

Population pharmacokinetics of morphine and its metabolites M3G and M6G in morbidly obese patients and healthy volunteers

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INTRODUCTION

- Obese patients are at increased risk of side effects of opioids, especially after surgery.
- The pharmacokinetics of morphine in morbidly obese patients are poorly studied.
- **AIM:** To investigate the pharmacokinetics of morphine and morphine metabolites (morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)) in morbidly obese patients and non-obese healthy volunteers.

METHODS

- 20 obese patients received 10 mg intravenous (I.V.) morphine for postoperative pain management after gastric bypass surgery, with additional morphine I.V. doses as needed.
- 20 healthy volunteers received an I.V. bolus morphine 0.1 mg/kg followed by an infusion of 0.030 mg/kg/hr for 1 hour.[1]
- Blood samples were collected per patient until 7 hours post dose.
- Population pharmacokinetic modeling using NONMEM 7.3.

Table 1: Patient characteristics, mean ± standard deviation and [range]

	Non-obese[1]	Morbidly obese
Male/Female	10/10	9/11
Age (years)	25.5 ± 4.1, [20 – 36]	44.1 ± 10.6, [33 – 59]
Body weight (kg)	70.6 ± 8.8, [56 – 85]	150.3 ± 30.3, [112 – 253]

RESULTS

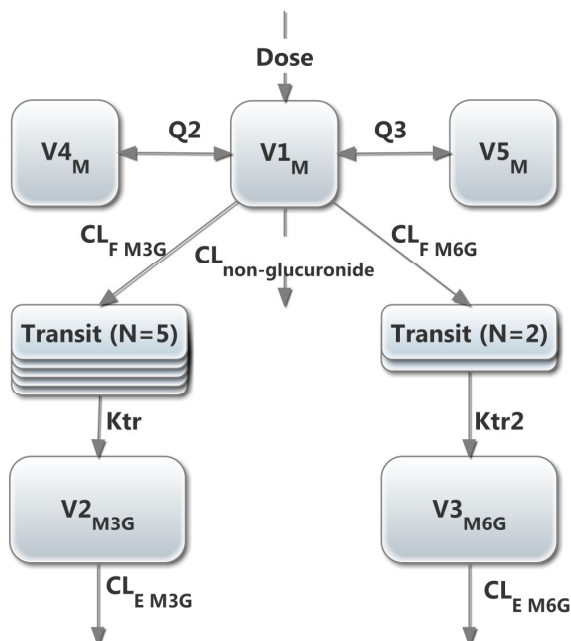


Figure 1: Schematic illustration of the PK model. V = Volume of distribution, $V_{3M6G} = V_{2M3G}$, CL_F = formation clearance, CL_E = elimination clearance, K_{tr} = transit rate constant, $CL_{unchanged}$ = 35% of CL_{total} (70 kg), $CL_{total} = CL_{non-glucuronide} + CL_F M3G, M6G + CL_F M6G$

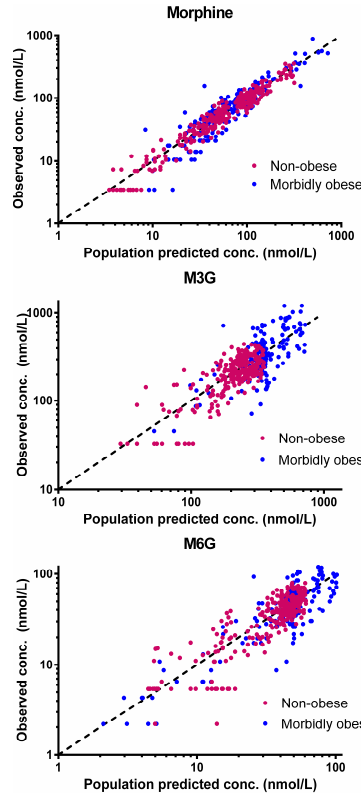


Figure 2: Observed vs population predicted concentrations of morphine, M3G and M6G.

- In the model (Figure 1) body weight was identified as covariate for V_{5M} ($P < 0.001$), K_{tr} ($P < 0.001$), $CL_F M6G$ ($P < 0.001$), $CL_E M3G$ ($P < 0.001$) and $CL_E M6G$ ($P < 0.001$).
- Mean transit time (MTT) for M3G and M6G were 3.05 and 12.7 min, respectively.

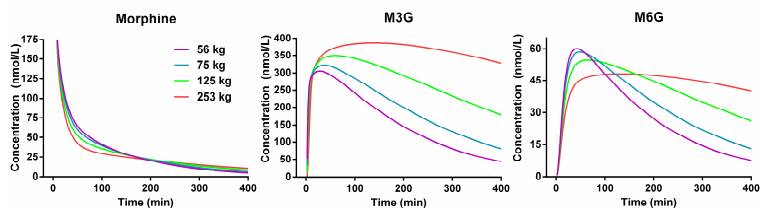


Figure 3: Simulation of a IV bolus dose of 10 mg morphine HCL in a 56 kg, 75 kg, 125 kg and 253 kg patient. Please note scale differences in y-axis

CONCLUSION

- No weight-based dosing adjustments are necessary in morbidly obese patients in terms of morphine exposure.
- However, increased concentrations of both M3G and M6G in obese patients could impact the efficacy of morphine and the occurrence of side effects.

REFERENCES

- [1] Sarton E, Olofsen E, Romberg R, den Hartigh J, Kest B, Nieuwenhuijs D, et al. Sex differences in morphine analgesia: an experimental study in healthy volunteers. *Anesthesiology* 2000 Nov;93(5):1245-54.