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ORIGINAL ARTICLE

Plasma ropivacaine concentrations after ultrasound-guided transversus abdominis plane block for open retropubic prostatectomy

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Abstract
Purpose Ropivacaine-induced vasoconstriction may affect the early absorption speed of ropivacaine; however, the effects of dose on pharmacokinetics following transversus abdominis plane (TAP) block have not been studied. In this study, we have examined plasma ropivacaine concentrations following TAP block with various ropivacaine concentrations (0.25, 0.5, and 0.75 %).
Methods With the approval of our University ethics committee and informed consent, 39 adult patients undergoing open retropubic prostatectomy were enrolled. Patients were randomly assigned to three groups ($n = 13$ each) receiving TAP block with 20 ml (10 ml each side) of different concentrations of ropivacaine. To determine plasma concentrations, blood samples were drawn before and 15, 30, 45, 60, 90, 120, and 180 min after completion of bilateral TAP blocks. Plasma ropivacaine concentrations were analyzed by gas chromatography with mass spectrometry.
Results We found that the peak plasma concentrations (C_{max}) increased dose dependently (0.41 ± 0.14, 0.89 ± 0.55, and 1.56 ± 0.50 μg/ml), but the times to C_{max} (23.0 ± 15.8, 23.1 ± 14.5, and 20.8 ± 11.5 min) were not different between 0.25, 0.5, and 0.75 % ropivacaine doses, respectively. Terminal elimination half-life ($t_{1/2}$), total body clearance (CL), and distribution volume (V_d) were also not different among the three groups.
Conclusion Ropivacaine concentration did not alter pharmacokinetic profile following TAP blocks.

Keywords Ropivacaine · Transversus abdominis plane block · Pharmacokinetics

Introduction

Since O'Donnell and McDonnell [1, 2] reported transversus abdominis plane (TAP) block for injection of local anesthetic agents between the internal oblique and the transversus abdominis muscles, this technique has increased in popularity in abdominal surgery to provide postoperative analgesia [2, 3]. The target site of this block is a relatively hypervascular plane; hence, potentially rapid absorption may cause local anesthetic toxicity following injection of large doses. Aminoamide local anesthetics are known to produce vasoconstriction both in vivo and in vitro [4–7] but act as vasodilators at high doses [4–6]. Although the pharmacokinetics of ropivacaine after bilateral TAP block has previously been reported [8–10], no study has been performed to assess the effects of injected ropivacaine time to peak plasma concentration. Therefore, we have determined the effects of varying concentration on ropivacaine pharmacokinetics following TAP blocks.

Patients and methods

With the approval of our University ethics committee and written informed consent, 39 adult patients (ASA 1–2)

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undergoing elective open retropubic prostatectomy were enrolled into this study. Patients with a bleeding tendency or coagulation disorders were excluded. All patients were premedicated orally with diazepam 4–10 mg and roxatidine 75 mg at 90 min before the induction of anesthesia. Anesthesia was induced and maintained with propofol, remifentanil, morphine, and rocuronium. Patients were randomly assigned to three groups ($n = 13$ each) receiving TAP block with 20 ml (10 ml each side) of 0.25, 0.5, or 0.75 % ropivacaine. Bilateral ultrasound-guided TAP block was performed following the method reported by Hebbard et al. [11, 12]. Briefly, we utilized a real-time and in-plane needle insertion technique using a portable ultrasound unit and a 6–12 MHz linear probe. The probe was positioned midway between the costal margin and the iliac crest and then adjusted with an identifying image of the three abdominal wall muscles. A 20-gauge Toughy needle was advanced to layer between transversus abdominis and internal oblique muscles using the in-plane technique, and 10 ml solution was injected to make a lens shape and a hypoechoic space. To determine plasma concentrations of ropivacaine, arterial blood (3 ml) was drawn from a radial artery catheter before and 15, 30, 45, 60, 90, 120, and 180 min after completion of bilateral TAP blocks. Blood samples were centrifuged to separate the plasma, which was stored at −20 °C until assay. Plasma ropivacaine concentrations were analyzed by gas chromatography with mass spectrometry (GC/MS) as previously described by Björk et al. [13]. The limit of determination for ropivacaine was 10 ng/ml. The within-day (intraassay) coefficient of variation of the assay varied from 3.7 % at 500 ng/ml to 3.1 % at 1,000 ng/ml. A sample size of at least 12 patients per group was needed to have a power of 80 %, with an SD of 0.5 μg/ml (C_{max})/or 8.9 min (T_{max}) of significance at the two-sided 5 % level on the basis of previous studies [14]. Following the pharmacokinetic parameter, C_{max}, time to peak plasma concentration (T_{max}), $t_{1/2}$, total body clearance (CL), and V_d were calculated and fitted using a computer program (Moment Analysis Program; Graduate School of Pharmaceutical Sciences, Kyoto University). Data are presented as mean ± SD. Statistical analysis was performed using two-way repeated-measures analysis of variance (ANOVA) with Dunnett's post hoc test.

Results

Patient characteristics did not differ among the three groups (Table 1). Plasma ropivacaine concentrations for the first 180 min following ultrasound-guided TAP block are shown in Fig. 1. There were no differences in the pharmacokinetic parameters among the three groups (Table 2). The highest individual plasma concentration was 2.78 μg/ml, observed 15 min after TAP block with 0.75 % ropivacaine. No patients developed symptoms suggesting systemic toxicity of local anesthetics such as remarkable changes of blood pressure, heart rate, or consciousness

Table 1 Patient characteristics

	Ropivacaine concentration		
	0.25 %	0.5 %	0.75 %
Number of patients	13	13	13
Age (years)	66 (60–71)	69 (61–74)	67 (57–75)
Height (cm)	163 ± 10	164 ± 11	164 ± 10
Weight (kg)	58 ± 4	67 ± 13	64 ± 7
Duration of surgery (min)	120 ± 22	121 ± 25	113 ± 25

Data are expressed as mean ± SD or mean (range). There are no significant differences between the groups

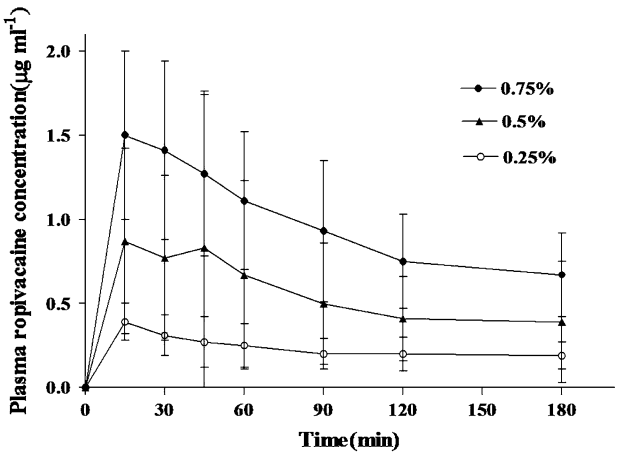

Fig. 1 Mean arterial plasma concentration of ropivacaine after administration of 20 ml of either 0.25, 0.5, or 0.75 % ropivacaine for bilateral transversus abdominis plane block. Data are mean ± SD ($n = 13$ per group)

Table 2 Maximum plasma concentration (C_{max}) and time (T_{max}) to reach C_{max} after transversus abdominis plane block with 0.25, 0.5, or 0.75 % ropivacaine

	Ropivacaine concentration		
	0.25 %	0.5 %	0.75 %
Number of patients	13	13	13
C_{max} (μg/ml)	0.41 ± 0.14	0.89 ± 0.55*	1.56 ± 0.50**
T_{max} (min)	23.0 ± 15.8	23.1 ± 14.5	20.8 ± 11.5
$t_{1/2}$ (h)	3.6 ± 2.1	5.4 ± 6.4	4.5 ± 3.2
CL (l/h)	27.7 ± 8.6	39.2 ± 20.2	42.8 ± 19.1
V_d (l)	135.1 ± 60.3	211.7 ± 92.4	233.7 ± 190.5

Mean ± SD

* $p < 0.05$

** $p < 0.01$ compared with group receiving 0.25 %

levels. In each group, no patients displayed serious adverse reactions such as systemic local anesthetic toxicity.

Main pharmacokinetic parameters of ropivacaine in each group are presented in Table 2. Absorption kinetics profile did not differ among the three groups ($p > 0.05$).

Discussion

In this study, the concentration of ropivacaine used for TAP block did not affect its pharmacokinetics within 180 min after injection. Ropivacaine has been reported to possess vasoconstrictor properties [4–6]. Cederholm and colleagues [5] studied the effects on skin blood flow of various concentration of ropivacaine. They found that ropivacaine showed an inverse dose–response relationship between the concentrations and its effect on skin blood flow. We therefore expected that the absorption of 0.75 % ropivacaine may have been delayed compared to 0.25 and 0.5 % ropivacaine. However, the pharmacokinetic profile did not differ between the groups in the present study and our ranges of ropivacaine doses do not affect absorption following TAP block. Sung et al. [6] found that ropivacaine produced a contraction of endothelium-intact vascular smooth muscle with maximum contraction from 3×10^{-4} to 10^{-3} M. In the present study, we gave 20 ml 0.25, 0.5, and 0.75 % ropivacaine for TAP block. Latzke and colleagues [10] showed that the concentrations of ropivacaine measured by microdialysis with the retrodialysis calibration method in the abdominal wall near the sites of injection of the TAP block were less than 100 μg/ml (300×10^{-4} mol/l) in most of the subjects [10]. It is likely that the concentrations in the injected tissue following TAP block with 20 ml 0.25 and 0.5 % ropivacaine may also be 3×10^{-4} mol/l or less, suggesting, together with the results by Sung et al. [6], that ropivacaine would not exert a vasoconstrictive effect,. Thus, ropivacaine-induced vasoconstriction in the injected tissue following TAP block with 0.25 to 0.75 % ropivacaine may be similar. Consequently, ropivacaine absorption should be similar between these doses used in TAP block.

We have previously reported the pharmacokinetic profile for a rectus sheath block (RSB) with 20 ml 0.25, 0.5, and 0.75 % ropivacaine [15]. In this study, T_{max} following TAP block was much shorter than that of RSB, whereas the C_{max} was similar to that of RSB. These data indicate that more rapid absorption after TAP blocks may occur compared to that after RSB. In general, local anesthetic absorption from injected tissues into the systemic circulation depends on several factors such as local anesthetic dosage, spread of injected solution, and tissue vascularity [16]. The target space for a TAP block is the neurovascular plane between the internal oblique and transversus abdominis muscles, which resembles the intercostal region revealing hypervascular perfusion with intercostal or subcostal arteries. Indeed, the T_{max} in the present study was similar to that after intercostal block (11 min) as previously reported [17]. In the present study, ropivacaine C_{max} increased dose dependently but did not reach a critically toxic level [9]. However, addition of epinephrine to ropivacaine solution should be considered to reduce its plasma concentration [16, 18], because a relatively large volume of local anesthetic solution (usually recommended, ≥15 ml for TAP block) is required in this kind of compartment block for abdominal wall muscles [1–3].

Weintraud et al. [19] reported faster absorption of local anesthetics following ultrasound-guided ilioinguinal/iliohypogastric nerve block when compared to a landmark-based technique in pediatric patients undergoing inguinal hernia repair. This finding indicates that local anesthetic absorption from the neurovascular plane such as in TAP block and ilioinguinal/iliohypogastric nerve block may be faster than from intramuscular sites. Weintraud et al. [19] explained this as follows: intramuscular injection causes a "sphere" of local anesthetic within the muscle while ultrasound-guided neurovascular plane injection produces a "pancake-shaped" disk of local anesthetic in the inter-muscle plane. The latter shape may produce a larger area for possible absorption.

In conclusion, the same amount (volume) of different concentrations of ropivacaine did not alter absorption kinetics following TAP block.

Conflict of interest None.

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