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Plasma ropivacaine concentrations after ultrasound-guided transversus abdominis plane block

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Key points

- Transversus abdominis plane (TAP) block involves injection of a large volume of local anaesthetic.
- TAP blocks using 3 mg kg^{-1} of ropivacaine result in venous plasma concentrations that are potentially neurotoxic.
- Ropivacaine levels peak at 30 min and remain high for several hours in some patients.

Background. The transversus abdominis plane block is a novel technique involving injection of local anaesthetic between the internal oblique and the transversus abdominis muscles of the abdominal wall. It is possible that injection of a large dose of local anaesthetic into a relatively vascular plane may result in toxic concentrations. One previously published study examined plasma lidocaine concentrations after transversus abdominus plane block and showed potentially toxic plasma concentrations. Although ropivacaine is most commonly used for this technique, plasma concentrations of ropivacaine after this block have not been reported previously.

Methods. Adult female patients undergoing elective open gynaecological surgery received bilateral ultrasound-guided transverse abdominal plane blocks before surgical incision (3 mg kg^{-1} of ropivacaine diluted to 40 ml). Venous blood was collected each 15 min for the first hour, each 30 min for the second hour, and then at 3, 4, 12, and 24 h post-block.

Results. Twenty-eight patients were recruited. The mean (SD) peak total ropivacaine concentration occurred 30 min post-injection and was 2.54 (SD 0.75) μg ml^{-1}. The highest measured concentration was 4.00 μg ml^{-1}, also 30 min post-injection. Mean total concentrations remained above 2.20 μg ml^{-1} for up to 90 min post-injection. The mean unbound peak venous concentration was 0.14 (0.05) μg ml^{-1}, and the peak was 0.25 μg ml^{-1}.

Conclusions. Transversus abdominus plane block using 3 mg kg^{-1} of ropivacaine produces venous plasma concentrations that are potentially neurotoxic, although broadly consistent with plasma levels found after injection at other comparable sites.

Keywords: anaesthetic techniques, regional; anaesthetics local, ropivacaine; toxicity, local anaesthetics

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The transversus abdominis plane (TAP) block is a newly described regional technique involving injection of local anaesthetic between the internal oblique and the transversus abdominis muscles of the abdominal wall. It has been shown in several clinical trials to be effective in reducing morphine consumption and improving postoperative pain relief.[1–5] The technique generally involves the injection of a large dose of local anaesthetic in the form of a single high-volume bolus into a relatively vascular plane. Potentially toxic plasma concentrations of local anaesthetic have been described after similar techniques, such as intercostal block.[6] Only one study has been previously published examining plasma local anaesthetic concentrations after TAP block[7] and showed that potentially toxic plasma concentrations of lidocaine were reached within 15 min after injection. Although ropivacaine is a much more commonly used local anaesthetic for TAP block, plasma ropivacaine concentrations after TAP block have not previously been reported.

This observational study aimed to quantify peak and mean venous plasma concentrations after ultrasound-guided TAP block using ropivacaine 3 mg kg^{-1} and to measure the time course of plasma concentration over 24 h after injection.

Methods

After institutional Human Ethics and Research Committee approval and informed written consent, female patients more than 18 yr of age undergoing elective open major gynaecological surgery and who were planned to receive TAP blocks were included. Patients were excluded if they had any allergy/sensitivity to local anaesthetic, significant renal or liver dysfunction, or were pregnant.

General anaesthesia was induced with fentanyl 1–2 μg kg^{-1}, propofol 2–3 mg kg^{-1}, a neuromuscular blocking agent of the treating anaesthetist's choice, paracetamol

1 g, and morphine 0.05–0.2 mg kg^{-1} i.v. Anaesthesia was maintained with sevoflurane. Bilateral ultrasound-guided TAP blocks were performed after induction of general anaesthesia, before surgical incision. Blocks were performed by a study investigator (or by a senior trainee experienced in the technique, under the direct supervision of a study investigator). Images were obtained using a Sonosite M-Turbo® ultrasound machine (Sonosite Inc., Bothell, WA, USA) with an L38x 10-5 MHz 38 mm broadband linear array probe. Blocks were performed with a 150 mm Stimuplex® needle (B-Braun Medical, Bethlehem, PA, USA) using an in-plane approach. Participants received a total dose of 3 mg kg^{-1} of ropivacaine (Naropin®, AstraZeneca, London, UK) diluted with 0.9% saline to a total volume of 40 ml (20 ml each side). The dose of ropivacaine of 3 mg kg^{-1} has been used in previous studies, demonstrating the efficacy of the TAP block.[4] The injections were performed midway between the costal margin and the iliac crest, between the junction of the anterior and middle thirds of the iliac crest. Postoperative analgesia included patient-controlled i.v. morphine, paracetamol and diclofenac.

After induction of anaesthesia, blood samples were obtained by aspiration from a large bore venous cannula, specifically placed in the antecubital fossa on the contralateral side to the cannula used for administering fluids and medications. Venous blood samples were obtained each 15 min for the first hour, each 30 min for the second hour, and then at 3, 4, 12, and 24 h after injection.

Assays were performed using a Shimadzu GC-17A gas chromatograph (Kyoto, Japan) equipped with a nitrogen–phosphorus detector and programmable temperature vaporizer and running a 25 m×0.25 mm SGE BPX-5 column (Melbourne, Victoria, Australia).

For total plasma concentration, 400 μl of plasma was added to a screw-capped borosilicate tube along with 50 μl mepivacaine 150 mg litre^{-1} and 50 μl KOH 3 M and extracted with 3 ml ethyl acetate. After vortex mixing and centrifugation, the ethyl acetate layer was transferred to a second borosilicate tube and evaporated to dryness under N_2 at 40°C. The residue was reconstituted in 100 μl of methanol and 6 μl injected into the gas chromatograph. The peak area ratio of ropivacaine to the mepivacaine internal standard was used to quantify the concentration of each plasma sample against a standard curve run with each batch. Unbound concentrations were determined after a single ultrafiltration of a single sample with Amicon (a trademark of Millipore, Carrigtwohll, Co., Cork, Ireland) Ultra 3K centrifugal filters. The extraction was similar except that 200 μl of ultrafiltrate was used and the KOH reduced to 25 μl. After reconstituting in 100 μl methanol, the sample was again evaporated to dryness under N_2 (at room temperature), reconstituted in 50 μl methanol, and 24 μl injected into the gas chromatograph. The method is linear to at least 20 mg litre^{-1} with a within-day coefficient of variation of <5% at 1 mg litre^{-1} on each analysis day. The limit of quantitation was 20 μg litre^{-1} for total levels and 5 μg litre^{-1} for unbound levels.

Sample size estimation

The sample size estimation was based on reported plasma levels with the potential for early neurotoxicity [2.2 (0.9) μg ml^{-1}] compared with scalp blocks as an exemplar of relatively high blood flow tissue block. For scalp blocks, peak plasma concentrations of mean 1.6 (0.6) μg ml^{-1} have been reported.[8] Using two-tailed analysis, α 0.05, and a power of 0.8, the minimum sample size was 28 patients in order to detect plasma ropivacaine levels 30% higher than scalp blocks, which would include the potentially toxic threshold of 2.2 μg ml^{-1}.

Results

We recruited 28 adult female patients. The median age was 43 yr (range, 19–86 yr) and the mean (SD) body weight was 67.1 (15.2) kg. The mean dose of ropivacaine administered was 201 (46) mg. All the patients underwent lower abdominal laparotomy for gynaecological procedures. The median surgical duration was 125 min (range, 71–206 min).

The time course of serum ropivacaine concentrations is shown in Figure 1. The mean peak total ropivacaine concentration was 2.54 (0.75) μg ml^{-1}, which occurred at the 30 min measurement. The highest individual peak plasma concentration was 4.00 μg ml^{-1}, also at 30 min after injection. Total mean concentrations remained above 2.20 μg ml^{-1} up to 90 min post-injection. Median concentrations were above 2.20 μg ml^{-1} for up to 45 min post-injection.

The mean unbound ropivacaine concentration measured at 30 min was 0.14 (0.05) μg ml^{-1}. The median unbound concentration was 0.13 μg ml^{-1}. The highest observed unbound ropivacaine concentration in any patient was 0.25 μg ml^{-1}. Ten patients exceeded the potentially toxic threshold concentration of 0.15 μg ml^{-1}.

We did not prospectively assess for subtle symptoms or clinical signs of neurological toxicity, but there were no seizures or persistent cardiovascular instability observed in any patient.

Discussion

Plasma concentrations of ropivacaine after large volume blocks in relatively high blood flow tissues have been reported previously, including scalp blocks for awake craniotomy [1.5 (0.6) μg ml^{-1}],[8] caudal [0.9 (0.31) μg ml^{-1}],[9] and ilioinguinal blocks [1.5 (0.93) μg ml^{-1}][10 11] in children. Knudsen and colleagues[12] published a study of volunteers receiving titrated i.v. infusions of ropivacaine and revealed the onset of neurological symptoms at a mean total plasma venous concentration of 2.2 μg ml^{-1} and an unbound ropivacaine concentration of 0.15 (0.08) μg ml^{-1}. Many case reports have been published measuring ropivacaine concentrations in the setting of local anaesthetic toxicity. Measured concentrations in the setting of overdosage tend to be much higher than levels in the setting of accidental intravascular injection, where the rapid increase in plasma concentrations makes toxicity more likely.[13] For

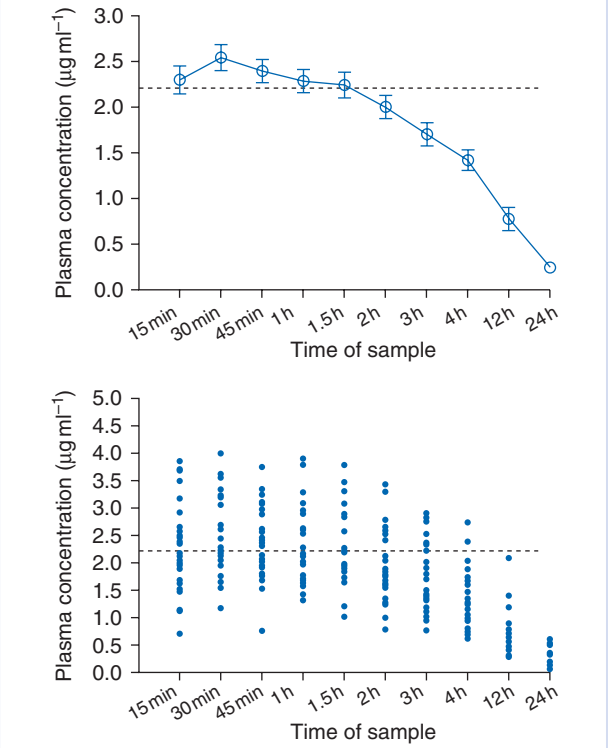

Fig 1 Total plasma ropivacaine.

example, a case where ropivacaine 6 mg kg^{-1} was injected as an interscalene nerve block resulted in an initial plasma concentration of 6.0 μg ml^{-1} and symptoms of neurological toxicity.[14] Whereas, brachial plexus block complicated by inadvertent intravascular injection (also with symptoms of neurological toxicity) resulted in measured plasma concentrations of only 2.70–3.3 μg ml^{-1}.[15 16]

This study revealed that mean peak total venous ropivacaine concentrations exceeded a potentially neurotoxic threshold value (2.2 μg ml^{-1}) after bilateral TAP block with 3 mg kg^{-1} ropivacaine at 15, 30, 60, and 90 min, with the highest individual value almost double this (4.0 μg ml^{-1}). The peak total concentrations found in our study exceeded those in previously published studies of scalp block for awake craniotomy,[8] ilioinguinal,[10] and caudal[9] blocks in children. The mean peak concentration was also higher than 2.2 μg ml^{-1}, which was the threshold level for the onset of minor neurotoxic symptoms as published by Knudsen and colleagues.[12] However, Knudsen's paper represents a different clinical scenario, where i.v. local anaesthetic infusions were titrated in volunteers, without supplemental anaesthetic agents which may reduce the likelihood of neurotoxic symptoms. Knudsen's study measured the onset of minor neurotoxic symptoms, rather than potentially life-threatening toxicity. There was also a marked arteriovenous difference in the samples, indicating high peripheral extraction in the limb used for measurement and making interpretation of the venous levels unreliable in respect of the venous levels associated with toxicity in a clinical scenario with slower absorption.

Plasma ropivacaine levels have also been studied in the context of other common regional techniques with a low incidence of clinically important toxicity. These reveal a range of results broadly consistent with our findings. Mean peak plasma ropivacaine levels after ilioinguinal block were 1.5 μg ml^{-1} (maximum level 2.6 μg ml^{-1}),[17] after axillary brachial plexus block 2.58 μg ml^{-1} (maximum level 3.4 μg ml^{-1})[18] and a single epidural bolus of 1.77 μg ml^{-1} (maximum level 2.94 μg ml^{-1}).[19]

In general, the free or unbound fraction of the drug is considered to be more predictive of toxicity than the total concentration. The median unbound venous concentration in our study (0.13 μg ml^{-1}) was lower than that which was associated with neurotoxicity in Knudsen's study in volunteers (0.15 μg ml^{-1}), although individual patients exceeded it.[12] Knudsen and colleagues, however, suggested that the peak unbound arterial concentration (0.56 μg ml^{-1}) may represent a more valid predictor of toxicity than the venous level due to the high peripheral extraction in their study.

In addition to the absolute plasma levels, the rate of increase in plasma local anaesthetic concentrations is implicated in resulting toxicity. In our study, plasma levels were seen to increase more slowly than in other settings. We found peak concentrations in most patients occurred at 30 min post-injection. This is slower than in the paravertebral block,[20] interscalene block,[18] and awake craniotomy,[8] where peak levels occurred at 7.5, 10, and 15 min, respectively. Our observed peak concentrations were also delayed compared with Knudsen's study, where infusions were stopped (with the onset of symptoms) after a median duration of 11.5 min. In contrast, after ilioinguinal block[17] and caudal anaesthesia in children,[21] peak venous levels were seen after 45 and 65 min, respectively.

In this study, we did not attempt to assess for clinical signs or symptoms of neurotoxicity. The duration of surgery in most patients exceeded the peak times that plasma concentrations were elevated. For this reason, we determined that it was highly unlikely that clinical neurotoxicity would be detected. This study does, however, have implications for TAP blocks performed at the conclusion of surgery for pain relief, or for brief operations, where potentially neurotoxic plasma concentrations could be present in conscious patients.

Also, the participants in this study were healthy adult female patients. It is possible that the measured concentrations would be different in males, children or the elderly, or in pregnancy (where levels of AAG are reduced and cardiac output is increased). Other conditions in which plasma concentrations may be unexpectedly increased could include renal or cardiac failure.[22]

Different anatomical locations display different pharmacokinetic characteristics influencing toxicity. Rosenberg and colleagues[22] propose that rather than publishing a single maximum safe dose of a local anaesthetic, dosage recommendations should be technique-specific. For example, different approaches to the brachial plexus result in

significantly different plasma concentrations of local anaesthetic.[18] Kato and colleagues suggest that local anaesthetic absorption after TAP block may in part result from leakage of injectate from the TAP out into the surrounding abdominal musculature. It is possible that ultrasound guidance may actually increase the accuracy of injection and decrease plasma levels compared with a blind technique.[7] Although we believe that clinically important toxicity with this technique is unlikely, the findings in our study raise the possibility that a dose of 3 mg kg^{-1} may be excessive in some patients. Consideration should be given to dose reduction, especially if there are medical conditions that may increase the unbound fraction of drug or increase the rate of absorption.

In conclusion, this study demonstrates that the use of 3 mg kg^{-1} of ropivacaine in the TAP block in adult females results in potentially toxic plasma concentrations of ropivacaine.

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Conflict of interest

None declared.

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