

Population pharmacokinetics of paracetamol and glucuronide, sulphate and CYP2E1 mediated metabolites in morbidly obese patients

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INTRODUCTION

- Paracetamol is metabolized via glucuronidation, sulphation and to a minor extent by CYP2E1, with the latter being responsible for hepatotoxicity.
- In obese patients, CYP2E1 activity is reported to be induced, thereby potentially changing the safety profile of paracetamol.
- AIM:** To determine the pharmacokinetics of paracetamol and its metabolites (glucuronide, sulphate, cysteine and mercapturate) in morbidly obese patients.

METHODS

- 20 morbidly obese patients received 2 gram of intravenous paracetamol.
- 15 blood samples were collected per patient until 8 hours post dose and one sample was collected at 24 hours.
- Population pharmacokinetic modeling using NONMEM 7.3.

Table 1: patient characteristics

	Morbidly obese patients (n=20)	
	Mean $\pm$ s.d.	Range
Female/Male	15/5	
Age (years)	39.2 $\pm$ 9.2	22 – 58
Body weight (kg)	142 $\pm$ 22.3	106 – 193.1
BMI (kg/m ²)	46.2 $\pm$ 4.4	40 – 55.2
Lean body weight (LBW)	69.4 $\pm$ 14.4	50.1 – 96.2

RESULTS

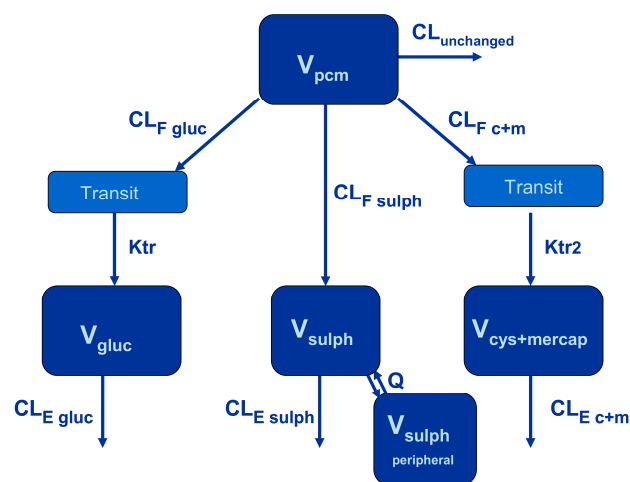


Figure 1: Schematic illustration of the PK model. CL_E = elimination clearance; CL_F = formation clearance; Ktr = transit rate constant. V_{sulph} = 5.66 FIX, $V_{cys+mercap}$ = 15.6 FIX [1], V_{sulph} = $V_{sulph\ periph}$, $CL_{unchanged}$ = 5% of CL_{total}

- For the glucuronide and the cysteine + mercapturate metabolites, a transit compartment model was identified to capture the delay in formation.
- The cysteine and mercapturate metabolites were modeled in one compartment [1]

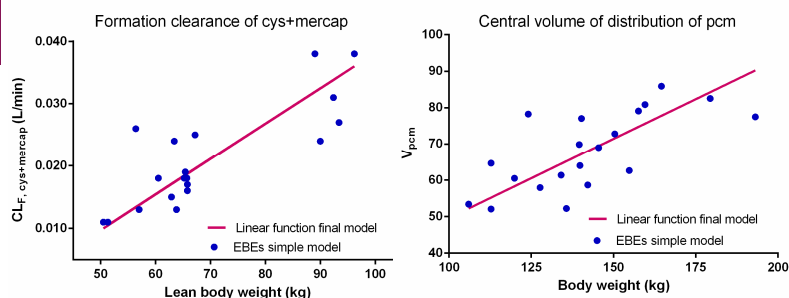


Figure 2: Empirical Bayes estimates (EBEs) for formation clearance of cysteine + mercapturate (CYP2E1) vs LBW and central volume of distribution of paracetamol vs weight of the simple PK model

- The formation clearance of cysteine + mercapturate metabolites ($CL_{F\ C+M}$) (CYP2E1) and central volume of distribution of paracetamol increased linearly with LBW and weight, respectively (Figure 2).
- Gender was found as a covariate for $CL_{F\ gluc}$ (0.356 vs 0.213 L/min male vs female) and $CL_{E\ C+M}$ (0.57 vs 0.24 L/min male vs female) $P < 0.001$

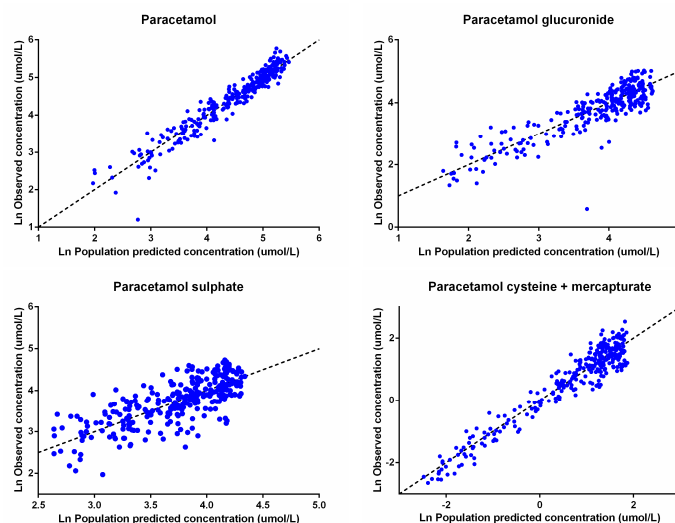


Figure 3: Observed vs population predicted concentrations of paracetamol, paracetamol glucuronide, paracetamol sulphate and paracetamol cys + mercap

CONCLUSION

- In morbidly obese patients, a substantial influence of (lean) body weight and gender was found on the formation clearance of the CYP2E1 mediated and glucuronide metabolites and central volume of distribution of paracetamol.
- These findings may potentially influence the efficacy and safety of paracetamol in morbidly obese patients
- Further study with inclusion of non obese patients is needed

REFERENCES

- Owens KH, Murphy PG, Medicott NJ, Kennedy J, Zacharias M, Curran N, et al. Population pharmacokinetics of intravenous acetaminophen and its metabolites in major surgical patients. J Pharmacokinet Pharmacodyn. 2014 Jun;41(3):211-21.