REDUCTION OF ORAL BIOAVAILABILITY OF LIGNOCAINE BY INDUCTION OF FIRST PASS METABOLISM IN EPILEPTIC PATIENTS

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- 1 The pharmacokinetics of lignocaine following single oral and intravenous doses have been investigated in six normal volunteers and in six patients receiving chronic antiepileptic drug therapy.
- 2 After intravenous administration, serum lignocaine levels declined biexponentially in all subjects. The serum clearance (mean $\pm$ s.d.) was slightly higher in the patients (0.85 ± 0.09 v 0.77 ± 0.07 l/min) but the difference was not statistically significant.
- 3 Lignocaine bioavailability after oral administration was more than two-fold lower in the patients than in the normal subjects (0.15 ± 0.06 v 0.37 ± 0.09 , $P < 0.001$).
- 4 It is suggested that the reduced bioavailability of lignocaine in the patients is a consequence of stimulation of hepatic first-pass metabolism by antiepileptic drugs.

Introduction

The perfusion limited pharmacokinetic model (Gibaldi, Boyes & Feldman, 1971; Rowland, 1972; Rowland, Benet & Graham, 1973; Wilkinson, 1975; Wilkinson & Shand, 1975) has recently been successfully applied to describe the disposition kinetics of high clearance drugs such as nortriptyline (Alván, Borgå, Lind, Palmer & Siwers, 1977), alprenolol (Alván, Piafsky, Lund & von Bahr, 1977) and paracetamol (Perucca & Richens, 1978) in man. According to this model, the systemic clearance of drugs subject to high hepatic extraction is mainly determined by the rate of liver blood flow (LBF) and only marginally influenced by changes in the activity of the hepatic drug metabolizing enzymes. On the other hand, when these drugs are administered orally, the fraction of the dose which escapes first-pass metabolism in the liver and reaches the systemic circulation is not limited by LBF and is totally dependent on the intrinsic metabolic activity of the organ (Perrier & Gibaldi, 1974) or *intrinsic clearance* as defined by Wilkinson & Shand (1975). It follows that induction of the hepatic microsomal enzymes will have negligible effects on the disposition of these drugs after intravenous administration but will result in marked reduction of bioavailability (Meikle, Jubiz, Matsukura, West & Tyler, 1969; Alván *et al.*, 1977) and steady state plasma levels (Alván, Lund, Mellström & von Bahr, 1977) on oral administration.

In the present study the perfusion limited model has been applied to describe the pharmacokinetics of the local anaesthetic and antidysrhythmic drug, lignocaine, in normal subjects and in patients treated

with enzyme-inducing agents. Lignocaine is almost ideal as a model drug because (i) it is subject to high hepatic clearance in man, as indicated by a high liver extraction ratio (Stenson, Constantino & Harrison, 1971) and evidence of extensive first-pass metabolism on oral administration (Boyes, Scott, Jebson, Godman & Julian, 1971; Bending, Bennett, Rowland & Steiner, 1976); (ii) it is metabolized by an enzymatic system in the liver which involves the mixed function oxidase (Hollunger, 1960; Krenaghan & Boyes, 1972; von Bahr, Fellenius & Fred, 1972; Strong, Parker & Atkinson, 1973) and which is induced by phenobarbitone treatment in the dog (Di Fazio & Brown, 1972); (iii) it has been previously selected to test the perfusion limited model in animal studies (Branch, Shand, Wilkinson & Nies, 1973; Benowitz, Forsyth, Melmon & Rowland, 1974a; Benowitz, Forsyth, Melmon & Rowland, 1974b; Rane, Wilkinson & Shand, 1977) and (iv) it is relatively safe at the plasma concentrations achieved in our subjects. This study adds further information to the question of lignocaine bioavailability on oral administration.

Methods

Experimental design

Six healthy subjects and six epileptic patients, resident at the National Hospitals-Chalfont Centre for Epilepsy, gave their informed consent to participate

in the study. Age, body weight and sex distribution were similar in the two groups (Table 1). None of the healthy subjects was taking any drug with the exception of AT who was occasionally taking lorazepam (4 mg) at night. One patient was treated with phenytoin alone (450 mg daily). The remaining five patients were receiving long-term treatment with a combination of at least two of the following drugs: phenobarbitone, primidone, phenytoin and carbamazepine (Table 1). All these agents are potent inducers of the hepatic microsomal enzymes (Richens, 1976). Prior to admission to the trial an electrocardiogram (ECG) was carried out in each of the subjects. No abnormalities were found. Each subject received in random order, and separated by an interval of approximately one week, a single oral dose of 750 mg lignocaine monohydrate and a single intravenous dose of 100 mg lignocaine hydrochloride (Xylocard, 2%, Astra). The oral dose (equivalent to 608 mg lignocaine base) was administered in aqueous solution (25 mg/ml) and was considered optimal for the purposes of the study after preliminary experiments in which the serum concentration of lignocaine was measured following different oral doses. The intravenous dose (equivalent to 86 mg base) was given into an antecubital vein over 2.5 min. On both occasions the drug was administered at approximately 08.00 h after an overnight fast. The subjects were kept supine during the injection and remained in a sitting position for most of the duration of the experiment. Food was not allowed during the

experiment but a small cup of weak tea was permitted after 2 h.

Blood samples (4 ml) were collected at 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min after dosing. Additional samples were collected 3 and 8 min when the drug was injected intravenously. The serum was kept frozen at -20°C until analysed for lignocaine concentration within 1 week.

The implications of the study were explained to each of the patients and volunteers, and the protocol was approved by a local Ethics Committee.

Analytical methods

The serum concentration of lignocaine was determined in duplicate by enzyme-immunoassay (EMIT, Syva) using a Syva-pipetter-diluter model 1500 and a Gilford 300-N spectrophotometer connected to a Syva timer-printer model 2400. Serum standards were made up containing from 0.4 to $8.5\text{ }\mu\text{mol/l}$ of lignocaine. An approximately six-fold increase in the sensitivity of the method was obtained by omitting one of the two initial sample dilutions described in the standard procedure (Syva Corporation, 1977). Apart from this modification, samples were analysed according to the manufacturer's instructions. The difference between the absorbance reading of each of the standards and the average absorbance reading of the zero calibrator ($\Delta A - \Delta A_0$) was plotted on the

Table 1 Details of subjects included in the study

<i>Healthy subjects</i>	<i>Sex</i>	<i>Age (years)</i>	<i>Drug treatment (mg/day)</i>
AT	F	36	Lorazepam 4
GM	M	21	—
MD	F	25	—
GS	F	28	—
TT	M	19	—
KE	F	21	—
Mean		25	—
s.d.		6	
<i>Epileptic patients</i>			
JK	M	37	DPH 450
AW	F	27	DPH 200 Pb 90
PC	M	27	DPH 100 C 800 Diazepam 20
EW	F	27	DPH 300 Pb 240
DT	M	31	DPH 300 Pmd 750 SV 800**
SH	F	22	DPH 400 Pmd 500
Mean		28	
s.d.		5	—

DPH = phenytoin, C = carbamazepine, Pb = phenobarbitone, Pmd = primidone, SV = sodium valproate, ** + pericyazine 15.

appropriate graph paper supplied with the reagent kit, allowing for the shift in concentration due to the omission of the dilution step. Samples containing more than $8.5 \mu\text{mol/l}$ were diluted prior to estimation.

Within assay variability was found to be 3.2% and 7.9% (coefficient of variation) for serum samples containing 1.1 and $8.5 \mu\text{mol/l}$ respectively ($n = 10$). Day-to-day variability estimated for a sample containing $2.4 \mu\text{mol/l}$ was found to be 6.5% ($n = 10$). No interference with the assay was found with carbamazepine ($40 \mu\text{mol/l}$), phenobarbitone ($340 \mu\text{mol/l}$), phenytoin ($120 \mu\text{mol/l}$) and primidone ($92 \mu\text{mol/l}$). Interference by monoethylglycinexylidide (MEGX) and glycine-xylidide (GX) was not tested. However, the cross-reactivity of the antiserum with the metabolites is reported to be negligible (Syva Corporation, 1977), concentrations above $150 \mu\text{mol/l}$ for MEGX and above $560 \mu\text{mol/l}$ for GX being necessary to produce a 30% measurement error in a sample containing $13.0 \mu\text{mol/l}$ of lignocaine (Chang & Bastiani, 1977). After oral administration of lignocaine in man, serum MEGX levels are comparable to those of the parent drug (Adjepon-Yamoah & Prescott, 1973; Bending *et al.*, 1976); lower MEGX concentrations are found after intravenous lignocaine (Bending *et al.*, 1976). Serum levels of GX after oral and parenteral administration are reported to be lower than those of MEGX (Adjepon-Yamoah & Prescott, 1973).

Pharmacokinetic analysis

The decline of the serum concentration of lignocaine after intravenous administration can be adequately described by a two compartment open model (Boyes *et al.*, 1971; Rowland, Thompson, Guichard & Melmon, 1971). According to this model, at time t after a single intravenous dose, the serum concentration C_t is given by the equation:

$$C_t = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

where α and β are the rate constants of the initial rapid and terminal slower phase respectively and A and B the contribution of the corresponding exponentials at $t = 0$. The β slope was obtained by linear regression from the terminal part of the serum concentration curve and extrapolated back to zero time. The α slope was calculated by linear regression from the values obtained after subtracting the β slope to the serum concentration of the early samples. Half-lives ($T_{1/2\alpha}$ and $T_{1/2\beta}$) were obtained by the relationships: $T_{1/2\alpha} = 0.693/\alpha$ and $T_{1/2\beta} = 0.693/\beta$. Areas under the serum concentration curves (AUC) were estimated by the trapezoidal rule and extrapolated to infinity by the relationship C_{tn}/β where C_{tn} is the concentration at the last sampling time. The added area (mean $\pm$ s.d.) comprised 11.6 ± 6.7 of the total area.

The oral availability (F) was calculated as $\text{AUC}_{\text{oral}}/\text{AUC}_{\text{iv}}$ corrected for the difference in dose. The systemic serum clearance (Cl_s) and the volume of distribution ($V_d\beta$) were calculated from intravenous data according to the formulae (Gibaldi, Nagashima & Levy, 1969; Rowland, 1972):

$$\text{Cl}_s = \text{Dose}/\text{AUC}_{\text{iv}} \quad \text{and} \quad V_d\beta = \text{Dose}/(\text{AUC}_{\text{iv}} \cdot \beta).$$

The serum clearance was converted to blood clearance (Cl) by using a conversion factor λ (= concentration of lignocaine in whole blood: concentration of lignocaine in serum) (Rowland, 1972):

$$\lambda = \text{PCV}/K + (1 - \text{PCV}) \quad (2)$$

Where PCV is the packed cell volume and K the partition coefficient for lignocaine between serum and red cells. A K value of 1.6 was used (Tucker & Mather, 1975).

The hepatic blood clearance (Cl_h) was calculated as:

$$\text{Cl}_h = \text{Cl} - \text{Cl}_r \quad (3)$$

Where Cl_r is the renal clearance of unchanged lignocaine which equals $f_u \times \text{Cl}$, where f_u is the fraction of the intravenous dose excreted unchanged in the urine. An average value for f_u of 0.01 (for normal conditions of urinary pH) was assigned from the literature (Lalka, Manion, Berlin, Baer, Dodd & Meyer, 1976). Equation 3 assumes that lignocaine metabolism is exclusively hepatic.

The hepatic blood flow (LBF) was calculated according to the relationship (Wilkinson & Shand, 1975):

$$\text{LBF} = \text{Cl}_h/E \quad (4)$$

Where E is the hepatic excretion ratio. The latter was estimated by the relationship $E = 1 - F$, which assumes complete absorption and first order kinetics. Equation 4 was also used to predict the oral availability from intravenous data, assuming a liver blood flow of 1.5 l/min (Wilkinson & Shand, 1975). The intrinsic clearance (Cl_{int}) was estimated according to Wilkinson & Shand (1975) as:

$$\text{Cl}_{\text{int}} = \text{Dose}_{\text{oral}}/\text{AUC}_{\text{oral}} \cdot \lambda \quad (5)$$

This term, which equals $\text{LBF} \cdot E/(1 - E)$ (or in terms of Michaelis-Menten kinetics the ratio V_{max}/K_m) assumes that absorption is complete and that elimination is exclusively by hepatic metabolism.

Results

Adverse effects

No serious adverse effects were encountered. Eight subjects (five normal volunteers and three epileptic

Figure 1 Mean serum lignocaine concentration ($\pm$ s.d.) after intravenous administration of lignocaine hydrochloride (100 mg) in six healthy subjects (●) and in six epileptic patients (○). ($1 \mu\text{mol/l} \equiv 0.23 \mu\text{g/ml}$.)

patients) complained of drowsiness, dizziness and/or disorientation and tinnitus during the injection. These symptoms disappeared completely 4 to 8 min after the injection. It was the observer's subjective impression that adverse effects were less prominent in the patients. Numbness of the tongue was common for 3–5 min following oral intake of the lignocaine solution. Five subjects (four normal volunteers and one epileptic patient) complained of moderate dizziness for a short period (usually between 30 and 90 min) after the oral dose. Invariably, a serum lignocaine concentration of $8.7 \mu\text{mol/l}$ or more was found at the time these symptoms were reported, and the only patient to complain of dizziness (AW) was also the only patient in whom a serum lignocaine concentration exceeded this value after oral intake (Table 7). Many subjects reported a feeling of tiredness for up to 12 h after drug administration. This symptom occurred as frequently after oral administration as after intravenous, and was noted by the volunteers and by the patients. No alteration was noted in the frequency or pattern of epileptic seizures in the patients.

Lignocaine kinetics after intravenous administration

The serum concentration values of lignocaine at various sampling times after intravenous administration in healthy subjects and epileptic patients are shown in Table 2. Mean values $\pm$ s.d. are illustrated in Figure 1 while calculated kinetic parameters are shown in Tables 3 and 4. In all subjects, serum lignocaine concentrations declined biexponentially following the injection. In subjects GS and EW, however, slight irregularities in the early part of the concentration curve prevented an accurate estimation of the α phase.

Within groups, terminal half-lives and systemic serum clearances showed low interindividual variability.

Comparison of data in Tables 3 and 4 indicates that the estimated kinetic parameters were similar in the two groups of subjects.

There was a trend for the systemic serum clearance to be higher in the epileptic patients but the difference was not statistically significant ($P \approx 0.1$).

Lignocaine kinetics after oral administration and comparison with intravenous data

Serum lignocaine concentration values after oral doses in normal subjects and epileptic patients are shown in Table 5. Mean values ($\pm$ s.d.) are illustrated in Figure 2. At all sampling times lignocaine concentrations were considerably lower in the epileptic patients resulting in an almost threefold difference in the areas under the curve between the two groups. Peak serum concentrations were reached after approximately 45 min in both groups; half-lives were similar to those calculated after intravenous administration and did not differ significantly in the two groups (Tables 6 and 7). Tables 6 and 7 illustrate kinetic parameters calculated by comparing oral and intravenous data. The mean oral availability was 37% in the normal subjects and 15% in the epileptic patients ($P < 0.001$). There was a good agreement between mean predicted and observed bioavailability in the normal subjects, but individual values were weakly correlated to those predicted ($r = 0.48$, $P > 0.05$). On the other hand, observed bioavailability values in the epileptic patients were found to be lower than but significantly correlated to those calculated from intravenous data ($r = 0.97$, $P < 0.01$). Estimated values for intrinsic clearance

Figure 2 Mean serum lignocaine concentration ($\pm$ s.d.) after oral administration of lignocaine hydrochloride (750 mg) in six normal subjects ($\bullet$) and in six epileptic patients ($\circ$). $P < 0.05$ at all sampling times except 0.25 and 0.5 h. (1 $\mu\text{mol/l} \equiv 0.23 \mu\text{g/ml}$.)

were approximately three times higher in the epileptic patients. Estimated values for hepatic blood flow ranged from 1.1 to 1.7 l/min and were lower in the patients than in the normal subjects.

Discussion

The two compartment open pharmacokinetic model proved to be adequate to describe the decline of the serum concentration of intravenously administered lignocaine in both normal volunteers and epileptic patients. Distribution was rapid and almost complete after 45–60 min in most of the subjects. A value of approximately 70 min for the terminal half-life in normal subjects is considerably lower than commonly reported (Rowland *et al.*, 1971; Rowland, 1974; Sasyniuk & Ogilvie, 1975), probably as a consequence of the relatively young age of the subjects studied (Nation, Triggs & Selig, 1977). Although knowledge of kinetic parameters such as half-life and systemic clearance is invaluable for a rational use of the drug, data derived from healthy volunteers should be extrapolated to patients cautiously. Factors such as age (Nation *et al.*, 1977), duration of administration (Le Lorier, Latour, Grenon, Caillé, Loiseau, Solignac & Du Mont, 1975; Le Lorier, Moisan, Gagné & Caillé, 1977) and disease (Thompson, Melmon, Richardson, Cohn, Steinbrunn, Cudihee & Rowland, 1973; Halkin, Meffin, Melmon & Rowland, 1975; Nation *et al.*, 1977) appear to play an important role

Table 2 Serum lignocaine concentration values after intravenous administration of lignocaine hydrochloride (100 mg) in six healthy subjects and in six epileptic patients

Time after administration (min)	Serum lignocaine concentration ($\mu\text{mol/l}$)											
	3	8	15	30	45	60	90	120	150	180	210	240
Healthy subjects												
AT	5.0	4.1	3.7	3.2	3.2	2.5	1.8	1.4	1.2	0.77	0.68	0.55
GM	11.9	7.7	4.7	3.8	2.4	1.9	1.4	1.0	0.7	0.68	0.51	0.38
MD	6.1	5.9	4.3	3.3	3.0	2.4	1.7	1.2	1.1	0.64	0.38	0.34
GS	8.9	5.6	5.0	3.9	3.7	2.9	2.1	1.2	0.6	0.47	0.34	0.21
TT	8.1	5.1	3.0	2.5	2.0	1.6	1.3	1.0	0.8	0.55	0.55	0.43
KE	13.7	9.2	5.3	3.4	2.9	2.2	1.6	1.3	0.8	0.73	0.51	0.43
Mean	8.9	6.3	4.3	3.4	2.9	2.3	1.6	1.1	0.9	0.64	0.50	0.39
s.d.	3.3	1.8	0.8	0.5	0.6	0.5	0.3	0.1	0.2	0.13	0.12	0.11
Epileptic patients												
JK	7.3	4.9	3.8	2.9	2.1	1.7	1.4	1.1	0.8	0.55	0.43	0.38
AW	11.9	6.8	4.7	3.3	3.1	2.6	1.5	1.4	1.1	0.73	0.60	0.34
PC	4.0	3.2	2.6	2.3	1.7	1.6	1.2	1.0	1.0	0.77	0.60	0.51
EW	8.3	5.1	4.1	3.4	3.2	2.4	1.4	1.1	0.7	0.43	0.30	0.17
DT	8.5	5.5	4.6	3.2	2.4	1.9	1.5	0.9	0.7	0.43	0.34	0.26
SH	10.2	7.4	4.7	3.6	2.6	2.4	1.7	1.2	0.8	0.51	0.38	0.26
Mean	8.4	5.5	4.1	3.1	2.5	2.1	1.4	1.1	0.8	0.57	0.44	0.32
s.d.	2.6	1.4	0.8	.5	0.6	0.4	0.2	0.2	0.2	0.15	0.13	0.12

Lignocaine 1 $\mu\text{mol/l} \equiv 0.23 \mu\text{g/ml}$.

Table 3 Kinetic parameters following intravenous administration of lignocaine hydrochloride (100 mg) in six normal subjects

Subject	A ($\mu\text{mol l}^{-1}$)	B ($\mu\text{mol l}^{-1}$)	α (min^{-1})	$T_{1/2}^{\alpha}$ (min)	β (min^{-1})	$T_{1/2}^{\beta}$ (min)	$AUC_{0-\infty}$ ($\mu\text{mol l}^{-1} \text{min}^{-1}$)	Serum clearance ($\text{l min}^{-1} \text{kg}^{-1}$)	Serum clearance ($\text{l min}^{-1} \text{kg}^{-1}$)	$V_d \beta$ (kg^{-1})
AT	1.6	4.0	0.1158	6.0	0.00832	83	507	0.74	0.012	1.44
GM	8.9	3.0	0.0662	10.5	0.00849	82	494	0.76	0.009	1.06
MD	3.3	5.0	0.1815	3.8	0.01133	61	466	0.81	0.015	1.32
GS	—	6.7	—	—	0.01435	48	493	0.76	0.011	0.77
TT	5.4	2.6	0.0937	7.3	0.00714	97	418	0.90	0.013	1.82
KE	12.5	3.7	0.1021	6.8	0.00924	75	525	0.71	0.011	1.19
Mean	6.3	4.1	0.1119	6.9	0.00981	74	489	0.77	0.012	1.27
s.d.	4.4	1.5	0.0429	2.8	0.00263	17	45	0.07	0.002	0.36

Table 4 Kinetic parameters following intravenous administration of lignocaine hydrochloride (100 mg) in six epileptic patients

Subject	A ($\mu\text{mol l}^{-1}$)	B ($\mu\text{mol l}^{-1}$)	α (min^{-1})	$T_{1/2}^{\alpha}$ (min)	β (min^{-1})	$T_{1/2}^{\beta}$ (min)	$AUC_{0-\infty}$ ($\mu\text{mol l}^{-1} \text{min}^{-1}$)	Serum clearance (l min^{-1})	Serum clearance ($\text{l min}^{-1} \text{kg}^{-1}$)	$V_d \beta$ (kg^{-1})
JK	4.4	3.0	0.0675	10.3	0.00889	78	412	0.91	0.013	1.46
AW	13.4	4.8	0.2077	3.3	0.01043	66	530	0.71	0.013	1.25
PC	2.4	2.3	0.0913	7.6	0.00604	115	409	0.92	0.018	2.98
EW	—	5.5	—	—	0.01403	49	428	0.88	0.017	1.21
DT	4.8	4.0	0.0818	8.4	0.01167	59	417	0.90	0.012	1.03
SH	10.8	5.1	0.1920	3.6	0.01244	56	480	0.78	0.014	1.12
Mean	7.1	4.1	0.1281	5.6	0.01058	70	446	0.85	0.014	1.51
s.d.	4.7	1.3	0.0663	3.0	0.00260	24	49	0.09	0.002	0.73

in modifying the disposition kinetics of lignocaine after intravenous administration.

The kinetics of lignocaine after oral administration have been less extensively investigated. Although the drug has been administered orally in a number of studies (Boyes *et al.*, 1971; Keenaghan & Boyes, 1972; Adjepon-Yamoah & Prescott, 1973; Adjepon-Yamoah, Scott & Prescott, 1974; Benowitz *et al.*, 1974a; Finlayson, Prescott, Adjepon-Yamoah & Forrest, 1974; Bending *et al.*, 1976) and therapeutic effectiveness of this route has been claimed (Parkinson & Margolin, 1970), available information on the plasma concentrations obtained after comparable doses is controversial (Eisinger & Hellier, 1969; Parkinson & Margolin, 1970; Boyes *et al.*, 1971; Adjepon-Yamoah, Scott & Prescott, 1973). Our value of 37% for lignocaine bioavailability in normal subjects is in extremely good agreement with recent studies (Boyes *et al.*, 1971; Bending *et al.*, 1976) in which the serum concentration of the drug was measured by specific gas-chromatographic techniques. Experimental data in animals and in man indicate that the low oral availability of lignocaine is due to extensive first-pass metabolism in the liver. The urinary recovery of radioactivity is similar after oral and intravenous treatment with tritium-labelled lignocaine in rats and dogs (Keenaghan *et al.*, 1972) and, in the latter species, infusion of lignocaine into the portal vein results in peripheral plasma

concentrations comparable to those obtained after oral administration (Boyes, Adams & Duce, 1970). In man, a kinetic analysis of the rate of appearance of lignocaine in the systemic circulation after oral administration also indicates that the drug is readily absorbed from the gastrointestinal tract (Boyes *et al.*, 1971).

In the present study, the perfusion limited model appeared to be adequate to describe the pharmacokinetics of lignocaine in the normal volunteers. There was a relatively good agreement between predicted and observed bioavailability and estimates of liver blood flow (LBF) for each subject were close to the commonly accepted physiological value. Although prolonged infusions of lignocaine may increase LBF (Wiklund, 1977), the effect is unlikely to be produced by brief (5–8 min) infusions (Lalka *et al.*, 1976) or at the serum concentrations attained in the present study.

In epileptic patients, the estimates of hepatic blood flow were lower than the average values described in the literature and, in turn, observed bioavailability was lower than predicted. Although, as discussed below, LBF values in epileptic patients may have been underestimated, our data support recent suggestions that hepatic blood flow may not increase significantly during enzyme-induction in man (Roberts, Jackson, Halliwell & Branch, 1976; Alván *et al.*, 1977), in contrast to animal findings (Ohnhaus,

Table 5 Serum lignocaine concentration values after oral administration of lignocaine hydrochloride monohydrate (750 mg) in six healthy subjects and in six epileptic patients

Time after administration (min)	Serum lignocaine concentration ($\mu\text{mol/l}$)									
	15	30	45	60	90	120	150	180	210	240
<i>Healthy subjects</i>										
AT	2.5	10.2	11.0	9.2	7.3	4.8	4.6	4.1	2.8	2.3
GM	10.1	15.5	11.7	8.9	6.9	4.5	3.8	2.7	2.2	1.6
MD	1.6	8.3	9.6	6.8	6.8	4.4	3.3	2.9	2.1	1.6
GS	7.0	8.5	7.3	6.6	3.7	2.7	2.0	1.5	0.9	0.6
TT	1.2	2.1	5.8	4.4	3.6	2.8	2.0	1.7	1.4	1.2
KE	1.2	3.4	6.4	7.8	8.5	6.7	4.8	3.8	2.9	2.1
Mean	3.9	8.0	8.6	7.3	6.2	4.3	5.4	2.7	2.0	1.6
s.d.	3.7	4.8	2.6	1.7	2.0	1.5	1.2	1.0	0.8	0.6
<i>Epileptic patients</i>										
JK	0.7	2.3	2.5	2.4	1.3	0.8	0.6	0.5	0.3	0.3
AW	2.6	7.3	9.6	7.7	5.1	3.2	2.1	1.5	1.2	0.6
PC	0.3	0.5	0.8	1.7	1.8	1.3	1.1	1.0	0.8	0.6
EW	1.4	3.0	2.7	2.6	1.7	1.4	1.0	0.9	0.4	0.3
DT	1.5	1.7	1.5	1.5	1.4	1.3	0.9	0.7	0.6	0.4
SH	3.2	5.8	5.5	4.8	3.8	2.4	1.9	1.4	1.0	0.7
Mean	1.6	3.4	3.8	3.5	2.5	1.7	1.2	1.0	0.7	0.5
s.d.	1.1	2.6	3.3	2.4	1.6	0.9	0.8	0.4	0.3	0.2

Lignocaine 1 $\mu\text{mol/l}$ $\equiv$ 0.23 $\mu\text{g/ml}$.

Table 6 Kinetic parameters following oral administration of lignocaine monohydrate (750 mg) in six normal subjects, and a comparison of oral and intravenous data

Subject	Single oral dose (750 mg)			Bioavailability				Intrinsic clearance (lmin ⁻¹)
	β (min ⁻¹)	$T_{1/2}$ (min)	Peak concentration ($\mu\text{mol l}^{-1}$)	Time of peak (min)	$AUC_{0-\infty}$ ($\mu\text{mol l}^{-1} \text{ min}$)	Predicted	Observed	
AT	0.00733	94	11.0	45	1655	0.42	0.46	1.9
GM	0.00937	74	15.5	30	1581	0.39	0.46	2.0
MD	0.00904	76	9.6	45	1258	0.37	0.38	2.5
GS	0.01171	59	8.5	30	898	0.41	0.26	3.4
TT	0.00651	106	5.8	45	792	0.29	0.27	4.0
KE	0.00928	74	8.5	90	1450	0.44	0.39	2.1
Mean	0.00887	80	9.8	47	1272	0.38	0.37	2.6
s.d.	0.00181	17	3.3	22	359	0.06	0.09	0.9

Table 7 Kinetic parameters calculated following oral administration of lignocaine monohydrate (750 mg) in six epileptic patients, and a comparison of oral and intravenous data

Subject	Single oral dose (750 mg)			Bioavailability				Intrinsic clearance (lmin ⁻¹)
	β (min ⁻¹)	$T_{1/2}$ (min)	Peak concentration ($\mu\text{mol l}^{-1}$)	Time of peak (min)	$AUC_{0-\infty}$ ($\mu\text{mol l}^{-1} \text{ min}$)	Predicted	Observed	
JK	0.00966	72	2.5	45	278	0.29	0.10	11.2
AW	0.01308	53	9.6	45	932	0.45	0.25	3.4
PC	0.00648	107	1.8	90	353	0.27	0.12	9.0
EW	0.00845	82	3.0	30	376	0.31	0.12	8.4
DT	0.00845	82	1.7	30	313	0.29	0.11	10.2
SH	0.01071	65	5.8	30	725	0.39	0.21	4.3
Mean	0.00947	77	4.1*	45	496**	0.33	0.15**	7.7*
s.d.	0.00226	18	3.1	23	268	0.07	0.06	3.2

* $P < 0.01$, ** $P < 0.001$ Student's t -test compared with parameters derived in normal subjects (Table 3).

Thorgeirsson, Davies & Breckenridge, 1971; Branch, Shand, Wilkinson & Nies, 1974). Indeed, the observation that serum clearance in the patients was only marginally greater than in the normal volunteers is evidence against a markedly increased LBF in the former group.

A slight shortening of the serum half-life of lignocaine has been previously described in epileptic patients (Heinonen, Takki & Jahro, 1970) and considered as evidence of induced metabolism. Although this conclusion is probably correct, it must be appreciated that the half-life and clearance of lignocaine are more dependent on the rate of LBF than on the metabolizing capacity of the organ (Stenson *et al.*, 1971). Provided the absorption is complete and the kinetics are first-order, the latter is best estimated by measuring the oral availability (*oral clearance*) which is equivalent to *intrinsic clearance* as defined by Wilkinson & Shand (1975) and as calculated by us. The oral availability was considerably lower in our patients and this (together with the strong correlation between experimental values and those calculated from intravenous data) provides evidence of induction of first-pass metabolism. However, the fact that the reduction in bioavailability was greater than predicted by the perfusion limited model suggests that other factors may be operating, some of which are not necessarily related to enzyme induction. These include reduced absorption, increased metabolism within the gastrointestinal wall, and decreased binding of the drug to red cells in the epileptic patients. Each of these possibilities would result in an underestimation of LBF in the former group. Alternatively, it might be argued that the oral availability was artificially elevated in the non-induced subjects by the occurrence of saturation kinetics during the absorption process. The agreement between predicted and observed bioavailability in the normal subjects does not support such an hypothesis and, although dose-dependent kinetics have been reported during intravenous infusions

(Lalka *et al.*, 1976) at least two separate multiple-dose studies failed to show any change in lignocaine bioavailability after single oral doses ranging from 100 to 500 mg (Boyes *et al.*, 1971; Bending *et al.*, 1976).

In the present study, therapeutic serum lignocaine concentrations ($\geq 6 \mu\text{mol/l}$) were obtained in five out of six normal subjects after a 750 mg oral dose. However, the critical issue determining the clinical usefulness of oral lignocaine is the possible toxicity of metabolites which accumulate in comparatively high concentrations when the drug is administered by this route. There have been an increasing number of reports suggesting that these metabolites, particularly MEGX, may be partly responsible for signs of central nervous system toxicity (Beckett, Boyes & Appleton, 1966; Boyes *et al.*, 1971; Blumer, Strong & Atkinson, 1973; Strong *et al.*, 1973; Nation *et al.*, 1977). In our study, however, adverse effects were less prominent after relatively large oral doses than after a single intravenous injection and appeared to be related to the concentration of the parent drug. We feel that further investigations are required to evaluate the potential toxicity of lignocaine metabolites.

Karlsson, Collste & Rawlins (1974) have reported a pharmacodynamic interaction between phenytoin and lignocaine, leading to potentiation of toxic effects when these agents are used in combination. Although this observation was not confirmed in our study, the experimental conditions were markedly different, particularly in respect of the lignocaine concentration achieved. Since both drugs can be used in combination for the treatment of cardiac dysrhythmias and status epilepticus (Bernhard, Bohm & Hojeberg, 1955) a possible interaction may have important clinical implications.

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Note added in proof:

Complete gastro-intestinal absorption of lignocaine hydrochloride has been recently demonstrated in five patients with hepatic cirrhosis and porto-caval shunt (Huet, Le Lorier, Pomier & Marleau, 1979).

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