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Short communication

Is the pharmacokinetics of bupivacaine equivalent after lumbar epidural administration through a needle or a catheter in male and female adults?

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ABSTRACT

We assessed possible pharmacokinetic modifications due to different epidural injection techniques using either a needle or a catheter. Adult patients ($n = 23$) undergoing lower abdominal or lower extremity surgery were randomly assigned a single bupivacaine epidural injection anesthesia (0.5%, 15 mL, 0.3 mL/s) through needle or catheter device. Plasma bupivacaine concentration was quantified using a validated HPLC method and non-compartmental pharmacokinetic parameters estimated. C_{MAX} and T_{MAX} were similar in both groups: 952 ± 346 ng/mL, 0.65 ± 0.51 h in the needle group; 810 ± 307 ng/mL, 0.43 ± 0.29 h in the catheter group respectively. Plasma $AUC_{0\rightarrow\infty}$ was also similar in both groups: 3868 ± 1687 ng h/mL for needle *versus* 4096 ± 1748 ng h/mL using catheter. The catheter group showed slower disposition than the needle group: $t_{1/2}$ = 3.9 ± 2.3 h, MRT = 6.0 ± 3.1 h versus 2.7 ± 1.03 h and 4.5 ± 1.2 h with needle administration respectively though it did not reach statistical significance, Cl/F and V/F were also similar. Lastly, female patients showed significant longer $t_{1/2}$ after administration through catheter (5.7 ± 2.0 h) than needle (2.7 ± 0.6 h) group ($P = 0.0279$). The device type does not affect the pharmacokinetics which is similar in both groups although sex-based differences might exist.

1. Introduction

Bupivacaine is widely used in epidural anesthesia. It is infused into the lumbar epidural space through a catheter or a needle, although administration through a catheter is generally preferred: the dose may be adjusted during surgery and postoperative analgesia may be provided [1]. In general, data suggests satisfactory regional anesthesia and analgesia [2] in male and female patients [3].

Bupivacaine may be administered alone or in combination with selected adjuvants [1,4,5], at doses ranging from 28 mg [6] to 187 mg [7] and at infusion rates as slow as 0.04 mL/s [7] or as fast as 1 mL/s [8], either through a needle [7] or a catheter [9,10] regardless whether patients are adults [7,10] or children [2,6]. The pharmacological effect is attained within a few minutes and lasts depending on the formulation used [1,11,12]. The pharmacokinetic analysis of bupivacaine has focused on the plasma concentration-time profile with primary data [8] or after compartmental analysis using non-linear regression and population approaches [13]. These analysis are mostly aimed to assess the maximum plasma concentration (C_{MAX}) and the time to reach C_{MAX} (T_{MAX}) post-administration and to correlate these two parameters with different administration techniques (catheter, needle injection, intermittent administration, etc.) or sampling procedures (arterial, peripheral or central venous blood) regardless of dose adjustment or infusion rates [7,10,14]. It was observed that earlier T_{MAX} values were achieved in children after administration via catheter than using a needle for the injection (5 min versus 20 min respectively) although C_{MAX} remained similar [6].

However, a clear understanding of the bupivacaine dose-response relationship after epidural administration is lacking due to difficulties to compare the various studies which present different conditions and designs [15]. This study aims to evaluate the pharmacokinetics of epidural bupivacaine in adults, using two infusion techniques, to assess whether differences in T_{MAX} and C_{MAX} as well as disposition parameters exist in systemic blood due

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Table 1
Validation parameters of the HPLC assay.

Nominal concentration (ng/mL)	Recovery (%)	Intraday assay ($n = 6$)			Interday assay ($n = 30$)		
		Exp. conc. (ng/mL)	CV (%)	ER (%)	Exp. conc. (ng/mL)	CV (%)	ER (%)
250	105.1	262.7 ± 17.6	6.7	5.1	249.5 ± 11.7	4.7	−0.2
800	96.9	774.8 ± 45.1	5.8	−3.2	809.8 ± 40.2	5.0	1.2
2000	99.8	1995 ± 161	8.1	−0.3	1992 ± 59	2.9	−3.9

to the different administration procedure, catheter or needle. An attempt to inquire whether sex-based differences exist is also made [3] and preliminary results reported here.

2. Material and methods

2.1. Ethics study approval

Ethical approval was obtained from the Institutional Ethics Review Board (Hospital de Viladecans, Barcelona, Spain) for a randomized clinical study in physical status classes 1–3 (American Society of Anesthesiologists), patients aged 18 years or older undergoing lower abdominal or lower extremity surgery under lumbar epidural anesthesia were included and excluded if epidural anesthesia was contraindicated for a condition like allergy to local anesthetics.

2.2. Study population and drug administration

Patients ($n = 23$) were enrolled after obtaining their written informed consent and simple-randomly allocated to 2 groups (catheter or a needle group) for administration of 75 mg single bupivacaine dose. All patients were premedicated with diazepan (0.05 mg/kg) the night before, and midazolam (0.03 mg/kg IV) prior to epidural anesthesia. Puncture of the epidural space at L3-L4 was performed with a Tuohy 18-gauge needle with the patient in a right or left lateral decubitus position and correct needle placement checked by loss of resistance to 2 mL of saline solution. Patients in the needle group were injected 15 mL of 0.5% bupivacaine (without epinephrine) directly through the needle at 0.3 mL/s flow rate. In the catheter group, a 20-gauge Perfix catheter (B Braun, Melsungen, Germany) was inserted 3 cm in a cephalad direction and bupivacaine infused (0.5%, 15 mL, 0.3 mL/s rate). No test dose was used in any group. Heart rate, blood pressure, arterial blood oxygen saturation and toxicity signs were monitored noninvasively as well as any bupivacaine toxicity signs (light headedness, dizziness, tinnitus, consciousness, respiratory depression/arrest amongst others). Two peripheral venous lines were established: one was used to deliver fluids and the other, placed in the antecubital vein of the contralateral arm, was used for sample collection.

2.3. Sample collection and HPLC analysis

Peripheral venous blood samples were collected into EDTA tubes at pre-dose, 1, 3, 5, 10, 20, 30, 60, 90, 120, 180 and 240 min after initiation of bupivacaine infusion. Plasma was separated, and stored at −21 °C until bupivacaine quantification using a validated HPLC method [16] carried out in a Kontron LC system (Kontron Instruments, Barcelona, Spain). In brief, plasma samples were injected (20 μl) in a Luna C_{18} column (150 × 6 mm, 5 μm) with a C_{18} ODS precolumn (octadecyl, 4 × 3 mm), eluted with a 40/60 mixture of 0.03 M acetonitrile and pH = 5.9 NaH_2PO_4 respectively at 1 mL/min flow rate and detected at 210 nm. Plasma samples were analyzed blindly and bupivacaine plasma concentration calculated with the aid of an external calibration curve and quality control samples, prepared daily from a bupivacaine standard stock solution (50 mg/mL). The method was linear ($r = 0.992$; LLOQ = 125 ng/mL, ULOQ = 2000 ng/mL); intra and inter-day accuracy and precision at three concentration levels (250, 800 and 2000 ng/mL) were within 10% and recovery within 5% (Table 1). The 24-h room temperature stability assay yielded 98.2% recovery, it was 100.6% after 1 month storage at −20 ± 1 °C and 98.6% after three freeze/thaw cycles.

2.4. Pharmacokinetic data analysis

Individual non-compartmental pharmacokinetic parameters were calculated using Excel®. The C_{MAX} and T_{MAX} were obtained directly from the deposition profiles, the elimination rate constant k_{el} was calculated using the log-linear regression of the terminal slope, the elimination half-life $t_{1/2}$ was $\ln 2/k_{el}$ and the area under the curve, $AUC_{0\to\infty}$ was calculated using the log-linear approach. The mean residence time (MRT) was calculated as the first moment of the curve divided by the AUC, oral clearance Cl/F was (Dose/AUC) and the apparent volume of distribution at steady state V_{SS}/F, was calculated as MRT × Cl/F. Lastly, Student's *t*-test was performed to assess differences between the groups after confirming normal distribution (Microstat®). Significance was set at $p < 0.05$.

3. Results and discussion

3.1. Study demographic data

Twenty seven patients were enrolled in the study but only 23 completed the study. There were 2 patients excluded due to insufficient blood samples; 1 patient was excluded due to intradural puncture and another patient due to epidural vessel puncture. There were 10 patients (7 male and 3 female) in the needle group and 13 patients (8 male and 5 female) in the catheter group available for full data analysis. Their demographics were analysed and no statistical differences between needle or catheter group were found. The age in the needle group ranged 51 to 76 years of age and in the catheter group from 45 to 82 years with a mean average age of 64.0 ± 7.4 years in the needle group and 62.2 ± 13.1 years in the catheter group ($P = 0.694$). Similarly, the mean average weight was 73.8 ± 13.7 (range 47–94 kg) in the needle group and 81.7 ± 14.4 (range 68–122 kg) in the catheter group

Table 2
Non-compartmental bupivacaine pharmacokinetic parameters in adult patients after epidural administration using a needle or a catheter. Data are mean ± SD.

Parameter	Needle	Catheter	*P*-value
C_{MAX} (ng/mL)	952 ± 346	810 ± 307	0.1560
T_{MAX} (h)	0.65 ± 0.51	0.43 ± 0.29	0.1060
k_{el} (h^{-1})	0.262 ± 0.085	0.269 ± 0.200	0.4566
$t_{1/2}$ (h)	2.70 ± 1.03	3.90 ± 2.25	0.0699
$AUC_{0\to t\ last}$ (ng h/mL)	2116 ± 568	1909 ± 822	0.2520
$AUC_{0\to\infty}$ (ng h/mL)	3868 ± 1687	4096 ± 1748	0.3782
MRT (h)	4.5 ± 1.2	6.0 ± 3.1	0.0900
V_{SS}/F (mL/kg)	1.44 ± 0.36	1.68 ± 0.79	0.1860
Cl/F (mL/h/kg)	0.343 ± 0.135	0.338 ± 0.243	0.4814