Symptomatic local anaesthetic toxicity and plasma ropivacaine concentrations after transversus abdominis plane block for Caesarean section

J. D. Griffiths, N. V. Le, S. Grant, A. Bjorksten, P. Hebbard and C. Royse

Background. The transversus abdominis plane (TAP) block involves injecting a large volume of local anaesthetic between the muscles of the abdominal wall. Plasma concentrations of ropivacaine after gynaecological laparotomy are potentially high enough to result in systemic toxicity, and there are pharmacokinetic reasons why pregnancy may increase susceptibility to local anaesthetic toxicity.

Methods. Adult female patients (n = 30) undergoing elective Caesarean section under spinal anaesthesia received bilateral ultrasound-guided TAP blocks after wound closure (2.5 mg kg⁻¹ of ropivacaine diluted to 40 ml). Venous blood samples were collected at 10, 20, 30, 45, 60, 90, 120, 180 and 240 min following the block. Blood samples were assayed for total and free ropivacaine concentrations. Patients were assessed for symptoms of local anaesthetic toxicity.

Results. The mean (standard deviation (SD)) peak total concentration of ropivacaine occurred at 30 min post-injection and was 1.82 (0.69) μg ml⁻¹. The maximum detected concentration in any patient was 3.76 μg ml⁻¹ (at 10 min post-injection). Three patients reported symptoms of mild neurotoxicity, and the mean (SD) peak levels were elevated in these patients, 2.70 (0.46) μg ml⁻¹.

Conclusions. TAP blocks can result in elevated plasma ropivacaine concentrations in patients undergoing Caesarean section, which may be associated with neurotoxicity.

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

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which may predispose to neurotoxicity, with seizures occurring at lower plasma concentrations of ropivacaine than for the non-pregnant. We are not aware of evidence to suggest that an increase in susceptibility to neurological toxicity necessarily corresponds to an increase in the risk of cardiovascular toxicity.

Caesarean section is a common surgical procedure where the TAP block may offer analgesic benefit. It is perhaps the most common surgical procedure for which TAP blocks are performed. The potential for local anaesthetic systemic toxicity in pregnant women undergoing neuraxial anaesthesia is well recognized, and frequently addressed in maternal resuscitation guidelines. It has been proposed that Intralipid should be available in obstetric centres. The potential for TAP blocks to cause local anaesthetic toxicity in recently pregnant women has not previously been studied.

This observational study aimed to quantify the peak and mean venous plasma concentrations after ultrasound-guided TAP block using ropivacaine in healthy women undergoing Caesarean section under spinal anaesthesia, and to measure the time course of plasma concentration over 4 h after injection. We also assessed the women for clinical symptoms and signs consistent with neurological local anaesthetic toxicity. We did not assess specifically for cardiovascular toxicity as animal studies suggest the CC/CNS ratio for ropivacaine is high (1.9–8.1), making the likelihood of observing overt cardiovascular toxicity very low.

Methods
After institutional Human Ethics and Research Committee approval and informed written consent, female patients over 18 yr of age undergoing elective Caesarean section under spinal anaesthesia were recruited. Patients were excluded if they had any allergy/sensitivity to local anaesthetic, significant renal or liver dysfunction, or weighed over 100 kg.

Patients received a spinal anaesthetic consisting of 11 mg of heavy bupivacaine and 15 µg of fentanyl. I.V. cephalolin 1 g, parecoxib 40 mg, and paracetamol 1 g were administered after cord clamping. A 5 unit bolus and 40 unit infusion regimen of syntocinon were administered. Rectal slow-release oxycodone 30 mg was given at the conclusion of the procedure.

TAP blocks were performed after wound closure 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 using a 150 mm Stimuplex needle (B-Braun Medical, Bethlehem, PA, USA) using an in-plane approach. Participants received a total dose of 2.5 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 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.

The dose of 2.5 mg kg⁻¹ was chosen as it represented a meaningful reduction from the concentration used in our previous study, while still being within the range shown to be efficacious in similar studies using the technique.

After the procedure, 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 collected at 10, 20, 30, 45, 60, 90, 120, 180, and 240 min following the block. Patients were asked whether they were experiencing perioral tingling, a metallic taste, tinnitus, visual disturbance, or slurred speech at the time that each blood sample was obtained. Local anaesthetic assays were performed using the method previously described. Unbound (free) ropivacaine concentration was measured on one sample, and the plasma binding fraction was calculated based on the corresponding total ropivacaine concentration in that sample.

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, the peak plasma concentrations of mean 1.6 (0.6) µg ml⁻¹ have been reported. Using two-tailed analysis, a 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. Student’s t-test was used to compare differences between numerical variables.

Results
We recruited 30 patients in this study. Patient characteristics are shown in Table 1. All participants underwent uncomplicated Caesarean section under spinal anaesthesia. The TAP blocks were performed after wound closure using a mean [standard deviation (SD)] dose of ropivacaine of 199 (27.8) mg.

The time course of total plasma ropivacaine concentrations is shown in Figure 1a (mean, so) and b (scatter plot). The mean peak total plasma ropivacaine concentration was 1.82 µg ml⁻¹. The mean (so) time of the maximum concentration was 35.5 (15.7) min. The highest individual plasma ropivacaine concentrations after TAP block for Caesarean section

Table 1. Patient characteristics according to symptoms of local anaesthetic neurotoxicity. Data are median (range) or mean (SD)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Asymptomatic (n=27)</th>
<th>Symptomatic (n=3)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34 (23–40)</td>
<td>34 (32–36)</td>
<td>0.034</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 (11)</td>
<td>91 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 (7.6)</td>
<td>163 (13.3)</td>
<td>0.75</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>30.8 (4.8)</td>
<td>34.8 (6.4)</td>
<td>0.097</td>
</tr>
<tr>
<td>Ropivacaine dose (mg)</td>
<td>196 (26.9)</td>
<td>229 (19.1)</td>
<td>0.025</td>
</tr>
</tbody>
</table>
concentration was 3.76 μg ml\(^{-1}\), which occurred at the 10 min sample. The mean (SD) peak free (unbound) ropivacaine concentration was 0.07 (0.034) μg ml\(^{-1}\), and the mean free drug fraction was 7.41 (3.66)%. This free drug fraction was comparable with the free drug fraction in our previous study of non-pregnant subjects [7.41 (3.66)% vs 6.13 (2.54)%; \(P=0.06\)].

In the first hour of observations, the total plasma concentrations of ropivacaine exceeded the potentially toxic threshold of 2.2 μg ml\(^{-1}\) in 12 patients. Three of these patients described symptoms attributable to local anaesthetic toxicity. The characteristics of these symptomatic patients are also shown in Table 1. Symptoms commenced at either the 20 or 30 min sample, and persisted for 10–70 min. The mean (SD) total peak ropivacaine concentrations for these three patients was 2.70 (0.46) μg ml\(^{-1}\), as shown in Figure 1c. The mean (SD) time to the maximum concentration in symptomatic patients was 26.7 (5.8) min, compared with 36.5 (16.1) min for asymptomatic patients (\(P=0.015\)). All symptoms resolved without treatment. Although we did not specifically monitor for manifestations of cardiovascular toxicity, no patients exhibited evidence of cardiovascular disturbance requiring medical intervention during the period of study. There were no other complications attributable to the TAP blocks.

### Discussion

This study aimed to prospectively assess for subtle symptoms of neurotoxicity in awake patients undergoing TAP block. We have demonstrated that healthy pregnant women receiving TAP blocks for Caesarean section can develop symptoms consistent with mild toxicity despite using modest doses of local anaesthetic. In our study, 12 patients had concentrations of total venous ropivacaine which exceeded the widely quoted toxic concentration of 2.2 μg ml\(^{-1}\) at some time after the block. All three patients who developed symptoms were in this group, which supports the acceptance of this plasma concentration as a reasonable threshold for clinical toxicity in patients undergoing TAP block.

Symptomatic patients had greater mean (SD) body weight than the asymptomatic [90.7 (6.7) vs 78.1 (11.2) kg; \(P<0.05\)]. Consequently, the mean (SD) total dose of ropivacaine in the symptomatic patients was significantly greater compared to the asymptomatic patients.

### Table 2

<table>
<thead>
<tr>
<th>Subject</th>
<th>Onset (post-block)</th>
<th>Total ropivacaine concentration (μg ml(^{-1}))</th>
<th>Maximum ropivacaine concentration (μg ml(^{-1}))</th>
<th>Approximate duration of symptoms (min)</th>
<th>Symptoms described</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>30</td>
<td>3.21</td>
<td>3.21</td>
<td>10</td>
<td>Perioral tingling; slurred speech</td>
</tr>
<tr>
<td>15</td>
<td>20</td>
<td>2.31</td>
<td>2.31</td>
<td>40</td>
<td>Perioral tingling; tongue paraesthesia</td>
</tr>
<tr>
<td>16</td>
<td>20</td>
<td>2.18</td>
<td>2.59</td>
<td>10</td>
<td>Metallic taste</td>
</tr>
</tbody>
</table>
with asymptomatic patients [229 (19.1) vs 196 (26.9) mg, 
$P<0.05$]. This suggests that further dose reduction may be 
required as patient weight increases, or perhaps that dosage calculation should be based on lean body mass.

The correct basis for selecting doses of local anaesthetic for TAP block is not yet fully established. However, it should 
be understood that the TAP block is a type of field block, 
with anatomical studies demonstrating the relationship 
between the location of local anaesthetic deposition and 
the resulting zone of anaesthesia. Thus, the anatomical 
region of desired anaesthesia dictates to some extent the 
volume required to cover the corresponding segmental ab-
dominal wall nerves. It may be preferable to obtain the 
spread of local anaesthetic solution by hydro-dissecting 
the plane and by progressively redirecting and advancing 
the needle within the TAP, rather than by relying on an exces-
sively large volume of injectate to achieve the same spread. 
Also, the concentration of local anaesthetic used will dictate 
the duration of analgesia achieved, and to some extent also 
the density of analgesia/anaesthesia obtained.

There are several potential limitations in our study. First, 
we did not assess the analgesic efficacy of the TAP blocks 
in our patients, nor did we record information regarding 
ultrasonographic evidence of successful local anaesthetic 
placement. It is possible that poor pain relief may indicate 
improper deposition of local anaesthetic into the desired 
anatomical plane, for example, excessive leakage of injectate 
into the surrounding musculature. This may in turn influence 
the extent of plasma uptake of local anaesthetic. The risk of 
unintended i.m. local anaesthetic deposition may also be 
higher for obese patients, which may have affected the 
results we obtained. Additionally, patients were asked directly 
whether they had specific symptoms associated with 
neurotoxicity. It is possible that, due to the subjective 
nature of these symptoms, suggestion bias may have been 
introduced and affected symptom reporting.

TAP blocks have been shown to reduce postoperative 
morphine consumption in the first 24 h after Caesarean 
section. The risk–benefit balance for TAP blocks either in 
addition to or as an alternative to other analgesic regimens 
(such as intrathecal morphine) in this setting is yet to be 
fully elucidated, although it must be noted that the symp-
toms of neurotoxicity in our patient sample were mild and 
of minimal clinical consequence.

Conclusion

This study confirms that the TAP block at Caesarean section 
may result in plasma ropivacaine concentrations associated 
with neurotoxicity.

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Declaration of interest

None declared.

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References

1 McDonnell JG, O'Donnell B, Curley G, Hefferman A, Power C, 
Laffey JG. The analgesic efficacy of transversus abdominis plane 
block after abdominal surgery: a prospective randomized con-

2 Corney J, McDonnell JG, Ochana A, Bhinder R, Laffey JG. The 
transversus abdominis plane block provides effective post-

ultrasound-guided transversus abdominis plane block in patients 
undergoing open appendicectomy. Br J Anaesth 2009; 103: 
601 –5

4 McDonnell JG, Curley G, Corney J, et al. The analgesic efficacy of 
transversus abdominis plane block after cesarean delivery: a ran-
of contents

5 Belavy D, Cowlishaw PJ, Howes M, Phillips F. Ultrasound-guided 
transversus abdominis plane block for analgesia after Caesarean 

6 Tan TT, Teoh WH, Woo DC, Ocampo CE, Shah MK, Sia AT. A 
randomised trial of the analgesic efficacy of ultrasound-
guided transversus abdominis plane block after caesarean delivery 
under general anaesthesia. Eur J Anaesthesiol 2012; 29: 
88 –94

7 Abdallah FW, Haipern SH, Margarido CB. Transversus abdominis 
plane block for postoperative analgesia after Caesarean delivery performed under spinal anaesthesia? A systematic review and 

8 Behnke H, Worthmann F, Cornelissen J, Kahl M, Wulf H. Plasma 
concentration of ropivacaine after intercostal blocks for 

9 Griffiths JD, Barron FA, Grant S, Bjorksten AR, Hebbard P, Royse CF. 
Plasma ropivacaine concentrations after ultrasound-guided 
transversus abdominis plane block. Br J Anaesth 2010; 105: 
853 –6

10 Torup H, Mitchell AU, Breindahl T, Hansen EG, Rosenberg J, 
Moller AM. Potentially toxic concentrations in blood of total 
ropivacaine after bilateral transversus abdominis plane 
blocks; a pharmacokinetic study. Eur J Anaesthesiol 2012; 29: 
235 –8

11 Kato N, Fujiwara Y, Harato M, et al. Serum concentration of lido-
23: 298 –300

12 Landy C, Gagnon N, Boulland P, Raynaud L, Plancade D. Seizures 
associated with local anaesthetic intoxication. Br J Anaesth 2012; 
109: 463 –4; author reply 64

13 Sakai T, Manabe W, Kamitani T, Takeyama E, Nakano S. Ropivacaine-induced late-onset systemic toxicity after transversus abdominis plane block under general anaesthesia: successful reversal with 20% lipid emulsion. Masui 2010; 59: 1502 –5
17 Santos AC, DeArmas PI. Systemic toxicity of levobupivacaine, bupivacaine, and ropivacaine during continuous intravenous infusion to nonpregnant and pregnant ewes. *Anesthesiology* 2001; **95**: 1256–64
21 Groban L. Central nervous system and cardiac effects from long-acting amide local anesthetic toxicity in the intact animal model. *Reg Anesth Pain Med* 2003; **28**: 3–11
24 Lee TH, Barrington MJ, Tran TM, Wong D, Hebbard PD. Comparison of extent of sensory block following posterior and subcostal approaches to ultrasound-guided transversus abdominis plane block. *Anaest Intensive Care* 2010; **38**: 452–60
25 El-Sharrawy E, Yagiela JA. Anesthetic efficacy of different ropivacaine concentrations for inferior alveolar nerve block. *Anesth Prog* 2006; **53**: 3–7

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