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Free and total bupivacaine plasma concentrations after continuous epidural anaesthesia in infants and children

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Summary

We measured free and total venous bupivacaine plasma concentrations in fourteen infants and children aged 6 days (2800 g) to 9 years (27 kg) undergoing epidural anaesthesia. An initial bolus of 0.5 $ml \cdot kg^{-1}$ bupivacaine 0.25% was followed by a continuous infusion administered one h after bolus over a period of seven h (first hour 0.25 $ml \cdot kg^{-1} \cdot h^{-1}$ 0.25%; then reduced to 0.125%). Although total bupivacaine plasma concentrations were within acceptable limits (<1.5 $\mu g \cdot ml^{-1}$), four of the seven infants showed adverse reactions. Maximum plasma concentrations of free bupivacaine were significantly higher in infants ($P<0.05$) than in older children. We conclude that toxicity may be underestimated when only measuring total bupivacaine concentrations. In young infants the bupivacaine dose administered for continuous epidural anaesthesia should be further lowered below recommended concentrations and the patients closely observed for possible adverse reactions.

Keywords: anaesthesia; epidural; bupivacaine

Introduction

Continuous postoperative epidural anaesthesia in infants and children has gained increasing acceptance in the past decade and bupivacaine's long duration of action makes it particularly suitable for this form of postoperative use (1). To date, various dosing guidelines have been published for continuous epidural administration of bupivacaine in children (2–6). Although attempts have been made to take into consideration the pharmacokinetic differences between adults and children, there is still no evidence to support these recommendations because plasma concentrations have only occasionally been studied. Clinical success with bupivacaine in epidural anaesthesia is offset by several disturbing reports of neurological side effects during continuous infusion in children, whose total plasma bupivacaine concentrations were below those regarded as borderline values in adults, namely 3–5 $\mu g \cdot ml^{-1}$ in plasma (6,7).

Although guidelines have been published for maximum total bupivacaine plasma concentrations in children (5,8,9), a definitive toxic threshold for infants and children with special regard to free plasma concentrations has not yet been defined.

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There is, however, evidence for age-dependent differences in pharmacokinetics, which means a search must be undertaken for optimal administration techniques to prevent inadvertent overdosing and toxic central nervous system side effects (8,10).

The aim of our study was to measure not only the total bupivacaine plasma concentrations but also the age-dependent free plasma concentrations after continuous epidural infusion and to determine safe dose guidelines for infants up to six months.

Materials and methods

After obtaining the approval of the local university ethics committee and parental informed consent we studied 14 ASA I infants and children planned for elective urological, abdominal or orthopaedic surgery. The patients were allocated to two groups (younger and older than six months). Premedication for infants consisted of oral atropine $0.02\,mg{\cdot}kg^{-1}$ and for older patients of oral midazolam $0.5\,mg{\cdot}kg^{-1}$ with atropine. Anaesthesia was induced via face mask with halothane, nitrous oxide and oxygen. After insertion of an intravenous line, vecuronium was given to facilitate intubation and controlled ventilation. Anaesthesia was maintained with halothane without systemic analgesics, and intraoperative fluids consisted of 5% glucose in lactated Ringer's solution at $10\,ml{\cdot}kg^{-1}{\cdot}h^{-1}$. Colloids were administered according to blood loss.

Epidural puncture was performed in the left lateral position via the caudal or lumbar route using a 19-gauge Tuohy needle (Portex Minipak®). A 22-gauge epidural catheter was inserted and a bolus dose of $0.5\,ml{\cdot}kg^{-1}$ bupivacaine 0.25% ($1.25\,mg{\cdot}kg^{-1}$) was given over a five-min period, followed by continuous infusion of $0.25\,ml{\cdot}kg^{-1}{\cdot}h^{-1}$, which was started one hour after bolus administration and lasted for seven h (eight h after bolus). One h after the infusion was started (two h after bolus) the bupivacaine concentration was reduced from 0.25% ($0.63\,mg{\cdot}kg^{-1}{\cdot}h^{-1}$) to 0.125% ($0.31\,mg{\cdot}kg^{-1}{\cdot}h^{-1}$). The level of analgesia was evaluated by means of the pin-prick method after recovery of inhalation anaesthesia.

Six venous blood samples (of 2.5 ml) were drawn 5, 8, 9, 10, 12 and 14 h after initial bupivacaine administration. Blood was centrifuged and plasma stored at −20°C. Total and free plasma concentrations of bupivacaine were measured using an ultrafiltration method and high pressure liquid chromatography (11). $Alpha_1$-acid-glycoprotein (AAG) plasma concentrations were measured in each patient at the end of the local anaesthetic infusion period. Plasma protein binding (PPB) was calculated using the equation: PPB (%) = (total bupivacaine concentration-free bupivacaine concentration/total bupivacaine concentration) × 100 (9). Heart rate, invasive or noninvasive blood pressure, oxygen saturation, endtidal carbon dioxide tension and body temperature were continuously monitored throughout the procedure. All patients except the two neonates were extubated after surgery.

Data were analysed using ANOVA for repeated measurements as well as Student's *t*-test and Mann-Whitney *U*-test with $P<0.05$ considered significant. Bonferroni-Holm procedure was used to correct for multiple comparisons. Values are shown as mean ± SEM (range).

Results

Fourteen infants and children were studied. Infants in group 1 had a mean age of 2.8 months (6 days–5.2 months) and a mean weight of 5.2 kg (2.8–7.2 kg) compared to 4.5 years (18 months–9 years) and 16.8 kg (11–27 kg) in group 2. Patient characteristics, diagnosis, level of epidural anaesthesia, maximum total and free bupivacaine plasma concentrations, AAG concentrations and adverse side effects are shown in Table 1. The time course of mean (SEM) total and free bupivacaine plasma concentrations during epidural infusion and after termination of drug administration for both age groups are shown in Figures 1 and 2.

No severe symptoms of central nervous toxicity (i.e. seizures) were seen during epidural infusion of local anaesthetic, but jitteriness and irritability were noticed in four infants after seven h of bupivacaine administration. Peak levels of free bupivacaine plasma concentrations were markedly higher in infants when compared to older children with a significant difference between groups after eight h of bupivacaine administration ($P<0.05$). In the infant group the neonates showed particularly high plasma concentrations of free and total bupivacaine during epidural infusion. The corresponding plasma protein

Table 1
Patient characteristics, maximum concentrations of total and free bupivacaine, alpha$_1$-acid-glycoprotein concentrations (AAG), neurological signs and postoperative drugs

Weight (kg)	*Age*	*Diagnoses*	*Level of analgesia*	C_{max} total bupivacaine ($\mu g \cdot ml^{-1}$)	C_{max} free bupivacaine ($ng \cdot ml^{-1}$)	AAG ($g \cdot l^{-1}$)	Neurol. signs postop. drugs
2.8	6 day	Diaphragmatic hernia	Th-4	1.47	72.5	0.46	— Midazolam
3.3	6 day	Duodenal membrane	Th-6	1.40	68	0.46	— Midazolam
5.3	5.2 mo	Hip dislocation	Th-8	0.46	16.5	0.53	— Nalbuphine
5.9	4.1 mo	Clubfoot	Th-10	0.63	18.2	0.47	Jittery Nalbuphine
6.2	3.1 mo	Clubfoot	Th-10	0.63	21.2	0.45	Jittery Nalbuphine
6.2	4.3 mo	Clubfoot	Th-10	0.65	21.6	0.71	Jittery Nalbuphine
7.2	3.2 mo	Clubfoot	Th-9	0.46	17.9	0.45	Irritable
11.0	1.5 yrs	Vesicureteral reflux	Th-7	0.51	9.2	0.74	— Nalbuphine
12.7	2.1 yrs	Vesicureteral reflux	Th-8	0.41	12.9	0.68	— Nalbuphine
14.0	3.2 yrs	Vesicureteral reflux	Th-9	0.25	9.9	0.57	— —
15.0	3.9 yrs	Vesicureteral reflux	Th-7	0.35	11.6	0.44	— Paracetamol
18.2	5.1 yrs	Vesicureteral reflux	Th-8	0.87	10.8	0.90	— —
19.5	6.5 yrs	Vesicureteral reflux	Th-8	0.44	8.9	0.52	— Nalbuphine
27.0	9.1 yrs	Vesicureteral reflux	Th-8	0.65	19	0.49	— —

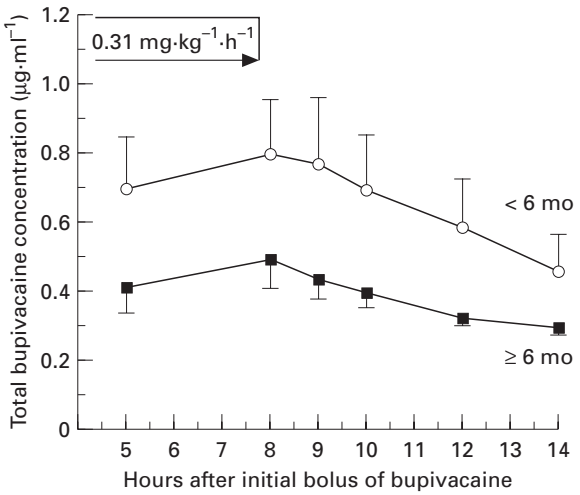

Figure 1
Total bupivacaine plasma concentrations during the last three h of continuous bupivacaine infusion (five and eight h after bolus) and after termination of infusion (9, 10, 12 and 14 h after bolus). Values are means ± SEM.

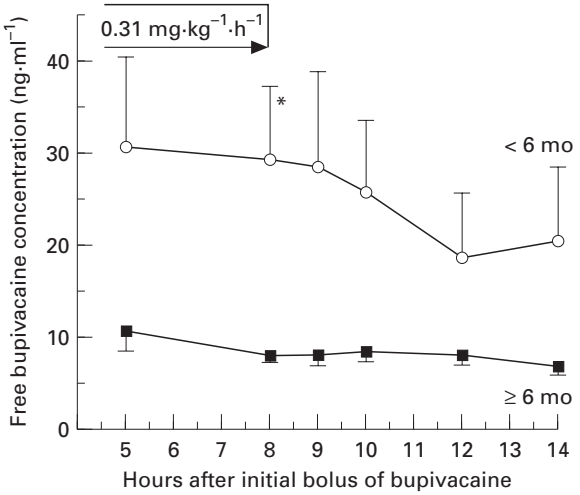

Figure 2
Free bupivacaine plasma concentrations during the last three h of continuous bupivacaine infusion (five and eight h after bolus) and after termination of infusion (9, 10, 12 and 14 h after bolus). Values are means ± SEM (*P<0.05 when compared to children).

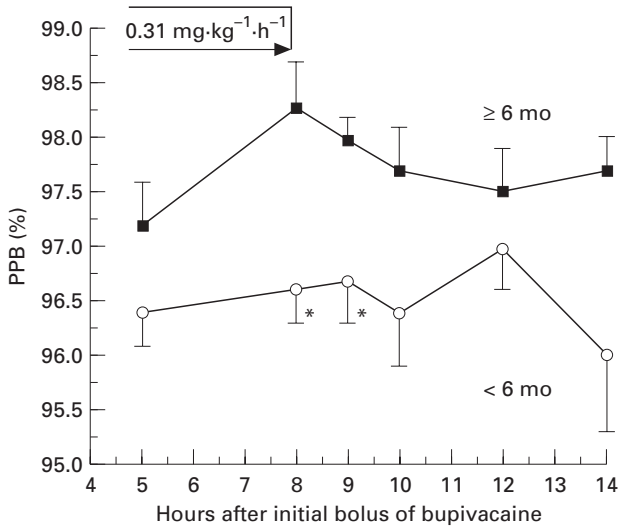

Figure 3
Plasma protein binding (PPB) during the last three h of continuous bupivacaine infusion (five and eight h after bolus) and after termination of infusion (9, 10, 12 and 14 h after bolus). Values are means ± SEM (*P<0.05 when compared to children).

binding was significantly lower in infants (P<0.05) than in children (Figure 3).

Surgical procedures did not cause major blood loss, so the perioperative infusion regimen was comparable for all our patients. No blood products were needed. Analgesia was adequate in every patient.

Discussion

An increase in the free bupivacaine plasma concentrations has primarily been deemed to contribute to toxic symptoms (1), but as most anaesthetic procedures are performed under general anaesthesia or sedation the early signs and symptoms of toxicity may be masked. In a previous study bupivacaine plasma concentrations during continuous epidural infusion of local anaesthetic over a period of four h were found to be higher in infants younger than four months when compared to children older than nine months (11). Using the same dosage regimen, we now investigated the more important, potentially toxic, free plasma concentration of bupivacaine in infants and children.

The loading dose of bupivacaine (1.25 mg·kg^{-1}) used was markedly lower than the dose recommended by both Berde (5) (2–2.5 mg·kg^{-1}) or the doses used in earlier case reports on bupivacaine-induced seizures (6,10). For all children the total bupivacaine dose administered by epidural bolus and infusion was within the particularly low range recommended by both Berde and Peutrell for infants (5,8). In a study in babies between four and 12 months one patient showed clear evidence of accumulation of bupivacaine (2.02 μg·ml^{-1}) after 32 h of infusion. The authors recommended not to exceed a maximum infusion rate of 0.375 mg·kg^{-1}·h^{-1} (8). At 1.47 μg·ml^{-1}, the highest plasma concentration of total bupivacaine measured in our study was clearly lower than the maximum plasma concentration of total bupivacaine of 2–2.5 μg·ml^{-1} (5,13), which Berde made the standard value for his dosing guideline.

We, however, found a markedly higher plasma level of free bupivacaine concentration in neonates and infants when compared to older children with a high rate of early symptoms of central nervous system toxicity (jitteriness). Four of the seven older infants in the group aged less than six months showed moderate central nervous system side effects and it seems surprising that the two youngest infants (6 d) demonstrated no adverse effects although they had the highest concentrations of total and free bupivacaine. This could be explained by the fact that these two neonates received midazolam sedation in the course of postoperative artificial ventilation in contrast to the five infants who had no midazolam perioperatively. Midazolam is able to suppress central nervous toxicity side effects. A possible midazolam-induced change in the plasma concentration of free bupivacaine is improbable, because Bruguerolle *et al.* demonstrated that the benzodiazepine has no influence on the protein-binding effect of bupivacaine following caudal anaesthesia (14,15).

Determination of the total and free fractions of bupivacaine in very young children is a methodologically involved procedure (11). Therefore, as a quality control the measuring time five in the present study was set identical to a measuring time in our earlier study (12). The measured values of total plasma bupivacaine and those of this earlier study were in close agreement. It would seem that the pharmacokinetics of local anaesthetics differ fundamentally for young individuals aged less than three months and for adults (16). Because of the lower serum concentrations of albumin and AAG,

the binding capacity of amide local anaesthetics in young infants is markedly diminished, and the proportion of the free fraction elevated (17). This is confirmed by the markedly lower plasma protein binding in infants younger than six months in the present study. Binding is pH-dependent, meaning that any episode of hypoxia or hypercapnia will increase the free fraction of local anaesthetic. Neonates and very young children are more prone to acidosis (18). Badgwell *et al.* demonstrated in an animal experiment that plasma concentrations of bupivacaine were higher in two-day-old pigs than in two-week- or two-month-old pigs (19). Mazoit *et al.* found an elevated free fraction of bupivacaine in infants between one and six months of age. In their study, AAG increased with age, whereas the elevated free fraction of bupivacaine showed a significant negative correlation with age (16).

When investigating the pharmacokinetics of bupivacaine following interpleural nerve block in infants of very low birthweight Weston *et al.* found half-life to be longer, clearance lower, and volume of distribution greater than in term infants and recommended caution when redosing because accumulation of the drug can be unpredictable (20). This also correlates with our observations in the two youngest infants in group 1, which exhibited a markedly elevated plasma concentration of total and free bupivacaine, that dropped faster than in older children following administration of local anaesthetic. In a study in neonates, no steady state of total bupivacaine concentration could be reached after 48 h of epidural infusion, but the free concentration of bupivacaine remained fairly stable within 24 h (9). This was explained by a stress-induced increase of AAG. In contrast, our infants did not show an increase of plasma protein binding after eight h of bupivacaine administration.

Mazoit *et al.* referred to the anatomical differences of infants, whereby the low fat content of the epidural space might promote faster resorption of the local anaesthetic and subsequently faster saturation of the AAG binding capacity (16). Pharmacokinetic behaviour in older children following administration of bupivacaine increasingly appears to resemble that in adults. For example, in children aged 11 months to 15 years Desparmet showed that a loading dose of 1.25 $mg \cdot kg^{-1}$ bupivacaine followed by an infusion of 0.25% bupivacaine at a rate of 0.08 $ml \cdot kg^{-1} \cdot h^{-1}$ produces adequate analgesia without complications over an infusion duration of 72 h (2). The toxic threshold of total bupivacaine for adults is still deemed 3–5 $\mu g \cdot ml^{-1}$ (5), that of free bupivacaine 0.2 $\mu g \cdot ml^{-1}$ (21). Central nervous system toxic effects have repeatedly been reported after administration of clinically accepted doses to neonates and infants although bupivacaine plasma concentrations were below the adult toxic threshold (6). The results of the present study show that if bupivacaine administration reflects this maximum bupivacaine plasma concentration, bupivacaine toxicity may be underestimated because only total drug concentrations are measured. Although none of the children in our study came even close to these previously published threshold values (5,8,9,12), the side effects observed in the children younger than six months infer that the dosage of local anaesthetic was too high for this age group.

The strategies recommended in the literature for postoperative analgesic therapy using epidural bupivacaine infusion are contradictory. Following a study in children younger than one year Murat *et al.* recommended repeated administration of bupivacaine as analgesia diminishes (22). This recommendation might be explained as a precaution against inadvertent overdosing during continuous infusion of local anaesthetic, but does not correspond with modern principles of postoperative pain therapy, which advocate sustained adequate dosing of analgesia.

Wolf *et al.* reported 0.0625% to be not as effective as 0.125% bupivacaine for caudal anaesthesia in children between six months and ten years (23). Nevertheless, in the light of the high plasma concentrations of free bupivacaine in children younger than six months as measured in our study we recommend that the concentration of bupivacaine for continuous epidural administration be further reduced corresponding to the child's age while maintaining infusion volume (0.1%). Addition of opioids or clonidine might contribute to reducing the necessary concentration of local anaesthetic and thus the danger of toxic side effects. These steps should make it possible to lower the plasma concentrations of free bupivacaine and thus lower the incidence of neurological side effects in infants younger than six months, while maintaining adequate analgesia.

References

1 Yaster M, Maxwell LG. Pediatric regional anesthesia. *Anesthesiology* 1989; **70**: 324–338.
2 Desparmet J, Meistelman C, Barre J *et al*. Continuous epidural infusion of bupivacaine for postoperative pain relief in children. *Anesthesiology* 1987; **67**: 108–110.
3 Ecoffey C, Dubousset AM, Samii K. Lumbar and thoracic epidural anesthesia for urologic and upper abdominal surgery in infants and children. *Anesthesiology* 1986; **65**: 87–90.
4 Murat I, Delleur MM, Levy J *et al*. Continuous epidural anaesthesia for major abdominal surgery in young children. *Eur J Anaesth* 1987; **4**: 327–335.
5 Berde CH. Convulsions associated with pediatric regional anesthesia. *Anesth Analg* 1992; **75**: 164–166.
6 Larsson BA, Olsson GL, Lönnqvist PA. Plasma concentrations of bupivacaine in young infants after continuous epidural infusion. *Paediatr Anaesth* 1994; **4**: 159–162.
7 Mather LE, Long GJ, Thomas J. The intravenous toxicity and clearance of bupivacaine in man. *Clin Pharmacol Ther* 1971; **12**: 935–943.
8 Peutrell JM, Holder K, Gregory M. Plasma bupivacaine concentrations associated with continuous extradural infusions in babies. *Br J Anaesth* 1997; **78**: 160–162.
9 Larsson BA, Lönnquist PA, Olsson GL. Plasma concentrations of bupivacaine in neonates after continuous epidural infusion. *Anesth Analg* 1997; **84**: 501–505.
10 McCloskey JJ, Haun S, Desphande JK. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. *Anesth Analg* 1992; **75**: 287–290.
11 Huy-Riem H, Funk B, Gerber HR *et al*. Determination of bupivacaine in plasma by high-performance liquid chromatography. *Anesth Analg* 1984; **63**: 448–450.
12 Luz G, Innerhofer P, Bachmann B *et al*. Bupivacaine plasma concentrations during continuous epidural anesthesia in infants and children. *Anesth Analg* 1996; **82**: 231–234.
13 Berde CH. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children (Letter). *Anesth Analg* 1992; **77**: 1305.
14 Giaufre E, Bruguerolle B, Morrison-Lacombe G *et al*. The influence of midazolam on the plasma concentration of bupivacaine and lidocaine after caudal injection of a mixture of the local anaesthetics in children. *Acta Anaesth Scand* 1990; **34**: 44–46.
15 Bruguerolle B, Giaufre E, Morrison-Lacombe G *et al*. Bupivacaine free plasma level in children after caudal anaesthesia: influence of pretreatment with diazepam. *Fundam Clin Pharmacol* 1990; **4**: 159–161.
16 Mazoit JX, Denson DD, Samil K. Pharmacokinetics of bupivacaine following caudal anesthesia in infants. *Anesthesiology* 1988; **68**: 387–391.
17 Booker PD, Taylor C, Saba G. Perioperative changes in alpha-1-acid glycoprotein concentrations in infants undergoing major surgery. *Br J Anaesth* 1996; **76**: 365–368.
18 Eyres RL. Local anaesthetic agents in infancy. *Paed Anaesth* 1995; **5**: 213–218.
19 Badgwell JM, Heavner JE, Kytta J. Bupivacaine toxicity in young pigs is age-dependent and is affected by volatile anesthetics. *Anesthesiology* 1990; **73**: 297–303.
20 Weston PJ, Bourchier D. The pharmacokinetics of bupivacaine following interpleural nerve block in infants of very low birthweight. *Paediatr Anaesth* 1995; **5**: 219–222.
21 Tucker GT, Mather LE. Clinical pharmacokinetics of local anaesthetics. *Clin Pharmacokin* 1979; **4**: 241–278.
22 Murat I, Montay G, Delleur M *et al*. Bupivacaine pharmacokinetics during epidural anaesthesia in children. *Eur J Anaesth* 1988; **5**: 113–120.
23 Wolf AR, Valley RD, Fear DW *et al*. Bupivacaine for caudal analgesia in infants and children: the optimal effective concentration. *Anesthesiology* 1988; **69**: 102–106.

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