Bupivacaine in Children: Pharmacokinetics Following Caudal Anesthesia

CLAUDE ECOFFEY, M.D.,* JOELLE DESPARMET, M.D.,† MARTINE MAURY, PHARM.,‡ ALAIN BERDEAUX, M.D.,‡
JEAN-FRANÇOIS GIUDICELLI, M.D.,§ CLAUDE SAINT-MAURICE, M.D.¶

Bupivacaine is used for caudal anesthesia in children.[1,2] No study has been devoted to the pharmacokinetic analysis of bupivacaine administered by this route. Only mean plasma concentrations following the caudal injection of bupivacaine are available.[3] Thus, the aim of our study was to evaluate the time course of the plasma concentrations and the pharmacokinetic parameters of bupivacaine following caudal anesthesia in healthy children.

PATIENTS AND METHODS

Six children, ages 7.25 ± 0.75 years, weighing 23.3 ± 2.3 kg (mean ± SEM), were studied. They were free of cardiac, renal, or hepatic disease and were to undergo orchidopexy surgery. This study was approved by the Human Investigation Committee, and parental consent was obtained. All patients had fasted 6 h before anesthesia and received no premedication. Heart rate was recorded continuously from the electrocardiogram, and arterial blood pressure was measured by standard sphygmomanometry every 5 min throughout the study. Anesthesia was induced by inhalation of nitrous oxide 70%, oxygen 30%, and halothane 1.0% in a partial rebreathing system while patients were in the lateral position. Once the lid reflex had disappeared, a 22-gauge needle was inserted in the caudal epidural space, and halothane administration terminated. A dose of 2.5 mg/kg of bupivacaine HCl in a 0.25% solution (58.3 ± 5.7 mg) was injected at a rate of about 1 ml/s. Blood venous samples of 1 ml were drawn from a catheter inserted in the antebrachial vein. Samples were collected at 1, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 90, 120, 240, 350, 600, and 840 min after the end of bupivacaine injection. Plasma was separated by centrifugation at 40° C, stored at −20° C, and assayed

in duplicate by high-pressure liquid chromatography.[4] This method measured bupivacaine between 0.05 and 10 μg/ml with a coefficient of variation of less than 10%. The best fit of the bupivacaine plasma concentration from each child was obtained by nonlinear regression least-squares analysis of the data according to a two-compartment equation model; this model describes the time course in plasma of bupivacaine following caudal injection assimilate to an extravascular administration model with a first-order administration model and described by the sum of at least two exponential terms. The nonlinear least-squares analysis was done with an iterative GRAPHAKIN program and run on Tektronix® 4052 computer. The various pharmacokinetic parameters, which include maximum concentration (Cp_{max}), time to Cp_{max} (t_{max}), vascular absorption ($t_{1/2}abs$) and terminal half-lives ($t_{1/2}\beta$), steady-state volume of distribution (Vd_{ss}), and total body clearance (Clt) were computed from the equations describing the data with the use of standard procedures.[5] The area under the plasma concentration time curve (AUC o → ∞) was calculated by the trapezoidal rule and the unknown area to infinity calculated from the slope and the last measured plasma bupivacaine concentration. All values are expressed as mean ± SEM.

RESULTS

Neither heart rate nor blood pressure was modified during the caudal anesthesia procedure. Table 1 summarizes the data. Figure 1 shows the mean time course of the plasma bupivacaine level following caudal anesthesia. The maximum concentration of drug in the plasma was achieved between 19.7 and 38.4 min (t_{max} = 29.1 $\pm$ 3.1 min), and the level ranged from 0.95 to 1.64 μg/ml (Cp_{max} = 1.25 $\pm$ 0.09 μg/ml). $T_{1/2}abs$ was 9.1 $\pm$ 0.6 min ($t_{1/2}abs$) (k_{abs} = 4.7 $\pm$ 0.4) and $t_{1/2}\beta$ was 277 $\pm$ 34 min. The Clt was 10.0 $\pm$ 0.7 ml·min⁻¹·kg⁻¹. There was no correlation between Clt with weight (r = 0.52, NS) or surface area (r = 0.45, NS) of the children. Vd_{ss} was 2.7 $\pm$ 0.2 l/kg. The AUC (o → ∞) was 260 $\pm$ 18 μg·min⁻¹·ml⁻¹.

DISCUSSION

Our results show that bupivacaine, like lidocaine,[6] is absorbed rapidly by the caudal route. According to Eyres et al.,[3] the short initial half-life of bupivacaine confirms that it is absorbed rapidly through the caudal epidural

* Assistant in Anesthesiology, Hôpital Bicêtre, Kremlin-Bicêtre.
† Assistant in Anesthesiology, Hôpital Saint-Vincent de Paul, Paris.
‡ Assistant in Pharmacology, Hôpital Bicêtre, Kremlin-Bicêtre.
§ Professor of Pharmacology, Hôpital Bicêtre, Kremlin-Bicêtre.
¶ Professor of Anesthesiology, Hôpital Saint-Vincent de Paul, Paris.

CLINICAL REPORTS

TABLE 1. Pharmacokinetic Parameters of Each Child and Mean ± SEM for the Group

	Weight (kg)	Age (yr)	Cp_{max} (μg/ml)	t_{max} (min)	$t_{1/2}$ abs (min)	K_{abs}	$t_{1/2}\beta$ (min)	AUC (0 → ∞) (μg·min⁻¹·ml⁻¹)	Vd_{ss} (l/kg)	Clt (ml·min⁻¹·kg⁻¹)
1	23	5.5	1.64	21.3	9.6	4.4	175	294	1.6	8.3
2	19	6	1.26	29.5	9.6	4.3	377	270	3.3	10
3	20	6	0.96	29.5	6.6	6.3	240	222	2.7	11.7
4	20	7	1.22	19.7	7.2	5.9	256	252	2.9	10
5	24	9	1.10	38.4	10.8	3.8	238	104	2.7	11.7
6	34	10	1.32	36.6	10.8	3.8	376	318	3.2	8.3
	23 ± 2.3	7.25 ± 0.75	1.25 ± 0.09	29.1 ± 3.1	9.1 ± 0.6	4.7 ± 0.4	277 ± 34	206 ± 18	2.7 ± 0.2	10 ± 0.7

space. The maximum bupivacaine concentration is almost similar to that previously reported by Eyres et al.[3] in children following caudal injection of 3 mg/kg of bupivacaine 0.25% and that reported in adults by Wilkinson and Lund,[7] following epidural injection of 2 mg/kg bupivacaine 0.5%. However, the maximum bupivacaine concentration is slightly higher than the value reported in adults following caudal administration of 2.2 mg/kg of bupivacaine 0.75 with epinephrine.[8] In adults, plasma bupivacaine concentrations greater than 4 μg/ml may cause convulsions.[9] In six children, the Cp_{max} value was far below this value, and no adverse cardiovascular or central nervous system side effects were observed.

Assuming an epidural bioavailability of 100%, we can calculate plasma values of total body clearance and volume of distribution from this study. Total body clearance of bupivacaine in the present study is of the same magnitude as previous values reported in adults,[10] although these control values for Clt in adults were obtained with different techniques. The lack of correlation of Clt with weight or surface area is probably due to individual variations in metabolism and excretion of bupivacaine, and since these children are representative of a relatively homogenous group (7.25 ± 0.75 years) and that it is well known that most maturational changes occur with the first year of life and then again at puberty. The steady

state volume of distribution of bupivacaine in children is as much as three times larger than in adults.[10] The terminal half-life of bupivacaine after caudal administration is longer than the values reported in adults following iv[10] and epidural[7] bupivacaine injections. Terminal half-life is linked closely to volume of distribution (Vd) by the formula $t_{1/2} = 0.693 \times Vd/Clt$.[11] Therefore, the combination of similar Clt and a larger Vd_{ss} can explain the longer terminal half-life, as it has also been reported with lidocaine in children.[6]

In summary, we found that our data show that pharmacokinetic parameters of bupivacaine after caudal anesthesia in children are similar to those reported after bupivacaine injection in adults, except for the larger volume of distribution and the slightly longer terminal half-life.

REFERENCES

1. Armitage EW: Caudal block in children. Anaesthesia 34:396, 1979
2. McGown RG: Caudal analgesia in children. Anaesthesia 37:806–818, 1981
3. Eyres RL, Bishop W, Oppenheim RC, Brown TCK: Plasma bupivacaine concentrations in children during caudal epidural analgesia. Anaesth Intensive Care 11:20–22, 1983
4. Bishop W, Oppenheim RC, Eyres RL: Analysis of lignocaine and bupivacaine in plasma by high pressure liquid chromatography. Asian J Pharmaceut Sci 2:91–94, 1980
5. Gibaldi M, Perrier D: Pharmacokinetics, Drugs and the Pharmaceutical Sciences, vol 1. Edited by Swarbrick J. New York, Marcel Dekker, 1975
6. Ecoffey C, Desparmet J, Berdeaux A, Maury M, Giudicelli JF, Saint-Maurice C: Pharmacokinetics of lignocaine in children following caudal anaesthesia. Br J Anaesth 56:1399–1402, 1984
7. Wilkinson GR, Lund PC: Bupivacaine levels in plasma and cerebrospinal fluid following peridural administration. ANESTHESIOLOGY 33:482–486, 1970
8. Freund PR, Bowdle TA, Slattery JT, Bell LE: Caudal anesthesia with lidocaine or bupivacaine: Plasma local anesthetic concentration and extent of sensory spread in old and young patients. Anesth Analg 63:1017–1020, 1984
9. Jorfeldt J, Löfström B, Pernow B, Persson B, Wahren J, Widman B: The effects of local anaesthetics on the central circulation and respiration in man and dog. Acta Anaesth Scand 12:153–169, 1968
10. Mather LE, Tucker GT: Pharmacokinetics and biotransformation of local anesthetics. Int Anesth Clin 16:23–51, 1978
11. Hull CJ: General principles of pharmacokinetics, Pharmacokinetics of Anaesthesia. Edited by Roberts CP, Hug CC Jr. Oxford, Blackwell Scientific Publications, 1984, pp 1–24
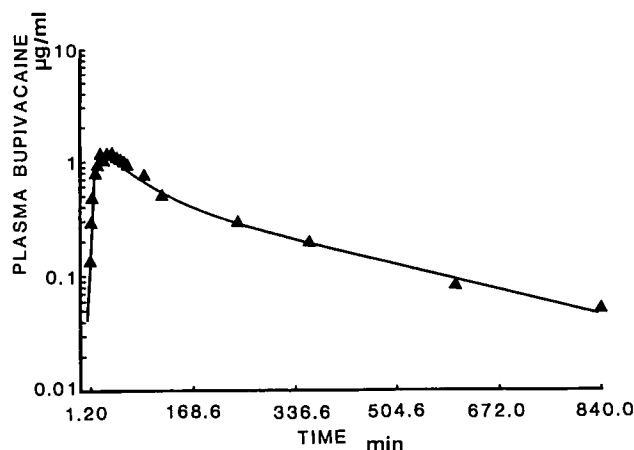

FIG. 1. Mean values for plasma bupivacaine following administration of 2.5 mg/kg into the caudal canal. The line represents the best fit as determined by nonlinear regression.