Comparative Circulating Serum Levels of Mepivacaine with Levo-Nordefrin and Lidocaine with Epinephrine

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ABSTRACT

Expected blood levels of common local anesthetics have been reported for numerous types of injections. Comparative levels of mepivacaine and lidocaine after dental injection have been only partially evaluated. A study was designed to compare the circulating serum level of 36 mgs. of mepivacaine with 1:20,000 levo-nordefrin (M) and 36 mgs. of lidocaine with 1:100,000 epinephrine (L) in 1.8 cc dental cartridges after standardized's bilateral maxillary infiltrations. Each of five subjects received 1.8 cc of (L) to the left maxillary second bicuspid and 1.8 cc of (M) to the right maxillary second bicuspid at a rate of one cc per minute. The serum was sampled before the injections and at 5, 15, 30, 60, 90, 120 and 240 minute intervals after the injections and analyzed by gas liquid chromatography. The results indicated that the serum level of (M) peaked at 30 minutes, 0.37 μg/ml of serum and (L) had peaks at 15 and 30 minutes, 0.22 μg/ml of serum. This difference was statistically significant, ($p < .01$) at all times sampled with (M) always resulting in a higher serum level. Serum levels persisted throughout the four hour test period.

Circulating levels of mepivacaine and lidocaine have been evaluated subsequent to numerous types of injections including caudal, epidural, brachial plexus, intercostal, sciatic, intramuscular, hernia infiltrations, and others.[1-11] Cannell and others[12-14] have studied lidocaine and Goebel et al.[15] have evaluated mepivacaine blood levels following dental injections.

Adult toxicity is noted in conscious patients at venous blood levels of 5μg/ml for both lidocaine and mepivacaine.[16-18] Routine dental injections are not expected to produce plasma levels of this magnitude although only recently, has information of expected blood levels been published.

Mepivacaine 2% with 1:20,000 levo-nordefrin and lidocaine 2% with 1:100,000 epinephrine are considered to be similar dental anesthetics in respect to efficiency, duration and safety.[19-21] Because of the different injection sites and dosage levels used in dentistry, as compared to general surgery, it would be speculative to attempt to predict serum levels of mepivacaine and lidocaine with vasoconstrictors after dental injections. Therefore, the purpose of this study was to establish comparative circulating levels of lidocaine with epinephrine and mepivacaine with levo-nordefrin in venous serum after dental injection. As to date these have not been determined.

Methods and Materials

Five healthy male and female adult volunteers average age 26.6 (21-32), average weight 60.7 Kg (51.3-72.6), who were fully informed as to the nature of the study, were used as test subjects and placed in the semi-reclined position for the evaluation. Each volunteer received a 1.8 cc injection of commercially available 2% mepivacaine with 1:20,000 levo-nordefrin* and 2% lidocaine with 1:100,000 epinephrine.** The first injection (mepivacaine) was given as a buccal infiltration at the apex of the right maxillary second bicuspid using an aspirating technique. The injection rate was constant at 1 cc per minute and no topical anesthetic was used. The second injection, (lidocaine) was given at the apex of the left maxillary second bicuspid in the same manner. The lidocaine injection was started two minutes after the start of the mepivacaine administration. A dose of one dental cartridge containing 36 mg of mepivacaine and 0.09 mg

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*Carbocaine® (brand of mepivacaine) and Neo-Cobefrin (levonordefrin) Cook-Waite Laboratories, Inc. N.Y., N.Y. 10016
**Xylocaine® (brand of lidocaine) and Epinephrine, Astra Pharmaceutical Products, Inc. Worchester, Mass. 01606

levo-nordefrin or 36 mg of lidocaine and 0.018 mg epinephrine was chosen as most dental practitioners use these fixed amounts of the anesthetics rather than a dose based on body weight. Peripheral venous samples were obtained from the antecubital fossa by means of an indwelling catheter. A control sample was drawn before the anesthetic injections and at intervals from the start of the injection of 5, 15, 30, 60, 90, 120 and 240 minutes. The patency of this catheter was maintained with 5% dextrose in saline and the dilutent removed with venous blood before drawing each sample. Samples were centrifuged and the serum stored at minus 4°C. Analysis of the serum was by gas liquid chromatography, with a rate of recovery that ranged from 87-95%.

The gas liquid chromatographic method was as follows:

Two cc of serum plus one μg of internal standard (Cyclizine)* were extracted with 10 cc of ether. The serum layer was discarded and the ether layer re-extracted with 2 cc of 0.2N HCl. The ether layer was discarded and the aqueous phase made alkaline with 2 cc of 0.5N NaOH. The latter was then extracted with 10 cc of ether. The extracted ether was evaporated and the residue dissolved in 20 μl of $CHCl_3$. Two μl of the latter was then injected into the gas liquid chromatograph. The GLC was fitted with a 6-foot, ¼" glass column packed with 3% OV-17 on Chromosorb W-HP††. Operating conditions were as follows: Column 215°C. Injector 280°C, and Detector 280°C.

Table 1

Sample	W.M. 69.0Kg	A.S. 59.0Kg	M.L. 51.8Kg	D.B. 72.6Kg	A.C. 51.3Kg	Mean 60.7Kg	S.E.	S.D.
Control	0μg/ml	0	0	0	0	0		
5 min	0.20	0.10	0.13	0.12	0.26	0.16	.03	.07
15 min	0.38	0.25	0.37	0.15	0.35	0.30	.04	.10
30 min	0.42*	0.34	0.40*	0.35*	0.33	0.37**	.02	.04
60 min	0.21	0.37*	0.38	0.27	0.39*	0.32	.04	.08
90 min	0.18	0.37	0.31	0.21	0.27	0.27	.04	.08
120 min	0.16	0.27	0.26	0.19	0.24	0.22	.02	.05
240 min	0.07	0.22	0.19	0.12	0.15	0.15	.03	.06
Dose In Relation To Body Weight (mg/Kg)	0.52	0.61	0.69	0.50	0.70	0.59		

*Individual subject peak serum value.
Mean of individual peaks — 0.39 μg/ml .01 .03
**Mean peak serum value — 0.37 μg/ml — —

1.8 cc, of 2% Mepivacaine with
1:20,000 Levo-Nordefrin
36 mg Total Mepivacaine Dose

*Cyclizine, IMC Pharmaceuticals, Inc., Life Science Group, Plainsview, N.Y.

††Chromosorb W-HP, Applied Science Laboratories, Inc., Inglewood, CA 90304

Results

The individual and mean values of the 36 mg mepivacaine with 1:20,000 levo-nordefrin injection are listed in Table 1. The mean serum level increased rapidly from the control sample to the 30 minute sample which was the mean peak level attained, 0.37 μg/ml. After the peak was reached, the level fell slowly through 60, 90 and 120 minutes and was still persistent at the end of the four hour test period. The mean dose in relation to body weight for this 36 mg injection was 0.59 mg/kg.

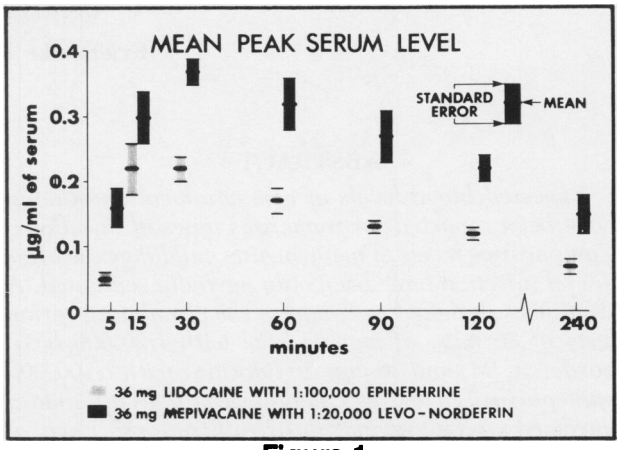

Figure 1

Figure 1 graphically depicts the mean serum value at each of the times sampled and the standard error. The mean is denoted by an asterisk. Despite intersubject variation, the mean values resulted in a relatively low, smooth curve that rose to a peak at 30 minutes and

Table 2

Sample	W.M. 69.0Kg	A.S. 59.0Kg	M.L. 51.8Kg	D.B. 72.6Kg	A.C. 51.3Kg	Average 60.7Kg	S.E.	S.D.
Control	0μg/ml	0	0	0	0	0		
5 min	0.05	0.04	0.01	0.05	0.10	0.05	.01	.03
15 min	0.23*	0.12	0.18	0.24	0.34*	0.22**	.04	.08
30 min	0.20	0.17*	0.20*	0.27*	0.25	0.22**	.02	.04
60 min	0.13	0.16	0.18	0.14	0.23	0.17	.02	.04
90 min	0.10	0.14	0.14	0.11	0.14	0.13	.01	.02
120 min	0.09	0.14	0.11	0.12	0.14	0.12	.01	.02
240 min	0.05	0.11	0.06	0.07	0.05	0.07	.01	.02
Dose In Relation To Body Weight (mg/Kg)	0.52	0.61	0.69	0.50	0.70	0.59		

* Individual subject peak serum value.
Mean of individual peaks — 0.24 μg/ml .03 .07
**Mean peak serum value — 0.22 μg/ml — —

1.8 cc, of 2% Lidocaine with
1:100,000 Epinephrine
36 mg Total Lidocaine Dose

then fell slowly with persistent levels remaining throughout the four hour sampling period. The individual peaks are underscored in Table 1.

The individual and mean results of the 36 mg lidocaine with 1:100,000 epinephrine injection are listed in Table 2. The mean serum level increased rapidly from the control sample to the peak level which was 0.22 μg/ml at 15 and 30 minutes. After the peak was reached the values fell slowly through 60, 90 and 120 minutes and persisted at 240 minutes, just as with the mepivacaine injection.

Figure 1 graphically depicts the mean serum value of the 36 mg lidocaine dose at each of the times sampled and the standard error. Not all subjects reached peak serum values at the same time and the individual peaks are underscored in Table 2. Despite this intersubject variation, mean values followed a relatively low, smooth curve, with peaks at 15 and 30 minutes and serum levels persisting throughout the four hour test period.

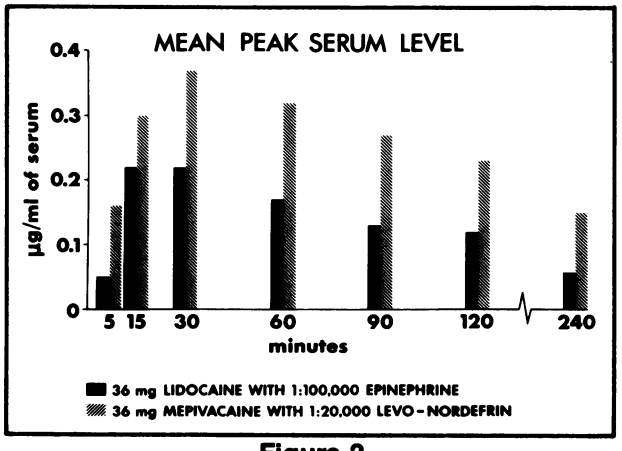

Figure 2

Figure 2 compares graphically the mean values of the mepivacaine and lidocaine doses for each of the times sampled and the percentage differences between each of the values are listed in Table 3. The five minute sample difference is considerable and should be discounted because the injections were given at a rate of 1 cc per minute, and measured from the start of the injection. The five minute sample is therefore approximately three minutes after completion of the mepivacaine dose, but only one minute after completion of the lidocaine injection. The effect of this 2 minute time differential is less noticeable in later samples.

Mepivacaine produced significantly higher serum levels than lidocaine at all intervals ($p < .01$). Analysis of variance was carried out on log serum levels. There was no significant difference in the absorption and clearance patterns of the two drugs.

All previously listed results are based on serum values at specific times yielding averages for those times. Individual test subject peak values, not related to time, may also be used to compute an average of the individual peak serum values. The values used for this comparison are denoted by an asterisk in Tables 1 and 2. When these are compared, the mean value of individual peaks not related to time, 0.39 μg/ml for mepivacaine and 0.24 μg/ml for lidocaine, results in a difference of 38% (Table 3). When the comparison is made on the mean peaks, 0.37 μg/ml for mepivacaine and 0.22 μg/ml for lidocaine, a similar difference is observed, 41% (Table 3).

Table 3

Comparison of Mean Venous Serum Values After Equal Dose Injections of 36 mg Mepivicaine with 1:20,000 Levo-Nordefrin and 36 mg Lidocaine with 1:100,000 Epinephrine

	36 mg Mepivacaine with Levo-Nordefrin	36 mg Lidocaine with Epinephrine	% Difference
Control	0μg/ml	0μg/ml	0%
5 min	0.16	0.05	69%
15 min	0.30	0.22**	27%
30 min	0.37**	0.22**	41%
60 min	0.32	0.17	47%
90 min	0.27	0.13	52%
120 min	0.22	0.12	45%
240 min	0.15	0.07	53%
Comparison of the Mean of Individual Peaks not related to Time	0.39*	0.24*	38%

**Mean Peak Serum Value
*Individual Subject Peak Serum Value Mean (not related to time)

Discussion

Results of this study are not directly comparable to other similar studies as not all use serum as the sample medium. Other evaluations have included arterial and venous whole blood, serum, and plasma. Serum and plasma yield similar values but whole blood levels are 80% of plasma levels.[2,22] Arterial plasma levels are also 20-30% higher than corresponding venous values.[23] Pratt, Warrington and Grego[24] reported a whole blood (presumably venous) peak level of 0.40 μg/ml after a 0.53 mg/kg injection of 2% mepivacaine with levonordefrin in the area of the mandible, which was reached at 60 minutes. The attained level was low, although the specific type of injection was not stated and the tested sample was whole blood, so a direct comparison is not possible. The dose however, is similar, 0.53 mg/kg compared to 0.59 mg/kg, and the resultant blood level although later, 60 minutes as compared to 30 minutes, was similar, 0.40 μg/ml compared to 0.37 μg/ml.

Cannell and associates[12,13] reported two evaluations of perioral injections of lidocaine with 1:80,000 adrenaline. The doses varied from 40 to 160 mg and the oral sites were randomized but one injection at an undefined site using 40 mg of lidocaine produced a blood level of almost 0.4 μg/ml, which is considerably different from the mean peak of 0.22 μg/ml of serum found in this study. The time of this peak is not stated, but occurred from 30 to 60 minutes after administration. One subject did have a peak value of 0.34 μg/ml which is closer to the individual peak reported by Cannell, et al.[12]

Lund and Cwik[25] studied comparative blood levels of mepivacaine and lidocaine, both with epinephrine, in equivalent doses after peridural injection and found that mepivacaine gave consistently higher venous blood levels. This is in agreement with the present oral evaluation where in every subject, the mepivacaine level was greater than the lidocaine venous serum level.

Vasoconstrictors, adrenalin in particular, are reported to be more effective in reducing plasma levels of a local anesthetic that is a vasodilator such as lidocaine, than they are with the less vasoactive drugs such as mepivacaine.[26] In comparing epidural lidocaine and mepivacaine without sympathomemitic amines, a higher blood level for lidocaine was found.[4] This is presumptive evidence to support the belief that vasoconstrictors are more effective in reducing blood levels when used with lidocaine than with mepivacine.

Unpublished data from Goebel and Allen, however, found that in dental injections of equal doses, the serum level without vasoconstriction for mepivacaine was always higher than for lidocaine. This would indicate that the role of the vasoconstrictor in reducing the serum level of the base anesthetic is poorly understood in dental injections and that the higher mepivacaine serum level in the present study is not solely related to vasoconstrictor action on lidocaine.

It is most apparent from the present evaluation that the two local anesthetic preparations in low doses do produce significantly different circulating serum-levels despite clinical evidence that considers them to be similar preparations.

Considerable intersubject variation in regard to time of peak serum level and attained peak value were also apparent in this study. From Tables 1 and 2, it can be seen that individual mepivacaine peaks varied from 30-60 minutes and individual lidocaine peaks from 15-30 minutes. The higher levels cannot be attributed to intravascular injections since the peak serum levels were not apparent at the initial 5 minute sample.

The 240 minute mean values show that persistent levels of mepivacaine and lidocaine exist for a considerable period after the injection, but is not necessarily related to the time or level of the peak. An explanation of this slow decline in the blood level has been proposed by Lurie and Weiss[4] who suggest it may result from continual release of the injected volume, slow metabolic degredation, or a combination of both, plus the effect of the vasoconstrictor additive.

Persistent serum levels could pose potential hazards in selected cases if large initial doses or reinjection of the same anesthetic is necessary, as cumulative effects of mepivacaine have been reported.[1] Lidocaine though, with adrenaline, on reinjection is reported to result in a decreased rate of plasma clearance rather than a new elevated peak.[13]

The mean peak serum levels at each time sampled for both anesthetics are shown in Figures 1 & 2. This illustrates the earlier peak from lidocaine with epinephrine and the slightly later but higher peak from mepivacaine with levo-nordefrin. The persistent serum level of both and the significant difference in serum levels of each are readily apparent at all the times sampled.

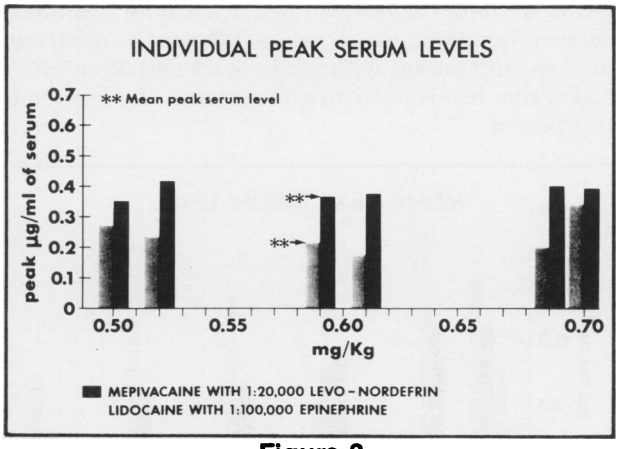

Figure 3

Figure 3 depicts the graphic comparison of how each individual's (n = 5) serum level and mean levels differed with each drug expressed as dose per body weight. It can be noted that there is no relationship in the limited dose range of this evaluation (0.5 mg/kg - 0.7 mg/kg), as to dose affecting attained serum levels. It is not possible from this evaluation to predict a serum level if an increased dose were given.

Scott, et al.[26] in an evaluation of prilocaine and lidocaine, reported a nonlinear dose curve below 200 mg and a linear dose curve from 200-700 mg. This linear relationship has a regression value of less than one (0.82) for lidocaine and 0.76 for prilocaine, so in doses above 200 mg, doubling the dose results in less than double the blood level and provides some margin of safety in large doses. A dose-serum level relationship using average values has been shown with 54 mg and 108 mg plain mepivacaine dental injection in a previous report.[15]

Summary and Conclusions

After standardized maxillary infiltrations of 36 mg of mepivacaine with 0.09 mg of levo-nordefrin and 36 mg of lidocaine with 0.018 mg of epinephrine in this group of patients, the following conclusions were reached.

1. Low peak peripheral venous serum levels were achieved.

2. A mean peak level was reached 30 minutes after the mepivacaine injection.
3. A mean peak level was reached at 15 and 30 minutes after the lidocaine injection.
4. Mepivacaine resulted in a significantly ($p < .01$) higher serum level than lidocaine.
5. Slow clearance of mepivacaine and lidocaine from the serum exists.
6. Considerable intersubject variation exists and makes predicting a serum level on a dose per body-weight relationship difficult.

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