Population pharmacokinetic analysis of ropivacaine and its metabolite PPX from pooled data in neonates, infants, and children

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Background

The aim was to characterize ropivacaine and 2',6'-pipecoloxylidide (PPX) pharmacokinetics and the factors affecting them in pediatric anaesthesia.

Methods

Population pharmacokinetics of ropivacaine (Naropin®) and its active metabolite PPX were estimated following single caudal block [1,2,3], continuous epidural infusion [4,5] and ilioinguinal nerve block [6] in 192 patients aged 0-12 years from six pooled published studies. Unbound and total ropivacaine and PPX plasma concentration and PPX urinary excretion data were used for non-linear mixed effects modeling by NONMEM. Covariates tested included age, body weight, gender, ethnic origin, ASA, method of administration and total dose.

The analysis was performed in the following steps:

(1) A population model was developed to describe the temporal change in AAG in order to impute missing AAG values.

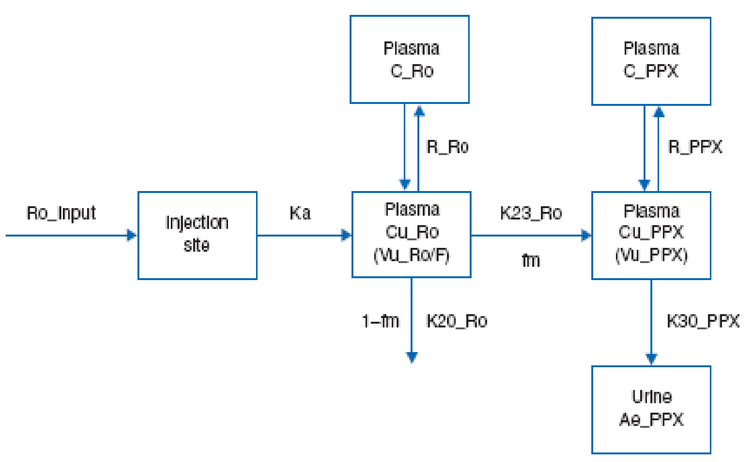
$$AAG = A_0 + \frac{(A_{max} - A_0) \cdot Time^{\gamma}}{TM_{50}^{\gamma} + Time^{\gamma}}$$

(2) A population model was developed to describe the apparent isotherm for binding of ropivacaine to AAG.

(3) A population model was developed to describe the apparent isotherm for binding of PPX to AAG.

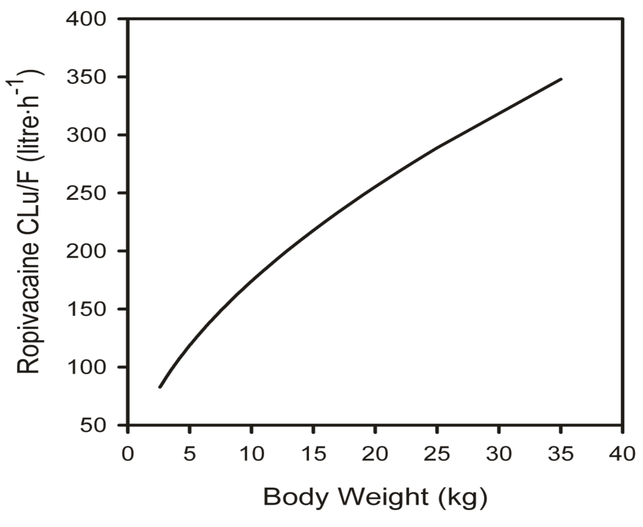
(4) A population pharmacokinetic model that simultaneously described total and unbound ropivacaine plasma concentrations, incorporating the protein binding isotherm for AAG, was developed.

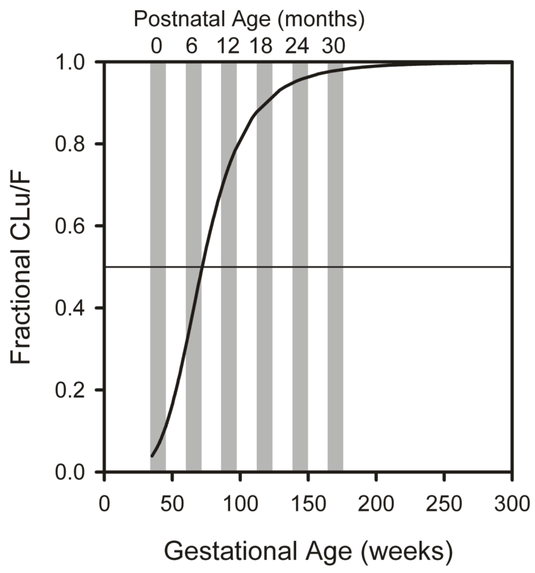
(5) A population pharmacokinetic model that simultaneously described total and unbound PPX plasma concentrations (incorporating the protein binding isotherm for AAG) and PPX amount excreted in urine data, was linked to the ropivacaine model.



Results

One-compartment first-order pharmacokinetic models incorporating linear binding of ropivacaine and PPX to α1-acid glycoprotein were used. After accounting for the effect of body weight, clearance of unbound ropivacaine and PPX reached 41% and 89% of their mature values respectively, at the age of 6 months.





$$CLu = Clu_{base} \times \left(\frac{BW}{10}\right)^{PWR} \times \frac{Age^{\gamma}}{TM_{50}^{\gamma} + Age^{\gamma}}$$

Figure 1 Effects of body weight and age on ropivacaine unbound clearance. Unbound ropivacaine clearance reaches a plateau at about 3 years, thereafter depends solely on body weight.

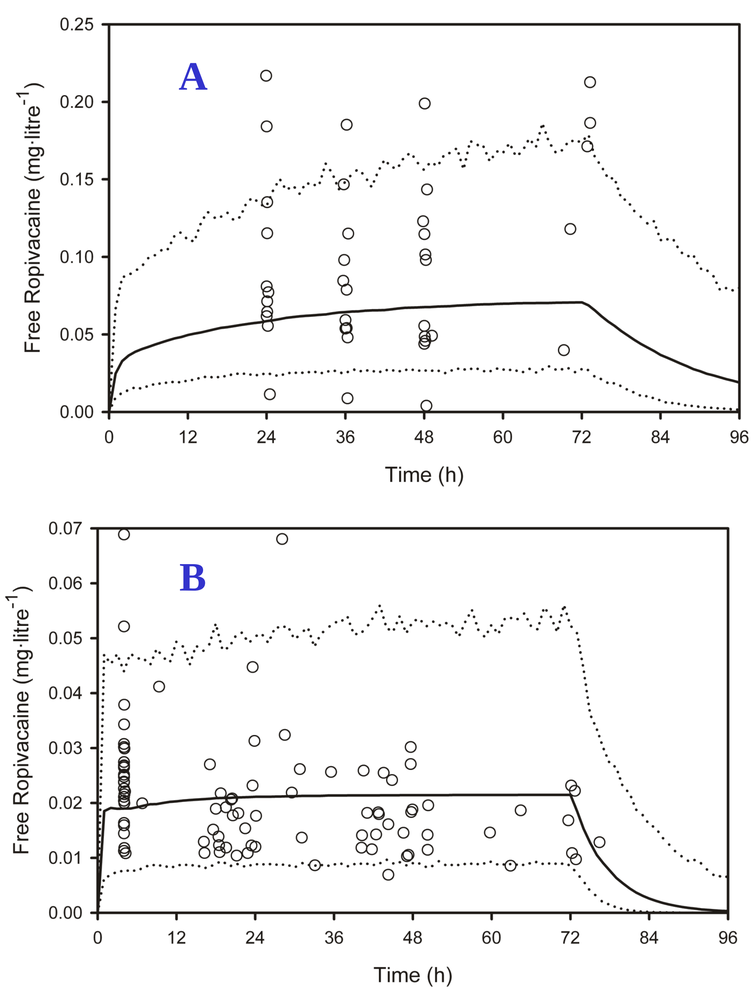


Figure 2 VPC of epidural bolus + continuous epidural infusion median profile and 90% prediction interval superimposed on ropivacaine observed unbound plasma concentrations for the A: 0-1 month group (median age 2 days, median weight 3.3 kg, median dose 1.54 mg kg^{-1} single caudal bolus plus 72 h continuous infusion 0.19 mg kg^{-1} h^{-1}) and B: 1-12 year age group (median age 4.5 years, median weight 18.0 kg, median dose 2.00 mg kg^{-1} single caudal bolus plus 72 h continuous infusion 0.40 mg kg^{-1} h^{-1}).

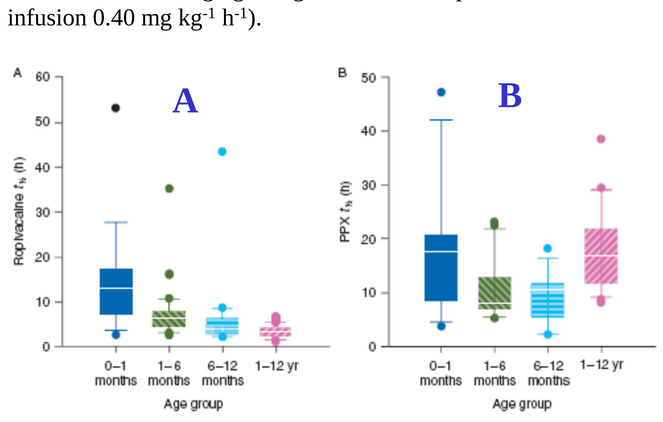


Figure 3 Individual half-life estimates of ropivacaine (A) and PPX (B) by age group. $t_{1/2}$ = half-life.

Simulations indicate that for a single caudal block the recommended dose has to be increased by a safety factor of 2.9 (0 to 1 month group) and 6.3 (1 to 10 year group) before unbound plasma ropivacaine concentrations cross the threshold for systemic toxicity, 0.34 mg/L[7].

Age group	Dose (mg kg^{-1})	Factor*	Ropivacaine equivalent maximum concentration (mgEq $litre^{-1}$) Population median	Lower 90% PI	Upper 90% PI	t_{max} (h)
0-1 m	5.8	2.9	0.1658	0.0796	0.3376	2.6
1-6 m	6.4	3.2	0.1469	0.0641	0.3307	2.0
6-12 m	12.0	6.0	0.1532	0.0671	0.3304	1.4
1-12 y	12.6	6.3	0.1544	0.0713	0.3320	0.9

Table 1 Simulated maximum unbound ropivacaine plasma concentration with corresponding time to maximum following maximum single caudal block non-toxic doses. .
* A factor by which the recommended dose could be increased in order for the upper PI of plasma concentration to approach the threshold for systemic toxicity. PI: Prediction interval, t_{max} = time of maximum unbound concentration.

Corresponding safety factors for continuous epidural infusion are 1.8 and 4.9 before the sum of unbound plasma ropivacaine and 1/12 of PPX concentrations cross the threshold for systemic toxicity, 0.34 mg/L [7]

Unbound ropivacaine clearance in children plateaus within the range of that reported in adults

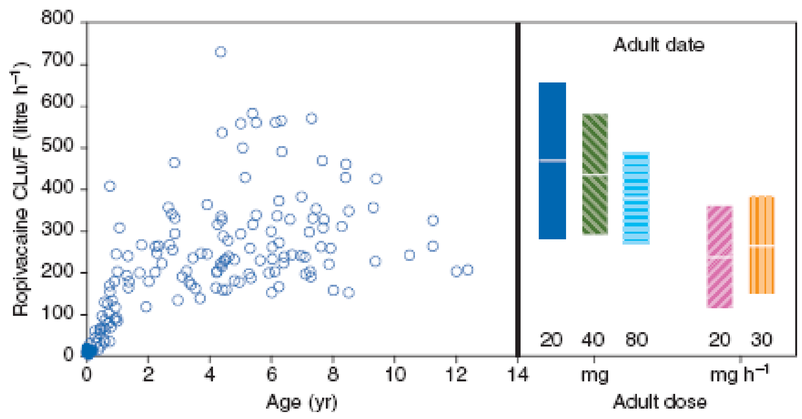


Figure 4 Estimated individual unbound ropivacaine clearance (L/min) in the present pediatric population compared to that in adults (mean±SD) [8, 9]

Conclusions

The population pharmacokinetic analysis support the dose recommendations of ropivacaine for single caudal block (2 mg kg^{-1}) as well as continuous 72-h epidural infusion in neonates, infants and up to 12-year-old children (dosing per kg body weight, with a 50% lower infusion rate in infants below 6 months), from a pharmacokinetic and systemic safety point of view.

Refereces

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