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IS INSTANT ALWAYS BETTER?

Pharmacokinetics of tablet vs. granulate formulation of paracetamol in frail older adults

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BACKGROUND & AIM

Pain is highly prevalent in old, frail adults with paracetamol as the mainstay treatment. Pain management is regularly suboptimal and using different paracetamol formulations might improve pain control. It is not known whether using faster dissolving formulations of paracetamol granulate will result in an improved exposure. Our objective was hence to determine the pharmacokinetics (PK) of two different formulations of oral paracetamol in old, frail adults.

METHODS

An observational monocentric pharmacokinetic study was conducted. Geriatric inpatients aged 80 years or older were included. All subjects received 1000mg paracetamol as a tablet or a granulate formulation at 8AM, 2PM and 8PM. After at least four consecutive gifts, paracetamol concentrations of the 8AM dose were quantified to estimate individual pharmacokinetics. Samples were collected at trough level (T0) and at +0.5 (T0.5), +1 (T1), +2 (T2), +4 (T4), +5 (T5) and +6hours (T6). Analysis of paracetamol concentrations was performed at the Clinical Chemistry Laboratory of the Erasmus MC Pharmacy Dpt. using an Ultra Performance Liquid Chromatography - tandem mass spectrometry (UPLC-MS/MS) method. Patient variables, displayed in Table 1, were retrieved from the electronic patient health record. Individual pharmacokinetic parameters were determined by non-compartmental analysis. The area under the plasma concentration-time curve (AUC0-6) was calculated by the linear up/log down trapezoidal method. Maximum plasma concentration (Cmax) and time to reach Cmax (Tmax) of paracetamol were observed directly from the data. Average (steady-state) plasma concentration (Css) was calculated as AUC0-6/6. Target attainment was determined as a Css above the analgesic target of 10mg/L. Differences in pharmacokinetic parameters between the different formulations of paracetamol were determined using the Mann Whitney U-test. The study was approved by the local Ethics Committee (S58396) and was registered on ClinicalTrials.gov (Identifier: NCT03617471).

RESULTS

Thirty-six patients were included with a mean age (±Standard Deviation (SD)) of 86.78 (±4.20) years. Other patient characteristics can be found in Table 1. The majority of the patients (N=26/36, 72%) received the tablet; 10 patients (28%) were prescribed the granulate formulation.

The median paracetamol plasma concentration-time curve of all patients is displayed in Figure 1. Only 7 (21%) patients had an average plasma concentration (Css) above the analgesic target of 10mg/L.

No statistically significant differences were found between the tablet group and granulate group for different pharmacokinetic parameters. More details are shown in Table 2.

Table 1: Characteristics of included patients

Age: mean (±SD)	86.78 (±4.20) years
Gender: male/female	16/20 (44%/56%)
BMI: mean (±SD)	26.04 (±4.33)
Total bilirubin: median [Q1-Q3]	0.52 [0.33-0.69] mg/dl
eGFR (CKD-EPI): mean (±SD)	60.42 (±18.31) ml/min/1.73m²
CrCl (CG): mean (±SD)	49.21 (±16.46) ml/min
Number of drugs: median [Q1-Q3]	8.50 [6.00-11.75]
MMSE (/30): mean (±SD)	21.79 (±4.80) (n=28)
Frailty (EFS)	(n=35)
0 (not frail)	1 (3%)
1 (slightly)	4 (12%)
2 (moderate)	12 (34%)
3 (severe)	18 (51%)

BMI: Body Mass Index, 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, SD: Standard Deviation, [Q1-Q3]: Interquartile range, n: number of patients

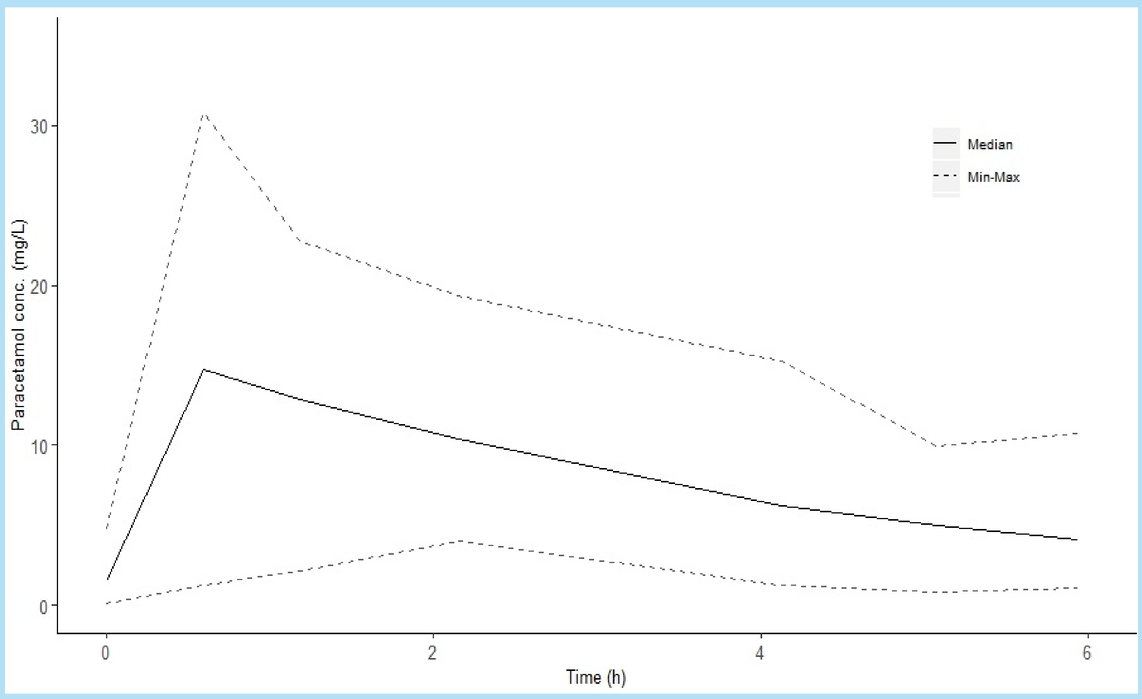

Figure 1: Median paracetamol plasma concentration-time curve.

Table 2: Pharmacokinetic parameters according to formulation

	Total group	Tablet group	Granulate group	P-value (tablet vs granulate)
Tmax (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)	P=1.000
Cmax (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)	P=0.698
AUC (0-6h) (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)	P=0.571
Css (mg/l) median [IQR]	8.00 [6.16-9.34] (n=33)	7.76 [6.31-9.08] (n=24)	9.27 [4.94-11.03] (n=9)	P=0.571

Tmax: Time to reach peak concentration, Cmax: Peak concentration, AUC: Area Under the plasma concentration-time Curve, Css: average (steady-state) concentration, IQR: Inter Quartile Range

DISCUSSION AND CONCLUSION

Large interindividual differences in PK parameters were found in a very old patient sample. Absorption parameters such as Tmax and Cmax were not significantly different between the tablet and granulate formulation group. A trend for a higher Css was observed for patients in the granulate group. Due to the large interindividual differences a population pharmacokinetic model is warranted in order to describe this variability and to determine an optimal dosing scheme where target attainment is met. Safety studies concerning hepatotoxicity are also needed to optimize the paracetamol dosage guidelines for frail older patients.

In conclusion, the granulate formulation of paracetamol did not differ significantly from the tablet formulation concerning PK parameters in a very old patient sample.