In children, the addition of epinephrine modifies the pharmacokinetics of ropivacaine injected caudally

[Chez les enfants, l'addition d'épinéphrine modifie la pharmacocinétique de la ropivacaïne administrée en injection caudale]

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Purpose: To describe the modification of the ropivacaine (R) pharmacokinetics produced by the addition of epinephrine (E).

Methods: After Institutional Review Board approval, 18 ASA I boys received a caudal block (1 mL·kg⁻¹) with either plain 0.2% R (Group E⁻) or with 0.2% R containing E (5 μg·mL⁻¹; Group E⁺). Venous blood samples were taken at zero, 15, 30, 60, 90, 120, 180, 240, 420, 720, 1440 min after caudal injection. Total R concentration in plasma was determined by high pressure liquid chromatography. Maximal concentration (C_{max}) and time to peak concentration (T_{max}) were obtained from the data, terminal half-life ($T_{1/2z}$), clearance (Cl) and volume of distribution (Vd) were estimated by a non-compartmental approach. Subsequently, in order to determine the absorption rate (Ka) and to reduce to number of blood samples, 25 other children, receiving plain R and another group of 25 receiving the E solution were studied using a population approach (NONMEM). A one compartment model with first order absorption was used. The effect of weight, age and E on Cl, Vd and Ka was estimated.

Results: C_{max} was significantly lower in Group E⁺ (0.93 mg·L⁻¹ ± 0.29 vs 0.61 mg·L⁻¹ ± 0.28, P = 0.05) and T_{max} occurred later (124 min ± 53 vs 47min ± 16, P = 0.003).

Weight was a significant covariate for Cl and Vd while E significantly slowed R Ka [Group I Ka 0.025 min⁻¹ [coefficient of variation (CV) 21%] vs 0.078 min⁻¹ (CV 25%) in Group II].

Conclusion: The addition of E significantly modifies the pharmacokinetics of R injected caudally.

Objectif : Décrire la modification de la pharmacocinétique de la ropivacaïne (R) induite par l'addition d'épinéphrine (E).

Méthode : Ayant reçu l'approbation du Comité d'examen, nous avons administré un bloc caudal à 18 garçons d'état physique ASA I (1 mL·kg⁻¹) avec, soit de la R simple à 0,2 % (Groupe E-), soit de la R à 0,2 %

contenant de l'E (5 μg·mL⁻¹ ; Group E+). Des échantillons de sang veineux ont été prélevés à zéro, 15, 30, 60, 90, 120, 180, 240, 420, 720, 1 440 min après l'injection caudale. La concentration plasmatique totale de R a été déterminée par chromatographie liquide haute pression. La concentration maximale (C_{max}) et le temps d'atteindre la concentration maximale (T_{max}) ont été obtenus des données; la demi-vie terminale ($T_{1/2z}$), la clairance (Cl) et le volume de distribution (Vd) ont été évalués par une méthode non compartimentale. Par la suite, dans le but de déterminer la vitesse d'absorption (Ka) et de réduire le nombre d'échantillons sanguins, 25 enfants, recevant de la R simple et un autre groupe de 25, recevant la solution d'E, ont été étudiés par une approche de population (NONMEM). Un modèle monocompartimental avec absorption du premier ordre a été utilisé. L'effet du poids, de l'âge et de l'E sur la Cl, le Vd et la Ka a été évalué.

Résultats : La C_{max} a été significativement plus faible dans le Groupe E+ (0,93 mg·L⁻¹ ± 0,29 vs 0,61 mg·L⁻¹ ± 0,28, P = 0,05) et le T_{max} a été plus tardif (124 min ± 53 vs 47min ± 16, P = 0,003). Le poids a été une covariable significative pour la Cl et le Vd tandis que l'E a significativement ralenti la Ka de la R [Groupe I, Ka 0,025 min⁻¹ [coefficient de variation (CV) 21 %] vs 0,078 min⁻¹ (CV 25 %) dans le Groupe II].

Conclusion : L'addition d'E modifie de façon significative la pharmacocinétique de la R en injection caudale.

R OPIVACAINE is an amide local anesthetic supplied as a pure enantiomer. This contributes to its decreased cardiotoxicity when compared to bupivacaine.[1] Ropivacaine has already been used widely caudally to provide per and postoperative analgesia in infants and children undergoing lower abdominal surgery;[2,3] its pharmacokinetics

have also been studied in various conditions demonstrating that toxic levels are rarely reached if no intravascular injection occurs.[4–6] However, as locoregional anesthesia is usually performed in children under general anesthesia or deep sedation, who are thus unable to report subjective signs of intravascular injection, strategies aiming at detecting early signs of accidental intravascular injection have been developed.[7] The addition of epinephrine at the concentration of at least 2.5 $\mu g \cdot mL^{-1}$ to the injected solution represents one of these.[8] Moreover, it has recently been demonstrated that adding epinephrine 1/400000 to bupivacaine prolongs its systemic absorption when injected caudally.[9] The aim of the two studies presented here was to describe the modifications of the ropivacaine pharmacokinetics induced by the addition of epinephrine to the solution.

Methods

Part 1: two-stage pharmacokinetic study using a non-compartmental approach

After approval of the Ethics Committee and signed informed parental consent, 18 ASA I boys undergoing minor lower abdominal surgery were included in the study. No premedication was given, general anesthesia was induced and maintained with sevoflurane 3 to 4% in an air/O_2 mixture delivered with a modified Ayre's T piece (Mapleson D breathing circuit). Fresh gas flow was adjusted to avoid any rebreathing as shown by capnography. Monitoring consisted in end-tidal CO_2 and sevoflurane, electrocardiogram (ECG), and pulse oximetry (AS3 monitor, Datex-Ohmeda, Helsinki, Finland). The children were allowed to breathe spontaneously through a face mask. An *iv* line was inserted to provide *iv* fluid maintenance according to Liu's formula[10] and to allow blood sampling.

The children were randomly allocated to receive a caudal block (1 $mL \cdot kg^{-1}$) with either plain 0.2% ropivacaine (Group E⁻) or with 0.2% ropivacaine containing epinephrine freshly added to the solution in order to obtain a 1/200000 concentration (5 $\mu g \cdot mL^{-1}$; Group E⁺). The caudal block was performed as already described[11] with a 22-gauge *iv* catheter after skin puncture with a larger needle to avoid any tissue coring. Careful aspiration was performed to exclude *iv* or intrathecal injection. The ECG waveform and the heart rate were monitored during the slow injection of the local anesthetic solution to detect any accidental *iv* injection: as the ECG changes caused in children by the *iv* injection of ropivacaine are not yet described, any change in either the ECG waveform or heart rate was to be followed by the immediate interruption of the injection.

Venous blood samples were taken just before and 15, 30, 60, 90, 120, 180, 240, 420, 720, 1440 min after the caudal injection. The collected blood was centrifuged and the plasma was kept frozen at -20°C until further analysis.

Total ropivacaine concentration in plasma was determined by high pressure liquid chromatography (HPLC) following a method already described for other local anesthetic agents.[12] This method is briefly summarized here. The plasma (500 μL) containing the ropivacaine was mixed with 1 mL of NaOH and 4 mL of diethylic ether during 15 min. This solution was then centrifuged at 3000 rpm to separate the phases. The diethyl ether was then decanted with 250 μL H_2SO_4 (0.05 N). The concentrations were determined by HPLC using a Lichrocart column 125-4 Superspher RP-selectB guarded by a precolumn. The mobile phase was a KH_2PO_4 buffer adjusted to a pH of 5.8 with NaOH (5 N), pumped at 1 $mL \cdot min^{-1}$. Detection was performed with a UV detector at 208 nm wavelength. Bupivacaine (50 μL of a 10 $\mu g \cdot mL^{-1}$ solution) was used as internal standard. The quantification limits were 25 $ng \cdot mL^{-1}$, with a precision of 6.7% at 50 $ng \cdot mL^{-1}$ and 2.7% at 1000 $ng \cdot mL^{-1}$.

Maximal plasma concentration (C_{max}) and time to peak plasma concentration (T_{max}) were obtained directly from the data. Terminal half-life ($T_{1/2z}$), clearance (Cl) and volume of distribution (Vd) were estimated by a non-compartmental approach as described by Gabrielsson[13] using WinNonLin 1.5 (standard edition; Pharsight Co, Mountain View, CA, USA).

Part 2: population analysis using NONMEM

The effect of adding epinephrine on the absorption phase was studied using a population approach as it was considered unethical to increase the number of blood samples compatible with an adequate description of this phase when using a classical two-stage approach. Again after approval by the Ethics Committee and signed informed parental consent, 50 additional children were included in this second part of our study. Plain 0.2% ropivacaine was administered to half of them while the others received the same solution with epinephrine (1/200000). The anesthetic technique, caudal block, surgical indications and the technique to measure the concentration of ropivacaine were similar to those described in part 1.

Six to ten blood samples were taken from each patient: at least five were drawn randomly during the first 120 min after injection, as this was the time in which T_{max} should occur as determined by the results presented in part 1; while the others were drawn at various times up to the 12th hr. We reduced the volume of the sample to 500 μL and the number of samples to six in the infants to maintain the total volume of sampling below 1 $mL \cdot kg^{-1}$.

Population kinetics was then determined using NONMEM (version V). A one compartment linear model with first order absorption (ADVAN2) was found to fit our data. Subroutine TRANS 2 was used to calculate the following pharmacokinetic parameter (PK): Cl absorption half-time was calculated assuming that $T_{1/2\ abs} = 0.693/Ka$. The introduction of covariates [age, weight and scaling factor for Ka] was made after visual inspection of the WRES *vs* the covariate; the covariate was kept in the model when a decrease of the objective function of six ($P \sim 0.01$) was observed. The different models introduced are summarized in Table II. Vd, Cl and absorption rate (Ka) were estimated using the following exponential interpatient error model:

$$PK_j = TVPK * (\exp \eta_j)$$

where PK_j is the individual parameter for the j patient (Vd, Cl, Ka), TVPK is the mean population parameter and η_j is the independently distributed variable with a mean of zero and a variance ω^2 and an additive intrapatient error model:

$$C_{ij} = C_{pred\ ij} + \epsilon_{ij}$$

where C_{ij} is the ith measured concentration for the jth patient, $C_{pred\ ij}$ is the predicted concentration and ϵ_{ij} is the residual variability randomly distributed with zero mean and a variance σ^2.

Randomization was performed for both parts of the study with sealed envelopes to be opened after the inclusion of the child in the study. Using the data from the previous studies summarized in Table IV, a power analysis found that a sample size of nine patients per group would result in a power of 80% to detect a modification of 50% of both C_{max} and T_{max} when $P \leq 0.05$ is considered as statistically significant.

Student's t test was used in part 1 to perform between group comparisons. Results are mean ± SD.

Results

None of the children studied developed any signs of toxicity or intravascular injection.

The results of the non-compartmental approach are summarized in Table I. The age, body weight and duration of surgery were similar in both groups. C_{max} was significantly lowered by the addition of epinephrine, which also significantly delayed the T_{max} (Figure). Terminal half-life, Cl and Vd were not modified by the addition of epinephrine.

Children included in the population analysis were aged from one day to 48 months with a weight ranging from 2.8 to 18 kg. The minimal objective function and the inclusion of the covariate in the model are found in Table II. Introducing the weight divided by

TABLE I Results of the first part of the study

	E- Group	*E+ Group*	*P*
n	9	9	
Age (months)	31 ± 9	38 ± 11	NS
Weight (kg)	14 ± 1.18	14 ± 2.21	NS
C_{max} (mg·L^{-1})	0.93 ± 0.29	0.61 ± 0.28	0.05
T_{max} (min)	47 ± 16	124 ± 53	0.003
$T_{1/2z}$ (hr)	4.32 ± 2.77	4.46 ± 1.26	NS
Cl (mL·kg^{-1}·hr^{-1})	406 ± 173	519 ± 271	NS
Vd (L·kg^{-1})	2.23 ± 0.9	3.49 ± 2.7	NS

E- Group = children receiving plain ropivacaine; E+ Group = children receiving a ropicavaine plus epinephrine; C_{max} = maximal plasma concentration; T_{max} = time to C_{max}; $T_{1/2z}$ = terminal half-life; Cl = clearance; Vd = distribution volume; NS = difference not statistically significant. Data are expressed as mean ± SD.
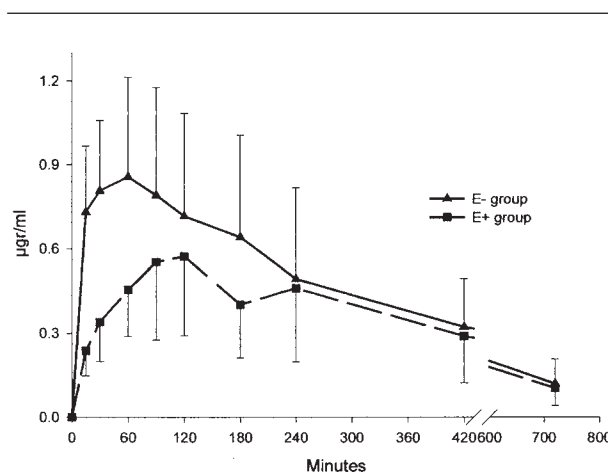

FIGURE Concentration *vs* time curves of children receiving caudal 0.2% ropivacaine (2 mg·kg^{-1}) either with (E+ Group) or without epinephrine (E- Group; mean ± SD).

the median value of our population (12 kg) into the model modified significantly the estimated values of both Cl and Vd but not Ka; however, age divided by the median age (34 months) had no effect on the fitting for Cl, Vd or Ka. The final introduction of a factor scaling for the presence of epinephrine (ADR = 1) again significantly improved the estimation by modifying the final value of Ka. The results of the final model described by NONMEM are summarized in Table III. The estimated absorption half-time of plain ropivacaine was nine minutes while the addition of epinephrine increased it up to 27 min.

TABLE II Models used for the population study

Model	Equation	MOF	Kept in model
Basic	$V = \Phi2$	-225	
	$CL = \Phi1$		
	$KA = \Phi3$		
Weight	$V = \Phi2*(weight/12)^{\Phi6}$	-254	Yes
	$CL = \Phi1*(weight/12)^{\Phi5}$		
	$KA = \Phi3$		
Age	$V = \Phi2*(AGE/34)^{\Phi6}$	-195	No
	$CL = \Phi1*(AGE/34)^{\Phi5}$		
	$KA = \Phi3$		
Final	$V = \Phi2*(weight/12)^{\Phi6}$	-292	Yes
	$CL = \Phi1*(weight/12)^{\Phi5}$		
	if ADR = 1 KA = $\Phi3$		
	Else KA = $\Phi4$		

MOF = minimal objective function; Vd = volume of distribution; CL = clearance; KA = absorption rate. The factors 12 and 34 have been selected as they represent respectively the median weight (kg) and age (months) of the children included in part 2. ADR = one means that the children are receiving an epinephrine containing solution.

TABLE III Parameters estimated by NONMEM in the final model

Parameter	Estimate	CV (%)
$\Phi1$ (mL·min^{-1})	91	45
$\Phi2$ (mL)	32500	35
$\Phi3$ (min^{-1})	0.025	21
$\Phi4$ (min^{-1})	0.078	25
$\Phi5$	1.35	
$\Phi6$	0.707	

$\Phi1$ = clearance; $\Phi2$ = distribution volume; $\Phi3$ = absorption coefficient in Group E+; $\Phi?4$ = absorption coefficient in Group E-; CV = coefficient of variation.

Discussion

This study shows that the addition of epinephrine to ropivacaine injected caudally modifies its pharmacokinetics. We found that adding a vasoconstrictor decreases the C_{max} of ropivacaine and delays its absorption from the epidural space as shown by the later occurrence of T_{max} and the longer absorption half-time.

Bupivacaine has been widely used to provide caudal analgesia in children. Although toxic concentrations are rarely obtained when a maximum of 1 mL·kg^{-1} of 0.25% bupivacaine is used, some authors have recommended that epinephrine should be added to facilitate the detection of intravascular injection as this remains a risk for acute intoxication.[14] It has recently been shown that the addition of epinephrine (1/400000) to a 0.25% bupivacaine solution did not modify the C_{max} nor the T_{max}: however the plasma concentrations measured at 360 min were significantly higher when a vasoconstrictor was added and the authors therefore concluded that epinephrine prolonged the systemic absorption of bupivacaine injected into the caudal space.[9]

Our results with ropivacaine, however, show more noticeable changes. The greater effects of epinephrine on ropivacaine may be due to the fact that ropivacaine is more liposoluble than bupivacaine and has some intrinsic vasoactivity. The slower absorption of ropivacaine from the caudal space when compared to bupivacaine has been described recently.[15] Its absorption from the epidural space is slow and has been described as biphasic; this is related to the high partitioning of ropivacaine into fat.[16]

Although the T_{max} observed in the epinephrine-group was similar to those obtained in other studies (Table IV), we found a greater C_{max}. However, there is a large variation of the latter parameter in each of those previous studies: this may also explain why the difference in ropivacaine C_{max} we measured with or without the addition epinephrine was less significant in our study ($P = 0.05$) than the modification observed for T_{max}. This is in accordance with the bupivacaine study where the main effect of adding epinephrine was mainly a longer absorption phase.[9]

The results we found for Vd and Cl are similar in both parts of our study and are comparable to those found in the two studies describing these parameters.[17,18]

The Ka of plain ropivacaine calculated by the population approach used in part two is similar to that found by Hansen et al. This parameter was not influenced by weight or age confirming the previously mentioned study;[18] although it has been described that the addition of epinephrine to bupivacaine significantly prolonged the duration of the block and that this was greatest in the younger children.[19] We found that weight was a significant covariate for Vd and Cl confirming the results of Lonnqvist et al. who described that age did not modify these parameters and that weight was probably the best variable to adjust dosage.[5] However, Hansen et al. were able to correlate Cl with age but their population was younger than ours: these authors indeed studied very young infants and their results are probably linked to the immaturity of the hepatic metabolic pathways in these patients. They also found that the percentage of free ropivacaine was a good covariate for Cl in infants.[18] We only determined total ropivacaine concentrations as its binding to plasma proteins or red cells should not be influenced by the addition of epinephrine and because the determination of unbound ropivacaine would require larger blood samples and increase the cost of the study.

TABLE IV Comparison of the ropivacaine pharmacokinetic parameters estimated by this study with those issued from other pediatric studies

	A	B	C	D	E	F	G	H	I
Dose (mg·kg⁻¹)	2 (plain)	2 (E⁺)	2 (plain)	2 (plain)	2.5 (plain)	2 (plain)	2 (plain)	2 (plain)	2 (plain)
Age (months)	31	38	48	56	25	96	8	2.6 (I) 35 (T)	32
T_{max} (min)	47	124	62 [16-125]	55 [10-120]	75 [20-125]	53 [30-240]	NA	60 [15-90] (I) 52.5 [30-120] (T)	60
C_{max} (mg·L⁻¹)	0.930	0.610	0.470 [0.32-0.75]	0.846 [0.538-1.22]	0.799 [707-1044]	0.640 [0.380-1.28]	0.748 [0.425-1.579]	0.73 (0.27) (I) 0.49 (0.21) (T)	1.03 (0.4)
Vd (L·kg⁻¹)	2.23	3.49	NA	NA	2.4	NA	2.12	NA	NA
Cl (mL·kg⁻¹·hr⁻¹)	406	519	NA	NA	456	NA	310	NA	NA
Ka (min⁻¹)	0.025	0.078	NA	NA	NA	NA	0.026	NA	NA

A and B = present study; C = Lonqvist *et al.*;[5] D = Ala Kokko *et al.*;[4] E = Habre *et al.*;[17] F = Bosenberg *et al.*;[6] G = Hansen *et al.*;[18] H = Wulf *et al.* (I = infants, T = toddlers);[21] I = Luz *et al.*[22] C_{max} = maximal plasma concentration; T_{max} = time to C_{max}; Cl = clearance; Vd = distribution volume; plain = plain ropivacaine; E⁺ = ropivacaine + epinephrine; NA = results not available.

Finally, as many other teams worldwide, we routinely use a 22-gauge *iv* cannula to perform a caudal block in infants and children.[11] We acknowledge that the use of a styletted needle, such as a lumbar puncture needle, a Crawford epidural needle or a special "caudal" needle, is recommended by many authors. However, it has been shown that the use of a styletted needle does not reduce the risk of tissue coring into the sacral epidural space providing that a small nick in the skin is made prior to insertion of the *iv* cannula.[20] Moreover, using a small *iv* cannula instead of a needle reduces the risk of intraosseus penetration and injection as well of displacement into a vessel or subarachnoid space during the injection. This should however not modify the pharmacokinetics of the drug injected caudally.

In conclusion, we have described the pharmacokinetic modifications occurring when epinephrine 5 µg·mL⁻¹ is added to ropivacaine injected caudally. Absorption is prolonged and T_{max} occurs significantly later; C_{max} is also decreased but to a lesser extent. Further studies are required to determine whether adding epinephrine to ropivacaine results in a prolonged duration of action and whether it effectively helps in detecting an *iv* injection.

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