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Pharmacokinetics and Cardiovascular Effects of Bupivacaine during Epidural Anesthesia in Children with Duchenne Muscular Dystrophy

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Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy. Children with this dystrophy often need orthopedic surgery to either extend their walking capacity or to facilitate nursing care. General anesthesia is associated with an increased risk in such patients, owing to poor cardiovascular and respiratory function and altered sensitivity to some anesthetics.[1–4] Although regional anesthesia is an appropriate choice for certain operations, the pharmacokinetics of local anesthetics are unknown in such patients. Some differences could be expected owing to the particular distribution of both fat and muscle compartments in these patients. Thus, this study was undertaken to assess the pharmacokinetics of bupivacaine following lumbar epidural injection in children with DMD.

MATERIALS AND METHODS

The study was carried out in five children with DMD scheduled for multiple tenotomies. Characteristics of the patients are shown in table 1. The index of obesity (OI) was calculated for each child using the following formula, especially designed for scoliotic patients:[5,6]

$$OI = \frac{WT}{S^3 \times 12.67}^{(6)},$$

where weight (WT) is expressed in kg and S is the armspan expressed in meters. The normal value is 1. In all patients, preoperative evaluation revealed severe pulmonary impairment with a marked reduction in both vital capacity and peak-flow values, when compared to normal predicted values for age. Systolic time intervals (STI) measured according to the criteria of Lewis *et al.*[7] were increased in two out of the five children (normal values 0.32 ± 0.03). The ejection fraction (EF) was measured by isotopic scintigraphy in three children, including one for whom the STI was prolonged, and was within the normal range (65 ± 5%). Both indexes have proved to be sensitive indicators of cardiac dysfunction in such patients.[8,9]

The children included in the present study were not premedicated. Informed consent was obtained from the parents during the preoperative visit. The study was approved by the Ethics Committee of the Hospital. General anesthesia was induced by Flunitrazepam (30 μg/kg) iv. Their tracheas were intubated, and ventilation controlled to maintain end-tidal CO_2 within normal limits (4–5 kPa). Epidural anesthesia was performed at a

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TABLE 1. Patient Characteristics

No	Weight (kg)	Age (yr)	Height (cm)	Obesity Index	Peak flow (l/min)	Vital Capacity %	Systolic Time Interval	Ejection Fraction %
1	35	9	135	1.12	—	41	0.32	59
2	35	10.5	149	0.83	29	53	0.33	—
3	30	12.2	150	0.67	61	56	0.43	74
4	40	9.9	140	1.2	50	81	0.34	63
5	19.5	7.5	120	0.98	44	64	0.39	—
Mean	31.9	9.8	139	0.96	46	59	0.36	65
SD	7.8	1.74	12.7	0.21	13.3	14.8	0.05	7.8

Individual data, mean values, and standard deviations (SD): weight (kg), age (yr), height (cm), index of obesity, vital capacity (VC), and peak flow (PF) expressed in percent of normal predicted values for age, systolic time intervals, and ejection fraction (%).

low lumbar interspace using a Tuohy 18-gauge needle. The local anesthetic used was, in all cases, 0.5% bupivacaine. The volume injected was 1 ml/10 cm height.[10] Mean dosage used was 2.3 mg/kg, ranging between 1.75 and 3.0 mg/kg. A hypnotic state was maintained during surgery using intermittent iv injections of flunitrazepam. Temperature, arterial blood pressure, and heart rate were continuously monitored throughout the surgery.

Venous blood samples of 2 ml were drawn from a short catheter inserted in an antebrachial vein. They were collected 1, 4, 7, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 180, 240, 300, and 360 min after the end of bupivacaine injection. Samples were kept at 4° C, and then plasma was separated and stored at −20° C. Bupivacaine plasma levels were assayed by high-performance liquid chromatography.[11] This method measures bupivacaine levels greater than 0.03 μg/ml with an intraday variation of 3–4%. During surgery, total blood loss was less then 10 ml/kg, so that no blood was replaced, and neither coloids nor vasoactive drugs were used. The following data were observed: maximum concentration (Cpmax), and time to Cpmax (Tcpmax). Bupivacaine plasma concentrations *versus* time were analysed with the non-linear regression computer program PHARM,[12] using the extended least square method for weighting the data. The equation of a two-compartment open model with first-order absorption was used to describe bupivacaine pharmacokinetics, except in one subject (5) whose data were best fitted with a single-compartment model with first-order absorption. The choice of the model was made using the F test applied to the sum of squared deviations observed between predicted and observed concentrations.[13] Thus, estimates were obtained of absorption rate, and the rate constants for a relatively rapid decay (alpha) and a slower decay (beta). The following parameters were calculated: vascular absorption (T½ abs), distribution half-life (T½ dist) and elimination half-life (T½ elim). The total area under the curve (AUC) was calculated by the trapezoidal rule, and extrapolated to infinity dividing the last measured bupivacaine concentration by the slope beta. Then, the total plasma clearance (Clp = Dose/AUC) and the apparent volume of distribution (Vdarea = Clp/beta) were calculated, assuming that the systemic bioavailability of the anesthetic from the lumbar interspace was 100%.

Statistical analysis of hemodynamic data was made using two-way variance analysis and, if statistical significance was reached, Newman-Keuls test for paired data. All results are expressed as mean ± standard deviation (SD).

TABLE 2. Hemodynamic Data (Mean ± SD)

	Control	5 Min Before Epidural	5 Min After Epidural	10 Min After Epidural	25 Min After Epidural	Skin Incision	15 Min After Incision
SBP	113	99	97	99	95	97	96
mmHg	14.8	11.4	14.8	12.4	10	10.9	11.4
		*	†	†	*	*	†
HR	106	91	90	83	78.6	81.6	78.4
bpm	20.7	13.4	15.8	10.9	10.7	11.5	10.6

* Mean values and standard deviation of systolic blood pressure (SBP) and heart rate (HR) measured before induction of anesthesia (control), 5 min before epidural anesthesia, 5, 10, and 25 min after epidural anesthesia, at skin incision, and 15 min after skin incision.
* $P < 0.05$ *versus* control.
† $P < 0.01$ *versus* control.

TABLE 3. Pharmacokinetic Data

No	Dose (mg/kg)	Maximum Conc. (μg/ml)	Time to Cpmax (min)	T1/2 abs Min	T1/2 distrib Min	T1/2 elim Min	Volume Distrib (l/kg)	Clearance (ml/kg/min)
1	2	1.29	25	7.7	16.3	192	2.02	7.3
2	2.14	1.65	20	9	13.6	341	2.49	5.07
3	2.5	1.09	15	7.6	12.2	321	3.29	7.1
4	1.75	1.59	20	6.2	36.7	452	2.0	3.07
5	3	1.5	20	3.7	—	92	2.14	16.16
Mean	2.28	1.42	20	6.8	19.7	279	2.39	7.74
SD	0.48	0.23	3.5	2.0	9.9	139	0.54	5.0

Individual data, mean values, and standard deviation:dosage (mg/kg), maximum concentration (Cpmax μg/ml), time to Cpmax (Tcpmax min), absorption half-life (T1/2 abs), distribution half-life (T1/2 distrib), elimination half-life (T1/2 elim), volume of distribution (Vdarea l/kg), and total plasma clearance (Clp ml/min/kg).

RESULTS

Mean duration of surgical procedure was 120 ± 20 min. Complete analgesia was obtained in all children during the whole surgical procedure. Heart rate remained statistically unchanged after epidural anesthesia, whereas a statistically significant decrease in systolic blood pressure (SBP) was observed ($P < 0.05$) (table 2). Significant changes in SBP were observed after induction of anesthesia, whereas epidural anesthesia did not produce significant additional changes. Individual results and mean values of pharmacokinetic parameters are shown in table 3. The mean plasma bupivacaine concentrations plotted against time (in minutes) are shown in figure 1. A significant correlation between Vdarea (1/kg) and the obesity index was observed (fig. 2) (Vdarea = $-2.34 \times OI + 4.63$; r = 0.93; $P < 0.05$).

DISCUSSION

The clinical practice of epidural anesthesia in myopathic children does not differ from that in normal children. However, the epidural space is sometimes difficult to reach owing to the spinal deformities existing in the older children. The DMD children are at greater risk for malignant hyperthermia (MH) compared with the general population.[2-4] The risk of triggering MH when using an amide local anesthetic has been suggested, but this hypothesis is unproven and controversial.[14] In the postoperative period, a particular benefit could be expected when using epidural anesthesia, especially in children with a marked impairment of pulmonary function. Complete postoperative analgesia allows easier chest physiotherapy, and epidural anesthesia itself avoids the need for mechanical ventilation during surgery in cooperative children.

The hemodynamic changes were moderate and well tolerated, even in children with cardiac impairment. The hemodynamic changes observed were similar to those reported in healthy children of the same age group.[10]

The maximum plasma levels obtained in the present study are below the presumed toxic levels (*i.e.*, 1.8–2 μg/ml).[15] The high volume of distribution of children, when compared to adults,[15] explains the lower Cpmax observed after an equivalent amount of drug (corrected for weight). In fact, in our study, Vdarea was two- to three-fold higher than that measured in adults, but similar to that of healthy children of same age group.[16-18] The difference between the mean calculated Vdarea and the mean volume of distribution at steady state (Vdss) computed using the fitted model was 3.3% (2.39 ± 0.54 *vs.* 2.31 ± 0.56 l/kg). There was an inverse correlation between degree of obesity and volume of distribution, when corrected for weight. This is interesting in view of previous data,[19] which suggest that, in obese adults, the elimination half-life of lidocaine is prolonged when compared with that of patients of normal weight. This increase was attributed to an increase in absolute drug volume of distribution. However, in this report, when Vd was corrected for body weight, no difference between obese and normal patients was observed.

The mean clearance value in the DMD children was similar to that recorded in adults,[15] but with marked individual variations. This results in a longer elimina-

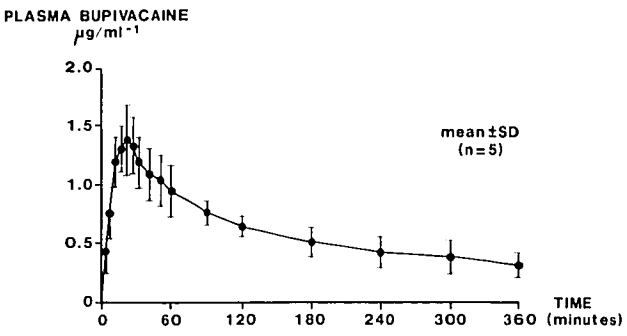

FIG. 1. Mean plasma bupivacaine concentrations and standard deviations *versus* time (min).

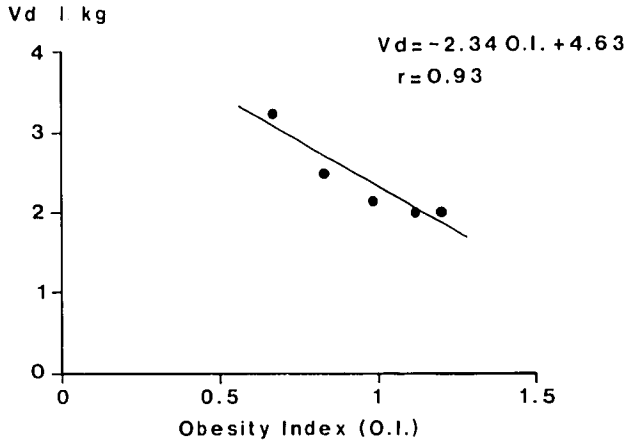

FIG. 2. Relationship between the index of obesity and volume of distribution.

tion half-life in these children. However, in our study and others in healthy children,[16-18] individual variations are wide, and the elimination half-life ranged between 92 and 452 min. The shortest elimination half-life was observed in the youngest child, and was related to a very high clearance. The elimination half-life of patient 4 (452 min) could be underestimated, because samples were only obtained during 360 min. This suggests that the eventual top-ups should be given on demand, according to clinical criteria, rather than systematically in such patients.

In conclusion, we found that the dosages routinely used in this study allowed excellent perioperative analgesia without deleterious side effects and with a maximum Cpmax in agreement with the correct saftey margin. This suggests that this technique can be safely used in DMD, as well as normal, children.

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