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PHARMACOKINETICS AND DISPOSITION

Levobupivacaine absorption pharmacokinetics with and without epinephrine during TAP block: analysis of doses based on the associated risk of local anaesthetic toxicity

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Abstract
Purpose Cases of local anaesthetic systemic toxicity (LAST) periodically occur following transversus abdominal plane (TAP) blocks. The aim of this study was to characterize levobupivacaine absorption pharmacokinetics, with and without epinephrine, and estimate the risk of LAST, based on a previously reported toxic threshold.
Methods Previously reported data from 11 volunteers receiving ultrasound-guided TAP blocks with and without epinephrine on two independent occasions were analysed. Serial venous concentrations were measured for 90 min. A pharmacokinetic analysis was performed using the NONMEM statistical programme. The use of epinephrine in the solution was included in the analysis of covariates. The associated risk of LAST symptoms associated with different levobupivacaine dose schemes with and without epinephrine was estimated in 1000 simulated subjects.
Results A one-compartment first-order input and elimination model adequately fit the levobupivacaine data. Epinephrine prolonged the levobupivacaine absorption half-life {4.22 [95 % confidence interval (CI) 2.53–6.50] vs. 7.02 [95 % CI 3.74–14.1]; $p < 0.05$} and reduced its relative bioavailability (0.84; 95 % CI 0.72–0.97; $p < 0.05$) The derived model predicts that levobupivacaine dose schemes should be halved from 3 mg kg^{-1} body weight with epinephrine to 1.5 mg kg^{-1} without epinephrine to obtain a comparable risk of anaesthetic toxicity symptoms of approximately 0.1 %.
Conclusions Our results strongly support the addition of epinephrine to the local anaesthetic solution, especially when doses of levobupivacaine of >1.5 mg kg^{-1} are required. Recommendations regarding the maximum allowable doses of local anaesthetics should consider population analysis to determine safer dosage ranges.

Keywords Levobupivacaine · Transversus abdominis plane block · Systemic toxicity · Pharmacokinetics

Introduction

Tranversus abdominal plane (TAP) blocks are widely used for postoperative analgesia following abdominal surgery [1]. During a TAP block, a local anaesthetic solution is injected between the internal oblique and transverse abdominis muscles. The addition of ultrasound guidance has facilitated anatomical plane identification, which has increased the popularity of TAP blocks. Despite the increased precision with ultrasound guidance, cases of high plasma levels of local anaesthetic and systemic toxicity have been reported with standard doses of ropivacaine and levobupivacaine [2–6].

To date, the levobupivacaine dose required for an effective TAP block has not been determined, and a wide range of doses have been reported in the literature [1]. In a study involving healthy male volunteers who received unilateral TAP blocks, Corvetto et al. demonstrated that the addition of epinephrine (5 μg ml^{-1}) to the local anaesthetic solution (20 ml 0.25 % levobupivacaine) reduced the peak venous levobupivacaine concentration from 0.49 μg ml^{-1} [95 % confidence interval

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(CI) 0.37–0.68] to 0.32 μg ml^{-1} (95 % CI 0.28–0.39) [7]. While these results strongly support the addition of epinephrine to prevent local anaesthetic toxicity at higher levobupivacaine doses, the analysis performed did not enable the formulation of dose recommendations based on formal pharmacokinetic (PK) model predictions.

Currently, there are no population PK models describing the absorption characteristics of levobupivacaine during TAP blocks. Such models can be used to investigate different levobupivacaine dose schemes with and without the addition of epinephrine to the local anaesthetic solution because they provide a better description of data variability and covariate effects [8]. The aim of this study was to characterize levobupivacaine absorption pharmacokinetics, with and without epinephrine, using a population modelling approach and estimate the risk of local anaesthetic systemic toxicity (LAST) using different dose schemes based on previously described toxicity thresholds [9].

Methods

We performed a secondary analysis of levobupivacaine PK data collected during a previous study by our group (ClinicalTrials.gov identifier: NCT01596998) [7]. Briefly, 11 healthy male volunteers underwent ultrasound-guided TAP blocks on two independent, randomly assigned occasions: at the first visit, subjects were administered 20 ml of 0.25 % levobupivacaine and at the second visit, subjects were administered levobupivacaine with epinephrine (5 μg ml^{-1}) added to the local anaesthetic solution. Serial venous blood samples were collected at 2, 5, 10, 30, 45, 60, and 90 min after completing the blockades. Plasma levobupivacaine concentrations at each time point were measured using high-performance liquid chromatography.

PK analysis

Population parameter estimations

A one-compartment model with first-order input and elimination was used to describe the time profile of serum levobupivacaine concentrations. Population parameter estimates were calculated using nonlinear mixed effects modelling implemented in the NONMEM statistical program (NONMEM 7.3; ICON Development Solutions, San Antonio, TX). The population parameter variability (F) was modelled in terms of random effect (η) variables. Each variable was assumed to have a mean = 0, and a variance, denoted by ω^2, was estimated. The between-subject variability for each model parameter was modelled using exponentiating random effects (Eq. 1) with the exception of levobupivacaine bioavailability. The variability of levobupivacaine bioavailability was calculated using a logistic transformation of the random effect to prevent generating individual values greater than 1 for the compound (i.e. >100 % compound bioavailability).

$$Pi = P_{TV}.e^{ni} \tag{1}$$

where P*i* is the value of the parameter (e.g., T_{abs}, CL, V) in the *i*th patient, P_{TV} is the value of the parameter after accounting for any predictable between-subject differences and η is the random variable. Random changes in model parameters between both study periods were explored using inter-occasion variability as described by Karlsson and Sheiner [10]. We described residual unidentified variability using a combined proportional and additive residual error model.

Size scaling of PK parameters

The parameter values were standardized for a 70-kg body weight using a theory-based allometric model with total body weight as the size scalar (Eq. 2). No other size metrics were used. The Power exponent (PWR) was 3/4 for CL, 1 for V, and 1/4 for T_{abs} [11, 12].

$$Pi = P_{TVSt} \cdot \left(\frac{W_i}{70}\right)^{PWR} \tag{2}$$

where P*i* is the parameter in the *i*th individual, W_i is the weight in the *i*th individual and P_{TVSt} is the population parameter estimate standardized for a 70-kg person.

Epinephrine effect

The effect of epinephrine on levobupivacaine absorption was explored for T_{abs} and levobupivacaine bioavailability parameters during the covariate analysis step. The bioavailability was assumed to be equal to 1 when epinephrine was not administered and estimated as a model parameter when epinephrine was administered.

Quality of fit

The quality of fit between the PK model and data was assessed using NONMEM's objective function value (OFV), parameter plausibility and visual predictive checks (VPC) functions. Nested and non-nested models were selected based on the decrease in OFV. An objective function change (ΔOBJ) of 3.84 was considered to be significant ($p < 0.05$). Parameter uncertainty was evaluated using bootstrap methods [13]. Parameter means and confidence intervals were estimated using a total of 1000 bootstrap replications.

Simulation analysis

Estimated PK parameters of levobupivacaine, both with and without epinephrine, and their estimated variability were used to investigate different dose schemes in a simulated population of 1000 patients. Levobupivacaine dose schemes and the associated risk of producing LAST symptoms were reported. If the maximum levobupivacaine concentration (C_{max}) reached a value >2.62 μg/ml, the simulated patient was assumed to experience toxicity symptoms. This threshold value was determined based on data reported in an earlier study [9]. For each dose tested, C_{max} values were calculated using the individual parameter estimates (V, Cl) of the 1000 simulated subjects (Eq. 3).

$$Cmax = \frac{F \cdot \frac{Dose}{V} \cdot e^{\left(-\frac{CL}{V} Tmax\right)}}{V} \quad (3)$$

where T_{max} corresponds to the time at the maximum levobupivacaine concentration, which was calculated using Eq. 4.

$$Tmax = \frac{\ln(Ka) - \ln\left(\frac{CL}{V}\right)}{Ka - \left(\frac{CL}{V}\right)} \quad (4)$$

Results

Data from 11 healthy male subjects were analysed. The mean age, weight and height of these 11 volunteers were 35 years (95 % CI 31–39 years), 76 kg (95 % CI 69–81 kg) and 179 cm (95 % CI 174–183 cm), respectively.

PK model

The one-compartment first-order input and elimination model adequately fit the levobupivacaine data and was selected to be our basic structural model. Biphasic absorption patterns were not observed during the relatively short observation period (90 min); consequently, no biphasic absorption models were tested. Incorporating inter-occasion variability (IOV) as a random effect in the T_{abs} variable improved model fit (ΔOFV = -26.026); no IOV effect was observed for any other model parameter. In the covariate analysis, including the effect of epinephrine administration on T_{abs} significantly decreased OFV by 20.659 points. We also tested the effect of epinephrine administration on levobupivacaine bioavailability and found this inclusion of this variable in the model further improved model fit to a ΔOFV of −62.834. Inclusion of age in the model did not affect model fit. The final model parameters are shown in Table 1. VPC diagnostic plots are shown in Figs. 1 and 2.

Simulation analysis results

The distributions of levobupivacaine C_{max} values obtained from simulations of two commonly recommended dose schemes, 3 mg kg^{-1} levobupivacaine with epinephrine and 2.5 mg kg^{-1} levobupivacaine alone, are shown in Fig. 3. The associated risks of LAST symptoms for the different dose schemes is shown in Table 2.

Discussion

The aim of this study was to determine the risk of LAST for levobupivacaine, administered either with or without epinephrine, for ultrasound-guided TAP blocks based on formal pharmacokinetic model predictions and previously reported toxic thresholds. These results provide relevant information to guide levobupivacaine dose schemes for TAP blocks.

At the present time there is no clear consensus on the appropriate drug mass or volume for the safe administration of TAP blocks. Several published studies use an arbitrary injection volume ("one size fits all" approach). In contrast, we used a weight-scaled model to describe levobupivacaine pharmacokinetics based on the assumption that the volumes and clearance of levobupivacaine change with body weight [11]. Our PK model assumed theoretical allometric relationships between estimated PK parameters and patient weight [14, 15]. Dose recommendations based on the present model will have the advantage of accounting for the nonlinear effect of weight on levobupivacaine pharmacokinetics in patients of varying weights. Allometric models have strong empirical support [16] and have been successfully used to adjust doses between different body sizes within species or between different species [16–18].

As a compartmental field block [19], the extension of the dermatomal area covered by TAP blocks depends on the volume of local anaesthetic injected. However, the maximum dose amenable to be safely administered may not be high enough to obtain effective analgesia due to the absorption profile of the specific local anaesthetic used, especially when bilateral injections are required. Too much local anaesthetic increases the risk of LAST, and too little will lead to inadequate analgesia. There is currently no data available on the minimum effective levobupivacaine dose needed to obtain analgesia in TAP blocks. Lahlou-Casulli et al. [20] determined the dose required to obtain adequate analgesia in 50 % of cases, i.e. the effective dose 50 (ED_{50}), of ropivacaine in TAP blocks for patients undergoing an ileostomy reversal. These authors reported that the ED_{50} is close to the toxic threshold described specifically for ropivacaine. Although

Table 1 Levobupivacaine population pharmacokinetic parameter estimates

Pharmacokinetic parameters	Estimate of structural parameter	Bootstrap estimate	95 % confidence interval	Population parameter variability (%)
V (L/70 kg)	109.4	110.0	76.6–133	40.0
CL (L/min/70 kg)	0.424	0.408	0.10–0.76	62.8
Tabs (min/70 kg)				
Without epinephrine	4.22	4.34	2.53–6.50	54.3
With epinephrine	7.02	7.47	3.74–14.1	54.3
F				
Without epinephrine	1 FIX	–	–	–
With epinephrine	0.842	0.90	0.72–0.97	26.1
Additive residual error (mcg/mL)	0.031		0.02–0.24	–
Proportional residual error (%)	12.2		0.1–14.5	–

V, volume; CL, clearance; Tabs, absorption rate half-time; F, bioavailablilty

Parameters are standardized for a 70-kg patient

Data are presented as mean estimates, and confidence intervals were estimated using the bootstrap approach

the ED_{50} is not as clinically relevant as the effective dose 95 (ED_{95}), i.e. the dose required to obtain adequate analgesia in 95 % of the cases, the authors still raised concerns about using TAP blocks because adherence to well-tolerated local anaesthetic limits could lead to insufficient dosing and block failure. One potential strategy to address this problem is to add epinephrine to the anaesthetic solution. In a previous study we showed that the addition of epinephrine to the levobupivacaine mixture administered during a unilateral TAP block resulted in lower arterial and venous plasma levels of levobupivacaine compared with the administration of levobupivacaine alone [7]. According to the PK model reported here, adding 5 μg ml^{-1} of epinephrine modifies the absorption kinetics of levobupivacaine following a unilateral TAP block, decreasing the absorption rate and relative bioavailability of levobupivacaine during the initial absorption period. Similarly, Chalkiadis et al. showed that the addition of epinephrine to the anaesthetic solution slowed systemic levobupivacaine absorption in the caudal epidural space in children [21]. In that study, levobupivacaine concentrations were halved when epinephrine was added as an adjuvant. Similar results have been described for paravertebral blocks using ropivacaine with and without epinephrine [22].

Based on our model, we propose the first formal recommended dose of levobupivacaine in TAP blockades administered to healthy adult patients. This recommendation accounts for the PK characteristics of the abdominal wall and the effect

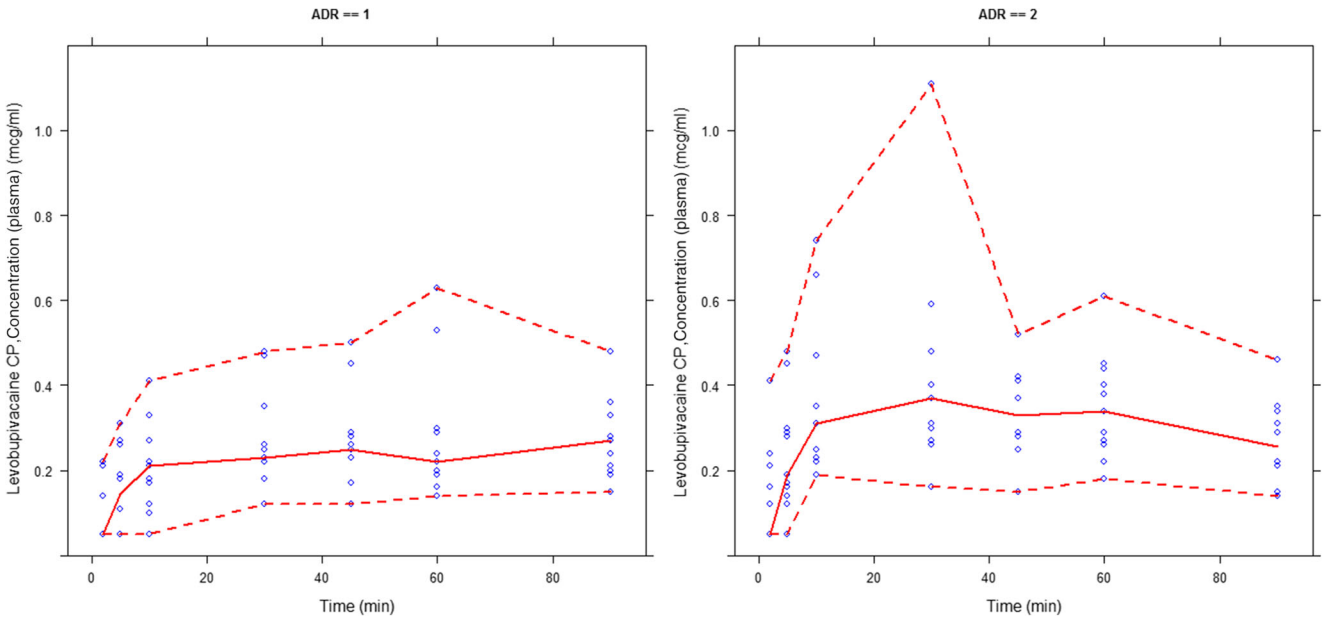

Fig. 1 Visual predictive check (VPC) plot of the pharmacokinetic (PK) data. *Blue circles* Observed plasma concentrations, *solid lines* median, *dashed red lines* 5th and 95th percentiles of the observed data

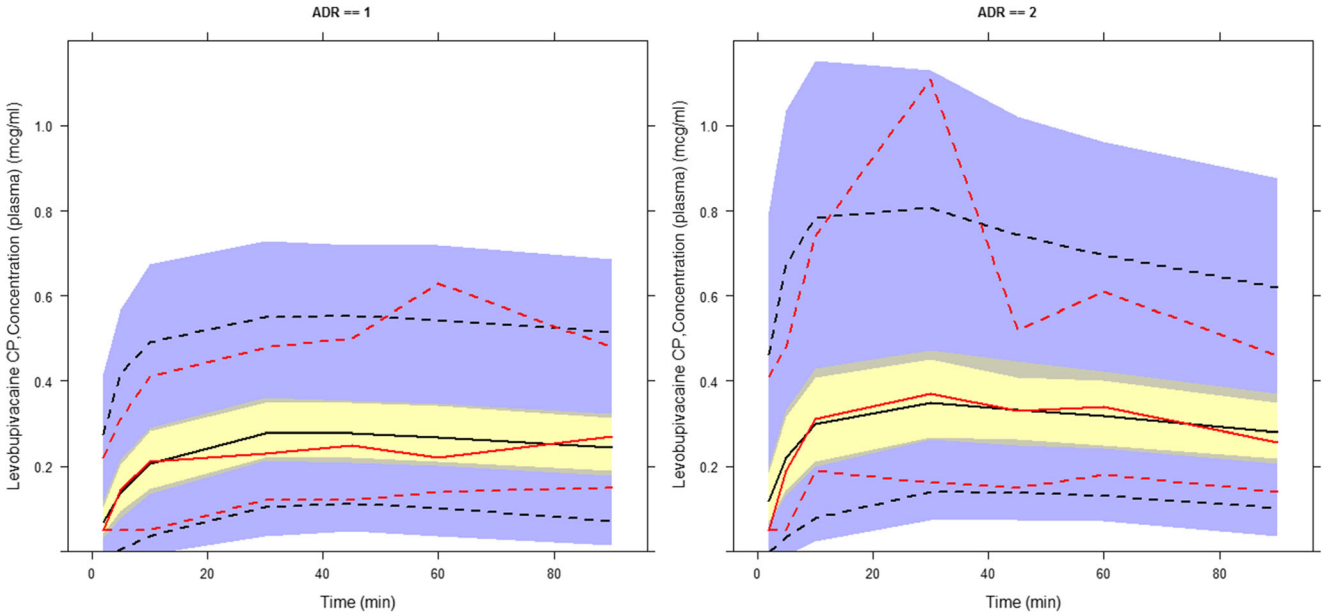

Fig. 2 VPC plot of the PK data. *Solid lines* Model's predicted median, *dashed black lines* predicted 5th and 95th percentiles. *Semi-transparent yellow field* Simulation-based 95 % confidence interval for the median, which reflects the uncertainty range in the median of the observations. *Dashed red lines* 5th and 95th percentiles of the observed data. *Semi-transparent blue fields* 95 % Confidence intervals for the corresponding model-predicted percentiles

of epinephrine when added to the local anaesthetic solution. Based on published safety thresholds for plasma levobupivacaine levels, the derived model predicts that levobupivacaine dose schemes should be halved from 3 mg kg^{-1} with epinephrine to 1.5 mg kg^{-1} without epinephrine to obtain a comparable risk of anaesthetic toxicity symptoms of approximately 0.1 %. Our results confirm the adequacy of the previously recommended dose scheme of 3.0 mg kg^{-1} of levobupivacaine with epinephrine for TAP blocks.[1] However, a further reduction from 2.5 to 1.5 mg kg^{-1} is suggested if levobupivacaine is used alone in order to reduce the risk of toxicity from 5.5 to 0.1 %. Further clinical studies evaluating plasma levels of levobupivacaine after different doses are warranted in order to test these proposed doses and test the degree of prediction of the proposed model. Due to safety

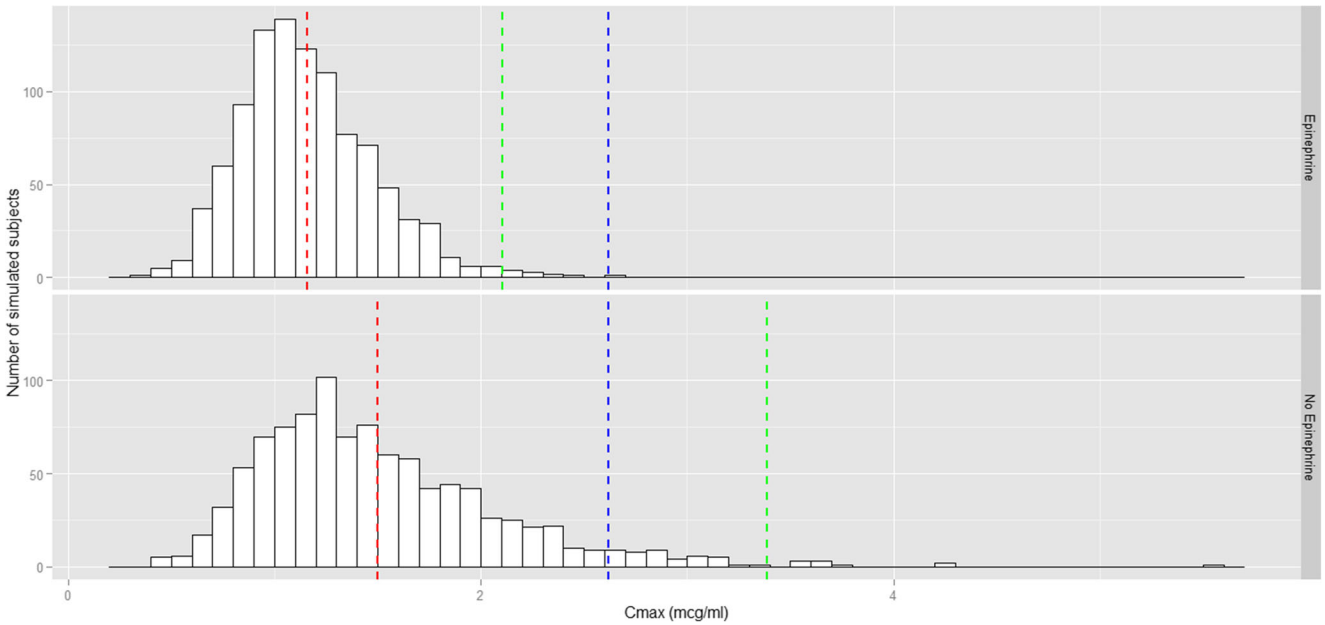

Fig. 3 Histogram showing the distribution of levobupivacaine peak plasma concentration (C_{max}) values obtained from the simulation of 1000 healthy subjects. *Upper graph* The 3 mg kg^{-1} levobupivacaine with epinephrine (5 μg ml^{-1}) dose scheme, *bottom graph* the 2.5 mg kg^{-1} dose scheme without epinephrine. *Red dashed line* Mean C_{max}, *green dashed line* 99th percentile of the C_{max} distribution, *dashed blue line* levobupivacaine toxic threshold (2.62 μg ml^{-1})

Table 2 Risk of local anaesthetic toxicity symptoms according to the simulation analysis in 1000 healthy subjects

Dose (mg kg^{-1})	Risk of LAST	
	With epinephrine	Without epinephrine
1.5	0 (0–3) %	0.1 (0–40) %
2.0	0 (0–23) %	1.1 (0.1–70) %
2.5	0 (0–53) %	5.5 (1–87) %
3.0	0.1 (0–78) %	13.3 (2.5–95 %)
3.5	0.5 (0–90) %	27.2 (5.7–98) %

Risk estimation (%) considered the mean estimated levobupivacaine concentration (2.62 mg ml^{-1}) at which local anaesthetic systemic toxicity (LAST) symptoms occurred and the inter-individual variability in the reported peak plasma levobupivacaine concentration (C_{max}) values (range 0.91–3.54 mg ml^{-1}) [9]

and ethical reasons, study protocols evaluating the effect of potentially toxic doses are technically impossible to implement.

One potential limitation of the model is the selection of a C_{max} of >2.62 μg/ml. To date, no studies have reported plasma levobupivacaine levels during episodes of LAST; therefore, we selected the most appropriate threshold based on the information available, namely the mean C_{max} reported in a study that administered intravenous infusions of levobupivacaine to 14 individuals until toxicity was reached. Toxicity in that study was defined as the "appearance of any subjective central nervous system symptoms", meaning that the toxic effects were mild manifestations. Notably, one of the subjects in that study received a 150 mg dose without exhibiting toxicity symptoms. Similarly, Bardsley et al. [9] reported substantial variability with respect to the dose administered (tenfold variation) and plasma concentrations at T_{max} (fourfold variation); thus, C_{max} is likely to have pronounced inter-patient variability. The effect of this variability is reflected in the values presented in Table 2, where the probabilities of occurrence of symptoms of LAST based upon individual C_{max} thresholds can range from 0 to 78 % when doses of levobupivacaine 3.0 mg kg^{-1} with epinephrine are administered and plasma levels of 3.54 or 0.91 mg ml^{-1} were used, respectively.

Another limitation to our study is that the data used to derive our model were collected from healthy male volunteers. Additionally, these data included total serum concentrations rather than unbound levobupivacaine. It is unbound (free) local anaesthetic in plasma that causes LAST; thus, the safe dose of local anaesthetic cannot be based exclusively on the total plasma concentrations. However, studies investigating plasma levobupivacaine levels only report total plasma concentrations. Given the lack of information, we assumed that the percentage of free levobupivacaine in our data set was not higher than 3 % in normal subjects and relatively constant [23]. Due to these limitations, extrapolation of the recommended dose schemes to other populations may be limited. Specifically, these schemes should likely not be extrapolated to elderly patients, who may require further dose reduction [24], or patients with medical conditions that could increase the unbound fraction of the drug or increase the rate of absorption [25, 26]. Ideally, future studies will investigate these populations; however, there are justifiable ethical considerations and restrictions to testing LAST symptoms in these patient groups. Despite these limitations, the results of this study represent the best evidence available for determining the levobupivacaine dose to administer for TAP blocks in a clinical setting.

In conclusion, our results strongly support the addition of epinephrine to levobupivacaine solution when the latter is used as a local anaesthetic, especially when doses of >1.5 mg kg^{-1} levobupivacaine are required. In the future, recommendations for the maximum allowable doses of local anaesthetics should consider formal population analysis methods to determine safer dosage ranges.

Author contributions PM wrote and planned the study, analysed the data and wrote the paper; AA wrote and planned the study and analysed the data; MAC wrote and planned the study and performed the research; GCE wrote and planned the study and performed the statistical analyses; LIC: wrote and planned the study, analysed the data and wrote the paper; FRA conceived the study, wrote and planned the study, analysed the data, and wrote the paper. All authors drafted and approved the final manuscript. The content is solely the responsibility of the authors.

Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to declare.

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