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Plasma mepivacaine concentrations in patients undergoing third molar surgery

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ABSTRACT

Background: Local anaesthetic-related systemic toxicity mainly results from elevated plasma concentrations of these drugs. We hypothesized that intraoral injection of submaximal doses of mepivacaine does not lead to toxic levels of this drug in blood. This study evaluated the plasma levels of mepivacaine in third molars surgeries.
Methods: Twenty-one patients were randomly assigned into two groups: group I (two unilateral third molars; submaximal dose of mepivacaine 108 mg with epinephrine 54 μg) and group II (four third molars; submaximal dose of mepivacaine 216 mg with epinephrine 108 μg). Blood samples were collected before anaesthesia, and 5, 10, 15, 20, 30, 40, 60, 90 and 120 min after anaesthesia.
Results: Individual peak plasma concentrations ranged 0.77–8.31 μg/mL (group I) and from 2.36–7.72 μg/mL (group II). An increase in the average dose of mepivacaine from 1.88 ± 0.12 mg/kg (group I) to 3.35 ± 0.17 mg/kg (group II) increased the mean mepivacaine peak plasma levels from 2.33 ± 0.58 to 4.01 ± 0.69 μg/mL, respectively. Four patients obtained plasma levels of mepivacaine above the threshold for toxicity (5 μg/mL).
Conclusions: Toxic levels of mepivacaine are possible, even when a submaximal dose is used. A twofold increase in the dose of mepivacaine caused the mean peak plasma concentration to increase proportionally, indicating that they may be predicted based on the relation of dose per bodyweight.

Keywords: local anaesthetics, mepivacaine, oral surgery, plasma levels, third molars.

Abbreviations and acronyms: CI = confidence interval; HPLC = high-performance liquid chromatography; LA = local anaesthetic.

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INTRODUCTION

Local anaesthetic (LA)-related systemic toxicity mainly results from elevated plasma concentrations of these drugs. It is noted that in adult patients mepivacaine induces toxicity when blood concentrations are above 5.0 μg/mL.[1] However, routine dental injection is not expected to reach blood concentrations of this magnitude.

In order to prevent systemic toxicity, a maximum adult dose of 6.6 mg of mepivacaine per kg of bodyweight has been recommended by manufacturers for a healthy individual.[2] In addition, when using anaesthetic solutions containing epinephrine, 400 mg is the maximum recommended dose of mepivacaine for adults.[1] In Australia, a maximum mg/kg dose of 2% mepivacaine with adrenaline 1:100 000 is not currently available; therefore, a maximum total of three dental cartridges containing 3% mepivacaine hydrochloride is safely recommended for adults (www.tg.org.au). These recommendations reinforce the importance of bodyweight, and its association

with LA dose in the prevention of systemic toxicity. However, factors such as biological variations, presence/absence of vasoconstrictor, injection speed, location of the injection site and intravascular injection of these drugs may also influence peak plasma concentrations, increasing the risk of LA toxicity.[3–9]

The wide variation of clinically administrated doses of LAs coupled with the scarce number of studies reporting on plasma concentrations of mepivacaine during third molar surgeries have raised our interest in this field. Hence, the present study aimed to evaluate the plasma levels of mepivacaine during impacted third molar surgery. We hypothesized that intraoral injection of submaximal doses of mepivacaine does not lead to toxic levels of this LA in blood.

METHODS

Study design

The present prospective, single-centre, randomized study was conducted as a collaboration between the School of Pharmacy, Dentistry and Nursing at the Federal University of Ceará and the Dr José Frota Institute Hospital (Fortaleza, Brazil). The approval for conducting this study was granted by the Ethics Committee on Human Research of the Dr José Frota Institute Hospital (protocol #02499/97). All patients freely consented to participate in this study, and Declaration of Helsinki guidelines were followed.

Participants and eligibility criteria

This study included 21 healthy individuals (American Society of Anesthesiologists classification I), both genders, aged 18–35 years, with an indication for removal of two or four third molars (Fig. 1). The subjects were able and willing to cooperate with the protocol and to sign an appropriate written informed consent form. Smokers, pregnant and/or lactating patients were excluded from the study. The withdrawal criterion adopted in the present study was a surgery exceeding 2 h. Patient data were recorded preoperatively and according to a standardized clinical examination. Panoramic radiographs were used to establish the need for surgery.

Surgical overview

Following recruitment, patients were randomly assigned into either one of two groups by using Microsoft Excel® software (Microsoft, Redmond, WA, USA): group I (N = 12, three men and nine women; aged 18–32 years [mean, 24]) received 108 mg of mepivacaine with 54 μg of epinephrine, and group II (N = 9, three men and six women; aged

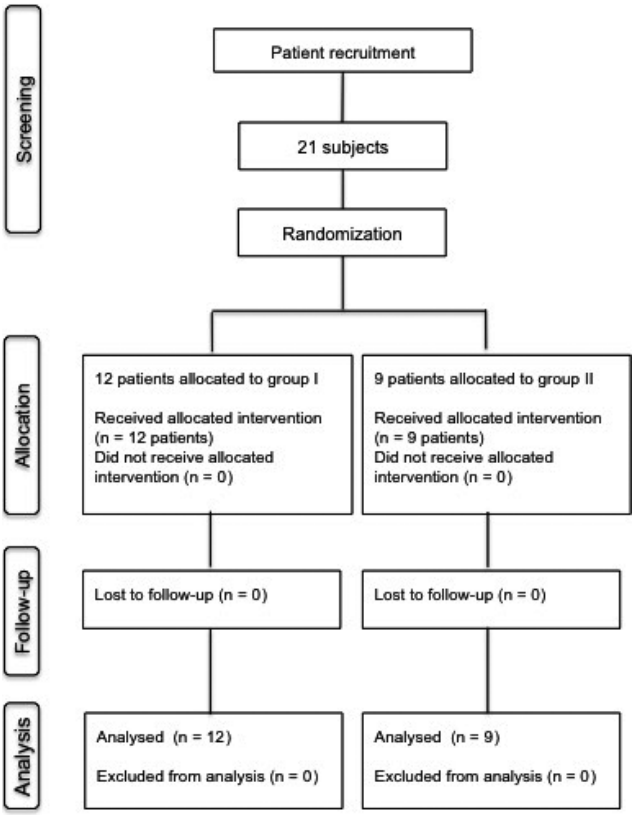

Fig. 1 Flow chart of patient recruitment into the study groups, according to the Consolidated Standards of Reporting Trials (CONSORT) statement.

20–35 years [mean, 25]) received 216 mg of mepivacaine with 108 μg of epinephrine. The established dose was below the recommended maximum limit of 400 mg of mepivacaine with epinephrine.[1] The required preoperative laboratory evaluation consisted of complete blood count, blood clotting tests, serum alanine aminotransferase test, serum aspartate aminotransferase, blood urea nitrogen, creatinine blood test and blood glucose test were performed at the Clinical Laboratory Analysis of the Dr Jose Frota Institute Hospital.

The same team performed all surgeries, and a standardized technique was used. The same surgical technique was used on the right and left sides of the mouth. Prior to local anaesthesia injection, vital signs were measured. Subsequently, LA was injected after careful aspiration for blood. A total amount of 5.4 mL (three dental cartridges) and 10.8 mL (six dental cartridges) of 2% mepivacaine solution with epinephrine 1:100 000 (DFL, Rio de Janeiro, Brazil) were respectively injected in a single session for the extraction of two unilateral or four third molars. All injections were sequentially performed in bilateral third molar surgeries. For the extraction of each maxillary third molar, a total quantity of 1.8 mL of anaesthetic solution were used as follows: 1.6 mL

were administrated over 60 s into the vestibular area, whereas 0.2 mL were administrated over 30 s into the greater palatine nerve region. The extraction of each mandibular third molar required a total amount of 3.6 mL of the anaesthetic solution, out of which 3.1 mL were administrated into the inferior alveolar and lingual nerve regions over 120 s, and 0.5 mL were infiltrated over 60 s to anaesthetize the long buccal nerve. After surgery, all patients were medicated with analgesic, anti-inflammatory and antibacterial agents.

Primary outcome measure

The peak plasma concentration of mepivacaine was established as the primary outcome measure for the present study, and was measured by obtaining 10 samples containing 4 mL of venous blood at times 0 (before anaesthesia), 5, 10, 15, 20, 30, 40, 60, 90 and 120 min following LA administration. These samples were placed into test tubes containing ethylenediaminetetraacetic acid (Dinâmica Química Contemporânea Ltda, São Paulo, Brazil), manually stirred and centrifuged at 590 *g* for 10 min to extract the plasma fraction, and kept at –70°C until processing and future analysis of mepivacaine concentrations by high-performance liquid chromatography (HPLC).[10]

In order to calibrate the HPLC system and validate the present method, calibrating solutions were prepared from a standard stock solution of mepivacaine at a concentration of 1.0 mg/mL (Sigma-Aldrich, St Louis, MO, USA), dissolved in MILLI-Q® water (Millipore, Bedford, MA, USA), diluted in white plasma (Hemocentro, Fortaleza, Brazil) to the final mepivacaine concentrations of 1, 5, 10, 20, 30, 40 and 50 μg/mL. These solutions were kept at –20°C and protected from direct light. Subsequently, 1 mL of acetonitrile was added to 1 mL of each of the diluted solutions to deproteinize the plasma, stirred on a vortex for 1 min, centrifuged at 1920 *g* for 10 min, and 1.5 mL aliquots of the supernatant were evaporated to dryness in a 40°C water bath under a flow of compressed air. The dry solid was reconstituted in 200 μL of Milli-Q water, stirred on a vortex for 30 s and then injected into the HPLC. Similarly, three isolated samples containing 1 mL of mepivacaine-free white plasma mixed with 1 mL of acetonitrile were processed, reconstituted and injected into the HPLC to investigate the presence of endogenous interferences in the plasma and reagents. This method was validated by the HPLC system calibration, assessing the precision, accuracies and linearity in the recovery of mepivacaine, demonstrating efficiency in the detection of small fluctuations in the mepivacaine plasma concentrations, as recommended by the Resolution 899/2003 of the Brazilian Sanitary Vigilance Agency based on the Food and Drug Administration regulation.[11–13]

Sample size

Sample size was calculated based on the study by Goebel *et al.*[9] When considering an increase in plasma mepivacaine concentration of 0.30 ± 0.35 mg after injection of 54 mg of mepivacaine, at least 12 patients would be needed per group in order to attain a statistical power of at least 80% within a 95% confidence interval (95% CI), and a type I error of 0.05 (χ^2-test without any correction). In addition, considering an increase of 0.80 ± 0.43 mg in the concentration of plasma mepivacaine following injection of 108 mg of mepivacaine, at least nine patients would be needed per group in order to attain a statistical power of at least 80% within a confidence interval of 95%, and a type I error of 0.05 (χ^2-test without any correction).

Randomization

The method to generate the random allocation sequence used the Microsoft Excel software RANDBETWEEN function. The type of randomization was simple without any restriction. In order to implement the random allocation sequence, a sealed envelope containing random numbers was used. An external collaborator (who was unaware of the study protocol and had no further participation in this study) implemented random allocation sequence generation and participant enrolment/assignment.

Blinding

In order to guarantee the blinding, the statistical analysis was initially carried out with coded groups. The information was only accessed once both the statistical analysis had been concluded. At this time, each experimental group was identified.

Statistical analysis

Data were initially submitted to the Kolmogorov–Smirnov normality test. Parametric data were analyzed by one-way repeated-measures ANOVA/Bonferroni test. All analyses were performed with GraphPad Prism 5.0 software (GraphPad Software, San Diego, CA, USA). The level of significance was set as $P < 0.05$ for all of the evaluations.

RESULTS

Table 1 shows the weights, doses, ages, genders, individual and mean plasma values observed after injecting a total of 108 mg of mepivacaine with 54 μg of

Table 1. Individual mepivacaine mean (μg/mL ± standard error of the mean) and peak plasma concentrations after injection of mepivacaine (108 mg) with epinephrine (1 μg/mL) in surgeries to remove two third molars (n = 12)

Time (min)	Patients												Averages (μg/mL ± SEM)	95% CI		*P*
	1	2	3	4	5	6	7	8	9*	10*	11	12		Min	Max	
Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0.00	0.00	
5	1.03	1.11	1.00	0.79	0.95	0.74	0.24	1.64	1.55	0.38	1.15	2.42	1.08 ± 0.17	0.71	1.46	
10	1.81	1.73	1.40	1.46	2.22	0.92	0.28	2.46	2.14	0.51	2.84	3.42	1.77 ± 0.27*	1.18	2.36	
15	1.99	1.88	1.24	**1.54**	2.70	1.16	0.33	**2.49**	**2.25**	0.59	3.15	4.84	2.01 ± 0.35*	1.24	2.79	
20	2.34	**2.04**	1.14	1.47	2.52	1.25	0.62	2.30	1.85	0.94	**3.21**	**8.31**	**2.33** ± 0.58*	1.05	3.62	< .001
30	**2.47**	1.77	**1.71**	1.29	2.59	**1.31**	0.74	2.19	1.74	0.79	3.16	4.04	1.98 ± 0.28*	1.37	2.60	
40	2.00	1.51	1.44	1.24	**2.72**	1.06	**0.77**	2.05	1.54	0.72	2.79	2.11	1.66 ± 0.20*	1.23	2.10	
60	1.46	1.37	1.32	1.17	2.14	0.77	0.73	1.94	1.43	0.67	2.81	1.34	1.43 ± 0.18*	1.03	1.83	
90	–	–	0.77	1.14	2.01	0.56	0.57	1.72	0.90	0.99	2.08	1.12	1.19 ± 0.18	0.78	1.59	
120	0.62	–	0.62	0.98	1.52	–	0.56	1.47	–	**1.03**	2.06	0.58	1.05 ± 0.18	0.64	1.46	
Weight (kg)	79	72	78	66	59	45	57	63	71	53	59	48	62.5	55.46	69.54	
Dose (mg/kg)	1.37	1.50	1.38	1.64	1.83	2.40	1.89	1.71	2.03	2.72	1.83	2.25	1.88 ± 0.12	1.616	2.142	
Age (years)	28	21	20	26	32	25	21	25	18	24	23	26	24.08	21.65	26.51	
Sex	M	F	M	F	F	F	F	F	M	F	F	F				

Numbers represents patients, and asterisk (*) represents individuals that received an additional dose of mepivacaine (36 mg). Underlined and bold typed values represent individual mepivacaine peak plasma concentrations and mean values of mepivacaine.
*$P < 0.05$ versus control (repeated-measures ANOVA/Bonferroni).
CI, confidence interval; F, female; M, male; Max, maximum; Min, minimum; SEM, standard error of the mean.

Table 2. Individual mepivacaine mean (μg/mL ± standard error of the mean) and peak plasma concentrations after injection of mepivacaine (216 mg) with epinephrine (1 μg/mL) in surgeries to remove four third molars (n = 9)

Time (min)	Patients									Averages (μg/mL ± SEM)	95% CI		*P*
	1	2	3	4	5	6	7*	8*	9		Min	Max	
Control	0	0	0	0	0	0	0	0	0	0	0.00	0.00	
5	2.85	1.35	1.09	1.26	2.00	3.26	3.62	0.87	5.63	2.44 ± 0.52*	1.25	3.92	
10	3.20	1.91	1.44	1.96	2.98	3.70	5.15	1.40	6.19	3.10 ± 0.56*	1.80	4.70	
15	**3.56**	2.20	1.75	2.70	5.10	**3.96**	**5.54**	**3.58**	6.46	3.87 ± 0.53*	2.67	5.37	
20	3.26	2.52	1.97	2.75	**7.72**	3.28	4.70	2.81	**7.04**	**4.01 ± 0.69***	2.37	5.95	<0.001
30	2.70	**2.72**	**2.36**	**2.76**	5.37	3.19	4.53	3.48	6.09	3.69 ± 0.44*	2.66	4.95	
40	2.57	2.30	2.03	2.32	4.68	2.91	4.44	2.98	6.29	3.39 ± 0.48*	2.30	4.75	
60	2.51	2.13	1.98	2.11	3.70	2.28	4.23	2.74	5.32	3.00 ± 0.39*	2.12	4.11	
90	2.45	2.05	1.85	1.40	3.06	2.00	3.98	2.11	5.28	2.69 ± 0.41*	1.83	3.86	
120	2.15	1.71	1.48	–	2.66	1.56	3.33	1.36	4.12	2.30 ± 0.35*	1.46	3.13	
Weight (kg)	65	65	64	75	59	94	64	71	57	68.22	57.72	77.03	
Dose (mg/kg)	3.32	3.32	3.38	2.88	3.66	2.30	3.94	3.55	3.79	3.35 ± 0.17	2.99	3.83	
Age (years)	23	20	24	21	35	27	21	23	31	25	21.17	29.83	
Sex	F	F	F	F	F	M	M	F	M				

Numbers represents patients, and asterisk (*) represents individuals that received an additional dose of mepivacaine (36 mg). Underlined and bold typed values represent individual mepivacaine peak plasma concentrations and mean values of mepivacaine.
*$P < 0.05$ versus control (repeated-measures ANOVA/Bonferroni).
CI, confidence interval; F, female; M, male; Max, maximum; Min, minimum; SEM, standard error of the mean.

epinephrine and monitoring patients over a 2-h period. The mean plasma concentration reached a maximum value of 2.33 ± 0.58 μg/mL (95% CI, 1.05–3.62) at 20 min in comparison with the levels of LA obtained before anaesthesia (control), subsequently decreasing to a residual level of 1.05 ± 0.18 μg/mL (95% CI, 0.64–1.46) at the end of the second hour. Similarly, Table 2 shows that following injections of 216 mg of mepivacaine with 108 μg of epinephrine, the mean serum level of LA increases to a peak plasma concentration of 4.01 ± 0.69 μg/mL (95% CI, 2.37–5.95) at 20 min and then decreases to a residual level of 2.30 ± 0.35 μg/mL (95% CI, 1.46–3.13). Hence, administration of 216 mg of mepivacaine renders peak plasma concentrations of approximately twice the amounts achieved after injecting 108 mg of mepivacaine. Both tables show that not all patients reached peak plasma levels 20 min after LA injection, as described in Tables 1 and 2 in bold underlined values.

Figure 2 shows the mean mepivacaine plasma values observed in different evaluation intervals. The mean peaks of 2.33 ± 0.58 and 4.01 ± 0.67 μg/mL occurred at 20 min, and this finding can be interpreted as a result of the injected mepivacaine doses of 1.88 and 3.35 mg/kg with epinephrine during extraction of two unilateral or four third molars, respectively. Despite the observed intrinsic variability in individual biological response, statistically, the mean values show the same pattern on the observed increase (due to higher peak plasma levels) and decrease (due to lower peak plasma levels) of the bars on Fig. 2 when doubling the dose of mepivacaine. This pattern was also noted when different patients received 108 or 216 mg of mepivacaine, demonstrating a certain proportionality between the mean values obtained in their respective evaluation intervals, which persisted throughout the 2 h of evaluation.

Figure 3 shows the peak plasma concentration for each study participant as it associates with bodyweight and dose (mg/kg). Patients identified with an asterisk (*) in Tables 1 and 2 received additional doses of 1.8 mL of LA (Table 1, patient #9 received a supplemental dose after 15 min and patient #10 after 11 min; Table 2, patient #7 received an additional dose after 20 min and patient #8 after 23 min). These individuals were maintained in the present study because they did not influence negatively the interpretation of the results, or the main study goal. Of the 12 patients who received 108 mg of mepivacaine, five individuals showed peak plasma values greater than the lowest peak plasma concentrations presented by those who received 216 mg of mepivacaine. Out of the nine patients receiving 216 mg of mepivacaine, three subjects reached peak plasma concentrations greater than 5.0 μg/mL, above the previously established levels of toxicity. Twenty-one patients showed peak plasma concentrations of 8.31 μg/mL after injection of 108 mg of mepivacaine. Patients did not show signs of toxicity throughout the 2-h follow-up period of this study, including those with peak plasma levels above 5 μg/mL.

Table 3 compares the differences in mean mepivacaine plasma levels (%) at different evaluation intervals. Throughout the various times of evaluation, the differences were statistically significant at $P < 0.05$ as

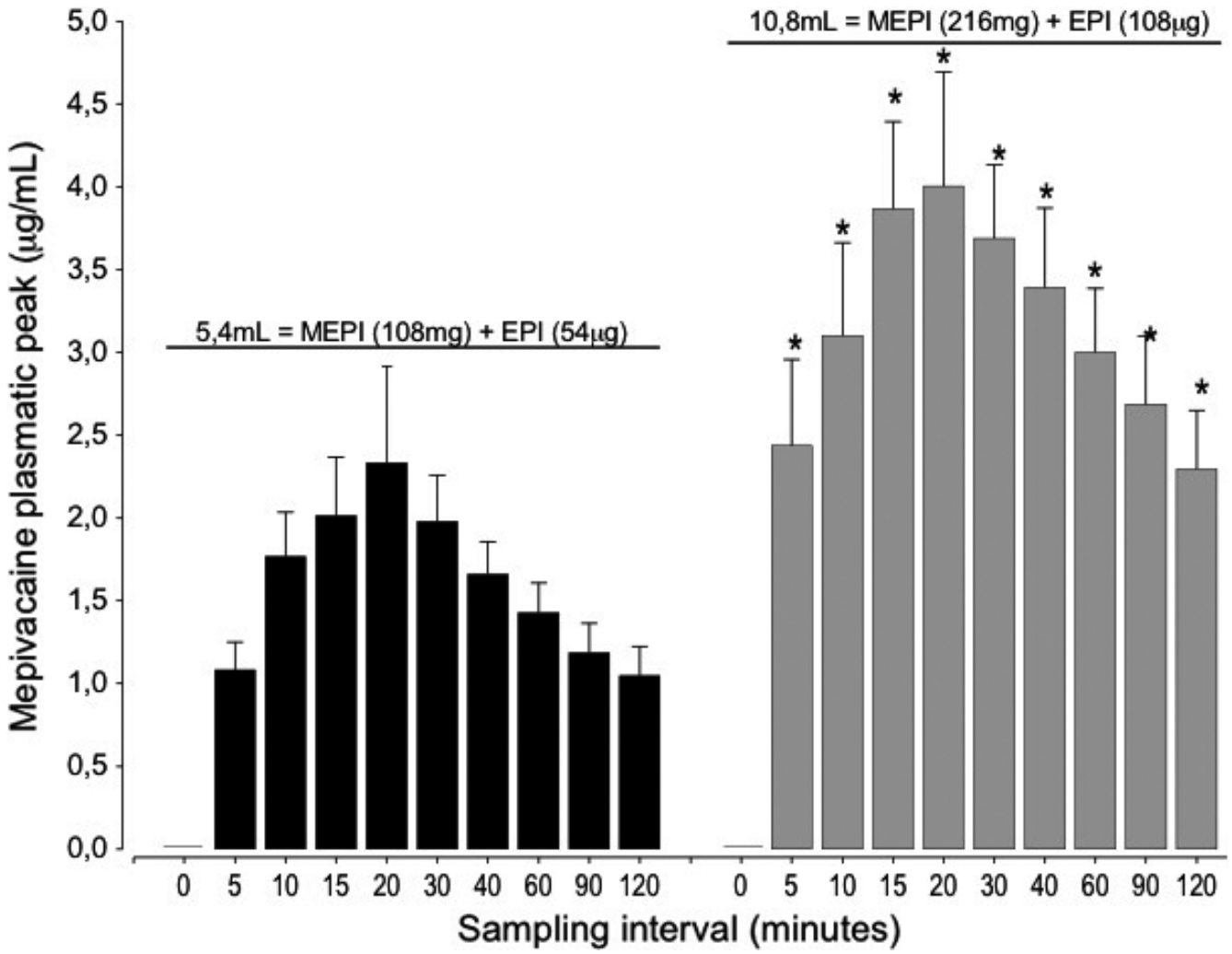

Fig. 2 Plasma mepivacaine (MEPI) concentrations after injection of 5.4 and 10.8 mL of mepivacaine at 2% with epinephrine (EPI) diluted to 1:100 000 in surgeries to extract two (black, n = 12) and four (grey, n = 9) third molars, respectively. Peak plasma values of mepivacaine are expressed in mean ± standard error of the mean (vertical bars), number of surgeries per patients is indicated by "n". Results are statistically significant at $*P < 0.05$, when compared with their respective intervals.

indicated with an asterisk (*) on the vertical bars seen in Fig. 2. A 44% increase in the mean dose generated a 43% rise in the mean peak plasma concentration, showing an increase of similar magnitude when doubling the amount of mepivacaine. In addition, this difference in percentage values is observed between the maximum peak concentration (42%) and the mean value of all individual plasma peaks (43%). This 1% difference can be neglected, because if the same patients had been exposed to these two different doses of mepivacaine (108 and 216 mg), the results would hardly differ. However, unlike the statistical analysis that shows mean doses of 1.88 ± 0.12 mg/kg (95% CI, 1.61–2.14) and 3.35 ± 0.17 mg/kg (95% CI, 2.99–3.83) leading to proportionally relative mepivacaine mean peak plasma concentrations of 2.49 and 4.36 μg/mL, individual results show that plasma peaks were not dose dependent. Thus, there was no direct relation between the attained plasma concentrations and bodyweight (Tables 1,2).

DISCUSSION

Local anaesthetics are the most widely used drugs in dentistry,[1,2,14–17] with an estimated number of 11 million dental cartridges containing LA solutions administrated per year in Australia.[14] A previous study that investigated dental LA adverse reactions from the Australian Office of Product Review of the Therapeutics Goods Administration showed that severe adverse reactions are rare and multifactorial in origin.[14] In this context, the present study evaluated the plasma levels of mepivacaine after injections of 108 and 216 mg of mepivacaine with epinephrine (1 μg/mL) for the respective extraction of two or four third molars. Four out of the 21 patients (group I,

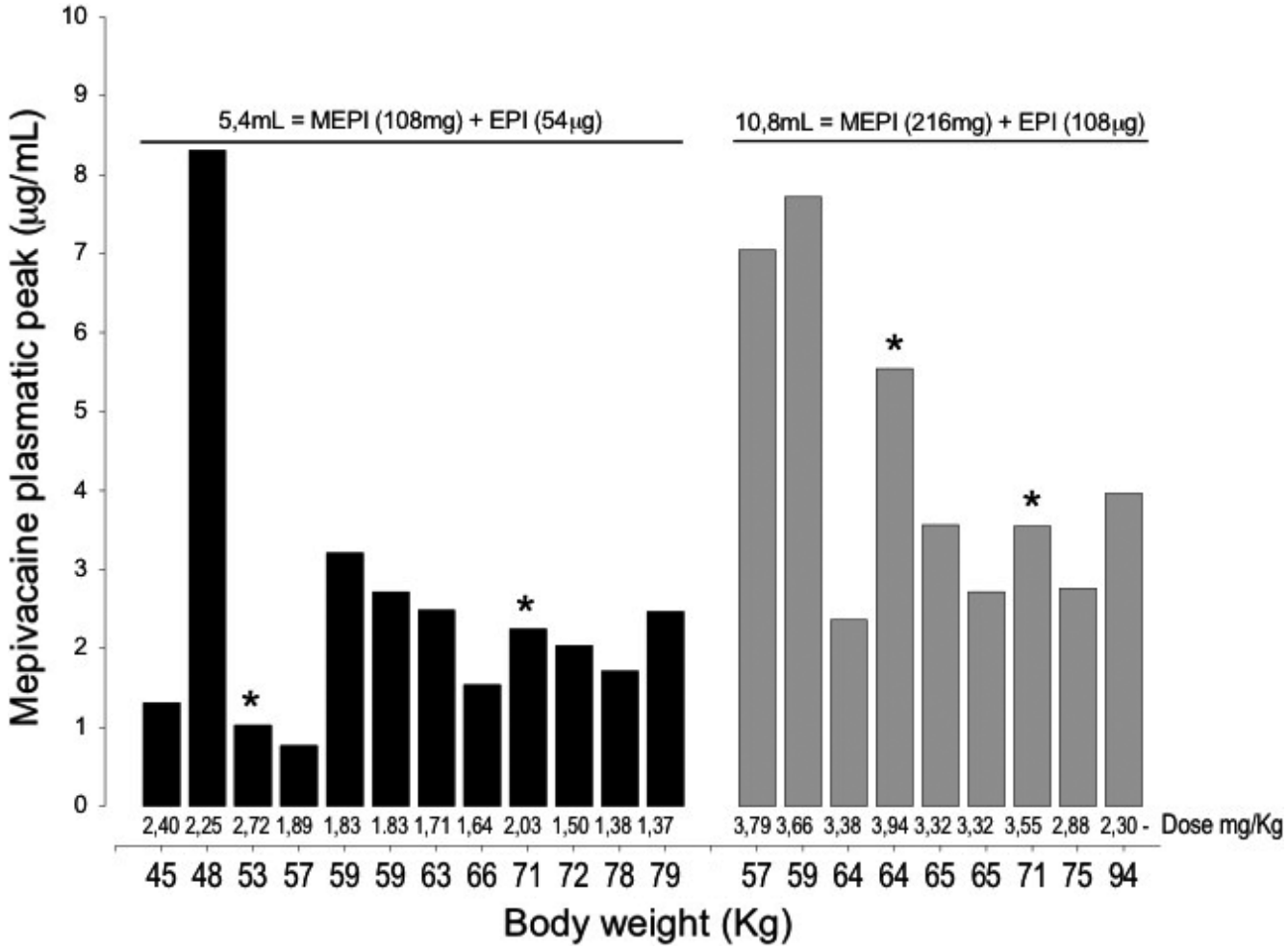

Fig. 3 Individual peak plasma concentrations of mepivacaine (MEPI) after injection of 5.4 and 10.8 mL of mepivacaine at 2% with epinephrine (EPI) diluted to 1:100 000 in surgeries to extract two (black, n = 12) and four (grey, n = 9) third molars, respectively. The number of procedures is indicated by "n" and the asterisk (*) identifies patients that received an additional dose of 36 mg of mepivacaine and 18 µg of epinephrine (1.8 mL). The values under the bars show the doses of mepivacaine in mg/kg of bodyweight.

N = 2; group 2, N = 2) received an additional dose of 1.8 mL of anaesthetic solution containing 36 mg of mepivacaine and 18 µg of epinephrine. Because the additional dose did not influence the analysis of the results, these subjects were not removed from the study sample.

The mepivacaine mean plasma values produced a graphic pattern that showed certain proportionality between the groups when compared with their respective experimental times. The same pattern of proportionality was obtained after the injection of 54 and 108 mg of 3% mepivacaine plain in the upper premolar region.[9] Similar curves have been previously obtained by gas chromatography[18] and in mepivacaine pharmacokinetic studies following epidural injection.[19] Similar plasma concentrations were observed after p.o. injection of mepivacaine following extraoral, epidural, intercostal, brachial plexus and sciatic femoral nerve blocks[3] in adults[20] and children.[8] These results were also reported in studies evaluating the plasma levels of lidocaine after p.o. injections.[6,21] In spite of the observed similarity between previous plasma concentration curves and our data, previous studies show discrepant peak plasma concentrations and demonstrate that many factors may influence LA absorption.

Previous studies investigated the circulating serum levels of lidocaine following dental infiltration injections.[6,7,20–23] In these studies, administration of lidocaine doses varying 20–160 mg rendered plasma concentrations ranging 0.22–2.00 µg/mL. These results differed from the present mepivacaine groups (group I, 0.77–8.31 µg/mL; group II, 2.36–7.72 µg/mL). Cannell and Beckett[5] showed that the application of a second dose of 2% lidocaine with epinephrine 60 min after the first dose induced an additional plasma peak when injected into the buccal region adjacent to the upper second molar; however, this finding was not observed after inferior alveolar nerve blocks. Interestingly, when the anaesthetic dose

increases twofold, but the injection site remains unchanged, plasma levels tend to increase at a similar rate. A study with five adult volunteers who received 54 and 108 mg of 3% mepivacaine plain injected into the buccal mucosa region of the upper premolars, respectively, reported 30 min after injection mean peak plasma concentrations of 0.59 and 1.11 μg/mL.[9] Wood *et al.*[23] evaluated intraosseous and infiltration injections for venous lidocaine and observed an approximate mean peak plasma level of 0.44 μg/mL. These results are in agreement with the present study, which demonstrated that a twofold increase in the dose of mepivacaine from 108 to 216 mg elevated the mean peak plasma concentrations from 2.33 to 4.01 μg/mL, 20 min after injection, respectively. However, to our knowledge no previous studies have shown the mean plasma levels of mepivacaine during third molar extractions, which did not allow a direct confrontation with our results.

There is strong evidence suggesting that the degree of vascularization in the injection site influences plasma levels of LAs.[3,5] Vasoconstrictors were added into anaesthetic solutions to compensate local vascularization and LA vasodilator effects by reducing the speed of absorption and plasma levels of these drugs. Epidural injection of mepivacaine with or without epinephrine showed that the presence of a vasoconstrictor did not reduce the plasma levels of mepivacaine.[24] Interestingly, in the present group I, mepivacaine injection resulted in a mean peak plasma concentration above 1.11 μg/mL. This concentration was obtained after injecting the same amount of mepivacaine without vasoconstrictor in the upper premolar region,[9] conflicting with the idea that the presence of a vasoconstrictor would reduce plasma levels of mepivacaine.

Individual biological variability is a remarkable feature among patients when considering time and peak plasma values. The present data showed that out of the 12 patients who received 108 mg of mepivacaine, three patients reached peak plasma levels 15 min after LA injection, three at 20 min, three at 30 min, two at 40 min and one individual achieved maximum plasma concentrations at 120 min after LA administration. These peak concentrations fluctuated from 0.77 to 8.31 μg/mL. Nine patients received 216 mg of mepivacaine, four of these patients achieved peak plasma levels of LA at 15 min, two at 20 min and three at 30 min after injection, with peak serum levels ranging 2.36–7.71 μg/mL. Statistically, patients who received 216 mg of mepivacaine expressed mean peak plasma levels higher than those who received 108 mg, both at 20 min. Unexpectedly, the individual data showed a lack of consistency between plasma levels of mepivacaine and the applied doses. Five of the patients who received 108 mg of mepivacaine reached higher peak plasma concentrations than the lowest peak serum levels observed after the injection of mepivacaine 216 mg. Extreme biological variability was also previously observed when one patient who received mepivacaine at 54 and 108 mg at different occasions, expressed the same peak serum concentration of 1.27 μg/mL, respectively, at 30 and 90 min after injection, showing that the dose does not influence the plasma peak.[9] These results emphasize that the dose can be standardized, but not the biological response. Thus, an imminent and unpredictable risk of systemic toxicity must always be considered, and no precautions can be previously suggested in these situations, while rigorously respecting the manufacturers' recommendations. The magnitude of risk is difficult to be safely quantified and caution should be exercised even with submaximal doses of LAs.

CONCLUSIONS

In summary, toxic levels of mepivacaine are possible, even when a submaximal dose is used. A twofold increase in the dose of mepivacaine caused the mean peak plasma concentration to increase proportionally, indicating that they may be predicted based on the relation of dose per bodyweight.

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