based on the published results so far, the occurrence of paracetamol-induced hypotension seems thus independent of route of administration or formulation. Whether the high incidence of hypotension is dependent on the specific population (ICU or MCU patients) in which it is administered is not clear. Mackenzie found in their study that MAP was lower in male than in female patients after administration of paracetamol and was correlated with age and baseline MAP [17]. We, however, did not identify any specific risk factors for the occurrence of hypotension. In particular, APACHE II score was not significantly related with an episode of hypotension (see Fig. 2).

In conclusion, we describe the pharmacokinetics of paracetamol after i.v. administration in a large population of patients admitted to the ICU or MCU. Overall, data were roughly comparable with earlier publications, but differences were noted in the ICU population. Further research on the importance of this finding in relation to paracetamol's analgesic or antipyretic effect might be needed. In addition, our data on paracetamol-induced hypotension confirms the subjective observations noted by our nursing staff. As its incidence is high, hypotension caused by paracetamol, a drug frequently used in the ICU/MCU population, must not be overlooked.

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Conflicts of interest The authors declare that they have no conflict of interest.

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