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PHARMACOKINETICS OF LIGNOCAINE IN HUMANS AFTER PERI-ORAL INJECTIONS

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ABSTRACT

Serum levels of lignocaine in ten healthy volunteers were determined after peri-oral injection of 36 mg lignocaine hydrochloride. Rapid absorption from injection site occured with a mean peak serum level of 46 ug/ml at 10 minutes.

In addition, lignocaine pharmacokinetics following peri-oral administration were studied. The serum concentration-time data were found to obey the one-compartment open model adequately with first-order absorption and elimination rates.

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INTRODUCTION

Expected circulating serum levels of common dental local anaesthetics is an area of dental pharmacology that has only recently been explored. Minimal baseline data is now being reported that evaluates expected serum levels after routine dental doses of commercially available local anaesthetic products.

Local anaesthetic solutions containing lignocaine hydrochloride are used as injections in conscious patients prior to most dental procedures.

The amount of lignocaine circulating in the blood after the injection into the body at sites other than the mouth has been studied widely (1-3). Blood levels following oral doses of lignocaine capsules for control of cardiac arrhythmias have been reported (4). Bergman et al (5) have reported studies of the transfer of C^{14}-labelled local anaesthetics across oral mucosa in vitro and in vivo.

It would appear that no much informations are available concerning the circulating levels of lignocaine after peri-oral injections as used by dental surgeons.

The purpose therefore of the present study is to find out whether significant circulating levels occured, and to calculate the pharmacokinetic parameters of lignocaine after peri-oral injections.

EXPERIMENTAL

Materials

Lignocaine hydrochloride (Astra Chemicals Ltd., Watford, U.S.A.), Analar diethylether freshly distilled (Prolabo, Paris, France), Sodium hydroxide (Chemapol, Czechoslovakia) and Hydrochloric acid (E. Merck, Darmstadt, W. Germany) were used in this study.

Methods

Subjects and injections

Ten healthy male adult volunteers, mean age 28 years (22 to 33) and mean weight 79.5 (68.0 to 92.0), who were fully informed as to the nature of the study, were used as test subjects. No subject had received any form of local or general anaesthetic or other drugs one week before the start of experiments and during the study. Each subject underwent physical

examination of his cardio-vascular and respiratory systems before the trial.

Each volunteer received a 1.8 ml injection of commercially available plain 2 per cent lignocaine hydrochloride. The preparation was without vasoconstrictor (adrenaline) and was from fresh multidose vial. An attempt was made to simulate a general dental, private practice, situation throughout. The solution was loaded into syringes equipped with 25 G needles. The injection was given as a buccal infiltration into the paraperiostean opposite to the maxillary second premolar. The injection was preceded in absence of blood confirmed a non vascular needle tip placement. The injection rate was constant with a mean deposition time of 40 seconds per injection.

Sampling and treatment of blood

Peripheral venous samples were obtained from the cephalic or basilic systems of the arm. A sample was drawn before local anaesthetic injection as a control and at intervals from the start of the injection of 2, 5, 10, 20, 30 and 60 minutes. Fresh, sterile, plastic syringes and needles were used for each sample, either by new intravenous puncture or by withdrawal through the diaphragm of a cannula previously inserted

into a vein. Where a cannula was used, this was kept clear by flushing with 2.0 to 4.0 ml amounts of sterile normal saline after each sample. Before a fresh sample was taken, the saline remaining in the cannula was drawn off and discarded.

Samples of peripheral venous blood were centrifuged and the serum was directly assayed for its drug content. Analysis of serum was performed by using a new spectrophotometric method with a good rate of recovery.

Analytical method

To 5 ml serum sample, 2 ml aliquot of 0.1 N sodium hydroxide was added. The solution was extracted with freshly distilled Analar diethyl ether (2 X 10 ml) and the serum layer was discarded. The basic drug contained in this ethereal extract was then partitioned into 0.2 N hydrochloric acid (4 ml) and the ethereal phase was then discarded. The acidic solution was then made alkaline by the addition of 0.5 N sodium hydroxide (4 ml) and extracted with freshly distilled Analar diethylether (10 ml). This ethereal solution was evaporated and the residual drug was dissolved in 1 ml 0.1 N hydrochloric acid and assayed spectrophotometrically at 235 nm for its lignocaine content.

A standard calibration curve was previously done by

spiking serum samples with different known concentrations of lignocaine. The spiked samples were analysed using the same previously mentioned procedure and their lignocaine contents were calculated.
It should be noticed that the time and rate of shaking overall the extraction processes were constant.

Pharmacokinetic analysis

Serum lignocaine concentrations were tabulated at each sampling time and plotted as a function of time on semi log papers. Individual serum data for each subject after each dose were fitted graphically to obtain initial estimates and by least-squares regression analysis to a one-compartment pharmacokinetic model defined by

$$C = \frac{FD}{Vd}\left(\frac{K_a}{K_a - K_E}\right)\left(e^{-K_E t} - e^{-K_a t}\right) \quad \text{. . Eq. 1}$$

where C is the procaine concentration at any time, t, after dosing; F is the fraction of dose, D, absorbed; Vd is the apparent volume of distribution; and K_a and K_E are the apparent first-order rate constants of absorption and elimination, respectively. From the graphical analysis, values of K_a, absorption half-life ($t_{½\text{-abs}}$), K_E, and elimination half-life ($t_{½\text{-elim}}$) were obtained.

The area under the individual serum concentration-time curve was calculated according to the following equation

$$AUC_o = \frac{FD}{Vd} \left(\frac{K_a}{K_a - K_E} \right) \left(\frac{1}{K_E} - \frac{1}{K_a} \right) \quad \text{Eq. 2}$$

where $(FD/Vd)\ K_a/(K_a - K_E)$ was the intercept of the best graphical fit of the individual data.

The amount of drug in the body at the steady state (A), i.e. when the rate of elimination equal the rate of absorption, was calculated according to equation 3.

$$A = C_{max} \cdot V_d \quad \ldots\ldots\ldots \quad \text{Eq. 3}$$

% Bioavailability of the peri-oral injection of lignocaine was calculated according to the following equation

$$\%\ \text{Bioavailability} = \frac{AUC_{\text{peri-oral}}}{AUC_{\text{i.v.}}} \quad \text{Eq. 4}$$

$AUC_{i.v.}$ could be easily theoritically calculated as follows,

$$AUC_{\text{i.v.}} = \frac{X_o}{V_d \cdot K_E} \quad \ldots\ldots \quad \text{Eq. 5}$$

where X_o is the initial dose injected.

RESULTS AND DISCUSSION

It was considered that, under general practice conditions, the entire contents of a local anaesthetic cartridge (2.0 - 2.2 ml) were not necessarily injected into the patient. It appeared that the wastage of solutions could occur in three ways. First, wastage of unkown amounts of solution by flushing the needle. Secondly, droplets of solution falled into the mouth during the injection process. Thirdly, it was found that from 0.1 to 0.2 ml of solution remained above each cartridge diaphragm after supposed complete delivery from the syringe.

The actual volume of local anaesthetic solution injected from a 2.0 ml cartridge during most dental studies was, therefore, less than 2.0 ml. For this reason, only 1.8 ml of 2 per cent lignocaine hydrochloride (36 mg) was sharply injected in this study.

In a separate investigation, the injection techniques of randomly selected dental practitioners in an extraction clinic (30 cases), showed a variation in the time taken to deposit one cartridge of local anaesthetic into the peri-iral tissues of between 16 and 80 seconds with a mean rate of injection of 40 seconds per cartridge. Dental surgeons performing nonextraction treatments on

supine patients at the London Hospital were found to take an average of 48 seconds to deposit a variable dose of lignocaine anaesthetic into peri-oral tissues (6).
Therefore, in the present study, a mean deposition time of 40 seconds per injection (1.8 ml) was used. The range of deposition time was 35 to 45 seconds per injection.

The individual and mean values of the 36 mg lignocaine peri-oral injections are listed in Table I. The mean values increased from the control sample and reached a peak venous serum level of 0.44 ug/ml at 10 minutes. This rapid achievement of peak serum level indicated a very high absorption rate from peri-oral injections. After the peak was reached, the value fell slowly and was still present at the end of the 60 minutes test period (0.26 ug/ml).

Figs. 1 & 2 showed the serum levels of lignocaine for each subject (10 subjects) at different time intervals. These figures showed different profiles of drug absorption and elimination for subjects. Accordingly, individual subjects did not reach peak levels at the same time. Therefore, a mean peak can be computed based on these individual peaks regardless the time. When the mean value

Table I - Individual and Mean Serum Levels After A 36.0 mg Dose of Lignocaine: Standard Error and Standard Deviation are Included.

Subject No.	I	II	III	IV	V	VI	VII	VIII	IX	X	Mean	S.E.	S.D.
Body weight (kg)	70	80	80	92	85	71	88	81	80	68	79.5		
Conc.(µg/ml) at different time intervals (min)													
0	0	0	0	0	0	0	0	0	0	0	0		
2	0.34	0.14	0.22	0.20	0.29	0.25	0.19	0.21	0.18	0.28	0.23	0.02	0.06
5	0.52[1]	0.21	0.38	0.26	0.36	0.44	0.27	0.37	0.30	0.58[1]	0.37	0.04	0.12
10	0.46	0.44[1]	0.47[1]	0.38[1]	0.40[1]	0.50	0.33	0.46[1]	0.46[1]	0.52	0.44[2]	0.02	0.06
20	0.41	0.38	0.40	0.33	0.34	0.52[1]	0.40[1]	0.44	0.39	0.47	0.41	0.02	0.06
30	0.36	0.32	0.35	0.28	0.30	0.44	0.35	0.41	0.34	0.43	0.36	0.02	0.05
60	0.25	0.21	0.25	0.18	0.20	0.33	0.26	0.36	0.23	0.31	0.26	0.02	0.06
Dose in relation to body weight (mg/kg)	0.55	0.48	0.48	0.42	0.45	0.54	0.44	0.48	0.48	0.56	0.48		

[1] Individual subject peak serum value: mean of individual peaks. 0.46 µg/ml 0.02 0.06

[2] Mean peak serum value : 0.44 µg/ml - -

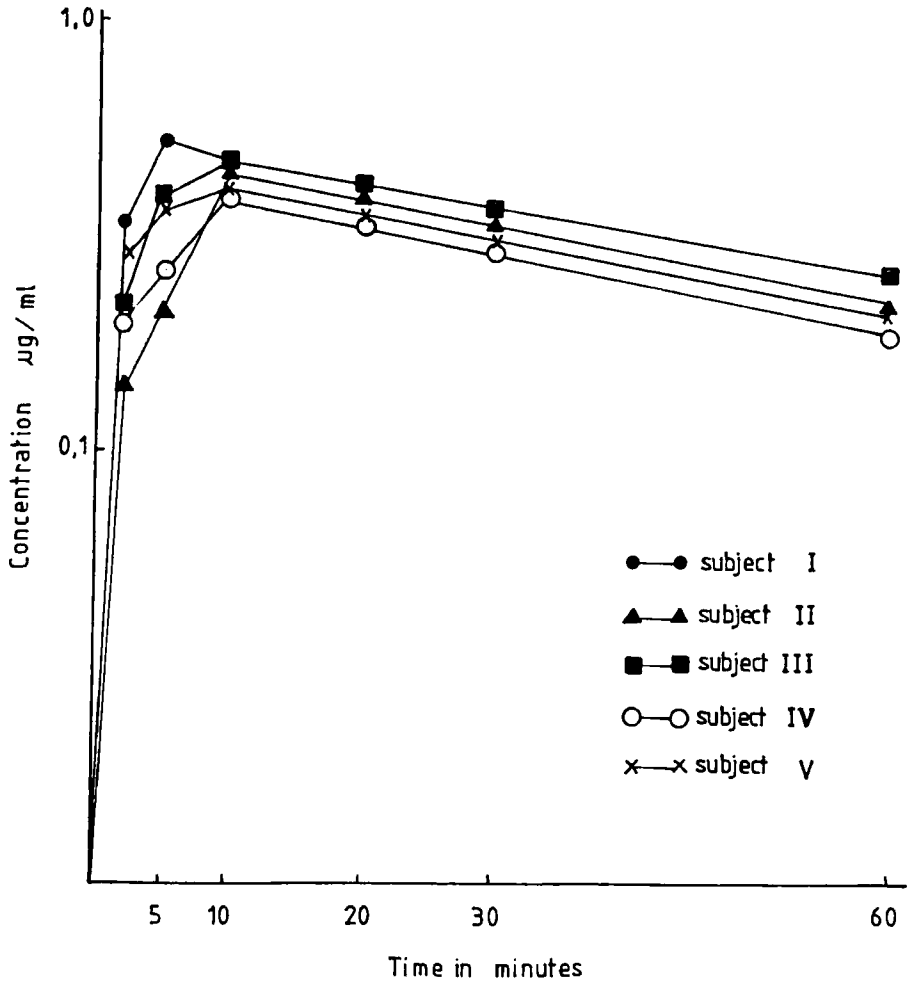

Fig. 1: A comparison of serum levels of lignocaine after a peri-oral dose of 36.0 mg.

produced by these individual peaks (0.46 ug/ml) was compared with the mean peaks (0.44 ug/ml), a small difference was obtained. This small difference indicated that a small number of subjects showed deviation in their maximum peak time (only 3) from the mean maximum peak time.

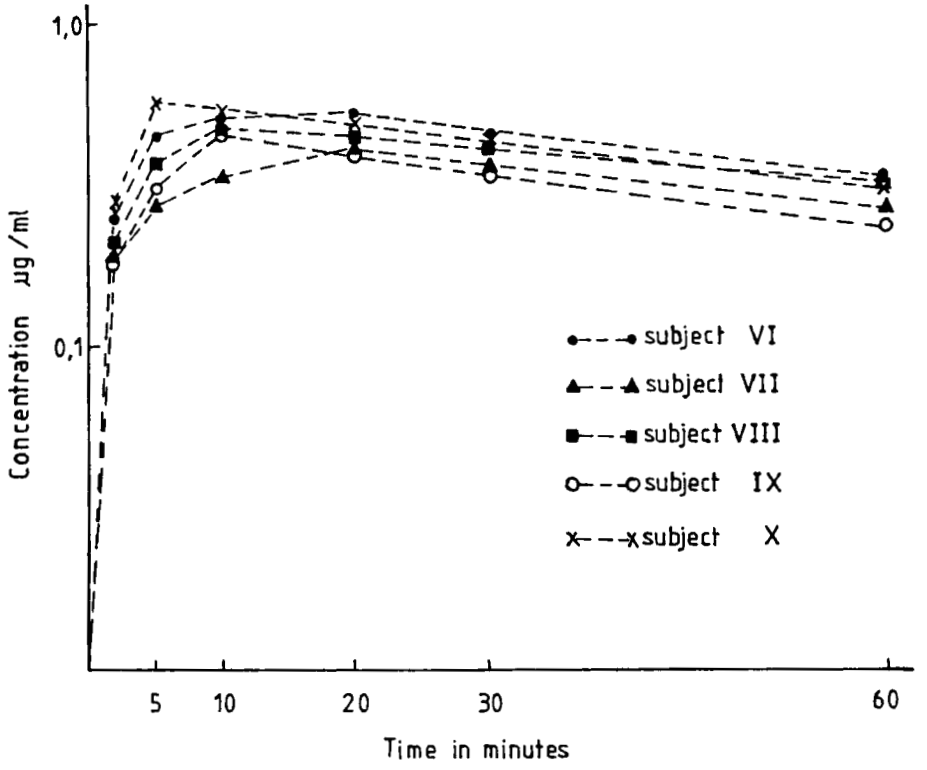

Fig. 2: A comparison of serum levels of lignocaine after a peri-oral dose of 36.0 mg.

Cannell et al. (6) reported 2 evaluations of peri-oral injections of lignocaine in a 40 mg dose and noted a peak blood level of approximately 0.4 ug/ml but the exact oral site is not stated. Serum and plasma evaluations are reported to yield similar values but whole blood levels are expected to be only 80 per cent of plasma levels (7) leading to the speculation that the blood level reported by Cannell et al. could translate into a 20 per cent greater value if reported as serum or plasma.

Therefore, such blood level of lignocaine (0.4 ug/ml) could be translated into serum level (0.48 ug/ml).

This peak of 0.48 ug/ml resulted from a 40 mg dose of peri-oral lignocaine injection is in a good accordance with the mean peak of 0.44 ug/ml for the present 36 mg lignocaine peri-oral injection.

Cannell et al. also found that the time of the 40 mg maximum peak was between 10 and 20 minutes. This is consistent with the time of the 36 mg maximum peak in the present study (10 to 20 minutes). A similar maximum peak time was also reported by Goebel et al. (8) but the plasma peak level was much lower (0.31 ug/ml) from the same peri-oral dose of lignocaine.

It is common practice to calculate drug dosage on a mg/kg body weight basis. This assumes that if distribution of the drug occurs evenly in the body then subjects of greater mass will achieve lower serum levels. When our data were put to the test, however, by plotting body weight against maximum serum level (keeping the dosage in mg constant), an excellent correlation could be seen between the two variables as shown in Fig. 3.

Semilogarithmic plots of serum lignocaine concentrations versus time revealed a monoexponential

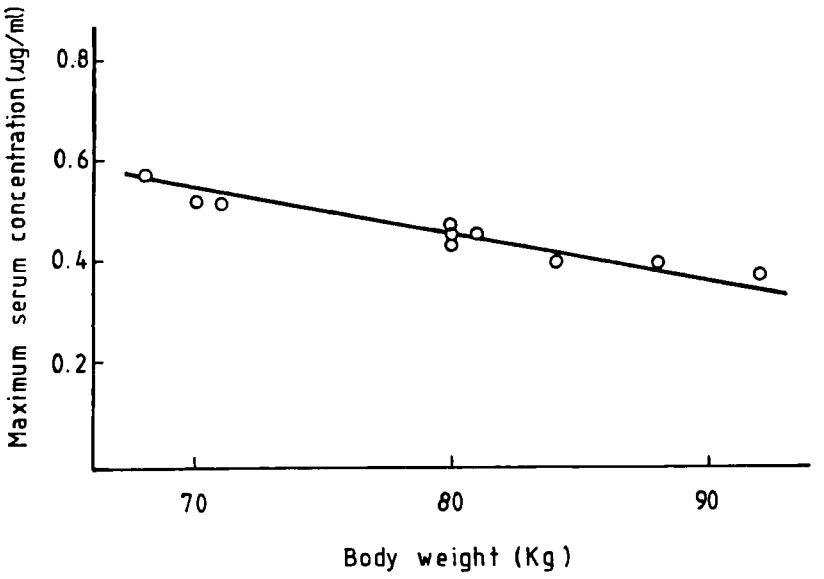

Fig. 3: Serum levels of lignocaine following peri-oral injection in 10 patients plotted against body weight.

decrease in observed serum levels after the peak with no significant distribution phase, indicating that a one-compartment open model is appropriate for evaluating the pharmacokinetics of these data.

The bioavailability parameters, i.e., the area under the serum level time curve (AUC_0), the maximum serum level (C_{max}), the time to maximum serum level (t_{max}), and the per cent bioavailability ($AUC_{peri-oral}$ / $AUC_{i.v.}$), of lignocaine after peri-oral injection of a 36 mg dose for the 10 subjects are listed in Table II.

Table II. Bioavailability parameter values for lignocaine after peri-oral injection of a 36 mg dose to 10 subjects.

Subject	AUC, μg.hr/ml	C_{max}, μg/ml	t_{max}, min	% Bioavailability
I	0.681	0.52	5	100
II	0.538	0.44	10	100
III	0.666	0.47	10	100
IV	0.466	0.38	10	100
V	0.509	0.40	10	100
VI	0.907	0.52	20	100
VII	0.689	0.40	20	100
VIII	0.895	0.46	10	100
IX	0.569	0.46	10	100
X	0.861	0.58	5	100
Mean	0.678	0.46	11	100
± SD	0.16	0.06	5.16	0.00
± SE	0.05	0.02	1.72	0.00

The area under the curve for the ten subjects ranged from 0.466 to 0.907 ug.hr/ml with a mean value of 0.678 ug.hr/ml.

The maximum serum concentration of lignocaine in this study for the shared subjects was 0.38 - 0.58 ug/ml with an average value of 0.46 ug/ml. The time to reach this maximum serum value was calculated. It was found to be in the range of 5-10 minutes with a mean value of 11 minutes. Concerning the bioavailability of lignocaine from peri-oral injection, all the subjects showed 100% bioavailability.

In order to make this in-vivo evaluation of the peri-oral injection of lignocaine of more biological significance, some pharmacokinetic parameters were computed. These parameters were computed for each subject, assuming first-order elimination from a single compartment (9).

The values of elimination rate constant (K_E) and elimination half-life ($t_{½\text{-elim}}$) are shown in Table III. The half-life for the 10 subjects was ranging from 0.783 to 1.200 hr with a mean value of 0.941 hr, which corresponded an elimination rate constant of 0.750 hr^{-1}.

Table III. Pharmacokinetic parameters in 10 healthy volunteers following a 36 mg peri-oral dose of procaine HCl.

Subject	K_a, hr-1	$t_{½-abs}$, hr	K_E, hr-1	$t_{½-elim}$, hr	Vd, liters/kg	A, mg
I	27.72	0.025	0.743	0.933	1.02	36.98
II	8.66	0.080	0.832	0.833	1.01	35.40
III	15.40	0.045	0.743	0.933	0.91	34.20
IV	13.86	0.050	0.885	0.783	0.95	38.41
V	16.50	0.042	0.866	0.800	0.96	32.68
VI	13.86	0.050	0.671	1.033	0.83	30.74
VII	9.90	0.070	0.676	1.025	0.88	30.91
VIII	13.86	0.050	0.578	1.200	0.86	32.00
IX	11.55	0.060	0.832	0.833	0.95	34.99
X	18.09	0.038	0.671	1.033	0.92	36.15
Mean	14.94	0.051	0.750	0.941	0.93	34.25
± SD	5.33	0.02	0.10	0.13	0.06	2.61
± SE	1.78	0.01	0.03	0.04	0.02	0.87

The values of absorption rate constant (K_a) and the absorption half-life are shown in Table III. The rate constant for absorption ranged from 8.66 to 27.72 hr^{-1} with an average value of 14.94 hr^{-1}, which corresponded to a half-life of 0.051 hr.

The volume of distribution (V_d) of lignocaine for the 10 subjects was also calculated (Table III). The mean value of the volume of distribution was 0.93 liters/kg.

Finally, the amount in the body at the steady state (A) was calculated. The mean value of A was 34.25 mg.

Concerning the variation in the results of the pharmacokinetic parameters of the ten subjects, the results showed a very little variation in their absorption half-life, elimination rate constant, elimination half-life, amount in the body at the steady state, and volume of distribution. Higher intrasubject variation was shown in their absorption rate constant.

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