British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2019) **85** 126–135 126

ORIGINAL ARTICLE

Population pharmacokinetic modelling of intravenous paracetamol in fit older people displays extensive unexplained variability

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Received 7 July 2018; **Revised** 10 September 2018; **Accepted** 16 September 2018

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Principle investigator: The authors confirm that the PI for clinical data reused in this paper is Klaus Olkkola and that he had direct clinical responsibility for patients

Keywords acetaminophen, aging, elderly, geriatric, pharmacokinetics, variability

AIMS

Paracetamol is the analgesic most used by older people. The physiological changes occurring with ageing influence the pharmacokinetics (PK) of paracetamol and its variability. We performed a population PK-analysis to describe the PK of intravenous (IV) paracetamol in fit older people. Simulations were performed to illustrate target attainment and variability of paracetamol exposure following current dosing regimens (1000 mg every 6 h, every 8 h) using steady-state concentration ($C_{ss\text{-}mean}$) of 10 mg l^{-1} as target for effective analgesia.

METHODS

A population PK-analysis, using NONMEM 7.2, was performed based on 601 concentrations of paracetamol from 30 fit older people (median age 77.3 years, range [61.8–88.5], body weight 79 kg [60–107]). All had received an IV paracetamol dose of 1000 mg (over 15 min) after elective knee surgery.

RESULTS

A two-compartment PK-model best described the data. Volume of distribution of paracetamol increased exponentially with body weight. Clearance was not influenced by any covariate. Simulations of the standardized dosing regimens resulted in a C_{ss} of 9.2 mg l^{-1} and 7.2 mg l^{-1}, for every 6 h and every 8 h respectively. Variability in paracetamol PK resulted in C_{ss} above 5.4 and 4.1 mg l^{-1}, respectively, in 90% of the population and above 15.5 and 11.7, respectively, in 10% at these dosing regimens.

CONCLUSIONS

The target concentration was achieved in the average patient with 1000 mg every 6 h, while every 8 h resulted in underdosing for the majority of the population. Furthermore, due to a large (unexplained) interindividual variability in paracetamol PK a relevant proportion of the fit older people remained either under- or over exposed.

DOI:10.1111/bcp.13770

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Physiological changes occurring with ageing influence the pharmacokinetics (PK) of intravenous paracetamol and its variability.
- Although PK of paracetamol have been described, no analysis in older people has been conducted trying to both explain variability in paracetamol PK as well as to illustrate target attainment (10 mg l^{-1}) following currently dosing regimens.

WHAT THIS STUDY ADDS

- The steady-state target concentration of 10 mg l^{-1} was achieved with 1000 mg every 6 h and every 8 h (9.2 and 7.2 mg l^{-1} respectively), resulting in underdosing for the average patient.
- Due to large (unexplained) interindividual variability in paracetamol PK, a relevant proportion of fit older people remained under- (every 8 h) or over-exposed (every 6 h).

Introduction

The proportion of older people (age > 65 years) in the world population has increased by 48% from 2000 to 2015 [1]. The number of older people is estimated to increase from 962 million in 2017 to 2.1 and 3.1 billion between 2050 and 2100, respectively [1]. It is expected, therefore, that the prevalence of diseases associated with advancing age, including pain syndromes, will rise.

Older people's pain management is still often suboptimal [2]. The most used analgesic in older people is **paracetamol** (acetaminophen, APAP) [3], prescribed not only for the management of chronic pain, but also for acute pain (e.g. postoperative pain) [4]. The paracetamol disposition can be affected, however, by specific physiological factors such as increased body fat and decreased renal function, which may explain suboptimal effect. In addition, great individual variability in drug disposition may be expected in this very heterogeneous population.

Drug trials usually exclude older subjects. Therefore, drug dosages for older people are mostly based on clinical experience, expert opinion or extrapolations from studies in younger adults. Intravenous (IV) paracetamol is currently registered for the short-term treatment of pain at a dose of 1000 mg every 6 h (maximum daily dose 4000 mg) in adults with a body weight of >50 kg and at a dose of 15 mg kg^{-1} (maximum daily dose 60 mg kg^{-1} or 3000 mg) in adults with a bodyweight of ≤50 kg [5, 6]. As old age in itself is a potential risk factor for paracetamol toxicity, it has been proposed to limit dosing to 3000 mg daily, even for adults weighing >50 kg [7] and to monitor safety parameters (e.g. liver function test) when IV paracetamol is used for longer than 48 h [7]. Although there is a lack of evidence supporting dose reduction in patients with risk factors [7], IV paracetamol (especially 1000 mg every 8 h) [8] is widely used in older people.

Several noncompartmental pharmacokinetic (PK)-studies comparing cohorts of fit older people with cohorts of young adults found a lower volume of distribution (Vd) of 22.9% and paracetamol clearance (CL) of 45.7% in the older people [9, 10]. As the PK analyses showed high variability in PK in the fit older people, the question is in what way this influences the exposure to (and thereby the efficacy of) the drug and if there is a reason to adjust paracetamol dosages.

Adequate analgesia in the paediatric population was achieved at steady-state concentration ($C_{ss\text{-}mean}$) of 10 mg l^{-1} [11]. Since this target concentration assumedly holds for older people as well, although with limited validation, it is therefore also used for the management of acute (postoperative) pain in older people. Using a population-PK modelling approach, we performed a study to estimate the PK of IV paracetamol and its variability in fit older people using a population PK-modelling approach. To illustrate target attainment and variability of paracetamol PK in fit older people simulations were performed with current dosing regimens (1000 mg every 6 h, every 8 h) and a $C_{ss\text{-}mean}$ of 10 mg l^{-1} as target for effective analgesia [11].

Methods

Patients, study design and drug dosing

Data on paracetamol concentrations from a previous observational study in older, fit subjects who underwent surgery were analysed [12]. The design of that study is summarized here, as it is relevant to this analysis. The study was conducted at the Turku University Hospital, Turku, Finland, following approval by the Finnish Medicines Agency and registration (EUDRACT 2006–001917-14) and included 30 older subjects who underwent elective knee prosthesis operations. The exclusion criteria were: use of strong inhibitors or inducers of cytochrome P450 enzymes, having a significant hepatic, renal, neurological, haematological, endocrine, metabolic or gastrointestinal disease, or a body mass index >35 kg m^{-2}. Patients with diabetes mellitus were eligible unless they had significant renal involvement [12]. The clinical characteristics of the subjects are shown in Table 1.

A single IV paracetamol infusion with a dose of 1000 mg was administered over 15 min according to the postoperative pain protocol. Blood was sampled at fixed time-points, namely before infusion (t = 0), during infusion (t = 7.5, 15 min), and after completion of the infusion (2.5, 5, 10, 15, 20, 30, 45, 60 min and 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24 h after infusion). In total 22 samples per patient were obtained.

Analytical assay

Paracetamol concentrations were determined by the high-performance liquid chromatographic method at the Department of Clinical Pharmacology, Helsinki and Helsinki University Central Hospital, Helsinki, Finland [12, 13].

The assay was linear over 0.5–250 μg ml^{-1}. The lower limit of quantification (LLOQ) was 0.25 mg l^{-1}. Intra- and interassay accuracies were < 5% and < 7%, respectively.

Table 1

Characteristics of 30 subjects

Variable	
Male, %	12 (40)
Age, years	77.3 [61.8–88.5]
Weight, kg	79 [60–107]
ASA physical status	
I	-
II	17 (56.67)
III	11 (36.67)
IV	2 (6.67)
Creatinine (μmol l^{-1})	75 [50–147]
MDRD (ml min^{-1} 1.73 m^{-2})	74.42 [29.56–116.8]

Values are presented as median [range] or *n* (%). ASA, American Society of Anesthesiologists; MDRD, modification of diet in renal disease

Intra- and interassay imprecision did not exceed 15%. Further details of the analytical assay are provided in the previous published papers [12, 13].

Population PK analysis

Paracetamol was analysed using nonlinear mixed effect modelling software NONMEM version 7.2 (ICON Development Solutions, Ellicott City, MD) using the first-order estimation method with the interaction option (FOCE-I) and subroutine ADVAN13, TOL6. Pirana (version 2.9.2), R (version 3.3.0) and PsN® version (version 4.4.8) software were used for graphical and numerical analysis of the output.

The model building process was performed stepwise as follows: (i) the structural population model; (ii) the statistical submodel; (iii) the covariate model; and (iv) internal validation. The different models were discriminated by the likelihood ratio test using the objective function value (OFV; i.e. –2*log likelihood), where a decrease in OFV of 7.8 points ($P < 0.005$ based on a χ^2 distribution) was considered statistically significant, between nested models with one additional degree of freedom. Furthermore, basic goodness-of-fit-plots were evaluated [14]. Additionally, the relative standard errors (RSE), the condition number and the η-shrinkage of the random effects were assessed during model evaluation. These should be as low as possible but preferably not exceed 60%, 1000 and 25% respectively [14].

Structural and statistical model. For the structural model, one, two and three compartment PK models for paracetamol were tested. For the statistical model, interindividual variability on the model parameters was assumed to be log-normally distributed and was tested for significance on all parameters. Variance were explored and included by an omega block if applicable. For the residual unexplained variability, a proportional, additive and a combined error model were tested.

Covariate model. The tested covariates were body weight, age, sex, creatinine concentration and creatinine clearance (using Modification of Diet in Renal Disease). To visualize potential relationships, covariates were plotted independently against the individual *posthoc* estimates of the PK parameters. Continuous potential covariates were tested using a linear or power equation (equation 1).

$$Pi = \theta 1 * \left(\frac{COV}{COVmedian}\right)^{\theta 2} + \theta 3 \quad (1)$$

In the equation, *Pi* represents the population parameter estimates; θ_1 and θ_3 represent the population parameters estimates (θ_1 population factor of proportionality, θ_3 population intercept) for the covariate relationship and *COV* represents the covariate value, which is normalized with the median covariate value (COV_{median}) representing the median value of the covariate for the full population. Θ_2 is the population exponent, which was fixed to 1 for a linear function or estimated for a power function. For the categorical covariate sex, the fractional change for one group compared to the other group was calculated.

Potential covariates were entered one by one using the bottom up inclusion method and considered statistically significant when the OFV decreased with at least 7.8 points ($P < 0.005$). When more than one significant covariate was identified, the covariate causing the largest drop in OFV was retained. For additional covariates to be retained in the model, this OFV had to be educed with the use of the same criteria. In addition, a reduction in interindividual variability of the parameter was evaluated upon inclusion of the covariate on the parameter.

Internal validation

For internal model validation, a bootstrap resampling method to test the stability of the model was conducted using 1000 replicates. Accuracy of the model was evaluated with visual predictive checks (VPC). For this VPC a set of 1000 simulated datasets were created to compare the observed concentration with the distribution of simulated concentrations.

Simulations

IV administration-dosing regimens were simulated, with 1000 replicates per simulation, using the final developed population PK model. The two dosing regimens frequently used in clinical practice, namely 1000 mg administered during 15 min every 6 h (max 4000 mg per day) and 1000 mg every 8 h (max 3000 mg per day) were simulated for 48 h [5, 6]. For each simulated concentration–time profile, the $C_{ss\text{-}mean}$ was calculated, based on the area under the plasma concentration–time curve and divided by the dosing interval during the final dosing interval. In addition, for each concentration time profile the 10, 25, 50, 75 and 90 percentiles of the C_{ss} were calculated.

Nomenclature of targets and ligands

Key ligand in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [15], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.

Results

Population PK analysis

The PK-model was based on 601 samples. Forty-seven samples (7.8%) were below the lower limit of quantification (LLOQ). The LLOQ occurred for samples taken after 10.25 h. These samples were excluded from the analysis.

Structural and statistical model. A two-compartment model best described the data (Figure 1). A three-compartment model improved the OFV significantly (dOFV = –53), but the estimation of the second peripheral compartment resulted in an unrealistic high volume of distribution (Vd >1000 l) for this compartment and was therefore not continued. A two-compartment model was estimated with high precision (low RSEs) and therefore preferred over the three-compartment model; the more so because the latter showed limited improvement in the goodness-of-fit plot.

Interindividual variability on all parameters significantly improved the model. Residual variability for paracetamol was best described with a proportional error model. A separate residual variability for paracetamol was estimated for the early sample time-points (t = 7.5 and 15 min) during infusion, due to a larger variability present.

Covariate model. For paracetamol, the systematic covariate analysis identified sex as the most significant covariate on the central Vd (dOFV –21), implying a lower Vd in females (1.8 times higher in males; Figure S1). As distribution of sex over the age range was skewed in favour of women aged >80 years; Figure S4), and as the relevance of this covariate in the clinical setting is undefined, this covariate was not included in the model. In addition, colinearity was present between body weight and sex (Pearson correlation of 0.69). Body weight, in an exponential relationship, was identified as the second-best explanatory variable for the Vd (dOFV = –17), implying that the Vd increases in an exponential relationship (Figure S2) with increasing body weight. Thereafter, age decreased the CL of paracetamol (dOFV = –10). However, this parameter could not be accurately estimated (RSE 141%), and age was therefore not included in the structural model (Figure S3). In addition, the ω^2 *vs.* the explored covariate plots did not alter after adding age as a covariate on clearance (Figure S3).

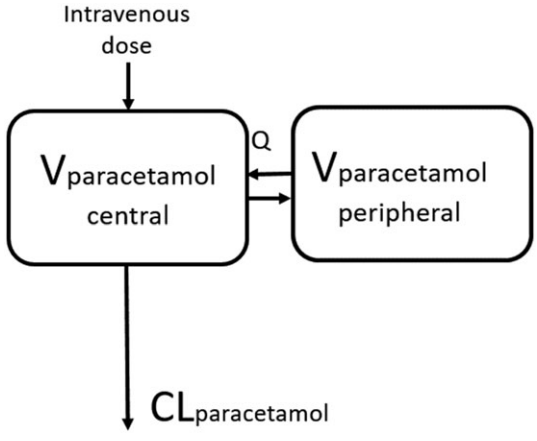

Figure 1
Schematic overview of the population pharmacokinetic model of paracetamol. V, distribution volume; CL, clearance of paracetamol; Q, intercompartmental clearance of paracetamol between the central and peripheral compartments

The parameter estimates of the developed model are shown in Table 2. Figure 2 demonstrates the goodness-of-fit plots. The data points show negligible bias around the line of unity, indicating that the model accurately describes the observations (Figure 2A,B,D). For the conditional weighted residuals over time after dose (Figure 2C), a small bias was retained in the model, which could not be further improved by additional model development.

Internal validation

The bootstrap analysis was successful in 99.6% of the runs and showed low variability in the stability of the model parameters (Table 2). The VPC plot, depicted in Figure 3, indicates an overall good predictive performance (Figure 3A). Figure 3B shows a small bias occurring in the time points <0.25 h after sampling, influencing the predictive performance. This small bias is due to the fact that sampling occurred during infusion.

Simulations

Body weight was defined as a major covariate contributing to paracetamol Vd variability. However, due to remaining large overlap in interindividual variability between a typical patient with the lowest interquartile range (66 kg), highest interquartile range (85 kg) and median body weight (79 kg), stratification on body weight was not relevant (Figure 4). Concentration–time profiles following the currently used dosing regimens (1000 mg every 6 h or every 8 h) were predicted based on simulations using the developed PK model (Table 3). After simulation of the currently used dosing regimens, $C_{ss\text{-}mean}$ of 9.2 and 7.2 mg l^{-1} were obtained after administration of 1000 mg every 6 h and every 8 h respectively. Table 3 shows the targets achieved for 10, 25, 50, 75 and 90% of the population. Variability in the population resulted in 90% of subjects being above a C_{ss} 5.4 and 4.1 mg l^{-1} and 10% above 15.5 and 11.7 mg l^{-1} at these dosing levels. When looking at target attainment with the currently used dosing regimens, 1000 mg every 8 h results in a C_{ss} far beneath the analgesic target of 10 mg l^{-1}.

Discussion

To our knowledge this is the first study using a population-PK approach that describes the PK of paracetamol and its variability in fit older people. Based on the final PK-model, simulations were performed to illustrate target attainment and variability to paracetamol PK following current dosing regimens using $C_{ss\text{-}mean}$ of 10 mg l^{-1} as a target. The CL of 17 l h^{-1} and Vd of 85.2 l 79 kg^{-1} of paracetamol obtained by this analysis are in line with those obtained from previous (noncompartmental PK) analysis, 22.04–36.97 l h^{-1} 79 kg^{-1} and 60.67–85.32 l 79 kg^{-1}, respectively [10]. Adequate

Table 2

Population pharmacokinetic parameters of the developed pharmacokinetic model for paracetamol in elderly and the values obtained after bootstrap analysis

	Final model: with covariates (RSE%) [shrinkage %]	Bootstrap mean [95%CI]
Population parameters		
$V_{APAP,\ central} = (\theta_1*((BW/79)^{**}\ \theta_2) + \theta_3)$		
θ_1 (l 79 kg^{-1})	20 (11.2)	20.42 [7.73–50.99]
θ_2 (l 79 kg^{-1})	5.15 (8.9)	5.85 [2.65–10.98]
θ_3 (l 79 kg^{-1})	34.9 (9.9)	34.05 [10.62–43.10]
$V_{APAP,\ peripheral}$ (l)	30.3 (35)	58.11 [14.38–88.31]
Q (l h^{-1})	3.54 (28.2)	4.03 [2.19–8.41]
CL_{APAP} (l h^{-1})	17 (6.4)	16.9 [14.63–19.64]
Interindividual variability [ω^2]		
ω^2 $V_{APAP,\ central}$	0.0976 (31.5) [0]	0.095 [0.04–0.155]
ω^2 $V_{APAP,\ peripheral}$	1.38 (49.8) [1]	1.39 [0.21–2.55]
ω^2 Q	2.01 (39.3) [29]	1.94 [0.66–3.35]
ω^2 CL_{APAP}	0.113 (24) [12]	0.12 [–0.14–0.37]
Residual variability [σ^2]		
σ^2 Proportional error (samples during infusion)	0.165 (37.3) [2]	0.167 [0.061–0.27]
σ^2 Proportional error (samples after infusion)	0.0068 (16.7) [10]	0.0067 [0.005–0.009]

CI, confidence interval; CL_{APAP}, elimination clearance of paracetamol; Q, intercompartmental clearance; RSE, relative standard error; $V_{APAP,\ central}$, central volume of distribution of paracetamol; $V_{APAP,\ peripheral}$, peripheral volume of distribution of paracetamol

achievement of the target concentration for a typical patient was obtained after simulation of 1000 mg every 6 h (9.2 mg l^{-1}), while the $C_{ss\text{-}mean}$ obtained with 1000 mg every 8 h was far below (7.2 mg l^{-1}) the target for the average patient. Due to the large variability in the PK, 10% of the subjects reached a target concentration above 15.5 and 11.7 mg l^{-1} and 90% were above 5.4 and 4.1 mg l^{-1} after administration of 1000 mg every 6 h and every 8 h, respectively. Other covariates besides body weight that could explain this variability were not identified. Identifying additional covariates, if any, is necessary to optimize the individual dosing of paracetamol in this highly heterogeneous population. Relevant issues concerning model development, simulations and applicability are discussed below.

Concerning the PK-model development, the current covariate analysis revealed that sex was the most significant covariate, resulting in a 1.8-times higher Vd in males than females. Five previous studies have investigated sex-related differences in PK parameters between fit older male and female adults [16–19]. In four, the Vd was lowest in females, by 8.5–17.5% compared with males. Nevertheless, in only one of these four studies the difference was statistically significant; $P < 0.05$), albeit not clinically relevant [20] The lower Vd in women is probably caused by the larger proportion of fat in women's total body weight. The most plausible explanation for the association between sex and Vd of paracetamol is that other factors than sex play a role, such as body weight (Pearson correlation of 0.69). Furthermore, the age group >80 years consisted almost exclusively of women, which might have contributed to the association (Figure S4). The other significant covariate that could (partly) explain variability between the older patients in the analysis was body weight on Vd. The last significant covariate was age on paracetamol CL. A large RSE (141%) was obtained when age was added as covariate on CL of paracetamol; age was therefore not included in the model. It is not surprising that age acts as a potential covariate on the CL of paracetamol. In younger subjects, clearance may be lower by the diminished phase II conjugation [21]. A lack of covariates on CL in this study could be due to the number of patients, which is relatively small (n = 30) to describe the *posthoc* observed large differences between individuals since it was not anticipated that variability, after IV administration in a fit population, would be so extensive. Furthermore, the lack of covariates could also be caused by the exclusion criteria in the study design. Future studies should therefore include more patients, primarily in the older age range (> 75 years), to further explore the exact influence of age and/or body weight on clearance. This would increase the statistical power in the identification of age-related effects. Our final PK-model showed great variability that could not be explained by the covariates available for this analysis. Therefore, we can only speculate about factors affecting the remaining unexplained paracetamol CL variability within the fit older people population.

Based on the final PK-model, simulations were performed with different dosing regimens currently used in clinical practice, using steady-state concentration ($C_{ss\text{-}mean}$) of 10 mg l^{-1} as target for effective analgesia. Although this adequate

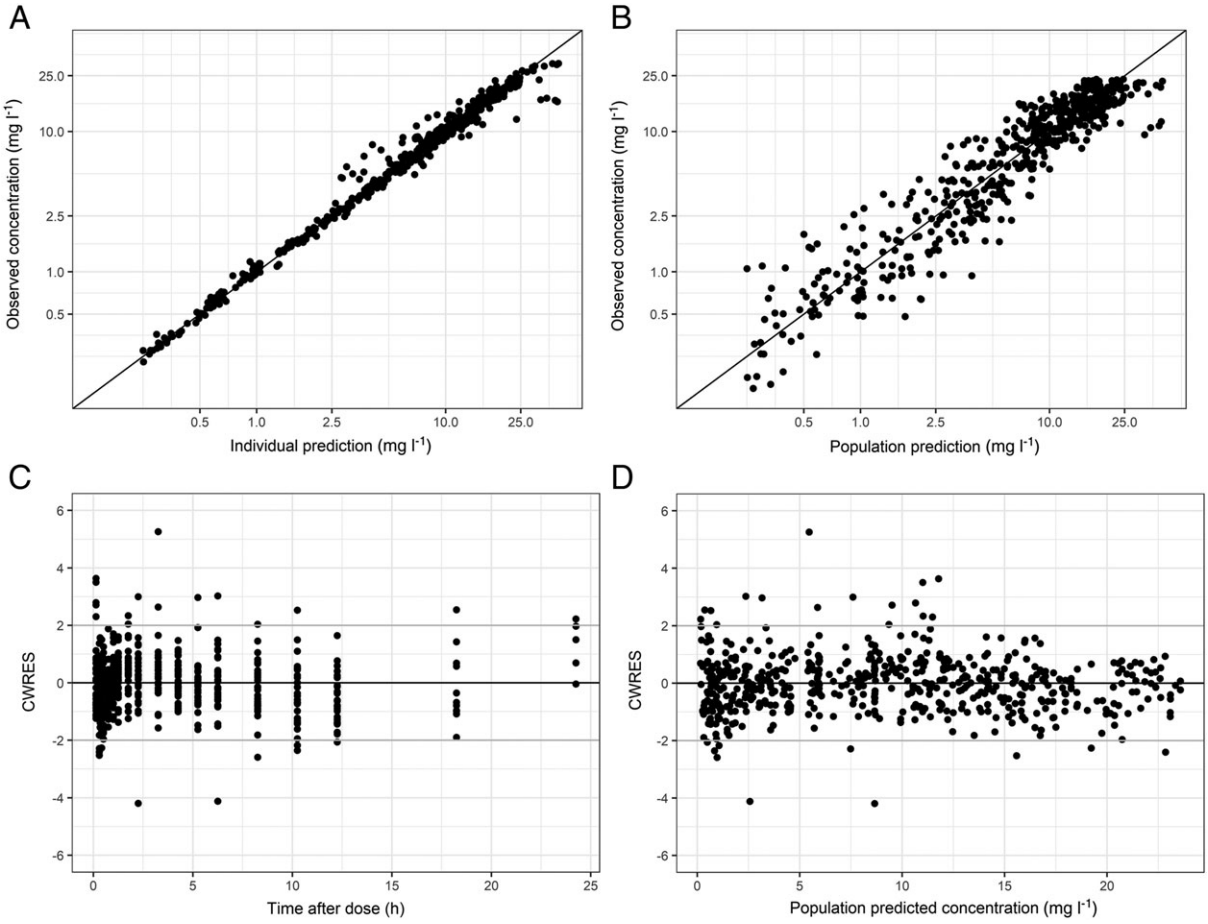

Figure 2

Diagnostic plots for the final pharmacokinetic model of paracetamol in older people: (A) observed concentrations *vs*. individual predicted concentrations; (B) observed concentrations *vs*. population predicted concentrations; (C) conditional weighted residuals (CWRES) *vs*. time after dose; (D) CWRES *vs*. population predicted concentrations

analgesia was reached in the paediatric population, the target concentration can be assumed to hold for older people as well, albeit with limited validation. In recent years, clinical experience has been gained with these regimens [5]. These seem to be well tolerated, but underdosing and subsequently suboptimal analgesia cannot be excluded. With 1000 mg every 6 h, the average patient reaches a concentration of about 10 mg l^{-1} but, due to the large remaining unexplained variability, a relevant portion of the fit older people remains off-target. For 1000 mg every 8 h, however, even the typical patient does not reach the Css target concentration (Table 3). Overall, we would argue that the administration of a higher daily dose could result in better pain management. This view was also supported by Piguet *et al*. [20] albeit in young adults only. The authors reported that higher dosing of paracetamol (1000 and 2000 mg in comparison with 500 mg) resulted in a more pronounced dose-dependent central anti-nociceptive effect in healthy adults [20]. Furthermore, obtaining the optimal target concentration with the exact dosing of paracetamol has the additional advantage that additional opiate use can possibly be reduced.

When dosing paracetamol it is equally important, however, to reach the target concentration and to consider safety. For older patients this safety aspect has resulted in the practice of dosing 1000 mg every 8 h [8]. Hepatotoxicity is common for paracetamol toxicity. Paracetamol is metabolized by different metabolic pathways [21]. In young adults, these are mainly the glucuronidation and sulfation pathways. A minor pathway through cytochrome P450 2E1 results in N-acetyl-p-benzoquinone imine (NAPQI), which is immediately neutralized by conjugation with glutathione [22]. After formation of paracetamol–glutathione, both paracetamol–cysteine and paracetamol–mercapturate are formed. However, at higher exposure or in situations where glutathione is depleted, such as malnourished state, glutathione will be depleted and NAPQI can bind covalently to cellular proteins and form toxic protein adducts. This will cause mitochondrial dysfunction and early oxidant stress. Ultimately, this will result in hepatocellular necrosis [22]. Several studies in older people [23, 24] reported differences in the contributions of the various metabolic routes as compared with younger adults, probably caused by the changing proportions of glucuronide and sulfate. When dosing 1000 every 6 h instead of every 8 h the exposure to NAPQI will be higher, although it has been suggested that the fraction to oxidative metabolite seems unchanged in older people as compared with younger

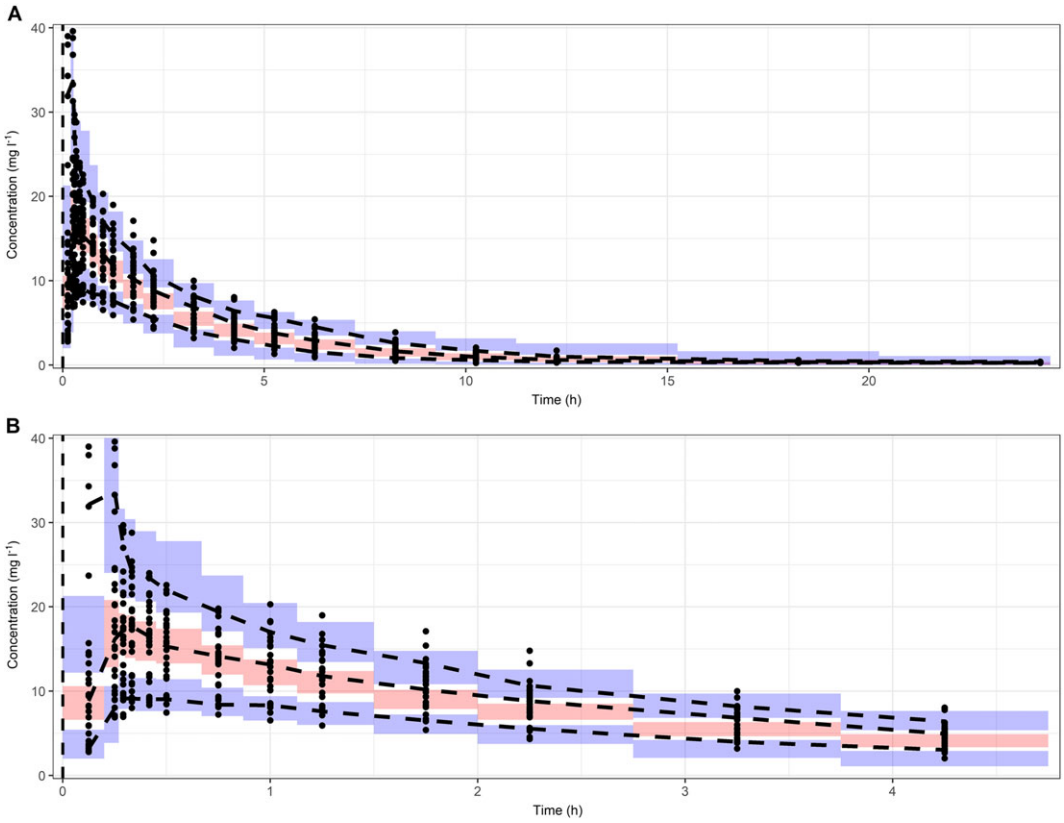

Figure 3

Visual predictive checks of the final pharmacokinetic model for paracetamol over the entire study period (A) and focus on the first 5 h after paracetamol administration (B). The open circles represent observed concentrations. The upper, middle and lower lines indicate the 95th, 50th and 5th percentile of observations, respectively. The shaded areas represent the 95% confidence interval of the corresponding percentiles of predictions

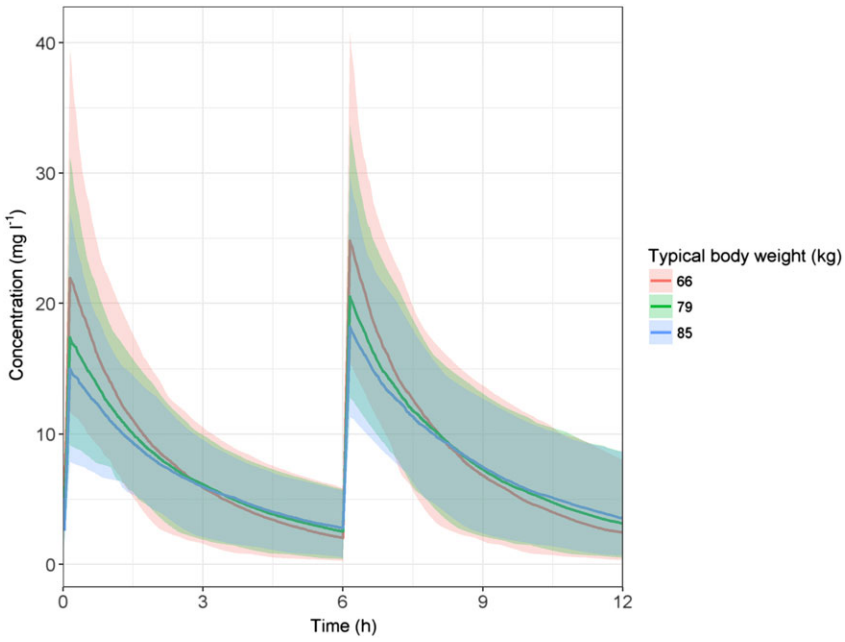

Figure 4

Concentration–time profiles of 1000 mg every 6 h intravenous paracetamol for individuals with a bodyweight of 66 kg (red), 79 kg (green) and 85 kg (blue) and the 95% confidence intervals, representing the lowest interquartile, median and highest interquartile body weight in this study

Table 3

Summary statistics of achieved steady-state concentrations (C_{ss}) for intravenous paracetamol in fit older people according to dosing regimens used in clinical practice. For concentration–time profiles of these dosing regimens for fit older people, refer to Figure 5

	C_{ss} (mg l^{-1})				
	50% of subjects above (mean concentration)	**10% of subjects above**	**25% of subjects above**	**75% of subjects above**	**90% of subjects above**
1000 mg every 6 h	9.2	15.5	12.4	7.4	5.4
1000 mg every 8 h	7.2	11.7	9.4	5.4	4.1

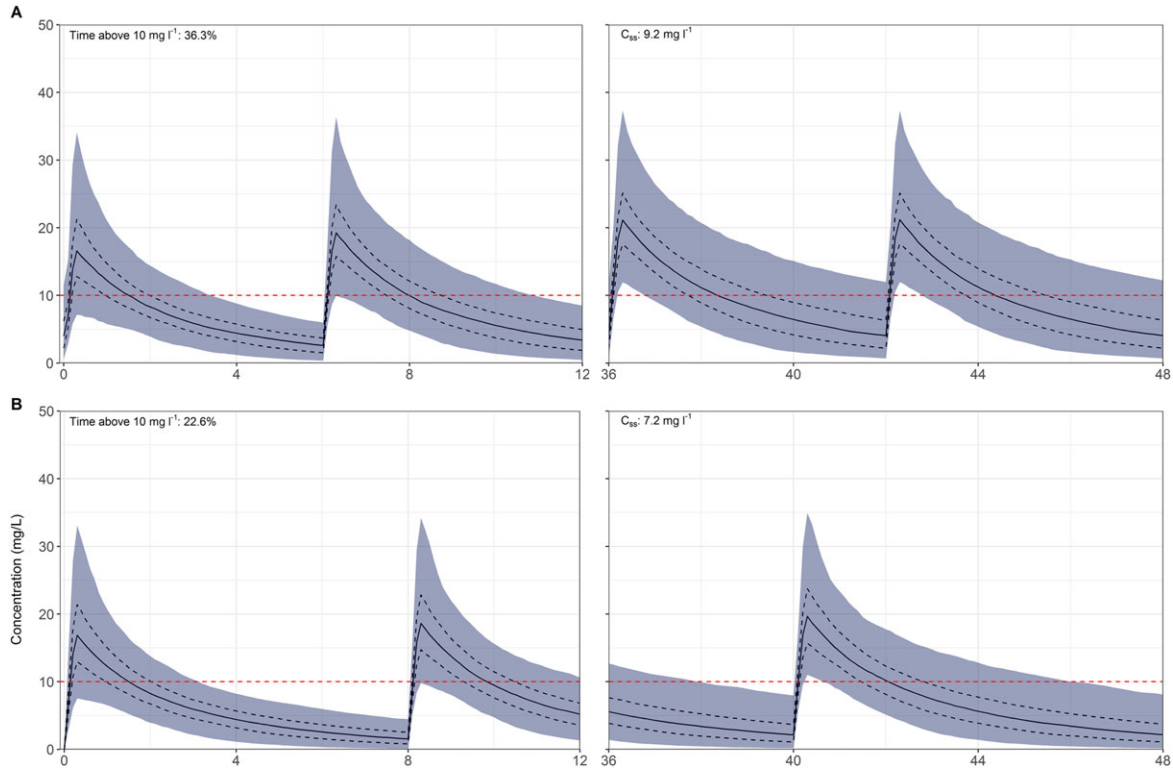

Figure 5

Concentration–time profiles based on 1000 simulations using the final PK model following the current dosing regimen every 6 h (A) and the current dosing regimen every 8 h (B) in the first 12 h dosing period (left) and the final 12 h dosing period (right). The black line corresponds with the median achieved concentration; the dotted lines represent the 25–75% prediction interval, the blue areas represents the 95% prediction interval of the simulated values. The red dashed line indicates the target concentration of 10 mg l^{-1}. The time above 10 mg l^{-1} is measured over the full simulated 48 h period

adults [10]. Due to a larger remaining unexplained variability, this can be a problem for a certain proportion of older people. With the current PK model, this group of patients cannot be identified. However, in this study, no information was available on all metabolites in order to investigate metabolite formation, and neither was information on (liver) safety values [12]. With 1000 mg every 6 h and every 8 h 10% was above 15.5 and 11.7 mg l^{-1}, respectively. However, it has to be noted that although the toxic reference of paracetamol has been reported to be 75 mg l^{-1} [25], hepatotoxicity can also occur with normal dosages administered to young adults. In addition, the toxic reference concentration of NAPQI is still unknown. Future research should take into account both PK and safety aspects. The postoperative clinical setting seems quite well-suited to study both PK/PD and the safety of IV paracetamol in fit older people, because they receive paracetamol usually no longer than 48–72 h and can be adequately monitored (pain relief, safety). Future studies should focus on extending this model to fit older people using paracetamol orally, taking into account that variability around the proposed target concentration will be very likely to be even larger due to variability in absorption rate constant and bioavailability. This model can also be extended to investigate if other covariates (e.g. type of surgery, those with several comorbidities and

comedication) can explain interindividual variability in PK in fit older people. The model will be less usable for other special populations within the older population, such as frail people, due to reported changed PK parameters between fit and frail older people [10, 24, 26]. However, a suggestion could be to perform a pooled-PK analysis of paracetamol in both fit and frail older people. Such a study has previously been done to explore covariates in adults. [27]. Using this approach, the impact of frailty as covariate can be further explored.

Conclusions

We conclude that paracetamol PK in fit older people can be best described with a two-compartment PK model. Body weight was found to be the most important covariate contributing to the paracetamol Vd variability. Simulations of the standardized dosing regimens (1000 mg) resulted in a C_{ss} of 9.2 and 7.2 mg l^{-1} for every 6 h and every 8 h respectively. Thus, 1000 mg every 6 h achieved the target concentration of 10 mg l^{-1} for the average patient, while every 8 h achieved far below the target. However, on account of a large (unexplained) interindividual variability in paracetamol PK, a relevant proportion of the fit older people remained either under- or overexposed, resulting in C_{ss} above 5.4 and 4.1 mg l^{-1}, respectively, in 90% of the population and above 15.5 and 11.7, respectively, in 10% at these dosing levels.

With the current analysis, a first step was made not only to describe the PK of paracetamol, but also to illustrate paracetamol exposure and variability with the currently used dosing regimens in the setting of fit older people. However, the older population is a very heterogeneous group and variability increases when a population is studied with different exclusion criteria. Besides exploring additional covariates in fit older persons, the next step is the expansion to a PK and safety study in complex older populations, for example frail older subjects or those with several comorbidities and comedication.

Competing Interests

There are no competing interests to declare.

The authors thank Ko Hagoort for editorial assistance. No sources of funding were used in the preparation of this manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13770/suppinfo

Figure S1 Eta values for central volume of distribution of paracetamol *vs*. sex in the base model
Figure S2 Eta values for volume of distribution of paracetamol *vs*. body weight in the base model (left) and in the final model (right)
Figure S3 Eta values for elimination clearance of paracetamol *vs*. age in the base model (after inclusion of bodyweight on the central volume of distribution) and after inclusion of age as a covariate on clearance
Figure S4 Distribution of body weight (A) and age (B) in the study population specified by sex