

Pharmacokinetics of levobupivacaine with epinephrine in transversus abdominis plane block for postoperative analgesia after Caesarean section

H. J. Lacassie¹, A. Rolle¹, L. I. Cortínez^{1,*}, S. Solari², M. A. Corvetto¹ and F. R. Altermatt¹

¹División de Anestesiología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile and ²División Imágenes, Laboratorios y Patología, Escuela de Medicina, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

*Corresponding author. E-mail: licorti@med.puc.cl

Abstract

Background: Transversus abdominis plane block is increasingly used for post-Caesarean section analgesia. Cases of toxicity and the limited pharmacokinetic information during pregnancy motivated this study. The objective of the study was to characterise and compare the pharmacokinetics of levobupivacaine with epinephrine in transversus abdominis plane block, in post-Caesarean section patients and healthy volunteers.

Methods: After approval by the Ethics Committee, we collected data from 12 healthy parturients after elective Caesarean section (Study 1) and data from 11 healthy male volunteers from a previous study (Study 2). Transversus abdominis plane block was performed under ultrasound guidance. The following injectates were used: levobupivacaine 0.25%, 20 ml with epinephrine 5 $\mu\text{g ml}^{-1}$ (Study 1) per side; 20 ml of the same solution (unilateral block) (study 2). The plasma venous concentration of levobupivacaine was measured serially for 90 min. Pharmacokinetic parameters (volume of distribution, clearance, and absorption half-life) were estimated using a non-linear mixed effects model (NONMEM). Simulation in 1000 patients estimated the maximum concentration and the time to reach it after bilateral transversus abdominis plane block.

Results: Venous concentrations were below toxic levels (2.62 mg L^{-1}). Levobupivacaine volume of distribution after Caesarean section was higher than in healthy volunteers [172 L (70 kg)⁻¹ (95% confidence interval: 137–207) vs 94.3 L (70 kg)⁻¹ (95% CI: 62–128); $P < 0.01$]. Clearance and absorption half-life were similar. The simulation showed that maximum levobupivacaine concentration is lower and occurs later in postpartum patients ($P < 0.01$). Postoperative analgesia was effective.

Conclusions: Postpartum women reached relatively low plasma concentrations of levobupivacaine after transversus abdominal plane block given a volume of distribution 80% higher than volunteers, which could confer a greater margin of safety.

Clinical trial registration: NCT02852720.

Keywords: analgesia; Caesarean section; levobupivacaine; pharmacokinetics; transversus abdominis

Editor's key points

- Transversus abdominis plane (TAP) block with levobupivacaine is commonly used for analgesia after Caesarean section.
- The aim of the current study was to investigate the influence of pregnancy on levobupivacaine pharmacokinetics.
- Administration of 100 mg levobupivacaine with epinephrine for TAP block resulted in plasma concentrations well below toxic levels.
- Volume of distribution and time to maximum concentration were significantly higher in pregnant females than in healthy male volunteers.

Caesarean section is among the 10 most painful surgeries performed on a regular basis.¹ Multiple strategies have been proposed for pain control after this surgery, including neuraxial analgesia, systemic opioids, non-opioid drugs, and peripheral nerve blocks, among others. In recent years, transversus abdominis plane (TAP) block has become a popular technique to provide post-Caesarean section analgesia and a reasonable alternative for patients who are unable to receive neuraxial morphine.²

Several studies have shown that this technique is highly effective and safe when used as part of a multimodal analgesic regime after abdominal surgery.^{3,4} However, TAP block requires a relatively large volume (40 ml) of local anaesthetic solution injected in the muscular plane, between the internal oblique and transversus abdominis muscles, to optimise the spread within a fascial plane.⁵ This fact has raised concerns about the safety of this technique in the obstetric population,^{6,7} as most of local anaesthetic toxicity cases have occurred in this population.⁸

A previous study of our group in healthy volunteers showed that the addition of epinephrine in TAP block was highly effective to reduce levobupivacaine peak plasma concentrations.⁹ Currently, there is scarce information on levobupivacaine pharmacokinetics (PK) after TAP block in pregnant patients. Dose schemes routinely used for pain control after Caesarean section have been extrapolated from studies in non-obstetric patients without considering possible differences in drug disposition because of pregnancy. A formal PK analysis, including data from healthy volunteers and pregnant patients, should allow a more comprehensive approach to guide dosing schemes in this population.

We hypothesised that levobupivacaine PK after TAP block is altered in post-Caesarean section patients because of body composition and cardiovascular changes associated with late pregnancy. Our objective was to generate a PK model derived with data from pregnant patients after Caesarean section and in healthy volunteers, to characterise and compare levobupivacaine with epinephrine disposition after TAP block in both populations.

Methods

Data from two sources were used in the analysis.

Study 1

After institutional Ethics Committee approval (School of Medicine, Pontificia Universidad Católica de Chile, Santiago,

Chile) and written informed consent, 12 term non-obese pregnant patients, ASA Physical status 1 or 2, scheduled for elective Caesarean section, were recruited in this prospective, single-blind PK study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02852720) identifier: NCT02852720). Patients were excluded if they had any allergy/sensitivity to the local anaesthetic, significant renal or liver dysfunction, or a BMI greater than 35 kg m⁻².

An i.v. catheter (18-gauge) was placed under local anaesthesia for co-hydration. After the initiation of standard monitoring (continuous electrocardiogram, non-invasive arterial blood pressure, and pulse oximetry), all patients received spinal anaesthesia with a 25G Whitacre needle (B. Braun Melsungen AG, Melsungen, Germany) at L3–L4 or L4–L5 interspace with hyperbaric bupivacaine 0.75%, 1.4 ml and fentanyl 20 µg to achieve bilateral anaesthetic level of at least T6, determined by pinprick. All surgeries were performed with a Pfannenstiel incision.

After surgery, a second i.v. catheter contralateral to the i.v. infusion was inserted for venous sample extraction. An ultrasound-guided TAP block was performed with levobupivacaine 0.25%, 20 ml with epinephrine 1:200 000 (5 µg ml⁻¹) on each side. One anaesthesiologist experienced in the technique performed all TAP blocks using a SonoSite M-Turbo ultrasound machine (SonoSite, Inc., Bothell, WA, USA) with a L38 × 10⁻⁵ MHz, 38 mm broadband linear array probe. Blocks were performed with a 21G, 110 mm spinal Quincke needle (Nipro Medical Industries, Ltd., Tatebayashi, Japan) using an in-plane approach.

The extent of bilateral sensory blockade of TAP blocks to temperature, light touch, and sharp touch was determined using ice, cotton wool, and pinprick, respectively, at 1, 2, 6, and 12 h post-block, and the metameric extent of the blockade was recorded. Venous blood samples (2 ml) were obtained at 2, 5, 10, 30, 45, 60, and 90 min after TAP block. The duration of blockade expressed as first dose of rescue pain medications (i.v. morphine 3 mg) was also recorded and symptoms of local anaesthetic systemic toxicity (LAST) were assessed on every control.

Levobupivacaine assay

Levobupivacaine was extracted from plasma using liquid–liquid extraction according to the methods described by Adams and colleagues.¹⁰ The internal standard solution (mepivacaine 30 µg ml⁻¹, 10 ml) was added to 0.2 ml of plasma, sodium hydroxide 100 µl (2 M solution), and diethyl ether 0.6 ml. The mixture was stirred for 1 min and centrifuged for 5 min at 3000 revolutions min⁻¹. Subsequently, the organic phase was transferred to another tube to which 0.05 N sulphuric acid 0.25 ml was added. The mixture was stirred again for another minute and centrifuged for 5 min at 3000 revolutions min⁻¹. The aqueous phase was transferred to another tube for subsequent injection. An aliquot of 100 µl was injected into the high-performance liquid chromatography system. The linearity of the method was evaluated in the range of 0.125–10 µg ml⁻¹, and three concentrations (0.75, 3, and 7.5 µg ml⁻¹) were extracted during each protocol as controls.

Study 2

Data from 11 healthy volunteers were obtained from a study by our group.⁹ Briefly, we characterised levobupivacaine PK after TAP block (levobupivacaine 50 mg) with and without epinephrine in healthy male volunteers. Each patient

underwent a unilateral TAP block twice, in a two-period crossover study, with and without epinephrine, assessed for 90 min after the injection.

In the current modelling analysis, we used the data of the epinephrine arm (77 levobupivacaine venous samples) of Study 2, in combination with the present data of post-Caesarean section women (Study 1).

Statistical analysis

A convenience sample of 12 subjects was enrolled in the study. The sampling design (seven samples per patient) was based on our previous study,⁹ where levobupivacaine PK parameters were described with good precision in a relatively similar scenario. Normally distributed interval data are reported as mean and standard deviation (SD), and non-normally distributed data with median and inter-quartile range (IQR).

PK analysis

A one-compartmental allometric model, with first-order absorption and elimination, was used to describe the time profile of levobupivacaine serum concentrations. Population parameter estimates [volume of distribution V (L), clearance Cl (L min⁻¹), and absorption rate half-time T_{abs} (min)] were obtained using the first-order conditional estimation method in NONMEM (NONMEM 7.3, Globomax LLC, Hanover, MD, USA).

Population parameter variability was modelled using random effect variables, each one with a mean=0 and a variance ω^2 ; the variability between subjects was modelled by exponentiating the random effect variables. Covariance analysis between random effect variables was accounted with an omega block. Residual variability was characterised using a proportional and additive error model. We assumed complete absorption of levobupivacaine from the compartment between transversus abdominis and internal oblique muscles (bioavailability=100%).

Parameter values were standardised to 70 kg total body weight (TBW), as expressed in equation (1):

$$P_i = P_{TVSt} \cdot \left(\frac{W_i}{70} \right)^{PWR} \quad (1)$$

where P_i is the parameter in the i th individual, P_{TVSt} is the population parameter estimate standardised for a 70 kg person, W_i is the weight in the i th individual, and PWR is the exponent for the allometric model, accounting for a value of 1 for volume of distribution, 0.25 for T_{abs} , and 0.75 for clearance.

The effects of age and pregnancy, as potential covariates of levobupivacaine PK parameters, were explored. Covariate testing of age was performed by an exponential model.

Quality of fit

Quality of fit was evaluated mainly by the objective function value (OFV), goodness-of-fit plots, and visual-predictive-check plots. An improvement in model fit was considered if the addition of a new parameter (nested models) produced a decrease in the OFV in at least 3.84 points, corresponding to $P=0.05$ (χ^2 distribution).

Simulation analysis

We performed a simulation analysis to investigate the distribution of maximum levobupivacaine serum concentrations

(C_{max}) and the time to maximal concentration (T_{max}), after a standard unique dose of levobupivacaine 100 mg with epinephrine 5 μ g ml⁻¹. For this, 1000 C_{max} [equation (2)] and T_{max} [equation (3)] values were simulated based on the final population PK parameter estimates and their estimated variability.

$$C_{max} = F \cdot \frac{\text{dose}}{V} \cdot e^{\left(-\frac{Cl}{V} \cdot T_{max}\right)} \quad (2)$$

$$T_{max} = \frac{\ln(K_a) - \ln\left(\frac{Cl}{V}\right)}{K_a - \left(\frac{Cl}{V}\right)} \quad (3)$$

where K_a is absorption rate constant.

Results

Twelve enrolled subjects completed the study. The general and demographic data of subjects and data from the 11 volunteers of Corvetto and colleagues,⁹ are shown in Table 1.

The time from the spinal block until the TAP block was considered the surgical time (Table 1). The highest level reached by the spinal blockade was T4 (IQR: T3–T4) bilaterally. Twelve healthy babies were born, eight males and four females, with a birth weight of 3276 g (SD 381.16) and height of 48.4 cm (SD 4.27). No patient required additional analgesics during surgery or complained of pain throughout the procedure. The anaesthetic level just before the TAP block was T8 (IQR: T7–T9).

All TAP blocks were uneventfully performed. The spinal anaesthesia blockade receded to T8 (IQR: T7–T9) and to T11 (IQR: T10–12) 1 and 2 h after the TAP block, respectively. After the spinal anaesthesia descended to the surgical incision level, the sensory blockade did not follow a consistent metameric pattern; therefore, it was not possible to map it throughout the study period. The TAP block duration determined by the first analgesic request followed a distribution depicted in Figure 1. Five patients from the cohort did not request supplemental analgesia. The maximum morphine use was 6 mg (median: 3 mg; IQR: 0–3.75 mg). The static and dynamic pain scores remained under 4 throughout the study.

Pharmacokinetic analysis

Seven blood samples were obtained from each patient, accounting for a total of 84 blood samples. The time profile of the measured levobupivacaine serum concentrations of the combined data set is shown in Figure 2. The mean measured

Table 1 Subject characteristics and general study data. Data expressed as mean (standard deviation).

	Post-Caesarean section (n=12)	Healthy volunteers ⁹ (n=11)
Age (yr)	34.1 (6.40)	34.8 (6.49)
Weight (kg)	74.9 (9.55)	77.2 (10.1)
BMI (kg m ⁻²)	28.4 (3.24)	24.1 (2.75)
Gestational age (days)	268.8 (5.69)	
Surgery duration (h)	1.06 (0.07)	
Phenylephrine dose (μ g)	1475 (504.83)	

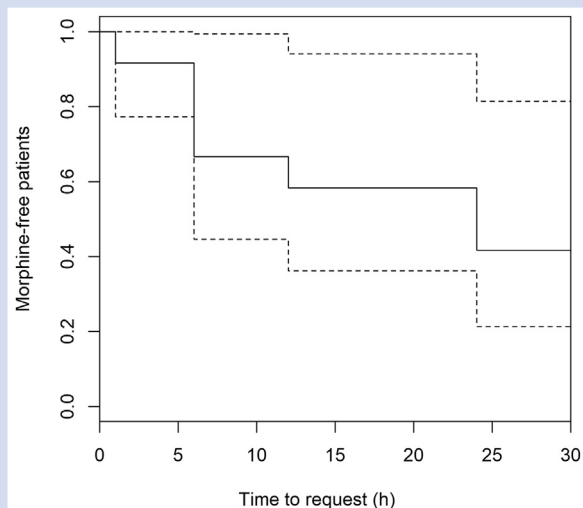


Fig 1. Survival curve for first morphine consumption. Follow-up was up to 24 h. The solid line is the absolute number of patients and the dashed lines are 95% confidence interval.

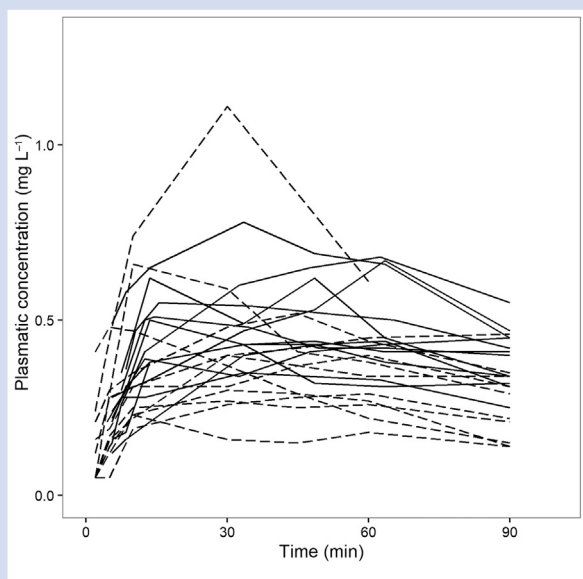


Fig 2. Levobupivacaine concentration profile (raw data). Solid lines, post-Caesarean section women (dose: 100 mg); dashed lines, healthy volunteers from Corvetto and colleagues⁹ (dose 50 mg).

venous C_{\max} of levobupivacaine for post-Caesarean section patients was 0.534 mg L^{-1} [95% confidence interval (CI) $0.4526\text{--}0.6157$], with a T_{\max} of 30 min (IQR: 25–60 min). The maximum peak levobupivacaine concentration measured in a patient was 0.78 mg L^{-1} .

A one-compartment model with first-order absorption and elimination adequately fits the levobupivacaine PK data and was selected as our base structural model. Parameters were scaled to TBW assuming allometric relationships. The

inclusion of pregnancy as a dichotomous covariate of the volume of distribution produced a significant improvement in model fit (OFV=−10.382). This covariate did not show a significant effect in clearance Cl (OFV=−1.26) nor in the absorption rate half-time T_{abs} (OFV=−2.65). The inclusion of age did not improve the model fit. No other covariates were tested. The final population parameter estimates, with their 95% CIs and coefficients of variation, are shown in Table 2. The diagnostic and visual-predictive-check plots can be seen in the Supplementary material (Supplementary Figures S1 and S2). The correlation of between-subject variability for the estimated parameters is presented in Supplementary Table S1.

Simulation analysis

We assessed the levobupivacaine C_{\max} and T_{\max} distribution in a simulated population of 1000 patients, after a unique dose of levobupivacaine 100 mg with epinephrine $5 \mu\text{g ml}^{-1}$. The mean C_{\max} was smaller and occurred later (T_{\max}) in post-Caesarean section women than in healthy volunteers: (0.493 mg L^{-1} (SD 0.13) vs 0.84 mg L^{-1} (SD 0.38); $P<0.01$) and (29.5 min (SD 14.7) vs 25.1 min (SD 11.8); $P<0.01$); respectively. A simulation of a typical post-Caesarean woman and a healthy volunteer patient (TBW=70 kg), receiving a bilateral TAP block (two i.m. doses of levobupivacaine 50 mg separated by 3.5 min), is presented in Figure 3.

Discussion

The main finding of the current study was the relatively low levobupivacaine plasma concentrations reached in post-Caesarean section patients after a bilateral TAP block with levobupivacaine 100 mg with epinephrine ($5 \mu\text{g ml}^{-1}$). The current modelling analysis found that post-Caesarean section patients have a mean volume of distribution 81% higher than that of healthy volunteers. Metabolic clearance and the rate of absorption from the muscular compartment were similar between pregnant patients and healthy volunteers.

Drug distribution is influenced by various factors, including tissue perfusion, tissue binding, lipid solubility, and plasma protein binding.¹¹ The higher volume of distribution of levobupivacaine observed in pregnant patients can be physiologically correlated with changes in body composition observed in late pregnancy, including an increase in plasma volume and total body water of around 40%, and an increase of approximately 4 kg in body fat.¹¹ The expansion of fluid compartments and fat mass will increase the volume of distribution of both hydrophilic and lipophilic drugs, leading to a decrease in their plasma concentrations.^{11,12} Levobupivacaine is a lipophilic drug, which is extensively bound to alpha-1 lipoproteins and albumin.¹³ The higher volume of distribution observed in late pregnancy can also be explained by a reduction in plasma protein concentration and protein binding observed in this period.^{14,15}

There is scarce information on levobupivacaine PK after a TAP block in pregnant patients to compare our results. A recent study by Trabelsi and colleagues¹⁶ reported mean bupivacaine C_{\max} values of 0.802 mg L^{-1} (95% CI: $0.232\text{--}3.505 \text{ mg L}^{-1}$) after bilateral TAP blocks (bupivacaine 50 mg each side) in post-Caesarean section patients. The mean value is very close to our mean levobupivacaine predicted concentration in male volunteers receiving a similar dose ($0.84\pm0.38 \text{ mg L}^{-1}$), and significantly higher than that predicted in pregnant patients ($0.493\pm0.13 \text{ mg L}^{-1}$). Considering that the

Table 2 Levobupivacaine pharmacokinetic parameter estimates. Bootstrap estimate is the median of 1000 bootstrap replications; 95% CI is the 95% confidence interval, obtained by bootstrap; CV (%) is between-subject variability, expressed as an apparent coefficient of variation; and T_{abs} is the absorption rate half-time. Pharmacokinetic parameters are standardised for a 70 kg typical patient.

	Estimate of structural parameter	Bootstrap estimate	95% CI	CV (%)
Clearance [L min^{-1} (70 kg) $^{-1}$]	0.674	0.665	0.36–0.96	40.4
Volume [pregnant, L (70 kg) $^{-1}$]	172	171	137–207	46.5
Volume [volunteers, L (70 kg) $^{-1}$]	94.3	95.4	62.8–128	55
T_{abs} [min (70 kg) $^{-1}$]	5.77	5.89	4.33–8.12	29.6
Additive residual error (mg L^{-1})	0.02	0.031	0.017–0.046	—
Proportional residual error (%)	10	9.5	3.89–12	—

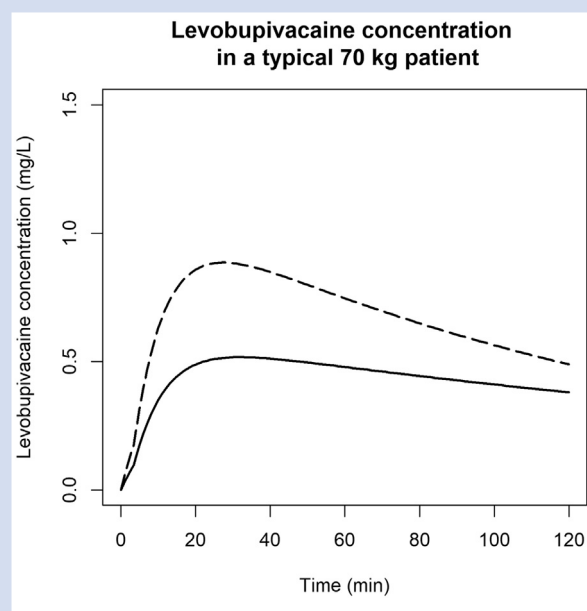


Fig 3. Simulation of a typical patient (TBW=70 kg) receiving bilateral TAP block (50 mg each dose, with time interval between procedures: 3.5 min). Solid line, post-Caesarean section women; dashed line, healthy male volunteers.

aforementioned study described parameters for the racemic mixture, instead of the levo-isomer, the most probable explanation for the lower concentrations found in our patients is the use of epinephrine in the local anaesthetic solution. In a previous study of our group,¹⁷ when performing unilateral TAP blocks in healthy volunteers, epinephrine prolonged the levobupivacaine mean absorption half-life by 65% and reduced its relative bioavailability to 0.84 (C_{max} local anaesthetic with epinephrine: 2.5 mg L^{-1} ; C_{max} local anaesthetic without epinephrine: 3 mg L^{-1}). These changes were associated with approximately 35% lower venous levobupivacaine concentrations in patients receiving epinephrine.

Our results support the safety profile of this analgesic block for post-Caesarean section patients, as the concentrations reached were approximately 60% lower than those predicted in healthy male volunteers receiving a similar dose scheme. In addition, in all patients, the observed maximum concentrations were below the previously reported threshold associated

to mild central nervous system symptoms of LAST.¹⁸ Lastly, none of our patients presented any symptoms suggesting toxicity. Recently, two cases of LAST in post-Caesarean section patients have been reported after bilateral TAP blocks.⁶ In these cases, the total mass of plain bupivacaine administered was 1.5 and 3 times higher than that used in our study. These considerations emphasise at least three aspects related to the safety for this procedure. First, dose adjustments should be taken in consideration when bilateral blocks are performed.¹⁷ Second, the relevance of adding epinephrine to the local anaesthetic solution is an efficient way to decrease potentially toxic levels.^{9,17,19} Third, the selection of local anaesthetics with relatively lower risk of cardiovascular and central nervous system toxicity, such as levobupivacaine or ropivacaine, instead of racemic bupivacaine, is highly desirable for bilateral blocks.²⁰

It should be noted that we have assessed levobupivacaine PK after TAP blocks after Caesarean delivery under spinal anaesthesia. The possible residual effects of spinal anaesthesia in levobupivacaine disposition should therefore be considered in the current results. The sympathetic blockade attributable to spinal anaesthesia might have contributed to the observed increase in volume of distribution caused by vasodilation and redistribution of regional flows. A potential decrease in cardiac output and liver blood flow caused by spinal anaesthesia might have a minor effect in levobupivacaine clearance. Although levobupivacaine is cleared from plasma by hepatic metabolism, primarily via oxidative dealkylation,²¹ as the levobupivacaine hepatic extraction ratio is relatively low (0.17), the clearance of unbound drug will depend more from the intrinsic activity of the liver enzymes than liver blood flow.²¹

Our study has several limitations. First, the levobupivacaine plasma concentrations were obtained from venous samples. We previously demonstrated a good correlation between venous and arterial plasma concentrations on this type of assays⁹; therefore, we opted for the simplest and less invasive approach of venous sampling. Likewise, although plasma concentrations from cases of LAST are not available, the only study reporting plasma thresholds associated with mild symptoms of central nervous system local anaesthetic toxicity contains venous samples.¹⁸ Second, the measured serum concentrations were from total levobupivacaine instead of the free moiety. During pregnancy, low plasma proteins increase the unbound fraction of local anaesthetics, potentially increasing the risk of LAST. It is difficult to address this specific concern because of the lack of information available regarding possible threshold values of the unbound

fraction in this population.^{6,16,22} Considering the relatively low C_{max} obtained, the absence of cases with LAST symptoms, and the good analgesic effect observed, in our opinion these results add new information to support the safety profile of this dose scheme and discourage the use of higher doses. Finally, to obtain a more comprehensive modelling analysis, we have pooled the data from two studies. It should be considered that healthy volunteers were only male subjects. There are numerous gender-related factors that can potentially affect drug disposition. Among others, women have a lower TBW, a higher proportion of body fat (25% vs 16% in men), lower muscle mass, smaller organ size, lower plasma volume, organ blood-flow rate, and alpha-1 glycoprotein concentration.²³ In addition, differences in transporters and drug-metabolising enzymes have also been reported, and women have up to 40% more in vivo CYP3A4 activity than men.²⁴ The net effect of these factors in levobupivacaine PK is uncertain, and it is possible that some of the differences observed between pregnant patients and healthy volunteers may be caused by gender differences.

In summary, our results suggest that pregnancy confers a further safety margin for local anaesthetic toxicity after a TAP block with levobupivacaine and epinephrine. The protective mechanism involves keeping plasma local anaesthetic concentrations well below toxic levels, mainly caused by the increase in central volume of distribution.

Authors' contributions

Study concept and design: H.J.L., L.I.C.

Study supervision: H.J.L., A.R., M.A.C.

Acquisition, analysis, and interpretation of data: all authors.

Full data access, responsibility for data integrity and data analysis accuracy: H.J.L., L.I.C.

Statistical analysis: H.J.L., A.R., L.I.C.

Drafting of the manuscript: H.J.L., L.I.C., A.R., M.A.C., F.R.A.

Critical revision of the manuscript: H.J.L., L.I.C., A.R., F.R.A.

Final approval of the manuscript: all authors.

Administrative, technical, and material support: H.J.L., A.R.

Agreement to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.bja.2018.02.070>.

Declaration of interest

The authors declare no conflict of interest related to the manuscript.

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