Pharmacokinetics of Bupivacaine following Caudal Anesthesia in Infants

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Pharmacokinetics and protein binding of bupivacaine were studied after caudal injection of 2.5 mg/kg in 13 ASA PS I infants (1–6 months of age) scheduled for elective hernia repair. Blood was sampled at frequent intervals from 5 min to 600 min in all but one patient. Additional samples were taken at 720 and 840 min in five patients. Bupivacaine concentration was measured using gas chromatography. Protein binding was measured using ultrafiltration. Peak serum concentrations ranged between 0.55 and 1.93 µg/ml. The time to reach the peak ranged from 10 to 60 min. Terminal halflife (T 1/2) was 7.7 ± 2.4 h (mean ± SD), the volume of distribution (Vd) was 3.9 ± 2.0 l·kg⁻¹, and the total body clearance (CL) was 7.1 ± 3.2 ml·min⁻¹·kg⁻¹. The free fraction was markedly increased (0.16 ± 0.07) when compared with published adult values, and showed a highly significant negative correlation with age. Alpha 1 acid glycoprotein measured in the same infants correlated significantly with age. In conclusion, pharmacokinetics of caudal bupivacaine in infants are characterized by Cmax of total drug similar to those observed in adults after epidural injection. The free fraction is increased at least until 6 months of life. This suggests caution in the use of bupivacaine in infants until we understand the clinical significance of this increased free fraction. (Key words: Anesthesia, pediatrics; caudal. Anesthetic techniques: caudal. Local anesthetics: bupivacaine; pharmacokinetics. Pharmacokinetics: bupivacaine.)

THE USE OF REGIONAL anesthesia in infants and children is increasing.¹ However, data regarding the pharmacokinetics of local anesthetics in infants and children are scarce. Peak plasma concentrations of bupivacaine after 2.5–3 mg/kg injected caudally in infants and children have been reported to be at the same levels as those observed after epidural injection of 150 mg in adults.²,³ Ecoffey et al. reported an increase in both the volume of distribution and apparent clearance in children aged 5–10 yr compared with adult values.³ Nevertheless, no information on terminal (elimination) phase is available in infants, and the effects of age on protein binding have not been carefully studied, even though it has been reported that binding of bupivacaine was markedly decreased in neonates.⁴ We, therefore, studied the pharmacokinetics and protein binding of bupivacaine in infants following caudal injection.

Materials and Methods

After institutional approval and parental consent, 13 ASA PS I infants scheduled for elective hernia repair were studied. Their mean age was 3.3 ± 1.6 months (mean ± SD) (range 1.1–6.0), and their mean weight was 5.66 ± 1.36 kg (range 3.30–7.55). They received no premedication. After induction of anesthesia with halothane up to 1.5% in 50% N₂O and 50% O₂ using a non-rebreathing circuit, caudal anesthesia was performed as previously described.¹,⁵ The solution used for caudal anesthesia was plain bupivacaine 0.5%, 2.5 mg/kg, injected over a 40-s period. Halothane was then decreased to 0.2% for the remainder of surgery.

SAMPLING AND ASSAYS

A separate venous access was used for sampling and patency was maintained with saline 1–2 ml/h. The sampling times were not identical in all infants because of clinical necessities and limitations of sample volume in young infants. In the seven infants of less than 6 kg body weight, 1.2 ml of blood was sampled at 5, 10, 20, 30 or 35, 50, 100, 180, and 360 min in three, and at 7.5, 15, 25, 40, 70, 120, 180, and 360 min in the other four. In all but one of the infants in this group, 0.6 ml of blood was taken at 540 and 600 min. In the six infants of more than 6 kg body weight, 1.2 ml of blood was taken at 5, 10, 15, 20 or 25, 30 or 35, 40, 60, 90, 120, 180, and 360 min, and 0.6 ml at 540 and 600 min. In addition, 0.6 ml of blood was taken at 720 and 840 min in five of the infants (two of less than 6 kg and three of more than 6 kg body weight). Blood was collected in silicized glass tubes and allowed to clot. The serum removed after centrifugation was kept at -18°C until the time of analysis. Bupivacaine was measured in aliquots of 200 µl using a gas chromatograph equipped with a 3 m x 2 mm ID column fitted with 3% OV-11 on 100/120 mesh chromosorb W, AW, DMCS, and equipped with a nitrogen specific detector. The internal standard used was prilocaine, and a single extraction in toluene was performed.⁶ The standard curve was run daily. The within-day coefficient of variation was less than 12% at 50 ng/ml, and less than 5% at 200 ng/ml. The free fraction was measured using ultrafiltration on

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YMT membranes (Amicon®). These membranes exhibited less than 1% adsorption for bupivacaine. pH was previously adjusted to pH 7.40 using water-saturated carbon dioxide in nitrogen at 37°C. Alpha-1-acid glycoprotein (AAG) and albumin concentrations were measured in serum collected just before bupivacaine injection, using radial immunodiffusion (Partigen, Behring). The blood/serum concentration ratio was measured in samples obtained in six additional infants 30 min after bupivacaine injection. The blood/plasma concentration ratio was measured in vitro at supra therapeutic concentration (5 μg/ml) in heparinized samples obtained in six additional infants before bupivacaine injection. Age and weight for these infants were in the same range as those of the previous infants described.

**Pharmacokinetic Analysis**

Pharmacokinetic analysis was conducted using a nonlinear regression program (PC NONLIN®). The data were fitted to a two-compartment open model as follows:

\[ C = Ae^{-\alpha t} + Be^{-\beta t} - (A + B)e^{-k_{at}}, \]

where C is the concentration measured in serum, t is time, A and B are the intercepts of the rapid and slow phase, and the hybrid rate constants for these two phases, and ka the absorption rate constant. ka was arbitrarily considered greater than \( \alpha \). Terminal half-life (T1/2\( \beta \)) was calculated as 0.693/\( \beta \), and total body clearance (CL) was calculated as \( \text{CL} = \text{DOSE/AUC} \), where AUC is the area under the serum concentration time curve from zero to infinity. The volume of distribution at steady-state (Vss) was calculated as \( \text{Vss} = \frac{k_{12} + k_{21}}{k_{21}} \).

\( x \) \( VC \) where \( k_{12} \) and \( k_{21} \) are rate constants, respectively, from central to peripheral compartments and from peripheral to central compartments, and \( VC \) is the volume of the central compartment. Peak serum concentration (Cmax) and time to reach the peak (Tmax) are reported as the maximum observed concentration and corresponding time. The average free fraction (Fuav) was calculated as the ratio of the corresponding areas under free and total concentration-time curves. The maximum free fraction (Fumax) was calculated as the ratio of free and total concentrations at Tmax. Linear regression was used to analyze the correlation between age and Fuav, AAG concentration, and albumin concentration. All results are expressed as the mean ± SD.

**Results**

The mean duration of anesthesia (from induction to end of surgery) was 56 ± 11 min, and the mean duration of the surgical procedure was 24 ± 8 min. Only 12 patients were sampled for sufficient time to permit the calculation of the slope of the terminal phase. Free fraction could only be measured in 11 of the 15 infants studied. All measured and calculated parameters showed wide variation (tables 1, 2; fig. 1). For example, Cmax ranged from 0.55 to 1.93 μg/ml and Tmax from 10 to 60 min. AUC varied from 201 to 1107 μg·min·ml⁻¹ and T 1/2\( \beta \) from 3.6 to 10.9 hours. Fuav varied from 0.31 to 0.075. However, Fuav showed a significant negative correlation with age (\( P < 0.01 \)) (fig. 2). AAG plasma levels correlated significantly with age (\( P < 0.001 \)), while albumin plasma levels did not correlate with age (fig. 3). Fu max was higher than Fuav in all but one infant, and the maximum free concentration observed (Cmax) varied from 0.05 to 0.21 μg/ml. The
blood/serum concentration ratio measured in vivo and the blood/plasma concentration ratio measured in vitro at higher concentrations were similar (Table 3).

Discussion

Total Bupivacaine Kinetics

We considered that bioavailability of epidural administration of bupivacaine in infants was complete since this had been demonstrated in adults. After epidural injection, bupivacaine kinetics represent absorption rather than elimination. This phenomenon, referred as the "flip-flop model," is due to a delayed absorption phase occurring during the usual terminal phase. This late absorption process which tends to increase the terminal half-life should be noted due to accumulation of drug in epidural fat. In the present study, T1/2, and Vss were increased when compared with the values published by Eoffey et al. 

Fig. 1. Concentration time curve of bupivacaine in serum. Patients 1 and 13 are, respectively, the youngest and the oldest infants. Patients 6 and 7 are representative infants of 2.9 and 3.1 months of age. — = Fitted concentration time curve; ▲ = measured concentration in serum.
BLOOD/SERUM AND BLOOD/PLASMA RATIOS

These values did not significantly differ, suggesting linear binding and/or diffusion into red blood cells over the range of concentrations studied (0.28–5 µg/ml of blood) (table 3). These results are in excellent agreement with those reported by Rothstein et al. in children with similar hematocrits and with those reported by Tucker et al. in adults. Hematocrits for all patients in the pharmacokinetic study ranged from 34 to 39%.

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§ Tretjakoff D: Das epidurale fettgewebe. Z Anat 79:100–101, 1926

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TABLE 3. Blood/serum (in Vivo) and Blood/plasma (in Vitro) Concentration Ratios Compared with the Values Reported in Adults and in Children.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>6 (3.1 ± 1.4 months)</td>
<td>6 (3.6 ± 2.3 months)</td>
</tr>
<tr>
<td>Ht</td>
<td>0.32 ± 0.03</td>
<td>0.32 ± 0.02</td>
</tr>
<tr>
<td>C(Blood)</td>
<td>0.53 ± 0.36 mcg/ml</td>
<td>4.99 ± 0.08 mcg/ml</td>
</tr>
<tr>
<td>B/S Ratio</td>
<td>0.82 ± 0.04</td>
<td>0.77 ± 0.05</td>
</tr>
</tbody>
</table>

Adults: B/P ratio = 0.75 ± 0.05; Children: B/P ratio = 0.69 + 0.11. Ht = Hematocrit, C = Measured concentration.
### Table 4. Bupivacaine Kinetics after Caudal Injection in Infants and Children in the Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Dose</th>
<th>Age</th>
<th>Cmax (μg/ml)</th>
<th>Tmax (min)</th>
<th>TV½ (hours)</th>
<th>Vd (l/kg)</th>
<th>CL (ml·min⁻¹·kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyres 1983²</td>
<td>3 mg/kg</td>
<td>1 yr</td>
<td>1.4</td>
<td>15-20</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.25%</td>
<td>n = 12</td>
<td>0.3 (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eccoifey 1985³</td>
<td>2.5 mg/kg</td>
<td>5.5-10 yr</td>
<td>1.25</td>
<td>29</td>
<td>4.6</td>
<td>2.7</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>0.25%</td>
<td>n = 6</td>
<td>(0.96-1.64)</td>
<td></td>
<td>(2.9-6.3)</td>
<td>(1.6-3.3)</td>
<td>(8.3-11.7)</td>
</tr>
<tr>
<td>Present study</td>
<td>2.5 mg/kg</td>
<td>3 months</td>
<td>0.97</td>
<td>28</td>
<td>7.7</td>
<td>3.90</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
<td>(1.1-6.0)</td>
<td>(0.55-1.93)</td>
<td>(10-60)</td>
<td>(3.6-10.9)</td>
<td>(1.42-7.97)</td>
<td>(2.3-12.4)</td>
</tr>
</tbody>
</table>

One infant had plasma concentration of 2 μg/ml at 5 min.

concentration dependance in free fraction. In the case of high concentrations in serum due to accidental intra-vascular injection, rapid absorption, or accumulation after repeated dosing, it would be expected that the free drug concentration will increase to a greater extent than the total. The observed maximum free concentration (Cumax) was greater than 0.2 μg/ml in two infants (numbers 2 and 9). This free concentration of 0.2 μg/ml may be considered as the toxic threshold for neurologic symptoms in awake adult. However, no clinical evidence of CNS toxicity was observed. A protective effect due to light general anesthesia in combination with regional anesthesia has been suggested. Nevertheless, it is not clear whether this protection is effective, or if adverse reactions due to local anesthetics are concealed by general anesthesia.

In conclusion, our results may be interpreted as an overview of the changes associated with early infancy, rather than as precise data leading to unique set of guidelines for regional anesthesia in infants. A great interindividual variability in kinetic parameters has often been reported in infancy, so that “a rational individualised dosage regimen becomes . . . a very difficult if not an impossible task.” Nevertheless, free fraction is increased at least until 6 months of life, and caution in the use of bupivacaine in infants must be exercised as long as we do not understand the significance of this increased free fraction.

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### References