Highly Variable Paracetamol Pharmacokinetics After Multiple Oral Dosing in Frail Older People

van der Heijden, L. T.; Mian, P.; Hias, J.; de Winter, B. C.M.; Tournoy, J.; Van der Linden, L.; Tibboel, D.; Walgraeve, K.; Flamaing, J.; Koch, B. C.P.

Published in:
Drugs and Aging

DOI:
10.1007/s40266-021-00912-z

Drugs & Aging (2022) 39:83–95
https://doi.org/10.1007/s40266-021-00912-z

ORIGINAL RESEARCH ARTICLE

Highly Variable Paracetamol Pharmacokinetics After Multiple Oral Dosing in Frail Older People: A Population Pharmacokinetic Analysis

L. T. van der Heijden[1,2] · P. Mian[1,3] · J. Hias[4] · B. C. M. de Winter[5] · J. Tournoy[6,7] · L. Van der Linden[4,8] · D. Tibboel[1] · K. Walgraeve[4] · J. Flamaing[6,7] · B. C. P. Koch[5] · K. Allegaert[5,8,9] · I. Spriet[4,8]

Accepted: 23 November 2021 / Published online: 17 December 2021

Abstract

Introduction Paracetamol pharmacokinetics (PK) is highly variable in older fit adults after intravenous administration. Frailty and oral administration likely result in additional variability. The aim was to determine oral paracetamol PK and variability in geriatric inpatients.

Methods A population PK analysis, using NONMEM 7.2, was performed on 245 paracetamol samples in 40 geriatric inpatients (median age 87 [range 80–95] years, bodyweight 66.4 [49.3–110] kg, 92.5% frail [Edmonton Frail Scale]). All subjects received paracetamol 1000 mg as tablet (72.5%) or granulate (27.5%) three times daily. Simulations of dosing regimens (1000 mg every 6 hours [q6h] or q8h) were performed to determine target attainment, using mean steady-state concentration ($C_{ss\text{-}mean}$) of 10 mg/L as target.

Results A one-compartment model with first order absorption and lag time best described the data. The inter-individual variability was high, with absorption rate constant containing the highest variability. The inter-individual variability could not be explained by covariates. Simulations of 1000 mg q6h and q8h resulted in a $C_{ss\text{-}mean}$ of 10.8 [25–75th percentiles 8.2–12.7] and 8.13 [6.3–9.6] mg/L, respectively, for the average geriatric inpatient. The majority of the population remained off-target (22.2% [q6h] and 52.2% [q8h] <8 mg/L; 31.3 [q6h] and 7.6% [q8h] >12 mg/L).

Conclusion A population of average geriatric inpatients achieved target $C_{ss\text{-}mean}$ with paracetamol 1000 mg q6h, while q8h resulted in underexposure for the majority of them. Due to high unexplained variability, a relevant proportion remained either above or below the target concentration of 10 mg/L. Research focusing on PK, efficacy and safety is needed to recommend dosing regimens.

1 Introduction

Pain is a frequent symptom, even more in older adults [1, 2]. Prevalence of pain increases with age, and is reported to be 25–75% among older persons [1, 2], with musculoskeletal (e.g. osteoarthritic back, chronic joint) and neuropathic pain syndromes as the most prevalent [2]. In addition, pain frequently is present during hospitalization in older inpatients.

Paracetamol (acetaminophen) is a commonly used analgesic [3]. It is registered for pain treatment in adults with a dose of 1000 mg q6h (maximum daily dose of 4000 mg) and for adults with a bodyweight ≤ 50 kg with a dose of 15 mg/kg/dose (maximum daily dose of 60 mg/kg or 3000 mg) [4, 5]. A maximum dose of 3000 mg daily is suggested for individuals with additional risk factors for paracetamol toxicity, such as old age itself and frailty [4]. Dosages for older adults, with or without risk factors for toxicity, have not been evaluated in clinical trials, and are therefore generally based on clinical experience, extrapolation of younger adult data and expert opinions. Yet, data collected in younger adults cannot be extrapolated with certainty to the older population due to physiological differences between the populations.

Age-related changes in physiology (e.g. increased body fat, decreased renal function [6, 7]) influence the disposition of paracetamol. Several studies have reported a lower volume of distribution (V_d) and lower clearance (CL) of paracetamol in fit older people in comparison with younger adults [8–10]. Next to age-related changes in physiology, frailty, which is a multifactorial biological syndrome characterized by a cumulative dysregulation of physiological

L. T. van der Heijden and P. Mian contributed equally.

✉ P. Mian
p.mian@umcg.nl

Extended author information available on the last page of the article

Key Points

Paracetamol pharmacokinetics (PK) in frail geriatric inpatients was best described by a one-compartment model. Inter-individual variability in paracetamol PK was high, with the absorption rate constant (K_a) displaying the highest variability. No covariates could explain this variability.

For average frail geriatric inpatients, simulations of dosing regimens (1000 mg every 6 hours [q6h] and q8h) resulted in a mean steady-state concentration ($C_{ss\text{-}mean}$), a commonly used marker for analgesic efficacy, of 10.8 and 8.13 mg/L, respectively. The target concentration of 10 mg/L was achieved with 1000 mg q6h, while q8h did not result in target attainment in the average patient.

Due to large unexplained inter-individual variability in paracetamol PK, a relevant proportion of the simulated patients remained either above (> 12 mg/L; 31.3% [q6h] and 7.6% [q8h]) or below (< 8 mg/L; 22.2% [q6h] and 54.2% [q8h]) the target of 10 mg/L. The resulting $C_{ss\text{-}mean}$ was > 8.2 mg/L (q6h) and > 6.3 mg/L (q8h) in 75% of the population and > 12.7 mg/L (q6h) and > 9.6 mg/L (q8h) in 25% of the population at these dosing regimens.

processes [11], might influence paracetamol pharmacokinetics (PK). While there is no consensus definition of frailty, two approaches are commonly used to define the frailty concept. The first approach defines frailty as a physical frailty phenotype determined by loss of strength/weight or speed, lack of energy, and/or inability to perform demanding activities such as domestic chores. The second quantifies frailty in a frailty index, representing the ratio of the deficits present in an individual divided by the number of evaluated deficits [12]. Accordingly, fit older people do not have a frailty phenotype and score low on a frailty index. Studies have found that paracetamol clearance was lower in frail versus fit older people [13, 14]. In addition, paracetamol PK was found to be more variable in fit older adults than in younger people [8–10]. Even after intravenous (IV) administration of paracetamol in fit older people, a high (unexplained) variability in PK occurred [15]. Frailty and oral administration of paracetamol will likely result in additional variability in PK [14].

Differences in PK between frail and fit elderly, but also high variability in PK parameters in older adults, can alter the exposure to (and thereby the efficacy and safety of) paracetamol. It is being debated, therefore, whether pain is indeed adequately treated in older adults [16]. A mean steady-state concentration ($C_{ss\text{-}mean}$) of 10 mg/L is associated with adequate analgesia in the paediatric population [17]. Although based on limited validation, this concentration is also used in the present study as the target for pain relief in older people.

The aim of this study was to develop a population PK model to describe paracetamol PK and its variability in (frail) geriatric inpatients during multiple oral dosing (tablet or granulate). Simulations were performed with dosing regimens (1000 mg q6h and q8h) to illustrate target attainment and variability of paracetamol PK in geriatric inpatients.

2 Methods

2.1 Patient Population, Study Design and Drug Dosing

Data analysis was performed on paracetamol plasma concentrations from a previously published observational study [17, 18]. The study design has been described in detail [17, 18] and is summarized here as relevant to this analysis. This study was conducted at the University Hospitals Leuven, Belgium, following approval by the medical ethics committee of UZ Leuven (EUDRACT 2015-004217-24). Inclusion criteria were as follows: aged ≥ 80 years, hospitalization on an acute geriatric ward, written informed consent, oral administration of paracetamol 1000 mg three times daily (8:00, 14:00, 20:00), and at least four consecutive doses of paracetamol before the start of the study. The exclusion criterion was end-of-life care.

All patients received paracetamol 1000 mg as tablet (Dafalgan® tablet forte) or granulate (Dafalgan® instant forte). Blood samples were taken at trough level before the study dose was administered and at 0.5, 1, 2, 4, 5 and 8 hours after the study dose. The median (interquartile range) number of samples was 7 in total (5–7). In the electronic supplementary material (ESM), Figure ESM_1 provides plots of the spread in sampling times relative to the first paracetamol dose during the complete study period (Figure ESM_1A) and during the first hour after dosing (Figure ESM_1B). Data available for analysis included 42 subjects. Two subjects were excluded because no samples were available after the study dose. The characteristics of the 40 subjects included are shown in Table 1. Contrary to our analysis, Hias et al. [18] included 36 patients, as patients without a complete PK profile were not excluded in the latter study.

2.2 Analytical Analysis

Paracetamol plasma concentrations were determined using an ultra-high performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) at the hospital

pharmacy of Erasmus Medical Centre Rotterdam, the Netherlands [19].

2.3 Population Pharmacokinetic Analysis

Paracetamol was analysed using non-linear mixed-effects modelling software NONMEM version 7.2 (ICON Development Solutions, Ellicott City, MD, USA) using the first-order conditional estimation method with the interaction option (FOCE-I) and subroutine ADVAN13 TOL9. Pirana (version 2.9.7), RStudio (version 1.1.423), [R] (version 3.4.3) and PsN (version 5.22.4) software were used for the numerical and graphical analysis of the output.

The model was built in a stepwise manner: (i) base model development, (ii) covariate model development and (iii) interval validation [20]. The likelihood ratio test using the objective function value (OFV) was used to discriminate between models. A decrease 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, goodness-of-fit (GOF) plots, relative standard error (RSE), confidence interval of the parameter estimates, condition number and eta-shrinkage were evaluated [20].

As aforementioned, at least four doses had been administered before administration of the study dose. While administration time of the study dose was known, exact times of administration of the previous doses were not known. As medication in hospital is distributed at standardised times (08:00, 14:00, 20:00), it was assumed that the previous paracetamol doses were administered at those times. In addition, the exact total number of received doses is unknown. In view of the inclusion criterion of at least four previous administrations, we included four previous doses with their assumed administration times in the analysis.

2.3.1 Base Model Development

For the structural model, one-compartment and two-compartment models were tested. Different approaches were tested to describe the absorption process: first order, zero order and Michaelis–Menten absorption. Lag time, a transit compartment model and a transit compartment model as described by Savic et al. [21] were also tested. Bioavailability (F) was fixed on 1.

It was assumed that the inter-individual variability of the apparent volume of distribution (V_d/F) and apparent clearance (CL/F) was log normally distributed. This was tested using the following equation:

$$Pi = \theta * e^{\eta_i}, \tag{1}$$

where Pi is the individual parameter estimate for the ith subject, θ is the population parameter estimate and η_i is the inter-individual variability with a mean of 0 and a variance of ω^2. The inter-individual variability of K_a was not log-normally distributed. A mixture model for K_a and logit, box cox and heavy tail transformations were tested to improve distribution of the inter-individual variability of K_a [22]. To optimize the PK model, correlations between random effects in the model were investigated using an omega block.

For the residual unexplained variability an additional (Eq. 2), proportional (Eq. 3) and a combined error model were tested (Eqs. 2 + 3).

$$Y_{ij} = C_{\text{pred},ij} + \varepsilon_{ij}, \tag{2}$$

$$Y_{ij} = C_{\text{pred},ij} \times \left(1 + \varepsilon_{ij}\right), \tag{3}$$

where Y_{ij} is the jth observed concentration for the ith subject, $C_{\text{pred},ij}$ the predicted concentration for the jth observation and ith subject and ε_{ij} is the random value from a normal distribution with a mean of 0 and a variance of σ^2.

2.3.2 Covariate Model Development

Lab values and patient characteristics were documented at the start of the study and were assumed to be constant over the study period of 8 h. If the documentation could not be performed at the start of the study period, the most recent values were extracted from the electronic patient file. If the percentage of missing data was < 10%, the missing values were replaced with the population mean (normal distribution population) or median (not-normally distributed). If the percentage of missing data exceeded 10%, the potential covariate was not tested (e.g. mini-mental state examination and direct bilirubin, and the use of any gastroprokinetic such as alizapride, domperidone, metoclopramide, ondansetron or erythromycin). Scores on the Edmonton Frail Scale (EFS) and Mini Nutritional Assessment (MNA) were sorted into the different scoring categories. For EFS: no impairment (0–5), vulnerable (6–7), mild impairment (8–9), moderate impairment (10–11) and severe impairment (12–17); for MNA: normal nutrition status (12–14), risk of underfeeding (8–11) and underfed (0–7).

The following covariates were tested: age, sex, MNA, EFS, bodyweight, lean body weight, renal function (both Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] and Cockcroft–Gault [C&G]), serum creatinine, international normalised ratio (INR), liver function parameters, total bilirubin, formulation (tablet or granulate), presence of fever, simultaneous opiate use (strong, weak, no), simultaneous proton-pump inhibitors use, the presence of

Table 1 Clinical characteristics of frail older adults ($n = 40$) included in this analysis

Variable (unit)	Value	Comments
Age, years	87 [80–95]	
Sex		
Female	22 (55)	
Race		
Caucasian	40 (100)	
Bodyweight, kg	66.4 [49.3–110]	
Height, cm	160.5 [142–185]	
Lean body weight, kg	49.84 [34.90–74.03]	Equations: Men: 1.10 × weight (kg) − 128 × (weight^2 [kg]/height^2 [cm]) Women: 1.07 × weight (kg) − 148 × (weight^2 [kg]/height^2 [cm])
Formulation (number of patients)		
Tablet	29 (72.5)	
Granulate	11 (27.5)	
Serum creatinine (mg/dL)	0.95 [0.51–2.10]	
Estimated GFR (CKD-EPI; mL/min/1.73m^2) [32]	65 [5.4–90.0]	Equations: Men: 141 × minimum (serum creatinine [mg/dL]/0.7)$^{-0.411}$ × maximum (serum creatinine [mg/dL]/0.7)$^{-1.209}$ × 0.993$^{\text{age (years)}}$ Women: 141 × minimum (serum creatinine [mg/dL]/0.7) $^{-0.411}$ × maximum (serum creatinine [mg/dL]/0.7) $^{-1.209}$ × 0.993$^{\text{age (years)}}$ × 1.018
Estimated GFR (Cockcroft-Gault; mL/min) [32]	46.9 [20.5–94.6]	Equations: Men: (140 − age (years) × weight (kg)/ 72 × serum creatinine (mg/dL) Women: (140 − age (years) × weight (kg)/72 × serum creatinine (mg/dL)
Sodium (mmol/L)	140 [129.4–147.6]	
Uric acid (mg/dL)	5.8 [1.9–15.2]	
ASAT (U/L)	19 [13–117]	
ALAT (U/L)	14 [7–52]	
Bilirubin total (mg/dL)	0.52 [0.18–1.71]	
Bilirubin direct (mg/dL)	0.25 [0.18–0.54]	
Gamma GT (U/L)	31 [12–289]	
Alkaline phosphatase (U/L)	70 [30–174]	
Albumin (g/L)	37.1 [26.5–45.7]	
Total protein (g/L)	66 [52–82]	
Haematocrit (volume % of red blood cells)	0.356 [0.241–0.480]	
International Normalised Ratio (INR)	1.2 [1–3.4]	
Use of weak opiates (no. of patients)		
Unknown	1 (2.5)	
No	28 (70)	
Yes	11 (27.5)	
Use of strong opiates (no. of patients)		
Unknown	1 (2.5)	
No	31 (77.5)	
Yes	8 (20)	
Use of proton pump inhibitors (no. of patients)		
Unknown	1 (2.5)	
No	24 (60)	
Yes	15 (37.5)	
Use of gastroprokinetics such as alizapride, domperidone, metoclopramide, ondansetron, erythromycin (number of patients)		
Unknown	4 (10)	
No	32 (80)	

Table 1 (continued)

Variable (unit)	Value	Comments
Yes	4 (10)	
Fever (number of patients)		Reference value: 38.5 °C
Unknown	2 (5)	
No	37 (92.5)	
Yes	1 (2.5)	
Type of feeding (number of patients)		
Unknown		
Oral	40 (100)	
Enteral		
Parenteral		
Mini-Mental State Examination (MMSE; unit)	22 [13–30]	
Concomitant administration with food (number of patients)		
Unknown	1 (2.5)	
Sober	4 (10)	
With food	35 (87.5)	
MNA; number of patients		Only the screening questions and not the research questions of MNA were used in this study. The screening questions encompass reductions in food intake and related causes, weight loss, mobility, critical illness or physiological stress, neurological problems, and calculation of the body mass index
Unknown	1 (2.5)	
Normal	9 (22.5)	
Risk of underfeeding	21 (52.5)	
Underfed	9 (22.5)	
EFS; number of patients		A validated questionnaire to assess frailty. Cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance are assessed to determine the EFS score
Unknown	2 (5)	
No impairment	1 (2.5)	
Vulnerable		
Mild impairment	4 (10)	
Moderate impairment	12 (30)	
Severe impairment	21 (52.5)	
Comorbidities associated with gastroparesis (number of patients)		
Unknown	4 (10)	
No comorbidities	18 (45)	
Diabetes mellitus	16 (40)	
Parkinson's disease	2 (5)	

Values are presented as median [range] or n (%) unless otherwise specified

ALAT alanine transaminase, *ASAT* aspartate aminotransferase, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *EFS* Edmonton Frail Scale, *GFR* glomerular filtration rate, *MNA* Mini-Nutritional Assessment

diseases known to be associated with gastroparesis such as diabetes mellitus and Parkinson's disease, and intake of paracetamol with or without food. To visualise potential relationships, the covariates were plotted against the individual PK parameter estimates. Covariates were tested if they were considered clinically relevant or if potential relationships were visible. The continuous covariates were included into the model with the following equation (Eq. 4):

$$Pi = \theta 1 \times \left(\frac{\mathrm{COV}}{\mathrm{COV}_{\mathrm{median}}} \right)^{\theta 2}, \quad (4)$$

where P*i* represents the individual parameter estimate and θ_1 represents the estimate for the covariate relationship. COV represents the covariate value and $\mathrm{COV}_{\mathrm{median}}$ the median value, by which the covariate is normalized. θ_2 is an estimated exponent. It was fixed on 1 for a linear function and estimated for a power function. From categorical covariates with two categories (sex, formulation, food conditions), the fractional change for one group compared to the other group was calculated. MNA and EFS have three and five categories, respectively. The fractional change of the different groups was estimated and compared with the first category.

Potential covariates were added separately to the model and were considered to be significant when OFV decreased

by at least 7.8 points ($p < 0.005$). When multiple covariates were found to be significant, the covariate causing the largest drop in OFV was retained in the model. In addition, a reduction in inter-individual variability of the parameter and improvement in GOF plots were evaluated upon inclusion of the covariate on the parameter.

2.3.3 Internal Validation

Bootstrapping, using 1000 replicates, was performed to check model stability. The parameter estimates obtained in the bootstrap were subsequently compared with the parameters estimated from the original dataset. To evaluate the accuracy of the model predictions, a normalized prediction distribution error (NPDE) method was performed in which the dataset was simulated 1000 times. The results were analysed with [R]. Distribution of NPDE was compared with a normal distribution.

2.3.4 Simulations

Simulations (1000 replicates) were performed to investigate target attainment and variability around the target (10 mg/L) in frail geriatric inpatients. Two dosing regimens (1000 mg q6h and q8h) were simulated for 72 h. For each simulated concentration–time profile, $C_{ss\text{-}mean}$ was calculated for the average patient. This calculation was based on the area under the plasma concentration–time (AUC) curve when steady-state was visually achieved and on the dosing interval (6h or 8h). For each concentration–time profile, the 10th, 25th, 50th, 75th and 90th percentiles of the C_{ss} were calculated. To quantify below and beyond the target concentration of 10 mg/L, we defined a range (8–12 mg/L) to investigate the extent of deviation from the target concentration.

3 Results

3.1 Population Pharmacokinetic Analysis

The PK model was based on 245 samples obtained from 40 subjects. None of these samples were below the lower limit of quantification.

3.1.1 Base Model Development

The data was best described by a one-compartment model with first-order absorption and first-order elimination (Fig. 1). The absorption phase was best described with lag time (−dOFV = −9.39).

The residual unexplained variability was best described by a combination of the additional and proportional error models. Inter-individual variability on V_d/F, CL/F and K_a further improved the model. Addition of inter-individual variability on F and lag time did not improve the model significantly.

A mixture model, box cox and heavy tail transformation did not improve the distribution of K_a. The logit transformation resulted in a lognormal distribution. However, the logit transformation resulted in a significantly higher OFV (−dOFV = 28.05) and the RSE of the inter-individual variability of K_a was 5000%. Therefore, the individual variability of K_a was left untransformed. An omega block for the inter-individual variability on V_d/F and CL/F resulted in more precise PK parameter estimates (lower RSEs) and a significant decrease in OFV.

3.1.2 Covariate Model Development

None of the tested potential covariates improved the model significantly (−dOFV ≥ 7.8). The parameter estimates of the final model are presented in Table 2. Parameters were estimated with high precision (RSE < 50%) [20]. Although overall accurately predicted (RSE = 44.4%), the highest variability was displayed in K_a (inter-individual variability of 4.14). This variability in absorption is also shown in the individual plots in Figure ESM_2. The GOF plots are shown in Fig. 2. Data points for paracetamol are randomly distributed around the line of unity, indicating that bias is negligible. The model is able to describe the observations, but contains high inter-individual variability in the predictions (Fig. 2A, B). The conditional weighted residuals (CWRES) were randomly distributed over the population predictions and over time and therefore bias was detected. It has to be noted that for some η-values the shrinkage was higher than 25%.

3.2 Internal Validation

The bootstrap mean and 95% confidence intervals (95% CI) are presented in Table 2. Overall, low variability and stability in V_d, CL and lag time is observed, while K_a is highly variable (95% CI 0.516–21.4 h^{-1}). The NPDE, presented in Fig. 3, shows high variability. A deviating peak in the histogram of the NPDE distribution can be seen in Fig. 3. However, NPDE distribution and its variability were not significantly different from a normal distribution ($p = 0.052$). No trend is observed in NPDE versus time and NPDE versus predicted concentrations, indicating that the model adequately quantifies both typical trend and variability in the observed concentrations.

3.3 Simulations

Concentration–time profiles of 1000 simulated frail older subjects for each of the currently used dosing regimens

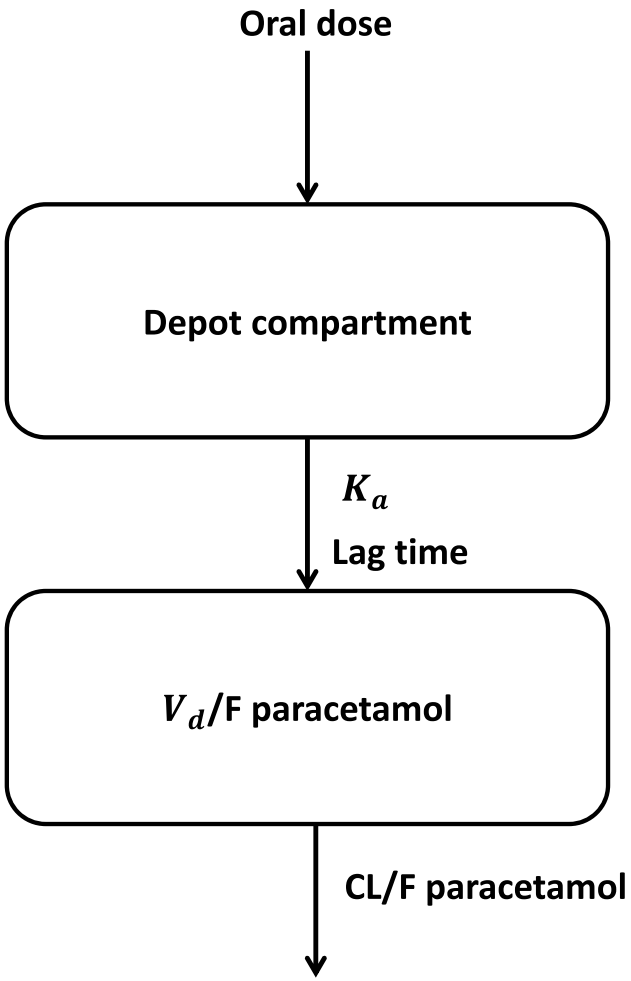

Fig. 1 Schematic representation of the structural model. *CL* clearance, *Ka* absorption rate constant, V_d volume of distribution

(1000 mg q6h and 1000 mg q8h) are presented in Fig. 4. The average subject achieved a $C_{ss\text{-}mean}$ of 10.8 mg/L for 1000 mg q6h and a $C_{ss\text{-}mean}$ of 8.13 mg/L for 1000 mg q8h. Table 3 shows the attained $C_{ss\text{-}mean}$ for 10, 25, 50, 75 and 90% of the subjects. The variability in PK resulted in 75% of the subjects being above a $C_{ss\text{-}mean}$ of 8.2 mg/L (q6h) and 6.2 mg/L (q8h) and in 25% above 12.7 mg/L (q6h) and 9.6 mg/L (q8h) for 1000 mg q6h and q8h. A relevant proportion remained either above (> 12 mg/L; 31.3% [q6h] and 7.6% [q8h]) or below (< 8 mg/L; 22.2% [q6h] and 54.2% [q8h]) the target of 10 mg/L.

4 Discussion

To the best of our knowledge, this is the first population PK model for oral paracetamol in frail geriatric inpatients. Oral paracetamol PK was best described with a one-compartment model. Despite the high inter-individual variability, none of the collected covariates could explain the high inter-individual variability. Simulations of 1000 mg q6h and q8h resulted in a $C_{ss\text{-}mean}$ of 10.8 (25–75th percentiles 8.2–12.7) and 8.13 (6.3–9.6) mg/L, respectively, for the average geriatric inpatient. The majority of the population remained off-target (22.2% [q6h] and 52.2% [q8h] < 8 mg/L; 31.3% [q6h] and 7.6% [q8h] > 12 mg/L). Relevant issues on model development, simulations and applicability are discussed below.

Concerning model development, the estimated CL/*F* and V_d/F were in line with previous research. Ellmers et al. studied paracetamol PK after administration of 1000 mg in 55 patients (47% frail; mean [SD] frail subgroup age: 83.5 [7.3] years; weight: not reported) and reported a CL

Table 2 Population pharmacokinetic parameters of the pharmacokinetic model for oral paracetamol in frail older people and the values obtained after bootstrap analysis

Parameter	Final model estimate (RSE %) [Shrinkage %]	Bootstrap mean [95% CI]
Fixed effects		
V_d/F (L)	69.7 (6.9)	69.5 [60.7–78.6]
CL/*F* (L/h)	16.1 (5.5)	16.1 [14.4–17.8]
K_a (1/h)	10.4 (6.6)	11.4 [0.516–21.4]
Lag time (h)	0.379 (5)	0.369 [0.277–0.480]
Inter-individual variability (ω^2)		
ω^2 V_d/F	0.0583 (30.7) [30]	0.0557 [0.0212–0.0955]
ω^2 V_d–CL/*F*	0.0466 (0.0201) [5]	0.0458 [0.00742–0.0856]
ω^2 CL/*F*	0.102 (29.5) [6]	0.0977 [0.0492–0.155]
ω^2 K_a	4.41 (44.4) [31]	4.82 [1.24–7.58]
Residual variability (σ^2)		
σ^2 (proportional)	0.464 (30) [13]	0.421 [0.160–0.769]
σ^2 (additional)	0.311 (13.4) [13]	0.310 [0.237–0.385]

CI confidence interval, *CL/F* apparent clearance, K_a absorption rate constant, *RSE* relative standard error, V_d/F apparent volume of distribution, *Vd-CL/F* the interaction of the inter-individual variability between apparent volume of distribution and apparent clearance

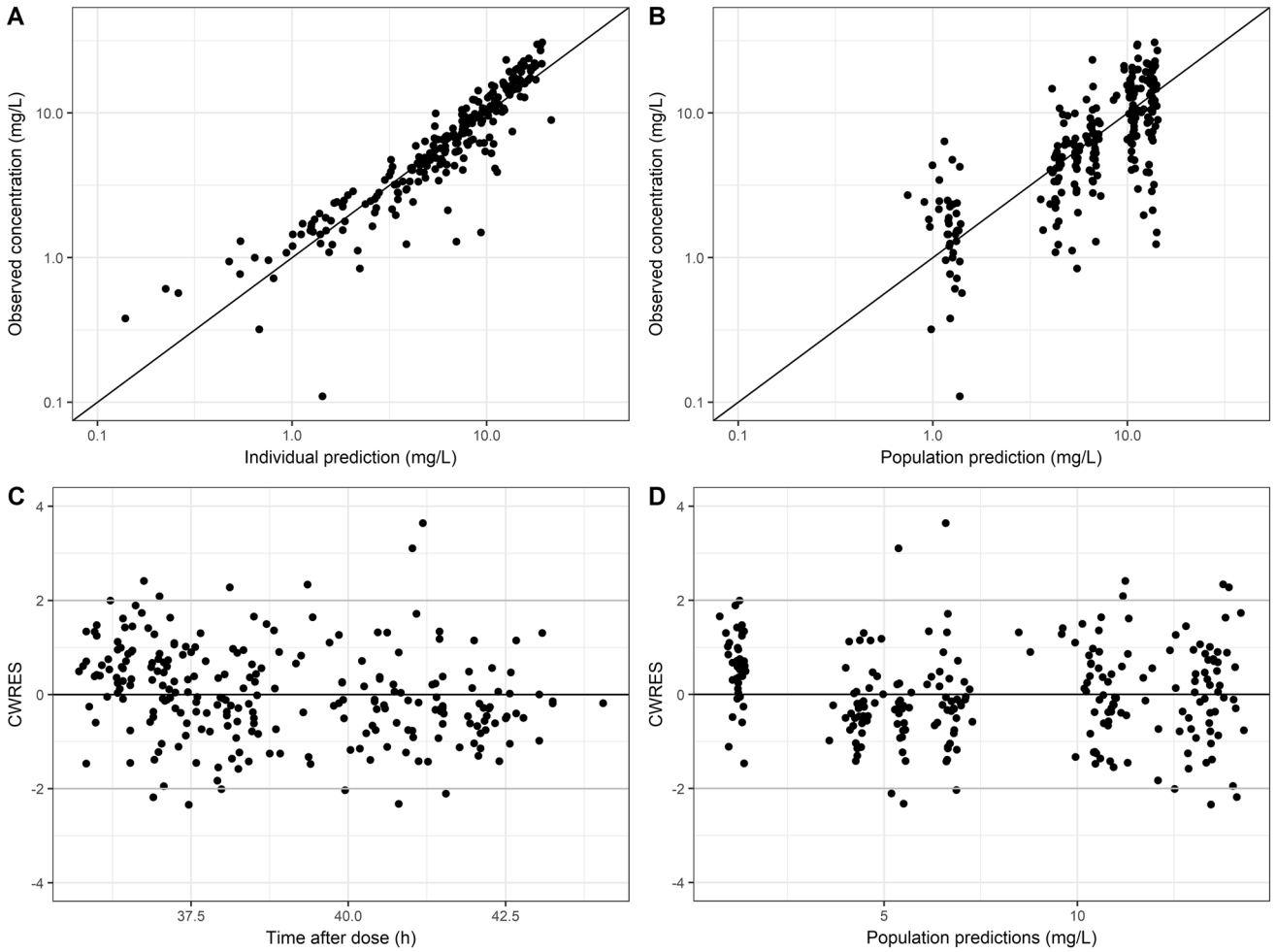

Fig. 2 Diagnostic plots for the final pharmacokinetic model of oral paracetamol in frail older people: (**A**) observed concentrations versus individual predicted concentrations; **B** observed concentrations versus population predicted concentrations; **C** conditional weighted residuals (CWRES) versus time after study dose; **D** CWRES versus population predicted concentrations

of 13.4 L/h and V_d of 65.7 L in the frail subpopulation [13]. Wynne et al., who studied paracetamol PK in 48 older subjects after administration of oral paracetamol 500 mg (18% frail, mean [SD] frail subgroup age: 82 [2] years; weight: 53 (4) kg), found less similarity in PK parameters in a similar population, namely a CL of 8 L/h and V_d of 32.5 L [14]. We will address some considerations that hamper comparing our results with those of the aforementioned studies. Firstly, those studies used a non-compartmental analysis [13, 14], whereas we used a compartmental analysis. Secondly, the definitions for frailty differed. Overall, frailty has a heterogeneous clinical presentation and a multitude of definitions [23]. Ellmers et al. defined frailty as not living independently [13], while Wynne et al. defined frail patients as patients who received continuous hospital care for chronic disabling conditions such as cerebrovascular and musculoskeletal disease [14]. In our study, frailty had been identified with the use of the EFS. This scale was chosen because it is validated to be applied in the acute setting by non-medically trained personnel with good inter-rater reliability [11]. Although frailty was not an inclusion criterion in this study, most of the included geriatric inpatients were considered to be frail (95%). The European Medicines Agency recognizes the need for an operational definition of frailty that can be used in research [24]. Thirdly, Ellmers et al. as well as Wynne et al. reported high variability in PK parameters [13, 14], thereby underlining the variability in PK in the frail geriatric inpatients from our study. A recent study investigating paracetamol PK in fit older people already observed high variability in a healthy younger older population, even with an IV formulation [15]. Therefore, the high variability found in our analysis (Figure ESM_2) in frail patients when using oral administration was expected.

An asset of this study is the fact that many potential covariates have been collected and tested in order to investigate if they could provide a partial explanation for the

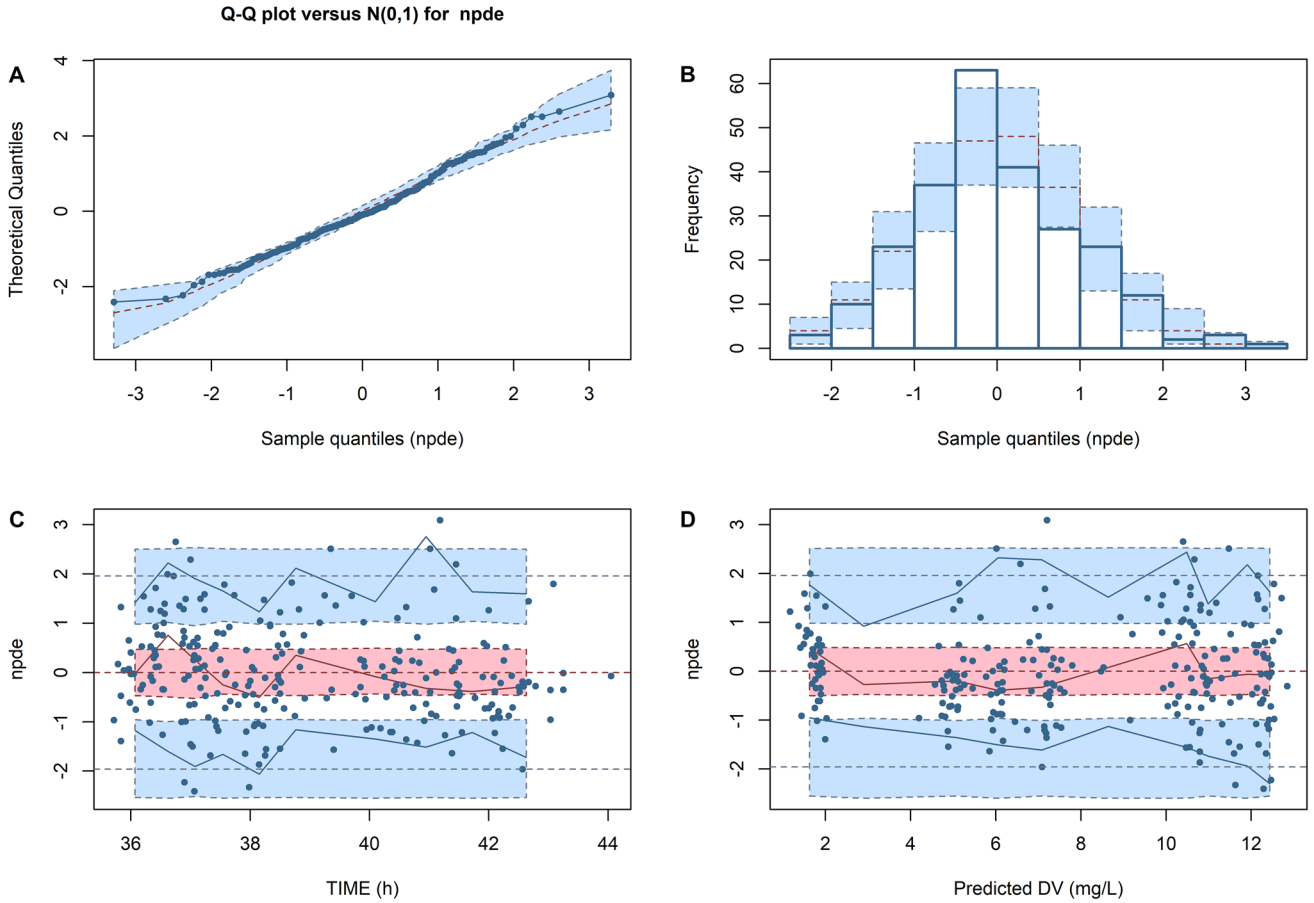

Fig. 3 Normalised prediction distribution error (NPDE) of the final model for oral paracetamol. **A** Quantile–quantile plot of NPDE versus the expected standard normal distribution; **B** histogram of the NPDE distribution (white bars), overlaid with the density of the standard normal distribution (blue bars); **C** NPDE over time with the NPDE for each observation (dots), and the lines indicate the mean (red) and the 90% percentiles (blue) of the NPDEs, and the shaded areas are the simulated 90% confidence intervals of the NPDE median (red) and 95% percentiles (blue) (middle graphs); **D** NPDE vesus the predicted concentrations, with dots and lines as described for C

inter-individual variability. There are several explanations why this study could not identify any covariate. One is the relative homogeneity of the study population with a small range for important potential covariates such as age, frailty, and nutritional status, although weight and renal function had a wide range. Other factors that cannot be quantified in a clinical setting (e.g. gastroparesis, gastric pH or epithelial integrity of the gastrointestinal tract) might have been of influence. However, diseases associated with gastroparesis such as diabetes and Parkinson's disease did not explain the observed variability. Additionally, several limitations of this study could have influenced the model development. For one, the sample period was too short to capture the complete concentration–time profile for a proportion of the subjects (Figure ESM_2). In addition, only a limited number of samples were taken during the absorption phase (Figures ESM_1, ESM_2). Furthermore, bioavailability was set to 1 due to lack of IV data. Still, despite the limitations, this model was able to adequately describe the observed concentrations, PK parameters and variability.

Both in clinical practice as well as in literature, a discussion is ongoing whether to administer paracetamol in a dose of 1000 mg q6h or q8h to the older population because of efficacy as well as safety issues [5]. Here we provide the pros and cons of the administration of paracetamol 1000 mg q6h vs q8h in relation to our analysis. Simulations were performed with the two dosing regimens (1000 mg q6h and q8h) using a $C_{ss\text{-}mean}$ of 10 mg/L as target. Importantly, the target concentration of 10 mg/L for both frail and fit older people has not yet been validated. It was used in this paper because it is the only known target concentration extrapolated from another special population (e.g. pediatrics) [17] and therefore the most feasible. Once the target concentration in older people is known, the model will still be accurate and simulations can be extended. With 1000 mg q6h, the average geriatric inpatients achieved a $C_{ss\text{-}mean}$ of

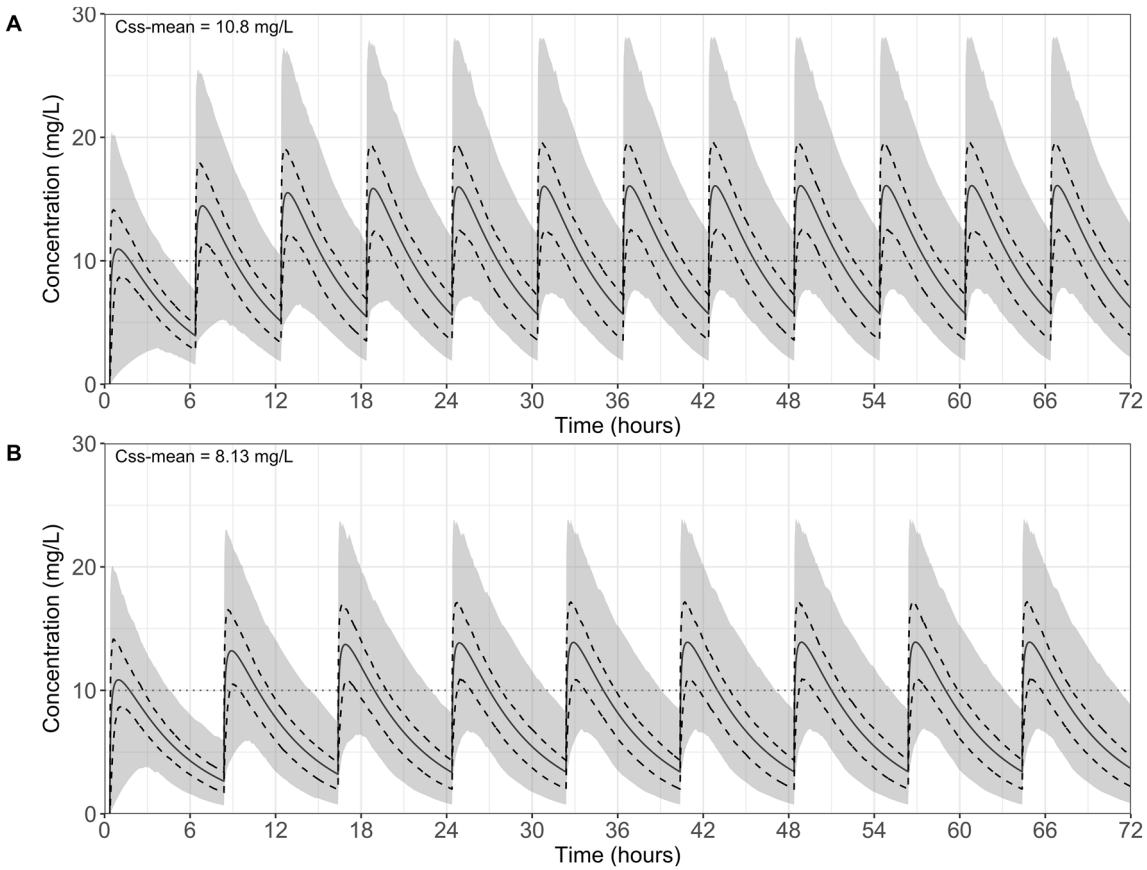

Fig. 4 Concentration–time profiles based on 1000 simulations using the final pharmacokinetic model following the current dosing regimens: **A** paracetamol 1000 mg every 6 h and **B** paracetamol 1000 mg every 8 hours. The black line corresponds with the median achieved concentration, the dashed lines represent the 25th to 75th prediction interval, and the grey areas represent the 95% prediction interval for the simulated values. The dotted grey line indicates the target concentration of 10 mg/L. For every dosing regimen, the mean steady-state concentration ($C_{ss\text{-}mean}$) is shown

Table 3 Mean steady-state concentrations ($C_{ss\text{-}mean}$) achieved by 90%, 75%, 50%, 25% and 10% of the frail older subjects with the currently used dosing regimens of paracetamol 1000 mg every 6 hours (q6h) and every 8 hours (q8h) based on 1000 simulations using the final pharmacokinetic model

	$C_{ss\text{-}mean}$ (mg/L)				
	90% of the subjects above	75% of the subjects above	50% of the subjects above (median concentration)	25% of the subjects above	10% of the subjects above
1000 mg q6h	6.8	8.2	10.2	12.7	15.5
1000 mg q8h	5.2	6.3	7.8	9.6	11.4

10.8 mg/L. The average geriatric inpatients did not achieve the target $C_{ss\text{-}mean}$ with 1000 mg q8h ($C_{ss\text{-}mean}$ 8.13 mg/L). However, due to the large unexplained variability, a relevant proportion of the frail older population remained off-target; 22.2% (q6h) and 54.2% (q8h) of the geriatric inpatients remained below 8 mg/L while 31.3% (q6h) and 7.6% (q8h) exceeded 12 mg/L. Based on these simulations, it could be stated that a higher daily dose (1000 mg q6h vs 1000 mg q8h) in frail geriatric inpatients would result in more patients achieving the target concentration.

Safety of treatment, however, is equally important as target attainment. Hepatotoxicity in particular is an issue in this context. In this study, we compared q6h and q8h administration based on $C_{ss\text{-}mean}$, which only reflects potential efficacy. Safety concerns have played a role in the recommendation of paracetamol 1000 mg q8h in older adults [25]. Paracetamol metabolism includes different metabolic pathways: paracetamol is mainly metabolized by sulphation and glucuronidation [26] and via a minor pathway by cytochrome P450 (CYP)2E1. This results in the formation of *N*-acetyl-p-benzoquinone imine (NAPQI), which under normal circumstances is neutralised by glutathione [26]. However, at high exposure or in situations where glutathione

is depleted, such as in a malnourished state, NAPQI will be able to bind covalently to cellular proteins. This results in the formation of toxic protein adducts, which can lead to hepatocellular necrosis [26]. A few studies have reported that formation of NAPQI seems unchanged in the fit older population [14, 27] but for the frail older population no data have been reported. Nonetheless, high dosing and reducing the dosing interval will result in high exposure to NAPQI. This can be a problem for a proportion of frail older adults considering the large variability in PK seen in the simulations (Fig. 4). With the current dosing regimens, the average patients achieved a concentration of 6.8 [3.1–11.5] mg/L (q6h) and 6.1 [2.3–9.5] mg/L (q8h) 4 h after oral paracetamol intake. Although the corresponding toxic reference of paracetamol, 4 h after intake, has been reported to be 75 mg/L [28], hepatotoxicity can occur with normal dosages administered to young adults [29] and fit older adults [30]. However, another study reported higher paracetamol concentrations in frail older patients (compared with fit older patients and young adults) after 5 days of therapeutic paracetamol dosage (3000–4000 mg/day), while no increased liver safety parameters were observed [31]. Additionally, the toxic reference for NAPQI is unknown. Currently, nothing is known about the relation between paracetamol concentrations, NAPQI concentrations and (elevated) liver function parameters in (frail) geriatric inpatients. To be able to recommend a dosing regimen, future studies should focus on PK, efficacy and safety for paracetamol, a drug frequently used in this subpopulation.

5 Conclusion

Oral paracetamol PK in frail geriatric inpatients was best described with a one-compartment model. Despite the high inter-individual variability, no covariates were identified to explain the high inter-individual variability. Simulations of 1000 mg q6h and q8h resulted in a $C_{ss\text{-}mean}$ of 10.8 [25–75th percentiles 8.2–12.7] and 8.13 [6.3–9.6] mg/L, respectively, for the average geriatric inpatients. The majority of the population remained off-target (22.2% and 52.2% < 8 mg/L; 31.3 and 7.6% > 12 mg/L). This current analysis is a first step towards description of paracetamol PK, and also to illustrate paracetamol variability with the currently used dosing regimens in frail geriatric inpatients. To be able to recommend a dosing regimen, future studies should focus on PK, efficacy and safety for paracetamol, a drug frequently used in this subpopulation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-021-00912-z.

Acknowledgements We greatly acknowledge K. Hagoort for editorial assistance.

Declarations

Funding All authors declare that no funding for this project has been received.

Conflict of interest All authors declare no conflicts of interest.

Ethics approval This study was conducted at the University Hospitals Leuven, Belgium, following approval by the medical ethics committee of UZ Leuven (EUDRACT 2015-004217-24).

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability The data that support the findings of this study are available on request from the corresponding author.

Code availability Available upon request to the corresponding author.

Author contributions LvdH and PM wrote the manuscript; LvdH, PM, LvdL, JH, BK, BdW, DT, JT, JF, KW, and IS edited the manuscript; LvdH and PM provided graphics for the manuscript; LvdH, PM, KA, BK and BdW performed research for the manuscript; LvdH, PM, KA, IS, BK and BdW designed the research; and IS, KA, BK and BdW supervised the research. All authors read and approved the final version of the paper.

References

1. Gibson SJ, Lussier D. Prevalence and relevance of pain in older persons. Pain Med. 2012;13(Suppl 2):S23–6. https://doi.org/10.1111/j.1526-4637.2012.01349.x.
2. Molton IR, Terrill AL. Overview of persistent pain in older adults. Am Psychol. 2014;69(2):197–207. https://doi.org/10.1037/a0035794.
3. Marcum ZA, Duncan NA, Makris UE. Pharmacotherapies in geriatric chronic pain management. Clin Geriatr Med. 2016;32(4):705–24. https://doi.org/10.1016/j.cger.2016.06.007.
4. Safe acetaminophen use guideline. Goverment Q. 2014. https://www.health.qld.gov.au/__data/assets/pdf_file/0030/147666/qh-gdl-415.pdf. Accessed 15 Jun 2018.
5. What dose of paracetamol for older people? Drug Ther Bull. 2018;56(6):69–72. https://doi.org/10.1136/dtb.2018.6.0636.
6. Boparai MK, Korc-Grodzicki B. Prescribing for older adults. Mt Sinai J Med. 2011;78(4):613–26. https://doi.org/10.1002/msj.20278.
7. ElDesoky ES. Pharmacokinetic-pharmacodynamic crisis in the elderly. Am J Ther. 2007;14(5):488–98. https://doi.org/10.1097/01.mjt.0000183719.84390.4d.
8. Allegaert K, Olkkola KT, Owens KH, Van de Velde M, de Maat MM, Anderson BJ, et al. Covariates of intravenous paracetamol pharmacokinetics in adults. BMC Anesthesiol. 2014;14:77. https://doi.org/10.1186/1471-2253-14-77.
9. Bannwarth B, Pehourcq F, Lagrange F, Matoga M, Maury S, Palisson M, et al. Single and multiple dose pharmacokinetics of acetaminophen (paracetamol) in polymedicated very old patients with rheumatic pain. J Rheumatol. 2001;28(1):182–4.

10. Liukas A, Kuusniemi K, Aantaa R, Virolainen P, Niemi M, Neuvonen PJ, et al. Pharmacokinetics of intravenous paracetamol in elderly patients. Clin Pharmacokinet. 2011;50(2):121–9. https://doi.org/10.2165/11537240-000000000-00000.
11. Johnston C, Hilmer SN, McLachlan AJ, Matthews ST, Carroll PR, Kirkpatrick CM. The impact of frailty on pharmacokinetics in older people: using gentamicin population pharmacokinetic modeling to investigate changes in renal drug clearance by glomerular filtration. Eur J Clin Pharmacol. 2014;70(5):549–55. https://doi.org/10.1007/s00228-014-1652-7.
12. Rockwood K, Howlett SE. Fifteen years of progress in understanding frailty and health in aging. BMC Med. 2018;16(1):220. https://doi.org/10.1186/s12916-018-1223-3.
13. Ellmers SEPL, Notarianni LJ, Jones RW. Excretion of paracetamol in fit and frail elderly people. J Am Geriatr Soc. 1991;31(596):597.
14. Wynne HA, Cope LH, Herd B, Rawlins MD, James OF, Woodhouse KW. The association of age and frailty with paracetamol conjugation in man. Age Ageing. 1990;19(6):419–24.
15. Mian P, van Esdonk MJ, Olkkola KT, de Winter BCM, Liukas A, Spriet I, et al. Population pharmacokinetic modelling of intravenous paracetamol in fit older people displays extensive unexplained variability. Br J Clin Pharmacol. 2019;85(1):126–35. https://doi.org/10.1111/bcp.13770.
16. Corsi N, Roberto A, Cortesi L, Nobili A, Mannucci PM, Corli O, et al. Prevalence, characteristics and treatment of chronic pain in elderly patients hospitalized in internal medicine wards. Eur J Intern Med. 2018;55:35–9. https://doi.org/10.1016/j.ejim.2018.05.031.
17. Gibb IA, Anderson BJ. Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. Arch Dis Child. 2008;93(3):241–7. https://doi.org/10.1136/adc.2007.126896.
18. Hias J, Van der Linden L, Walgraeve K, Gijsen M, Mian P, Koch BCP, Allegaert K, Annaert P, Tournoy J, Spriet I. Pharmacokinetics of 2 oral paracetamol formulations in hospitalized octogenarians. Br J Clin Pharmacol. 2021. https://doi.org/10.1111/bcp.15049
19. Flint RB, Mian P, van der Nagel B, Slijkhuis N, Koch BC. Quantification of acetaminophen and its metabolites in plasma using UPLC-MS: doors open to therapeutic drug monitoring in special patient populations. Ther Drug Monit. 2017;39(2):164–71. https://doi.org/10.1097/FTD.0000000000000379.
20. Nguyen TH, Mouksassi MS, Holford N, Al-Huniti N, Freedman I, Hooker AC, et al. Model evaluation of continuous data pharmacometric models: metrics and graphics. CPT Pharmacometrics Syst Pharmacol. 2017;6(2):87–109. https://doi.org/10.1002/psp4.12161.
21. Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2007;34(5):711–26. https://doi.org/10.1007/s10928-007-9066-0.
22. Petersson KJ, Hanze E, Savic RM, Karlsson MO. Semiparametric distributions with estimated shape parameters. Pharm Res. 2009;26(9):2174–85. https://doi.org/10.1007/s11095-009-9931-1.
23. Rodriguez-Manas L, Feart C, Mann G, Vina J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci. 2013;68(1):62–7. https://doi.org/10.1093/gerona/gls119.
24. Cerreta F, Eichler HG, Rasi G. Drug policy for an aging population–the European Medicines Agency's geriatric medicines strategy. N Engl J Med. 2012;367(21):1972–4. https://doi.org/10.1056/NEJMp1209034.
25. Booker SS, Bartoszczyk DA, Herr KA. Managing pain in frail elders. Am Nurse Today. 2016;11(4). https://www.americannursetoday.com/managing-pain-frail-elders/
26. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol. 2002;40(1):3–20.
27. Miners JO, Penhall R, Robson RA, Birkett DJ. Comparison of paracetamol metabolism in young adult and elderly males. Eur J Clin Pharmacol. 1988;35(2):157–60.
28. Bos JC, Misticio MC, Nunguiane G, Mathot RAA, van Hest RM, Prins JM. Paracetamol clinical dosing routine leads to paracetamol underexposure in an adult severely ill sub-Saharan African hospital population: a drug concentration measurement study. BMC Res Notes. 2017;10(1):671. https://doi.org/10.1186/s13104-017-3016-8.
29. Sabate M, Ibanez L, Perez E, Vidal X, Buti M, Xiol X, et al. Paracetamol in therapeutic dosages and acute liver injury: causality assessment in a prospective case series. BMC Gastroenterol. 2011;11:80. https://doi.org/10.1186/1471-230X-11-80.
30. Ging P, Mikulich O, O'Reilly KM. Unexpected paracetamol (acetaminophen) hepatotoxicity at standard dosage in two older patients: time to rethink 1 g four times daily? Age Ageing. 2016;45(4):566–7. https://doi.org/10.1093/ageing/afw067.
31. Mitchell SJ, Kane AE, Hilmer SN. Age-related changes in the hepatic pharmacology and toxicology of paracetamol. Curr Gerontol Geriatr Res. 2011;2011: 624156. https://doi.org/10.1155/2011/624156.
32. Valente MA, Hillege HL, Navis G, Voors AA, Dunselman PH, van Veldhuisen DJ, et al. The Chronic Kidney Disease Epidemiology Collaboration equation outperforms the Modification of Diet in Renal Disease equation for estimating glomerular filtration rate in chronic systolic heart failure. Eur J Heart Fail. 2014;16(1):86–94. https://doi.org/10.1093/eurjhf/hft128.

Authors and Affiliations

L. T. van der Heijden[1,2] · P. Mian[1,3] · J. Hias[4] · B. C. M. de Winter[5] · J. Tournoy[6,7] · L. Van der Linden[4,8] · D. Tibboel[1] · K. Walgraeve[4] · J. Flamaing[6,7] · B. C. P. Koch[5] · K. Allegaert[5,8,9] · I. Spriet[4,8]

1 Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

2 Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

3 Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Hanzeplein 1, Groningen 9713 GZ, The Netherlands

4 Pharmacy Department, University Hospitals Leuven, Leuven, Belgium

5 Department of Hospital Pharmacy, Erasmus University Medical Centre, Rotterdam, The Netherlands

6 Department of Geriatric Medicine, University Hospitals Leuven, Leuven, Belgium

7 Department of Chronic Diseases, Metabolism and Ageing, KU Leuven, Leuven, Belgium

8 Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

9 Department of Development and Regeneration, KU Leuven, Leuven, Belgium