Plasma ropivacaine concentrations during bilateral transversus abdominis plane infusions


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Editor’s key points

- Bilateral transversus abdominus plane (TAP) blocks with continuous infusion require relative high doses of local anaesthetic.
- Plasma ropivacaine concentrations were determined in patients receiving postoperative TAP blocks and infusion for analgesia after laparotomy.
- Potentially toxic ropivacaine concentrations were observed, with wide variability between patients requiring individualized dosing and close monitoring for toxicity.

Background. The transversus abdominis plane (TAP) block is a regional anaesthetic technique that blocks abdominal wall somatic afferent nerves. We conducted a prospective observational study to evaluate the venous plasma concentrations of ropivacaine during a continuous TAP infusion.

Methods. Twenty patients who were planned to undergo intra-abdominal cavity surgery requiring a mid-line laparotomy incision were enrolled. Patients were excluded if they had a history of chronic pain, opioid tolerance, renal or hepatic impairment, or contraindication to study medications. Subjects received a standardized general anaesthetic, and at the completion of surgery, ultrasound-guided subcostal or posterior TAP blocks and catheters. A TAP infusion of 2 mg ml⁻¹ ropivacaine was administered for 72 h after operation. Data collection during the 72 h included morphine requirements, pain scores, and plasma ropivacaine levels.

Results. TAP blocks and catheters were successfully inserted in all recruited subjects. The fourth subject experienced neurological symptoms attributed to local anaesthetic toxicity, but did not have high plasma ropivacaine concentrations. However, the protocol was amended for the subsequent 16 subjects, to a weight-based dosing regimen. The range of total plasma ropivacaine concentrations was 0.98–3.41 mg litre⁻¹ for posterior infusions and 0.96–3.48 mg litre⁻¹ for subcostal infusions. Four subjects had total ropivacaine levels >3.4 mg litre⁻¹. The range of unbound plasma ropivacaine concentrations was 0.022–0.135 mg litre⁻¹ for posterior infusions and 0.031–0.120 mg litre⁻¹ for subcostal infusions.

Conclusion. Given the potential for high plasma concentrations from a bilateral TAP infusion technique, attention should be paid to individualized dosing strategies.

Keywords: anaesthetics local, ropivacaine; analgesia postoperative; analgesic techniques, infusion; surgery, abdominal; toxicity, local anaesthetics

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The TAP block is a regional anaesthetic technique that blocks abdominal wall somatic afferent nerves.¹ McDonnell and colleagues demonstrated improved visual analogue scores and decreased morphine requirements within the first 24 h after bowel resection via a mid-line laparotomy in patients receiving bilateral TAP blocks. Other studies have demonstrated efficacy of TAP blocks in a variety of surgeries.²–⁸ The use of local anaesthetic infusions to provide postoperative analgesia is common.³ One consideration in selecting a dosing regimen for any infusion is the potential for toxicity because of high intravascular concentrations of local anaesthetic. Because the TAP block is generally a bilateral block,¹⁰ involving a relatively large plane containing multiple nerves,¹¹ higher volumes of local anaesthetic have traditionally been used to ensure successful blockade of multiple dermatomes.¹²⁻¹³ Consequently, it is not unusual for local anaesthetic administration to approach maximum recommended doses. A single injection followed with an infusion technique has the potential to result in high intravascular local anaesthetic plasma concentrations.

Although there are data evaluating plasma concentrations of local anaesthetics after TAP block,¹⁴ there is no published literature describing levels resulting from TAP block followed by continuous infusion. In preparation for a randomized controlled trial looking at the efficacy of TAP infusions, we conducted a prospective observational study to evaluate peak and mean plasma concentrations of ropivacaine during a continuous 72 h TAP ropivacaine infusion.
**Methods**

This study was approved by the Melbourne Health Human Research and Ethics Committee. Ropivacaine is approved for neural blockade by Therapeutics Goods Administration Australia. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12608000291381). Written informed consent was obtained from the participants.

Twenty adult subjects planned for intra-abdominal cavity surgery requiring a mid-line laparotomy incision were recruited over a 1-year period. Patients were excluded if they had a history of chronic pain, opioid tolerance, renal or hepatic impairment, allergy or contraindication to ropivacaine, or the other agents included in the pain management protocol: morphine, tramadol, acetaminophen, or parecoxib.

All subjects received a standardized general anaesthetic. Before operation, subjects were given weight-determined dose of between 1 and 2 g oral acetaminophen. Fentanyl was the major intraoperative analgesic, with dose determined by the treating anaesthetist. Intraoperative analgesic adjuncts were 40 mg parecoxib and 2–3 mg kg \(^{-1}\) tramadol depending on age. Anaesthesia was maintained with sevoflurane or desflurane in oxygen/air mix, with positive pressure ventilation in a circle system. Choice of neuromuscular blocking agent was at the discretion of the treating anaesthetist.

At the conclusion of the surgery, the anaesthetist placed bilateral TAP blocks and inserted TAP catheters. Blocks were performed or supervised by one of three experienced operators.

**Insertion of TAP blocks and catheters**

TAP blocks were inserted with ultrasound guidance under sterile conditions using an 18 gauge Portex Tuohy (Smiths Medical Australasia, Brisbane, Australia) needle. The appropriate approach for the TAP block was selected depending on the location of the surgical incision. Where the incision was predominantly sub-umbilical, a posterior approach TAP block was performed, with the needle insertion point midway between the costal margin and the iliac crest, on the anterior axillary line. For surgical incisions that were supra-umbilical or full abdominal length, an oblique subcostal approach TAP block was performed, which involves imaging the TAP plane in the supero-medial abdominal wall.\(^ {14} \) The ultrasound probe is placed parallel to the costal margin, and the needle inserted lateral and caudal to the xiphoid process. Local anaesthetic is deposited posterior to the rectus abdominis muscle, anterior to either the transversus abdominis muscle or the posterior rectus sheath, depending on which structure is present at this point. The needle is then advanced parallel to the costal margin, and progressive injections of the local anaesthetic are used to hydrodissect the plane between transversus abdominis and internal oblique muscles. This approach allows blockade of intercostal nerves as they emerge to run into the transversus plane.

This decision to target different surgical incisions with either the posterior or subcostal approach has been validated by recent studies demonstrating different dermatomal spread of local anaesthetic for the two TAP block approaches.\(^ {11,13} \)

The insertion site for the blocks was prepared with chlorhexidine 0.5% in isopropyl alcohol 70% solution and surrounded by sterile drapes. The abdominal wall was imaged using a GE Logiq E ultrasound (GE Medical Systems, Jiangsu, China) with a linear 12LRS probe (GE Yokogawa Medical Systems, Tokyo, Japan).

After successful visualization of the needle tip between the internal oblique and transversus abdominis muscles, the potential TAP space was expanded with 20 ml of ropivacaine 5 mg ml\(^{-1}\). Infusion catheters (open ended catheter with three lateral eyes) were then inserted via the Tuohy needle.

**TAP block and infusion ropivacaine dose**

For the first four patients, the dosing regimen was as follows:

- **Bolus of ropivacaine 200 mg** (20 ml ropivacaine 5 mg ml\(^{-1}\) each side).
- **With infusion of 14 mg h\(^{-1}\)** (7 ml h\(^{-1}\) of ropivacaine 2 mg ml\(^{-1}\) each side (total infusion rate 28 mg h\(^{-1}\)).

Following development of potential local anaesthetic toxicity in the fourth recruited patient, the protocol was amended to reflect a weight-based dosing regimen (Table 1). Infusions were commenced in the recovery room, \(\sim\)10–20 min after the initial TAP block.

**Data collection and plasma ropivacaine sampling**

Data collection occurred at 6, 24, 48, and 72 h after operation. The following parameters were collected: patient controlled analgesia morphine use in total milligrams; verbal pain scores on rest and movement (0=no pain and 10=worst pain imaginable); and signs or symptoms of local anaesthetic toxicity including sensory disturbance, muscle twitching, hallucinations, and peripheral numbness or tingling.

Peripheral venous blood samples (7 ml) were taken at 0, 2, 6, 12, 24, 48, and 72 h after TAP block. The blood was centrifuged within 1 h of sampling and the plasma frozen at

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Dosing regimen TAP blocks and infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight &lt;70 kg</strong></td>
<td><strong>Weight ≥70 kg</strong></td>
</tr>
<tr>
<td><strong>Loading dose</strong></td>
<td>Ropivacaine 150 mg (20 ml ropivacaine 3.75 mg ml(^{-1}) each side)</td>
</tr>
<tr>
<td><strong>Infusion dose</strong></td>
<td>Ropivacaine 2 mg ml(^{-1}) 0.1 ml kg(^{-1}) h(^{-1}) each side, rounded down to nearest integer. For example, a 58 kg subject would receive an infusion of 5 ml h(^{-1}) each side. Maximum dose of 7 ml h(^{-1}) each side</td>
</tr>
</tbody>
</table>
– 20°C until assayed. Total and free ropivacaine levels were assayed using gas chromatography. 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 3 M KOH, 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 nitrogen at 40°C. The residue was reconstituted in 100 μl of methanol and 6 μl was injected into the gas chromatograph. The gas chromatograph was a Shimadzu GC-17A (Shimadzu, Kyoto, Japan) equipped with a nitrogen-phosphorus detector and programmable temperature vaporizer with a 25 m × 0.25 mm SGE BPX-5 column (SGE Analytical Science, Melbourne, Australia). 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. The method is linear to at least 20 mg litre⁻¹; within day coefficient was variation of <5% at 1 mg litre⁻¹ on each analysis day.

Unbound ropivacaine concentrations were determined after ultrafiltration with Amicon Ultra 30K centrifugal filters (Millipore, County Cork, Ireland). 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 nitrogen (at room temperature), reconstituted in 50 μl methanol, and 24 μl injected into the gas chromatograph.

Mean and standard deviation (SD) of the total and unbound plasma ropivacaine concentrations at each time-point were calculated.

### Results

Thirty-five patients eligible for the trial were identified. Twenty patients consented to participation in the trial and were recruited. The reasons for failure to recruit were patient refusal (10), trial on-hold during protocol amendment (3), and rebooking of surgery date and subsequent loss to the follow-up (2). Two subjects’ results were excluded from the analysis because they did not receive the ropivacaine regimen described above.

All subjects were scheduled to undergo laparotomy requiring a mid-line surgical incision. Subject characteristics, procedures, and TAP block approach are listed in Table 2.

At the conclusion of the surgery, TAP blocks and catheters were inserted. The TAP block approach was posterior in 7 subjects and subcostal in 11 subjects. The median (inter-quartile range) time taken to place the catheters (measured from placement of the ultrasound probe to placement of the dressings over the catheters) was 24 (18–35) min.

Visualization of the TAP, placement of the needle and insertion of bilateral catheters was successful in all subjects. Where difficulties were encountered advancing the catheter into the TAP plane, an additional 10–20 ml of normal saline was used to further expand the TAP space.

### Ropivacaine plasma concentrations

Total and unbound plasma ropivacaine levels for subcostal and posterior infusions over the 72 h of infusion are shown in Figures 1–4. Figures 1 and 2 demonstrate total ropivacaine plasma concentrations rising rapidly after the initial ropivacaine bolus of the TAP block. Thereafter, there is a second

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**Table 2** Subject characteristics and operations. *Results excluded from analysis. BMI, body mass index*

<table>
<thead>
<tr>
<th>Operation</th>
<th>Gender</th>
<th>Age</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>BMI (kg m⁻²)</th>
<th>TAP approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversal of Hartmann’s procedure</td>
<td>M</td>
<td>45</td>
<td>1.77</td>
<td>77</td>
<td>24.6</td>
<td>Subcostal</td>
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<tr>
<td>Right hemicolectomy</td>
<td>F</td>
<td>83</td>
<td>1.56</td>
<td>59</td>
<td>24.2</td>
<td>Posterior*</td>
</tr>
<tr>
<td>Abdominoperineal resection</td>
<td>M</td>
<td>58</td>
<td>1.80</td>
<td>95</td>
<td>29.3</td>
<td>Posterior</td>
</tr>
<tr>
<td>Gastrectomy</td>
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<td>25</td>
<td>1.63</td>
<td>45</td>
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<td>Subcostal*</td>
</tr>
<tr>
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<td>M</td>
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<td>1.60</td>
<td>70</td>
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<td>Posterior</td>
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<tr>
<td>Anterior resection</td>
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<td>71</td>
<td>1.93</td>
<td>87</td>
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<tr>
<td>Anterior resection</td>
<td>M</td>
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<td>1.65</td>
<td>78</td>
<td>28.6</td>
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<td>Right hemicolectomy</td>
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<td>1.58</td>
<td>60</td>
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<td>Right hemicolectomy</td>
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<td>1.60</td>
<td>68</td>
<td>26.6</td>
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<td>95</td>
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<td>Splenectomy</td>
<td>M</td>
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<td>25.8</td>
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<tr>
<td>Anterior resection</td>
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<td>1.78</td>
<td>70</td>
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<tr>
<td>Right hemicolectomy</td>
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<td>1.49</td>
<td>54</td>
<td>24.3</td>
<td>Subcostal</td>
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<tr>
<td>Abdominoperineal resection</td>
<td>M</td>
<td>68</td>
<td>1.79</td>
<td>114</td>
<td>35.6</td>
<td>Posterior</td>
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<tr>
<td>Reversal of Hartmann’s procedure</td>
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<td>1.68</td>
<td>85</td>
<td>30.1</td>
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<td>105</td>
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</tr>
<tr>
<td>Anterior resection</td>
<td>M</td>
<td>75</td>
<td>1.63</td>
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<td>22.2</td>
<td>Posterior</td>
</tr>
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</table>
Subcostal TAP total plasma ropivacaine concentration
Black line represents mean, error bars one standard deviation

Total plasma ropivacaine concentration (mg litre⁻¹)

Subcostal TAP infusions.

Posterior TAP total ropivacaine concentration
Bold line represents mean, error bars one standard deviation

Total plasma ropivacaine concentration (mg litre⁻¹)

Posterior TAP infusions.
phase of more gradual increase in total plasma ropivacaine concentration. This result has been observed before in other local anaesthetic pharmacokinetic trials, and is thought to result from a gradual increase in binding proteins that occurs in response to surgical stress.\textsuperscript{15–18} The mean (±SD) peak total ropivacaine for subcostal infusions was 2.64 (0.39)
mg litre\(^{-1}\), which was reached at the 48 h time point. The mean (so) peak total ropivacaine level for posterior infusions was 2.50 (0.60) mg litre\(^{-1}\), which was reached at the 72 h time point. The range of total plasma ropivacaine concentrations was 0.98–3.41 mg litre\(^{-1}\) for posterior infusions and 0.96–3.48 mg litre\(^{-1}\) for subcostal infusions. Four subjects, one in the first cohort and three in the second cohort, experienced total ropivacaine levels $>3.4$ mg litre\(^{-1}\).

Figures 3 and 4 illustrate the unbound plasma ropivacaine levels from 24 to 72 h. The plateau observed has been previously reported. As the local anaesthetic binds to increasing levels of protein, specifically \(\alpha\)-acid glycoprotein, the unbound local anaesthetic level plateaus at a level dependent on the clearance rate. The mean (so) peak plasma concentration of unbound ropivacaine for posterior infusions was 0.078 (0.039), which occurred at the 24 h time point. The mean (so) peak plasma concentration of unbound ropivacaine for subcostal infusions was 0.070 (0.025) mg litre\(^{-1}\), which occurred at the 24 h time point. The range of unbound plasma ropivacaine concentrations was 0.022–0.135 mg litre\(^{-1}\) for posterior infusions and 0.031–0.120 mg litre\(^{-1}\) for subcostal infusions.

### Analgesia

The mean (so) morphine use in the 72 h after operation was 154 mg (138). The large so illustrates the significant individual variability in morphine use, highlighting one of the difficulties in using analgesia requirements as a surrogate marker for levels of pain.

The median pain scores are listed in Table 3, and show consistently higher values on movement compared with at rest.

### Complications

The fourth subject recruited, a young 45 kg woman, reported symptoms of facial and arm numbness and tingling at 6 h, which she noticed following her return to the ward from recovery. Her infusion was stopped, and no signs of intravascular catheter placement were observed.

Following resolution of symptoms, the infusion was restarted at 4 ml h\(^{-1}\) each side. However, symptoms recurred the following day, including some muscle twitching, and the catheters were removed. Symptoms of numbness of the tip of the tongue, chin, and arms did not fully resolve until around 48 h after final cessation of the infusion.

Consequently, recruitment was suspended on December 16, 2008 and an amended protocol (incorporating a weight-based dosing regimen) was submitted for ethics committee approval. Recruitment recommenced on April 3, 2009.

### Discussion

This is the first study assessing ropivacaine plasma concentrations during a continuous infusion into the TAP. Relatively high cumulative doses of ropivacaine (up to 2216 mg $>72$ h) and marked individual variability in responses were observed.

The toxicity of local anaesthetic agents is typically determined by studying i.v. infusions in healthy volunteers. These data are extrapolated to clinical scenarios involving extravascular local anaesthetic infusions; however, because the pharmacokinetics of local anaesthetics vary depending on the site of injection, plasma concentrations causing toxicity during i.v. infusion might not be analogous to plasma levels observed during extravascular infusion.

Knudsen and colleagues evaluated toxic plasma concentrations of ropivacaine after infusions of i.v. ropivacaine in healthy volunteers. Neurological symptoms were observed at venous total ropivacaine concentrations as low as 0.5 mg litre\(^{-1}\); however differences in arterial and venous drug concentrations were observed because of a delay in establishment of a steady-state across tissue compartments. As the authors note, ‘peripheral venous blood returning from poorly perfused sampling tissues during rapid i.v. administration is not representative of the distribution to, and concentration at, the site of action for central effects of local anaesthetics’. We believe that the more clinically relevant ‘neurological toxicity range’ for ropivacaine are the arterial sampled ropivacaine levels observed in Knudsen’s study.

The arterial sampled levels during i.v. infusion better approximate venous sampled levels after slower absorption from an extravascular location such as the TAP. In Knudsen’s study, symptoms attributable to toxicity commenced in the arterial sampled range of 3.4–5.3 mg litre\(^{-1}\).

The role of protein binding is important in local anaesthetic toxicity. After surgery, levels of \(\alpha\)-acid glycoprotein increase, and consequently, there is increased protein binding capacity for local anaesthetics. This has been shown to stabilize unbound local anaesthetic concentrations in the presence of increasing total drug concentration during continuous infusion. As it is unbound local anaesthetic that determine pharmacodynamic and toxic effects, it is more useful to quote unbound plasma concentrations in discussing
‘safe’ plasma concentrations. The quoted unbound ropivacaine range causing neurological toxicity in Knudsen’s study was 0.34–0.85 mg litre\(^{-1}\) (arterial sample).

How do these ranges relate to our study? Four subjects had a total ropivacaine level between 3.4–4.0 mg litre\(^{-1}\) on at least one occasion. None of these subjects reported symptoms of neurological toxicity, despite targeted questioning at the time of venesection. For the other 136 time-points sampled, total drug concentrations remained <3.4 mg litre\(^{-1}\). In a paper examining the ropivacaine plasma concentrations after single injection TAP blocks, Griffiths and colleagues demonstrated a peak in unbound ropivacaine levels occurring 30 min after injection, with a mean peak unbound ropivacaine concentration of 0.14 mg litre\(^{-1}\) and a highest observed level of 0.25 mg litre\(^{-1}\). Although some of the reported ropivacaine levels exceed the venous toxicity level recorded in the Knudsen paper (0.15 mg litre\(^{-1}\)), the authors also acknowledge their arterial measurement: plasma concentration (0.56 mg litre\(^{-1}\)) to be a more valid threshold predictor of toxicity. In our study, all unbound ropivacaine levels were well below the Knudsen arterial sampled range for toxicity of 0.34–0.85 mg litre\(^{-1}\).

The subject who developed symptoms consistent with local anaesthetic toxicity demonstrated an interesting, and previously reported phenomenon, of symptoms despite presumably safe drug concentrations. This subject had symptoms consistent with local anaesthetic neurotoxicity, but demonstrated low plasma concentrations of both total and unbound ropivacaine levels (<1.5 and 0.08 mg litre\(^{-1}\), respectively, for the duration of the infusion). Other authors have identified that symptoms of systemic toxicity correlate poorly with plasma concentrations of local anaesthetics.

A potential explanation for this phenomenon is that patients vary in their sensitivity to local anaesthetics.

There are several limitations of this study. First, we did not objectively assess degree of nerve blockade. Therefore, there is no certainty that all the catheters remained in the TAP plane. Potentially catheters could have migrated into highly vascular muscle during the infusion period.

Secondly, we did not analyse unbound ropivacaine levels for the first 24 h of infusion. However, the study by Griffiths and colleagues complements our study in providing more detailed consideration of the first 24 h after TAP blocks.

In conclusion, given the potential for high plasma concentrations from a bilateral infusion technique, attention should be paid to individualized dosing strategies. Further studies into the safety and efficacy of this technique are justified.

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**Declaration of interest**

None declared.

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