

PHARMACOKINETICS OF FREE HYDROMORPHONE CONCENTRATIONS IN PATIENTS AFTER CARDIAC SURGERY

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Objectives: Hydromorphone (HM) is an opioid analgesic used to relieve moderate-to-severe pain. The published pharmacokinetic models [1] consider young healthy volunteers but not postoperative patients. We conducted a clinical trial to externally validate the population model, based on a previously published model with a new dataset collected from patients undergoing cardiac surgery.

Methods:

- After IRB approval and written informed consent; 50 patients undergoing coronary artery bypass surgery were recruited.
- HM was administered postoperatively on the ICU (Fig. 1):
 - target controlled infusion (TCI) with the PK model described by Westerling et al. [1] and plasma target concentrations of HM between 1 and 2 ng/ml;
 - patient controlled analgesia with TCI (TCI-PCA) for the following 6.5 hrs with the pharmacokinetic model described by Westerling et al. [1] and plasma target concentrations between 0.8 and 10 ng/ml;
 - patient controlled analgesia (PCA) for the following 8.5 hrs delivering 0.2 mg (0.5 ml) bolus doses in 1 min with a lock time of 10 min.
- Arterial blood samples were drawn during and up to 12 h after TCI. Free and total HM plasma concentrations were measured after ultrafiltration by LC/MS/MS [2].
- Linear PK-model was determined with NONMEM 7.2 using FOCE-I. The influence of patient characteristics on the elimination clearance and volumes of distribution were tested.
- Statistics: Goodness-of-fit plots, bootstrap, Prediction error (PE) = $(C_{p,PRED} - C_{p,PRED})/C_{p,PRED}$; MDPE = Median{PE}, MDAPE = Median{|PE|}

Results:

- 49 patients (40-81 yrs) received HM, and the data from 44 patients were analysed.
- Median free fraction was 0.90 with a range of 0.37 - 0.98.
- The PK of free HM were best described by a three compartment model (MDPE = -4.5%). (Tables 1 and 2; Fig. 2)
- The elimination clearance (CL₁) and the central volume of distribution (V₁) decreased with age (Fig. 3).
- Context-sensitive half-time increases with increasing age (Fig. 4)

$CL_1 = \theta_1 \cdot \left(\frac{Wt}{70}\right) \cdot (1 + \theta_7 \cdot (Age - 67))$
$V_1 = \theta_2 \cdot \left(\frac{Wt}{70}\right) \cdot (1 + \theta_8 \cdot (Age - 67))$
$CL_2 = \theta_3 \cdot \left(\frac{Wt}{70}\right)$
$V_2 = \theta_4 \cdot \left(\frac{Wt}{70}\right)$
$CL_3 = \theta_5 \cdot \left(\frac{Wt}{70}\right)$
$V_3 = \theta_6 \cdot \left(\frac{Wt}{70}\right)$

Table 1: Final population model. Wt, weight

Parameter	Value	SE	IIV
θ_1 (L/min)	1.14	0.06	24%
θ_2 (L)	3.89	0.32	23%
θ_3 (L/min)	1.41	0.21	36%
θ_4 (L)	14.6	3.6	0 (fixed)
θ_5 (L/min)	1.58	0.22	44%
θ_6 (L)	149	18.2	46%
θ_7	-0.012	0.005	-
θ_8	-0.017	0.007	-

Table 2: Results, population analysis

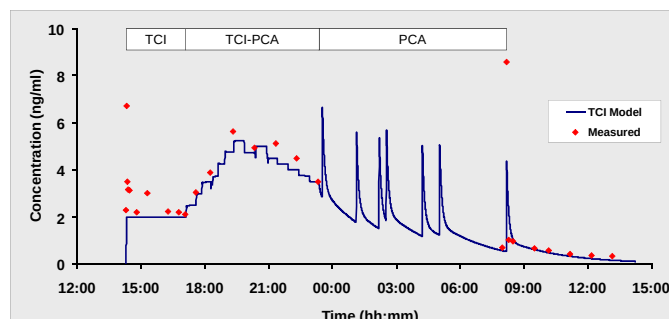


Fig. 1: Concentration-time course in one patient during pain therapy on the ICU: measured total C_p (red dots), predicted total C_p by the model of Westerling et al. (blue line)

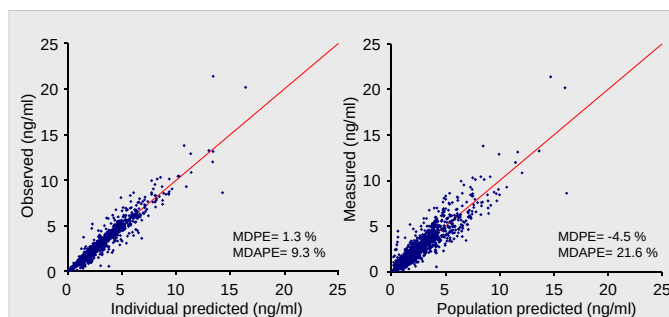


Fig. 2: Measured vs. model predicted sufentanil concentrations with individual (left) and population (right) PK-parameters. MDPE=Median{PE}, MDAPE=Median{|PE|}

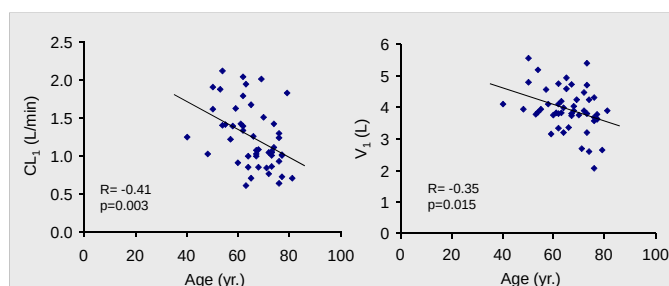


Fig. 3: Individual estimates of elimination clearance (left) and central volume of distribution (right) vs. age

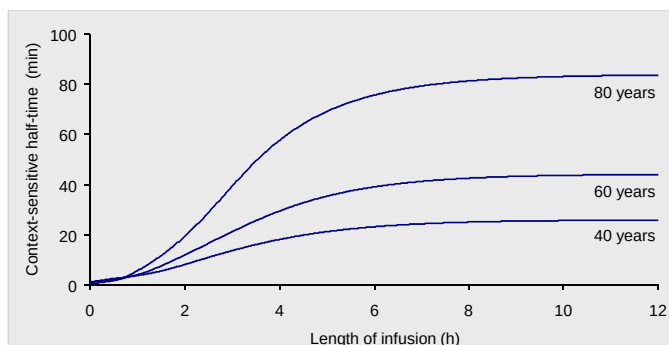


Fig. 4: Simulated context-sensitive half-time for different age groups

Conclusions: Our model indicates that age and body weight influence HM pharmacokinetics strongly. Protein binding of HM in cardiac surgery patients was similar to the values reported in the literature.

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Literature: [1] Westerling et al. Pain Res Manag 1996; 1: 86-92
[2] Saari et al. J Pharm Biomed Anal 2012; 71: 63-7

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