Plasma concentration of ropivacaine after intercostal blocks for video-assisted thoracic surgery

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Background. Absorption of local anaesthetics following intercostal blocks is rapid. Therefore, plasma concentrations of ropivacaine during intercostal blocks with ropivacaine 2, 5, 7.5 and 10 mg ml^{-1} (ropivacaine 5 ml injected into each of four intercostal spaces) in patients undergoing video-assisted thoracic surgery were determined.

Methods. After informed consent and ethics committee approval, 64 patients were randomly allocated to four groups for intercostal nerve block (ropivacaine 2, 5, 7.5 or 10 mg ml^{-1} at the end of surgery). Central (mixed) venous and arterial plasma samples were collected before the start of intercostal application, and 2, 5, 10, 15, 20, 30, 45, 60 and 90 min afterwards. Plasma concentrations of ropivacaine were measured by high performance liquid chromatography.

Results. Maximum venous plasma concentrations occurred after the mean times of 10.7 (range, 5–15), 10.8 (5–20), 11.3 (5–20) and 12.2 (5–45) min, respectively for each group. The groups had mean concentrations of 1.3 (SD, 0.6; range, 0.3–2.3), 2.1 (1.0; 0.5–4.5), 2.4 (1.0; 1.2–5.1) and 2.5 (0.9; 1.7–5.6) μg ml^{-1}, respectively. Maximum arterial plasma concentration following 1.0% ropivacaine occurred after 16 (5–45) min with a mean of 2.3 (0.6; 1.5–3.6) μg ml^{-1}. No signs of central nervous system or cardiac toxicity were observed.

Conclusions. After intercostal blocks the absorption of ropivacaine is rapid compared with other techniques for regional anaesthesia and results in relatively high venous and arterial plasma concentrations, especially if a dose of 100 mg or more is used.

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Absorption of local anaesthetics following intercostal blocks (ICB) is known to be rapid.[1] Ropivacaine is a new long acting amide local anaesthetic available as a pure S-enantiomer.

Several studies have demonstrated that S-ropivacaine is less toxic compared with bupivacaine in preclinical studies[2–5] and is suitable for epidural anaesthesia.[6–9] However, information about the absorption kinetics of ropivacaine following ICB is lacking. In the present study, we measured plasma concentrations of ropivacaine following intraoperative ICB for pain prophylaxis after thoracic surgery using increasing concentrations of ropivacaine (0.2–1.0%).

Methods

Patients (n=64) with ASA classifications of I–III, who were undergoing elective video-assisted thoracoscopic surgery, were enrolled in this prospective study (Table 1). The study protocol had been approved by the ethics committee. After written informed consent had been obtained, patients were premedicated orally with a benzodiazepine. For the induction and maintenance of anaesthesia, propofol, remifentanil and mivacurium were used, and a double lumen tube was inserted for single lung ventilation. A pulmonary artery catheter and an arterial cannula were inserted. After the completion of surgery, but before extubating the trachea, four intercostal blocks were performed as indicated for an appropriate block of the involved nerves. In a prospective randomized manner, 20 ml of the following commercially available solutions of ropivacaine were injected (n=16 in all groups). Group 0.2 received 0.2% ropivacaine (2 mg ml^{-1}), group 0.5, 0.5% ropivacaine (5 mg ml^{-1}), group 0.75, 0.75% ropivacaine (7.5 mg ml^{-1}) and group 1.0, 1.0% ropivacaine (10 mg ml^{-1}).

Table 1 Patient characteristics and type of video-assisted surgery. Data are presented as mean (range) for age and as mean (SD) for weight and height

Group	Patients	Sex	Age	Weight	Height	Type of surgery (*n*)		
	(*n*)	(M/F)	(yr)	(kg)	(cm)	Pleurodesis	Wedge-resection	Lobectomy
0.2	15	11/4	56 (44–67)	73 (12)	175 (13)	9	2	4
0.5	15	9/6	57 (46–67)	77 (14)	176 (9)	6	4	5
0.75	15	9/6	59 (48–72)	70 (10)	171 (10)	4	2	9
1.0	16	13/3	59 (48–69)	84 (15)	179 (7)	6	4	6

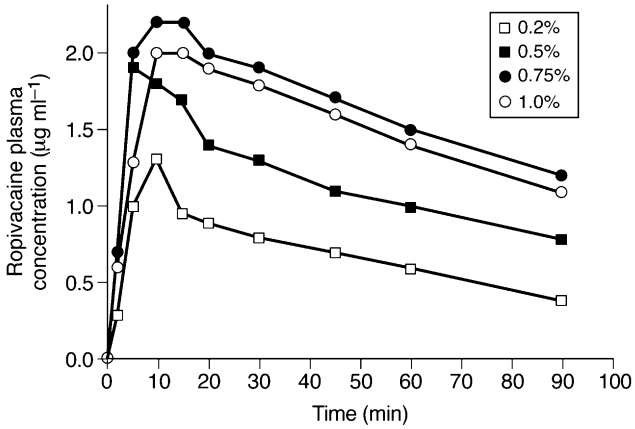

Fig 1 Mean venous plasma concentration of ropivacaine in 61 patients following intercostal blocks (5 ml of either 0.2, 0.5, 0.75 or 1.0% ropivacaine were injected into each of four intercostal spaces). SD is omitted for clarity but see Table 2 for C_{max} and T_{max}.

Intercostal injections were all administered within 2 min. Central mixed venous blood samples from the pulmonary artery catheter were collected before the first intercostal injection and 2, 5, 10, 15, 20, 30, 45, 60 and 90 min after completion of the fourth injection of ropivacaine. In addition, in group 1.0, arterial blood was sampled in order to compare arterial and venous data. Blood samples were centrifuged within 1 h after collection and then stored at –20°C before analysis.

A high performance liquid chromatographic (HPLC) method previously described[10] was modified in order to determine plasma concentrations of ropivacaine. All concentrations were determined in duplicate. The absorption was measured at a wavelength of 203 nm and integrated using HPLC-Manager, D-6000 A Interface. The coefficient of variation showed acceptable precision of the assay in the range of 0.01–10 μg ml^{-1} (<5%).

Data are presented as median, mean, SD and range. For the comparison of maximum plasma concentrations, ANOVA with Dunnett's post-hoc test was performed using GraphPad Prism, version 3.02 for Windows (GraphPad Software, San Diego, CA, USA). For comparison between arterial and venous plasma concentrations a paired *t*-test was used. Alpha was set at 0.05. Thus, the study had an 80% chance of detecting an absolute difference of 1 SD within the unpaired comparisons.

Table 2 Maximum plasma concentration of ropivacaine following four intercostal blocks with 5 ml of either 0.2, 0.5, 0.75 or 1.0% ropivacaine. Data for the maximum venous plasma concentration (C_{max}), and the time point of that maximum after the start of the injection (T_{max}), are given as median (range). For the highest ropivacaine concentration (1.0%), values from venous as well as arterial samples are presented. *P<0.05, **P<0.01 and ***P<0.005 compared with group 0.2

Ropivacaine group	C_{max} (μg ml^{-1})	T_{max} (min)
0.2	1.0 (0.3–2.3)	10 (5–15)
0.5	1.8 (0.5–4.5)*	7.5 (5–20)
0.75	2.2 (1.2–5.1)**	10 (5–20)
1.0 (arterial)	2.2 (1.5–3.6)	12.5 (5–45)
1.0 (venous)	2.3 (1.6–5.6) ***	10 (5–45)

Results

Three patients (one in each of the groups 0.2, 0.5 and 0.75) were excluded from further analysis because their sampling processes were incomplete.

On average, maximum central venous plasma concentrations occurred after 11 min, without significant difference between the groups. Mean maximum plasma concentrations were 1.3 (0.6; 0.3–2.3), 2.1 (1.0; 0.5–4.5), 2.4 (1.0; 1.2–5.1) and 2.5 (0.9; 1.7–5.6) μg ml^{-1} in groups 0.2, 0.5, 0.75 and 1.0, respectively (Fig. 1). The highest individual plasma concentration was 5.6 μg ml^{-1} 5 min after intercostal injection of 1.0% ropivacaine 200 mg. Maximum plasma concentrations were not significantly different between groups 0.5, 0.75 and 1.0 but were significantly higher compared with group 0.2 (P<0.05, P<0.01 and P<0.001, respectively) (Table 2).

Central (mixed) venous plasma concentrations were higher compared with arterial concentrations (group 1.0) 2 min after completion of the blocks (P=0.02), while no significant differences were found in the further time course (e.g. P=0.07 at 5 min) (Fig. 2).

No signs of central nervous system or cardiac toxicity were observed in the patients of the present study.

Discussion

Intercostal blocks are associated with rapid absorption of local anaesthetics and, therefore, result in early and relatively high peak plasma concentrations compared with other techniques of regional anaesthesia. The present study shows that this assumption holds true for the new local

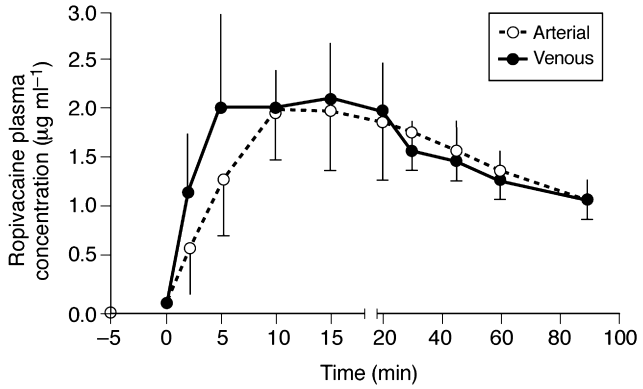

Fig 2 Time course of the plasma concentration of ropivacaine analysed from central venous and simultaneously drawn arterial blood samples (mean±SD) in 16 patients after intercostal blocks with 1.0% ropivacaine 5 ml injected into each of four intercostal spaces. At 2 min after completion of the blocks, central venous plasma concentrations were significantly higher (P=0.02) compared with arterial plasma concentration.

anaesthetic S-ropivacaine. For example, the mean maximum plasma concentrations after 150 mg epidural ropivacaine were reported to be 1.1–1.4 μg ml^{-1} after 17–40 min.[11–14] After an identical dose given for intercostal block (0.75% ropivacaine 20 ml), considerably higher maximum plasma concentrations (2.4 μg ml^{-1}) of ropivacaine were found in the present study with a shorter time to the maximum (11 min).

We found one previous study on the pharmacokinetics of ropivacaine after intercostal blocks in the literature.[15] Maximum plasma concentration was 1.1 (0.4) μg ml^{-1} with 56 ml of 0.25% ropivacaine (140 mg) after 21 min. In our study, peaks occurred somewhat earlier and were considerably higher. This discrepancy could be due to the fact that in the previous study, bilateral blocks (14 blocks each) were performed in awake healthy male volunteers without premedication (n=7; mean age, 34 yr) using 0.25% ropivacaine (a concentration not commercially available). In contrast, we performed four unilateral blocks each in patients of both genders (age range, 44–72 yr) under general anaesthesia.

Toxic plasma ropivacaine concentrations for humans are still not well characterized. Scott and colleagues[16] reported mild central nervous symptoms at venous plasma concentrations ranging from 1 to 2 μg ml^{-1} after i.v. administration of ropivacaine in unpremedicated volunteers. Despite rather high individual plasma concentrations (>5 μg ml^{-1}) no signs of central nervous system or cardiovascular toxicity were observed in our patients, confirming a higher threshold for toxic reactions compared with racemic bupivacaine. A limitation of the present study with regard to toxicity is that our patients were premedicated with a benzodiazepine and general anaesthesia was just finished (blocks were performed before extubating the trachea) at the time of maximum plasma concentrations. Therefore, any signs of central nervous system toxicity could have been suppressed.

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