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ORIGINAL ARTICLE

Pharmacokinetics of 2 oral paracetamol formulations in hospitalized octogenarians

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Aims: It is currently unclear how paracetamol should be dosed in order to increase its efficacy while warranting safety in very old adults. The objective was to evaluate the pharmacokinetics of 2 oral paracetamol formulations and its metabolites in hospitalized octogenarians.

Methods: Geriatric inpatients aged 80 years and older received a 1000-mg paracetamol tablet or granulate at 08.00, 14.00 and 20.00. After at least 4 consecutive gifts, plasma samples were collected around the 08.00 dose (trough, +0.5, +1, +2, +4, +5 and +6 h). Plasma concentrations of paracetamol and its metabolites were determined and individual pharmacokinetic parameters were derived. The Edmonton Frail Scale was used to assess frailty. An analgesic plasma target was defined as an average plasma concentration (C_{avg}) of 10 mg/L.

Results: The mean (±standard deviation) age was 86.78 (±4.20) years. The majority (n = 26/36, 72%) received the tablet, 10 (28%) the granulate. Thirty patients (85%) were classified with moderate to severe frailty. Seven (21%) patients had a C_{avg} above 10 mg/L. The median [interquartile range] time to reach the peak concentration was 50.5 [31.50–92.50] and 42.50 [33.75–106.75] min for the tablet and granulate, respectively. The coefficient of variation was 95% for time to reach the peak concentration and 30% for C_{avg} of paracetamol. A correlation of C_{avg} of paracetamol was observed with female sex and total serum bilirubin.

Conclusion: Large interindividual differences were found for pharmacokinetic parameters of oral paracetamol in frail inpatients after multiple dosing. Female sex and higher total serum bilirubin concentrations were associated with paracetamol exposure. No significant differences were observed between the tablet and granulate.

KEYWORDS
older inpatients, paracetamol, pharmacokinetics

The authors confirm that the Principal investigator for this paper is Jos Tournoy and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

The prevalence of chronic pain is high in very old adults and inadequate pain control remains a significant issue in this population.[1–4] Multiple causes can be identified. First, pain in very old adults is often underreported and might be related to cognitive impairment, which can lead to difficulties in pain assessment. Secondly, a lacking knowledge of healthcare professionals on how to provide appropriate pain treatment might further impact pain control. Thirdly fear of potential adverse drug events might add to the overall issues of undertreatment in very old adults.[5] Most mild-to-moderate pain syndromes in very old adults are initially managed with **paracetamol** (acetaminophen), which is in accordance with the World Health Organization analgesic ladder. The World Health Organization recommends using nonopioid minor analgesics such as paracetamol as first-line treatment of pain. Addition of a weak opioid, such as tramadol or codeine, is suggested if pain is not properly controlled. Next, weak opioids can be substituted by more potent opioid, such as oxycodone or morphine.[6] As nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk for adverse drug events, these are not considered first-line agents in this patient population.[7]

Dosing recommendations for paracetamol are available, yet none with a specific focus on patients aged 80 years and older.[2] As a result, paracetamol is mainly dosed according to clinical experience, expert opinion or based on pharmacokinetic data extrapolated from studies in younger adults.[2] Previous research by Mian et al. showed that ageing coincided with a decreased volume of distribution (Vd) and total paracetamol clearance from plasma (CL). However, a clear impact of age on paracetamol absorption was not observed.[2] More data are urgently needed to better understand how physiological changes during ageing impact the pharmacokinetics as well as the analgesic effects of oral paracetamol, in particular in frail older inpatients.[2]

Furthermore, it has been suggested to aim for a target plasma concentration of 10 mg/L to manage pain adequately. Similarly, this target has never been studied or validated in adults aged 80 years and older.[2,8] A population pharmacokinetic study has proposed practical dosing guidelines for older adults receiving intravenous paracetamol. In this single-dose pharmacokinetic study, investigators mostly enrolled fit and robust older adults with a median age of 77.3 years following orthopaedic surgery.[9] In summary, there is a need for data on paracetamol pharmacokinetics in frail adults aged 80 years and older receiving oral paracetamol during multiple dosing. These data might then be used for pharmacodynamics studies and subsequently to inform an evidence-based dosing regimen of oral paracetamol in older adults.

The aims of this study were hence to determine exposure and pharmacokinetics of oral paracetamol and its metabolites in geriatric inpatients aged 80 years and older during multiple dosing and to investigate whether a tablet *vs*. granulate formulation may affect absorption and subsequent exposure.

What is already known about this study

- Oral paracetamol is the agent of choice for managing pain in older adults and dosing recommendations are extrapolated from data in younger adults.
- Ageing is associated with altered pharmacokinetics of intravenous paracetamol.
- Pharmacokinetics of oral paracetamol in very old frail patients are insufficiently characterized.

What this study adds

- Large interindividual variability in pharmacokinetics was observed.
- No difference in absorption was observed between the granulate and tablet formulation.
- Female sex and higher total serum bilirubin concentration were associated with an increased paracetamol exposure in an exploratory analysis.

2 | METHODS

2.1 | Design and setting

An observational monocentric pharmacokinetic study was conducted. The study was organized at the 80-bed acute geriatric department of the 1950-bed University Hospitals Leuven in Belgium. The study was approved by the local Ethics Committee (S58396) and was registered at ClinicalTrials.gov (Identifier: NCT03617471).

2.2 | Study participants

Patients were eligible for study participation if the following criteria were met: written informed consent provided by the patients or their relatives in case of inability to provide the consent themselves; a minimum age of 80 years; admission to the acute geriatric ward; oral intake of paracetamol, treatment with 1000 mg in tablet or granulate formulation at the discretion of the treating physician, 3 times daily (08.00, 14.00, 20.00); at least 4 consecutive doses of paracetamol administered before sampling. Patients were excluded in case of a do-not-resuscitate code corresponding to active withdrawal of care (= end of life care).

2.3 | Pharmacokinetic sampling

Blood sampling for paracetamol and its metabolites was performed during 1 dosing interval of oral paracetamol starting at 08.00 after at

least 4 confirmed consecutive intakes. During a first inclusion period (November 2015–January 2016) only patients taking the tablet formulation (Dafalgan Forte, tablets, Bristol-Myers Squibb Belgium N.V., Brussels, 1000 mg) were included. During a second inclusion period (July–November 2016) a new formulation (Dafalgan Instant forte, granulate, Bristol-Myers Squibb Belgium N.V., Brussels, 1000 mg) was introduced; patients taking this formulation were also included.

In the first study period, 6 blood samples were collected via a peripheral venous catheter: within 15 minutes before intake of the 08.00 dose (trough level, T0, i.e., 12 hours after intake last paracetamol) and at +0.5 (T0.5), +1 (T1), +2 (T2), +4 (T4) and +6 hours (T6, trough level before intake of second paracetamol at 14.00) after oral administration of paracetamol. In the second study period (July–November 2016) a seventh sample drawn at +5 hours (T5) after paracetamol intake was introduced allowing for a better estimation of the elimination phase. Samples were centrifuged at 1500*g* for 15 minutes immediately after collection. Plasma was stored at −20°C until bioanalysis.

2.4 | Bioanalysis

Analysis of paracetamol concentrations and its major metabolites paracetamol-glucuronide, paracetamol-sulfate, paracetamol-mercapturic acid and paracetamol-cysteine was performed at the Hospital Pharmacy Laboratory of the Erasmus MC Pharmacy department using an ultra-performance liquid chromatography (UPLC)–tandem mass spectrometry method. The equipment used was a Dionex Ultimate UPLC system consisting of an Ultimate 3000 RS UPLC pump, an Ultimate 3000 RS autosampler, and an Ultimate 3000 RS Column Compartment. The UPLC was connected to a triple quadrupole Thermo TSQ Vantage mass spectrometer with HESI probe (Thermo Scientific, Waltham, MA, USA). The software programs Chromeleon (version 6.8; Dionex, Thermo Scientific), Xcalibur (version 2.1; Thermo Scientific) and LCquan (version 2.6; Thermo Scientific) were used to control the system and analyse the data. The assays were linear from 0.020 to 25.0 mg/L, 0.047 to 47.0 mg/L and 0.043 to 43.0 mg/L for paracetamol, paracetamol-glucuronide and paracetamol-sulfate, respectively, and from 0.020 to 10.0 mg/L, and 0.010 to 15 mg/L for paracetamol-cysteine and paracetamol-mercapturic acid. The lower limit of the ranges represents the lower limits of quantification. Intra- and interassay accuracies ranged from 93.6 to 130.9%. Intra- and interassay imprecision did not exceed 15%. More details are described in an earlier validation article. The method was validated according to Food and Drug Administration guidelines.[10]

2.5 | Patient variables

The following patient variables were retrieved from the electronic patient health record: age, sex, body length, body weight and body mass index. Biochemical parameters from the last available blood sample prior to paracetamol sampling were acquired as follows: serum albumin concentrations, estimated glomerular filtration rate according to the Chronic Kidney Disease–Epidemiology Collaboration formula and estimated creatinine clearance according to the Cockcroft and Gault ($CrCl_{CG}$) formula, serum creatinine total serum bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase (GGT) and alkaline phosphatase concentrations. The values were documented as reported in the electronic health record. Comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease, heart failure, chronic kidney disease, dementia, chronic pain, liver disease, anorexia and Parkinson's disease were also registered. Additional variables were collected as follows: the indication for paracetamol administration (pain, fever or both); the number of concomitant drugs; the use of other analgesics; the pain score determined by the numeric rating scale (NRS) or the Pain Assessment in Advanced Dementia (PAINAD) tool at each sample moment (T0–T6); the Mini Mental State Examination score; and frailty status determined by the Edmonton Frail Scale.[11,12]

2.6 | Pharmacokinetic parameters

Individual pharmacokinetic parameters were determined by noncompartmental analysis using Microsoft Excel Windows 2016 (16.0.6366.2062 21 January 2016). The terminal elimination rate (k_e) constant was estimated by linear regression of the natural logarithms of mean plasma concentrations *vs*. time. The area under the plasma concentration–time curve (AUC_{0-6}) was calculated by the linear up/log down trapezoidal method. The half-life ($t^1/_2$) was calculated as $\ln 2/k_e$. Oral plasma clearance (CL/F) was calculated as dose/AUC_{0-6}. Volume of distribution (Vd) was calculated as dose/(ke. AUC_{0-6}). Maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) of paracetamol were observed directly from the data. Average plasma concentration (C_{avg}) was calculated as $AUC_{0-6}/6$. The AUC of the metabolites (in mg*h/L and mmol*h/L) and the metabolite-to-parent drug AUC ratios ($AUCm_{0-6}/AUCp_{0-6}$) were also calculated (in mg and mmol).

Pharmacokinetic parameters were compared to previously reported study findings, where paracetamol, in a dose of 1000 mg or 14 mg/kg, administered intravenously or orally, was examined in patients with a mean age of 75 years or older and to their comparison groups of younger adults.

Target attainment was determined as a C_{avg} above the analgesic target of 10 mg/L.[8]

2.7 | Statistical analysis

Normality of the continuous variables was evaluated by visual inspection of the histograms and QQ plots. Variables were reported as mean (±standard deviation [SD]) or median [interquartile range, IQR = Q1–Q3], as appropriate. Proportions and counts were represented as *n* (%). The coefficient of variation (CV) was reported for T_{max}, C_{max} and C_{avg} for paracetamol. CV is defined as the ratio of the SD to the

mean and expressed as a percentage. Differences in pharmacokinetic parameters between the different formulations of paracetamol were determined using the Mann–Whitney *U*-test.

Univariate linear regression analyses with C_{avg} of paracetamol and each of the metabolites as separate outcome variables were performed to investigate the relationship with body weight, body mass index, total serum bilirubin concentrations, sex, $CrCl_{CG}$, GGT and serum albumin concentrations. The variables showing a statistically significant relationship were included along with the type of formulation in the multivariable regression analysis. Statistical significance was established as $P < .05$, with all tests being 2-tailed.

Data were analysed using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) and R software (R version 3.5.1; The R Foundation for Statistical Computing, Vienna, Austria).

2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in. http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[13]

3 | RESULTS

In total, 36 patients were included for pharmacokinetic analysis. The patient selection process is summarized in Figure 1.

The patients' mean age was 86.78 (±4.20) years. Paracetamol was prescribed for pain in 89%, fever in 8% and for both indications in 3% in patients. Almost half of the patients (49%) received other analgesics during paracetamol treatment and in 33% chronic pain was mentioned in their medical history. Other demographic characteristics are shown in Table 1.

A decrease in pain score determined by the NRS between the moment before the intake of paracetamol and 1 hour after the intake was observed in 40% ($n = 10/25$) of patients, the score remained the same in 36% ($n = 6/25$) of patients and increased in 24% ($n = 9/25$). The median paracetamol plasma concentration-time curve of all patients is displayed in Figure 2.

A minority of patients, i.e. 7/33 (21%), had a C_{avg} exceeding the predefined analgesic target of 10 mg/L. Pharmacokinetic parameters are summarized in Table 2, which also contains data from previously published studies on the use of paracetamol in older adults aged 75 years or older and their comparator groups of fit younger patients. CVs were 95% for T_{max}, 35% for C_{max} and 30% for C_{avg} of paracetamol.

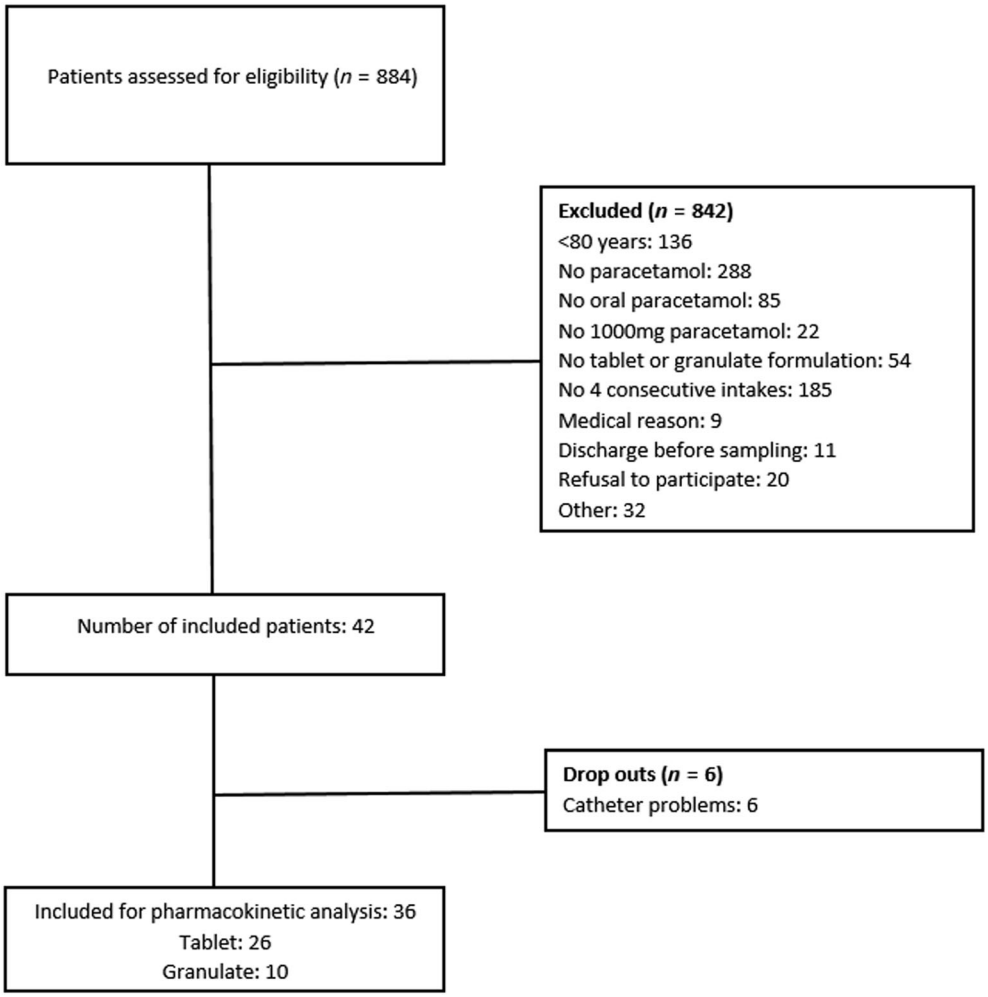

FIGURE 1 Patient selection process

TABLE 1 Characteristics of included patients

Age	**86.78 (±4.20) y**
Formulation: tablet/granulate	26/10 (72%/28%)
Reason for paracetamol administration	
Pain	32 (89%)
Fever	3 (8%)
Combination pain and fever	1 (3%)
Male/female	16/20 (44%/56%)
Body weight	68.67 (±13.14) kg
Height	1.62 (±0.09) m
BMI	26.04 (±4.33)
Bilirubin (total)	0.52 [0.33–0.69] mg/dl
Bilirubin (direct)	0.24 [0.18–0.36] mg/dl
AST	19.5 [17.00–23.75] U/L
ALT	14 [11.00–21.00] U/L
γ-GT	31 [16.25–54.75] U/L
Alkaline phosphatase	69.50 [61.75–91.00] U/L
eGFR (CKD-EPI)	60.42 (±18.31) mL/min/1.73m^2
$CrCl_{CG}$	49.21 (±16.46) mL/min
Number of drugs [a]	8.50 [6.00–11.75]
Other analgesic drugs	17 (49%)
NSAIDs	1 (6%)
Mild opioids	9 (53%)
Strong opioids	7 (41%)
MMSE (/30)	21.79 (±4.80) ($n = 28$)
Albumin	37.25 (±4.73) g/L
Frailty (EFS)	($n = 35$)
0 (not frail)	1 (3%)
1 (slightly)	4 (12%)
2 (moderate)	12 (34%)
3 (severe)	18 (51%)
Comorbidities	($n = 36$)
Diabetes mellitus	16 (44%)
Chronic obstructive pulmonary disease	12 (33%)
Heart failure	16 (44%)
Atrial fibrillation	22 (61%)
Chronic kidney disease	18 (50%)
Dementia	17 (47%)
Chronic pain	12 (33%)
Liver disease	24 (67%)
Anorexia	9 (25%)
Parkinson disease	2 (6%)
NRS score	
t0	4 [0–6]
t1	2 [0–5]
t2	2 [0–5]
t3	2 [0–5]
t4	2 [0–5]

(Continues)

TABLE 1 (Continued)

Age	**86.78 (±4.20) y**
t5	2 [0–5]
t6	3 [0–4.5]

Data was reported as mean (± standard deviation) or median [interquartile range] unless stated otherwise
[a]Number of administrations not taken into account
BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GT: γ-glutamyltransferase; eGFR (CKD-EPI): estimated glomerular filtration rate according to Chronic Kidney Disease–Epidemiology Collaboration; $CrCl_{CG:}$ Creatinine clearance according to Cockcroft and Gault; MMSE: mini mental state examination; EFS: Edmonton Frail Scale; numeric rating scale; t0: before intake paracetamol; t1: 30 min after intake; t2: 60 min after intake; t3 120 min after intake; t4: 240 min after intake; t5: 300 min after intake; t6: 360 min after intake of paracetamol.

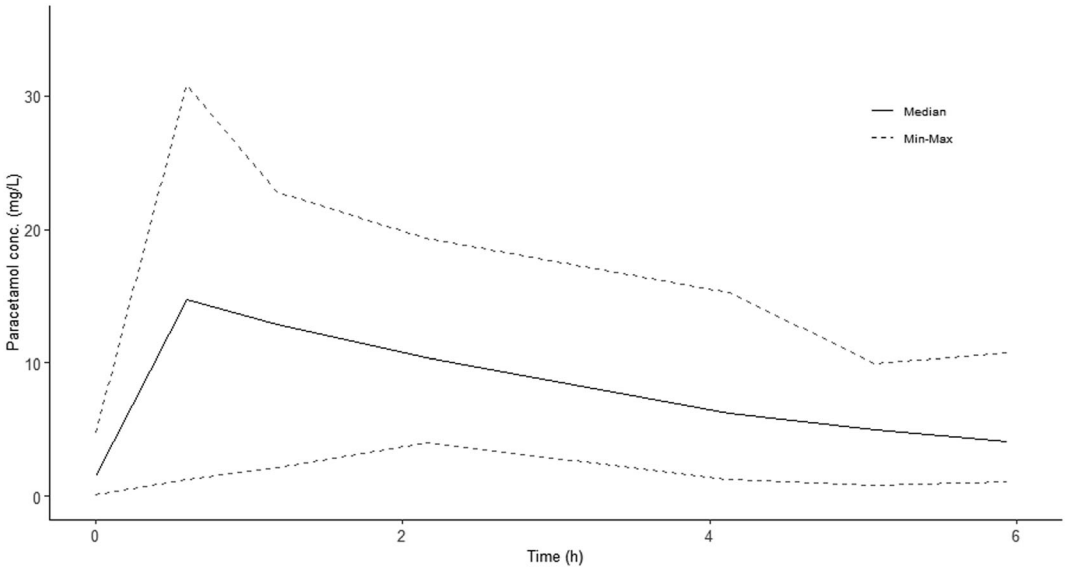

FIGURE 2 Median paracetamol plasma concentration–time curve. Dosing regimen: 1000 mg 3 times daily in tablet or granulate formulation. Population: patients aged 80 years or older. Min-Max: the minimum and maximum determined concentrations at each time point

Ten patients took the granulate formulation. Pharmacokinetic parameters did not differ significantly between patients receiving a tablet or a granulate formulation. Details are shown in Table 3.

The AUCs for the main paracetamol metabolites and the metabolite/paracetamol ratio are summarized in Table 4. Data from Liukas et al. are also shown in the table. The AUC_{0-6} expressed in mmol*h/L were 0.3 [0.02–0.04], 0.59 [0.48–0.76], 0.006 [0.004–0.008] and 0.28 [0.20–0.37] mmol*h/L for the cysteine, glucuronide, mercapturic acid and sulfate conjugates, respectively. The metabolic ratios expressed in mmol were 0.07 [0.05–0.15], 1.73 [1.47–2.94], 0.019 [0.012–0.024] and 0.79 [0.64–1.52] for the cysteine, glucuronide, mercapturic acid and sulfate conjugates, respectively.

Total serum bilirubin concentrations and sex were included in the multivariable regression analysis along with the type of formulation. A higher total serum bilirubin concentration and female sex were significantly associated with an increased C_{avg}.

For C_{avg} of the paracetamol metabolites GGT, $CrCl_{CG}$ and the type of formulation were included in the separate multivariable regression analyses for each metabolite. $CrCl_{CG}$ showed an inverse association with C_{avg} for each of the metabolites in the multivariable model. For the cysteine metabolite, increased GGT was also associated with an increased C_{avg}. The results of the multivariable regression analyses are shown in Table 5.

4 | DISCUSSION

In this study we determined pharmacokinetics and exposure of oral paracetamol and its metabolites in frail geriatric inpatients aged 80 years or older during multiple dosing. To the best of our knowledge, our study is presently the largest dataset in this complex patient population (Table 2). Importantly, we observed a large interindividual variability, as demonstrated by the wide IQR for all pharmacokinetic parameters and relatively high CVs for T_{max}, C_{max} and C_{avg}. In the majority of patients (26/33, 79%) the concentration at steady state was below the predefined analgesic target of 10 mg/L as shown by a median [IQR] C_{avg} of 8,00 [6.16–9.34] mg/L, resulting in an overall low exposure. No significant differences were seen in exposure

TABLE 2 Pharmacokinetic parameters of paracetamol compared to literature data

	Study population	Published data – Frail older patients	Published data – Fit older patients					Published data – Younger adults		
		Ellmers et al.[14]	Triggs et al.[15]	Liukas et al.[16]	Miners et al.[17]	Bannwarth et al.[18]	Ellmers et al.[14]	Liukas et al.[16]	Miners et al.[17]	Triggs et al.[15]
Dosing information	1000 mg, orally	1000 mg, orally	14.3 mg/kg, orally	1000 mg, intravenously	1000 mg, orally	1000 mg, orally	1000 mg, orally	1000 mg, intravenously	1000 mg orally	14.3 mg/kg orally
Setting information (mean age, sample size, population)	86.78 y, $n = 36$, frail geriatric inpatients	83.5 y, $n = 26$, frail elderly	80.9 y, $n = 7$, healthy elderly	84 y, $n = 10$, fit elderly	79.3 y, $n = 8$, fit elderly	89 y, $n = 12$, mobile patients	77.3 y $n = 29$, fit elderly	27 y, $n = 10$, fit younger subjects	20.8 y, $n = 8$, healthy male subjects	24 y, $n = 6$, healthy young subjects
T_{max} (h)	0.83 [0.54–1.60] ($n = 36$)		0.74 (±0.17)	0.26 (±0.05)	0.76 (±0.32)	0.9 (±0.5)		0.31 (±0.07)	0.87 (±0.38)	0.67 (±0.19)
C_{max} (mg/L)	15.6 [12.35–20.89] ($n = 36$)			25.8 (±9.2)	14.5 (±3.4)	23.9 (±5.4)		16.3 (±4.5)	13.9 (±3.5)	
$AUC_{0-\infty}$ (mg/L*h)				74 (±16)		82.54 (±21.09)		44 (±3)		
AUC_{0-t} (mg/L*h)	47.97 [36.99–56.06] ($n = 33$)	74.62 [95%CI: 42.39–311.72][a]			38.48 [95%CI: 30.16–53.15][a]		56.50 [95%CI: 32.43–219.01][a]		36.48 [95%CI: 27.02–56.15][a]	
CL/F (D/AUC/kg) mL/min/kg	5.19 [4.46–6.20] ($n = 33$)			3.3 (±1.0)	5.61 (±0.79)	3.68 (±0.85)		4.6 (±1.1)	6.1 (±1.09)	
CL/F (D/AUC) (L/h)	20.85 [28.84–27.04] ($n = 33$)	13.4 (±5.2)					17.7 (±6.7)			
CL/F (mL/min/1.73m^2)	349.11 [299.79–425.62] ($n = 33$)		379 (±35)							477 (±36)
Vd (L/kg)	0.95 [0.75–1.40] ($n = 22$)		1.05 ± 0.08	0.92 (±0.26)				1.04 (±0.22)		1.03 (±0.08)
$t_{1/2}$ (h)	2.08 [1.83–2.75] ($n = 22$)	3.4 (±1.2)	2.17 (±0.13)	3.6 (±1.9)	2.2 (±0.3)	2.74 (±0.48)	2.7 (±0.5)	2.7 (±0.6)	2.1 (±0.4)	1.82 (±7)

T_{max}: time to reach peak concentration, C_{max}: peak concentration, AUC: area under the plasma concentration–time curve, CL/F: total drug clearance from plasma, Vd: volume of distribution, $t^1/_2$: half-life, median [interquartile range], mean (± standard deviation), 95%CI: 95% confidence interval

[a]The mean AUC and 95% confidence interval were calculated based on mean Cl/F, dose and mean weight

TABLE 3 Pharmacokinetic parameters according to formulation

	Total	Tablet	Granulate	*P*-value (tablet *vs.* granulate)
T_{max} (min) median [IQR]	49.5 [32.25–95.75] ($n = 36$)	50.5 [31.50–92.50] ($n = 26$)	42.50 [33.75–106.75] ($n = 10$)	>.999
C_{max} (mg/L) median [IQR]	15.6 [12.35–20.89] ($n = 36$)	15.95 [12.38–21.19] ($n = 26$)	15.59 [10.80–21.77] ($n = 10$)	.698
AUC_{0-6} (mg/L*h) median [IQR]	47.97 [36.99–56.06] ($n = 33$)	46.56 [37.83–54.50] ($n = 24$)	55.64 [29.65–66.16] ($n = 9$)	.571

T_{max}: time to reach peak concentration; C_{max}: peak concentration; AUC: area under the plasma concentration–time curve; C_{avg}: average concentration; IQR: interquartile range

TABLE 4 Pharmacokinetic parameters of paracetamol and its metabolites

	AUC_{0-6} (mg/L*h) median [IQR]	Liukas et al.[16] $AUC_{0-\infty}$ (mg/L*h) mean (±SD)	Liukas et al.[16] $AUC_{0-\infty}$ (mg/L*h) mean (±SD)	AUCm/AUCp (mg/mg) median [IQR]	Liukas et al.[16] AUCm/AUCp (mg/mg) mean (±SD)	Liukas et al.[16] AUCm/AUCp (mg/mg) mean (±SD)
Dosing information	1000 mg, orally	1000 mg, intravenously		1000 mg, orally	1000 mg, intravenously	
Setting information	86.78 y, $n = 31$, frail geriatric inpatients	84 y, $n = 10$, fit elderly	27 y, $n = 10$, fit younger subjects	86.78 y, $n = 31$, frail geriatric inpatients	84 y, $n = 10$, fit elderly	27 y, $n = 10$, fit younger subjects
Paracetamol	47.97 [36.99–56.06]	74 (±16)	44 (±13)	NA	NA	NA
Paracetamol-cysteine	6.84 [3.91–9.52]	NA	NA	0.12 [0.9–0.25]	NA	NA
Paracetamol-glucuronide	194.28 [155.71–247.61]	272 (±131)	117 (± 34)	3.74 [3.18–6.36]	3.81 (±1.87)	2.8 (±0.95)
Paracetamol-mercapturic acid	1.74 [1.18–2.58]	NA	NA	0.04 [0.02–0.05]	NA	NA
Paracetamol-sulfate	64.21 [46.45–85.85]	84 (±39)	31 (±8)	1.21 [0.97–2.33]	1.13 (±0.39)	0.70 (±0.18)

m: metabolite; p: parent drug; AUC: area under the plasma concentration–time curve; IQR: interquartile range; SD: standard deviation

TABLE 5 Determinants associated with exposure of paracetamol and its major metabolites

Regression coefficient	C_{avg} PCT	C_{avg} PCT-CYS	C_{avg} PCT-GLUC	C_{avg} PCT-MERC	C_{avg} PCT-SULF
Form, granulate	−0.62	0.09	1.41	0.03	1.46
Sex, female	1.92*	NA	NA	NA	NA
Bilirubin total (mg/dl)	3.26*	NA	NA	NA	NA
CrCl $_{CG}$ (mL/min)	NA	−0.02*	−0.95*	−0.006**	−0.25***
GGT (U/L)	NA	0.01*	0.39	0.002	0.05

C_{avg}: average plasma concentration; PCT: paracetamol; PCT-CYS: paracetamol-cysteine; PCT-GLUC: paracetamol-glucuronide; PCT-MERC: paracetamol-mercaptopuric acid; PCT-SULF: paracetamol-sulfate, NA: not applicable; $Crcl_{CG}$: creatinine clearance according to Cockcroft and Gault; GGT: γ-glutamyltransferase

*Statistically significant (*P*-value * <.05; ** <.01; *** <.001)

following the tablet *vs.* granulate formulations. The pain levels of the majority of patients remained the same or decreased 1 hour after paracetamol intake.

We believe that our study results are valid, yet some limitations have to be taken into consideration. First, only patients aged 80 years or older were included, hence no direct comparison with fit younger adults (i.e. younger than 80 years) was possible. However, we compared our results to already published data. Second, all included published data extrapolated their AUC to infinity which made the comparison with our data challenging. Extrapolation to infinity is usually done in studies reporting single dose pharmacokinetics, however, in our study sampling was performed when the patient had taken at

least 4 consecutive doses of paracetamol. This pragmatic study design allows for better insights into paracetamol pharmacokinetics during multiple dosing, which is closer to the daily clinical practice. Third, paracetamol was prescribed at 08.00, 14.00 and 20.00. The intervals between consecutive doses were hence different: the first trough level taken at 08.00 was 12 hours after the last paracetamol intake and the last trough level taken at 14.00 was 6 hours after the morning intake of paracetamol. However, this represents daily practice in most hospital settings, since oral therapy is commonly administered throughout the day, thus further adding to the external validity of our data. Fourth, mean and SD were often used to describe data in the literature. In contrast, we reported median and IQR since none of our evaluated pharmacokinetic parameters were distributed normally. We believe that median and IQR better represent the highly variable pharmacokinetics of paracetamol in our cohort. Fifth, the analgesic target of 10 mg/L is debatable. It is based on studies predominantly performed in paediatric patients after surgery and was not validated for geriatric patients. Based on the available body of evidence, Gibb et al. concluded, however, that a target of 10 mg/L for pain control could be used for adults. Since this cut-off is the only 1 reported to be associated with adequate analgesia, this was applied to define target attainment.[8] However, no hard conclusions should be drawn based on target attainment as its clinical relevance in our patient population remains uncertain. A formal exposure (e.g. C_{avg}) *vs.* response (pain assessment, using NRS or PAINAD) relationship analysis should be carried out in older adults with a geriatric profile in order to identify validated targets.

The following strengths add to the value of our data. First, the sample size of our study population ($n = 36$) exceeds that of other pharmacokinetic studies with paracetamol, which ranged from 6 to 26 patients.[14–18] Second, 2 different oral formulations of the study drug were compared. This strengthens the belief that variability is rather linked to the oral route of administration than to the formulation. Third, the major metabolites of paracetamol, i.e. the sulfate, glucuronide, mercapturic acid and cysteine conjugates, were also analysed, allowing for more detailed insights regarding the elimination of paracetamol in frail patients aged 80 years and older.

Table 2 shows a comparison with published data of paracetamol pharmacokinetic parameters. Compared to younger adults, the AUC was similar in our frail elderly population.[16] The CL/F found in this study was lower than those reported by Triggs et al. and Miners et al.[15,17] Mian et al. also concluded in their review that CL/F decreased with age and frailty.[2] The Vd was slightly lower than the values as reported by Liukas et al. and Triggs et al.[15,16] A decrease in Vd with increasing age and frailty was also described by Mian et al.[2]

The population investigated by Ellmers et al. was comparable to ours. They enrolled frail older patients with an average age of 83.5 years taking oral paracetamol 1000 mg. Compared to their results, our average AUC was reduced, CL/F was increased and $t_{1/2}$ was prolonged.[14] Furthermore, our average AUC was reduced and CL/F increased in comparison to other previously published findings in fit patients aged 75 years or older.[14,16,18] T_{max} was prolonged compared to most other investigations on oral paracetamol in fit older patients aged 75 years and older.[17] C_{max} was lower compared to the results of the fit older adults included by Bannwarth et al.[18] and comparable to the results found by Miners et al. in the same population.[17] Vd and $t_{1/2}$ were comparable to other trial results in fit older adults.[14–18]

Since CL/F is directly linked to AUC (CL = D/AUC), we hypothesize that the lower paracetamol exposure in our study population might be explained by reduced absorption, reflected by a delayed T_{max} and lower C_{max}. In the granulate group, a shorter average T_{max} and higher average C_{avg}, hinting toward increased absorption, were observed. However, no statistically significant differences between the tablet and granulate groups were observed for any of the pharmacokinetic parameters. Patients who received the granulate formulation had an average C_{avg} of 9.27 [4.94–11.03] mg/L, which is closer to the target of 10 mg/L. Results were nonetheless highly variable as demonstrated by the wide IQR and relatively high CVs. Importantly, although explorative, these results suggest that facilitating the dissolution of paracetamol, by using a granulate formulation, did not affect absorption of paracetamol in a meaningful manner. Other factors such as the rate of gastric emptying could perhaps explain the delayed and reduced absorption and the subsequent lower exposure in our study sample.[19] The lack of a statistically significant difference between the 2 formulations might be explained by the small sample size and deserves further investigation. More research is necessary for factors influencing the absorption process of paracetamol and other drugs in frail older patients.

Female sex and a higher total serum bilirubin concentration were statistically associated with an increase in C_{avg} of paracetamol. Liver toxicity is a known adverse drug reaction of paracetamol overdose, but it is also described with therapeutic doses.[20] A higher serum bilirubin concentration could be a sign of liver toxicity and could be a result of an increased paracetamol exposure after multiple dosing. However, only 2 patients had a total bilirubin concentration above the upper limit of normal of 1.18 mg/dL. Female patients had a higher exposure, which was also observed by Liukas et al.[16] This is an exploratory analysis for covariates influencing paracetamol exposure. Therefore, these results need to be confirmed in a larger patient group to allow for a robust multivariable analysis of the correlation between patient characteristics and paracetamol exposure.

Pain scores were determined, yet interpretation was difficult and not linked to any of the pharmacokinetic parameters of paracetamol or its metabolites. Firstly, while both the NRS or PAINAD tools were are regularly used on our geriatric wards to determine the pain scores, only the NRS score results were registered for all included patients. Knowing that 47% of patients included in our study were diagnosed with dementia, using the NRS was not considered appropriate. Secondly, it was not clear for which type of pain paracetamol was prescribed. In very old patients, paracetamol is often prescribed instead of NSAIDs for musculoskeletal pain, owing to the negative benefit/risk ratio of the latter, even though they have shown to be more effective analgesics.[21] Thirdly, the majority ($n = 17$, 49%) of patients also received other analgesics, such as NSAIDs (6%) and mild (53%) or strong (47%) opioids. This complicates the evaluation of the

correlation between pharmacokinetic parameters and pharmacodynamic effects such as analgesic effects for paracetamol.

The major metabolites of paracetamol are the sulfate and glucuronide conjugates, but a minor fraction is converted to a highly reactive metabolite, N-acetyl-p-benzoquinone-imine (NAPQI). Normally, this metabolite is rapidly inactivated by conjugation with reduced glutathione and is excreted in urine as cysteine and mercapturic acid conjugates.[22] In our population, the metabolite/paracetamol ratio was the highest for the glucuronide conjugate, followed by the sulfate conjugate. The ratios were similar compared to the ratios found by Liukas et al. in their group aged 80 years and older. However, we should refrain from overinterpreting the comparison to the Liukas data. Our study was performed in the setting of multiple dosing and hence steady state was assumed to be reached.[16] Very low ratios for the mercapturic acid and cysteine conjugates were found in our cohort. The analytic method was not able to discern NAPQI concentrations and toxic effects were not evaluated. An inverse correlation was found between the $CrCl_{CG}$ and the AUCs of all conjugates. This association is in line with previous results by Liukas et al. for the sulfate and glucuronide conjugates.[16] In sum, decreased renal function might be associated with an accumulation of paracetamol metabolites. Further research should determine the clinical significance of this accumulation.

Due to the large interindividual differences, a population pharmacokinetic model is warranted in order to explain the variability and to determine an optimal dosing regimen for this specific population of octogenarians. Safety studies concerning hepatotoxicity are also needed to optimize the paracetamol dosage guidelines for frail older patients.[23]

5 | CONCLUSION

Exposure to paracetamol and its metabolites, after administration of multiple oral doses of the tablet *vs*. granulate formulation, was documented for the first time in a large cohort of frail inpatients aged 80 years and older. A large interindividual variability in exposure and pharmacokinetic parameters was found. The granulate formulation did not lead to significantly higher exposure; pharmacokinetic parameters were not significantly different when comparing both formulations. Female sex and higher total serum bilirubin concentrations were found to be associated with increased paracetamol exposure. Ideally, a well-designed pharmacokinetic–pharmacodynamic modelling and simulation analysis, in which exposure is analysed in relation to pain assessment scores, is needed to understand the relation between exposure and response and the need for dosing optimization.

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COMPETING INTERESTS

The authors declare that they have no conflict of interest.

CONTRIBUTORS

J.H., L.V.d.L., I.S., J.T. and K.W. have made substantial contributions to the concept and design, acquisition of data, analysis of data, interpretation of data and were involved in drafting the manuscript. K.A., P.M., P.A. and B.C.P.K. were involved in revising the manuscript critically for important intellectual content. M.G. was involved in revising the manuscript by running the multivariable analysis. All authors gave final approval of the version to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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