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The metabolism and excretion of lignocaine in man

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The urinary excretion of lignocaine and monoethylglycinexylidide (MEGX) has been studied in man. The finding that MEGX is a major metabolite of lignocaine in man is discussed in relation to studies in animals reported by other workers. An analogue computer model was constructed to simulate the metabolism and excretion of lignocaine. By varying the model parameters it was possible to obtain good agreement between the calculated and empirical excretion data for both lignocaine and its metabolite MEGX. Because of this good agreement, the computer was used to predict body levels of the compounds after a dose of lignocaine.

DESPITE the extensive clinical use of lignocaine, little is known of its biological fate in man, although extensive studies, both *in vivo* and *in vitro*, have been made in animals. Sung & Truant (1954) reported that in man (two subjects) only 3–11% of an administered dose of lignocaine was excreted unchanged in the urine. More recently, Eriksson & Granberg (1965) found that the renal clearance was affected markedly by changes in urinary pH but not significantly by urine flow rate.

After intravenous administration of lignocaine to dogs, McMahon & Woods (1951a) found no evidence for the splitting of the amide bond but, based on an increase in the excretion of organic sulphate, they suggested ring hydroxylation followed by conjugation with sulphate (1951b). However, Geddes & Douglas (1956) incubated ^{14}C-labelled lignocaine with rat liver slices and suggested that hydrolysis of the amide bond occurred, resulting in diethylaminoacetic acid as the main metabolite (Geddes, 1958). Hollunger (1960a, b) studied the properties of the liver enzyme system responsible for the metabolism of lignocaine in rabbits and found that lignocaine was dealkylated to the monoethyl derivative, which was then rapidly hydrolysed at the amide bond. The secondary amine was much more susceptible to hydrolysis than either the tertiary (lignocaine) or the primary (glycinexylidide) amine, and little or no primary amine was produced as a metabolite of lignocaine.

The present paper correlates previous results obtained in animals with the elimination of lignocaine in man.

Experimental

Materials and Apparatus. Lignocaine hydrochloride. Monoethylglycinexylidide hydrochloride (MEGX). Glycinexylidide hydrochloride. Analar diethyl ether, freshly distilled. Internal marker solution: chlorpheniramine maleate 5·7 μg/ml. 5N Sodium hydroxide. 0·5N Hydrochloric acid. Perkin Elmer Model F 11 Gas Chromatograph. TR-20R Analogue Computer (Electronics Associates Ltd.).

URINE EXCRETION TRIALS

Three male volunteers were given 5 ml intravenous injections of lignocaine hydrochloride, and on a separate occasion a 5 ml injection of MEGX, both equivalent to 50 mg of lignocaine base. The urine was maintained

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at a constant acid pH by the oral administration of ammonium chloride according to the following regimen: 2 g every 4 hr for half a day before the injection, 2 g 2 hr, and 1 g 1 hr before the injection, and 1 g every 4 hr thereafter. Urine was collected hourly for 12 hr after the dose, and one overnight sample was taken the following morning. Lignocaine and MEGX were determined in urine by the method of Beckett, Boyes & Parker (1965). Glycinexylidide, added to urine, was also detected by this procedure.

ANALYSIS OF BLOOD SAMPLES

After each lignocaine injection blood samples were taken at regular intervals for 1 hr (Beckett & others, 1965).

The extraction procedure was improved by the following modification. Blood (2 ml), water (3 ml), carbon tetrachloride (1 ml) and 5N sodium hydroxide (0·5 ml) were placed in a glass-stoppered centrifuge tube. The mixture was shaken (5 min), centrifuged, and as much as possible of the aqueous layer was carefully removed and discarded. To the residual carbon tetrachloride were added 0·5N hydrochloric acid (2 ml) and 1 ml of the internal marker solution. The tube was shaken (5 min), centrifuged, and the aqueous layer transferred to a second centrifuge tube. The carbon tetrachloride layer was further extracted with 0·5N hydrochloric acid (2 ml). The combined acid extracts were made alkaline with 5N sodium hydroxide (1 ml) and the remainder of the extraction and chromatography was carried out using the previously described procedure.

COMPUTER ANALYSIS OF RESULTS

In view of the work of Hollunger (1960a, b) and Geddes (1958) with animals, the model shown in Fig. 1 is proposed as a basis for studying the

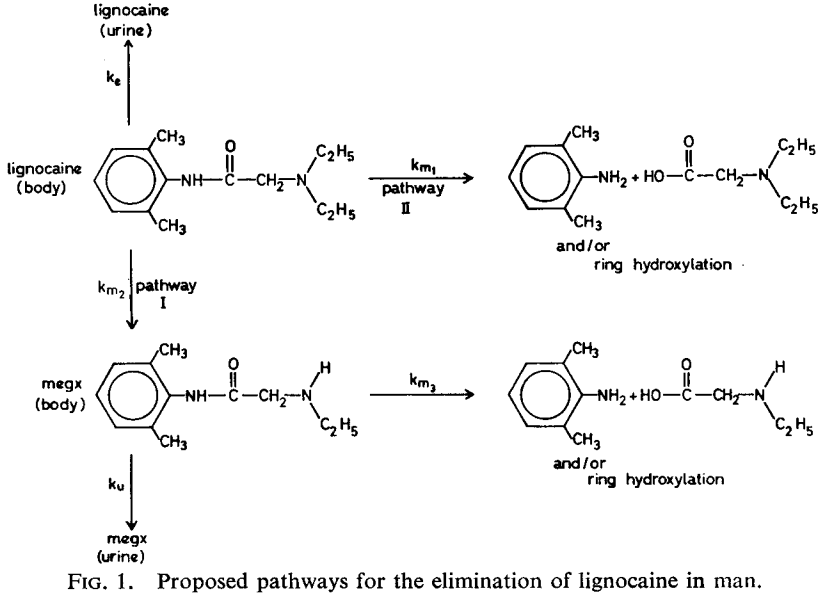

FIG. 1. Proposed pathways for the elimination of lignocaine in man.

elimination of lignocaine in man. Assuming first-order rate processes and a constant volume of distribution, the analogue computer was programmed, as illustrated diagramatically in Fig. 2, to evaluate the various rate processes involved in the model. The various rate constants were systematically altered on the computer until a fit was obtained between the computer output and the experimentally determined excretion values

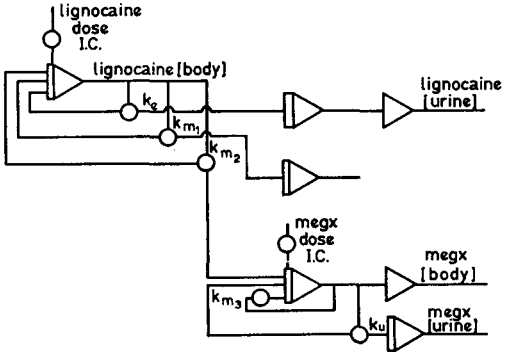

FIG. 2. Analogue computer programme for the elimination of lignocaine in man.

for lignocaine and MEGX for each subject. The MEGX excretion data were analysed by placing the initial dose value directly into the MEGX (body) compartment. When a fit was obtained between the experimental and computer curves, rate constants were determined from the appropriate potentiometer settings.

Results

The rates of excretion of lignocaine and its metabolite, MEGX, after an intravenous dose of lignocaine, alone are shown in Fig. 3. Although glycinexylidide could not be detected in any of the urine samples analysed, the primary aromatic amine (xylidine) was detected gas chromatographically after doses of lignocaine and MEGX. However, due to the very small quantities observed and the instability of this compound in aqueous solution no attempt was made to draw conclusions of a quantitative nature from these results. The 12 hr recoveries of lignocaine and MEGX in urine, after single doses of each drug, are summarised in Table 1. The

TABLE 1. THE 12 HR RECOVERIES OF LIGNOCAINE AND MEGX IN URINE EXPRESSED AS PERCENTAGES OF THE TOTAL DOSE ADMINISTERED

Subject	Dose	% of dose recovered as: Lignocaine	MEGX
P.A.	Lignocaine	7·2	3·5
	MEGX		12·5
D.E.	Lignocaine	4·1	5·0
	MEGX		12·5
J.H.	Lignocaine	6·9	4·0
	MEGX		12·3

blood levels of lignocaine, in all cases, declined rapidly from about 1 μg/ml such that after 45 min the concentration was below the limit of accurate determination by the method used.

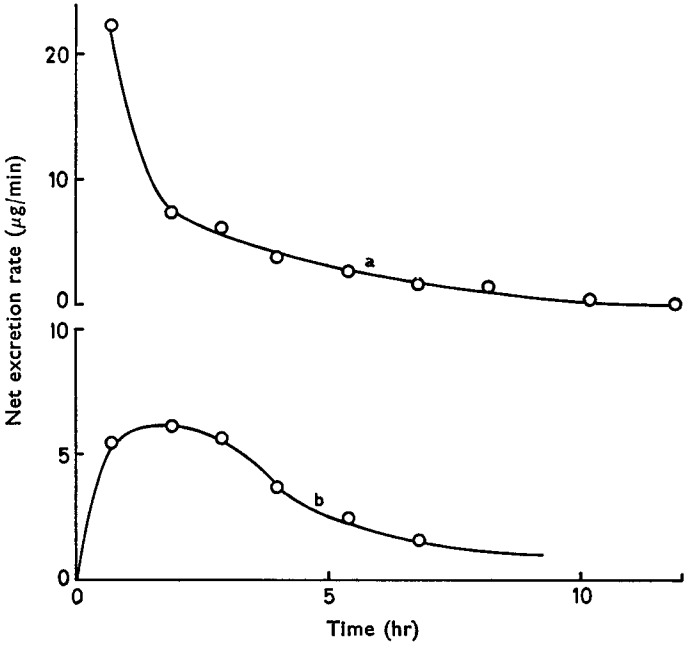

FIG. 3. Rates of urinary excretion of lignocaine (a) and MEGX (b) after an i.v. dose of lignocaine HCl equivalent to 50 mg lignocaine base. Subject P.A.

Agreement between the curves produced by the computer (continuous curves) and the experimental excretion data (points) for lignocaine and MEGX after a single dose of lignocaine is illustrated by curves (a) and (b), respectively, of Fig. 4 (subject P.A.). Similar agreement was also obtained for the other subjects. The good agreement suggested extrapolation of the excretion data to describe the amounts of the compounds in the other compartments of the model. For example, curves (c) and (d) of Fig. 4

TABLE 2. CALCULATED RATE CONSTANTS FOR THE ELIMINATION OF LIGNOCAINE AND MEGX FROM MAN AND THE PERCENTAGE OF THE TOTAL DOSE OF LIGNOCAINE METABOLISED IN EACH PATHWAY

Subject	Dose	k_e*	k_{m1}	k_{m2}	k_{m3}	k_u	Pathway: I	Pathway: II
P.A.	Lignocaine	0·027	0·190	0·161	0·771	0·074	42·8	50·2
	MEGX				0·414	0·060		
D.E.	Lignocaine	0·016	0·200	0·169	0·606	0·071	43·8	52·4
	MEGX				0·465	0·068		
J.H.	Lignocaine	0·030	0·209	0·200	0·780	0·077	45·6	47·6
	MEGX				0·425	0·061		

* Units: hr^{-1}.

represent the changes in the body levels of lignocaine and MEGX respectively with time. These are complementary to the excretion curves (a) and (b) in this figure.

Table 2 shows the rate constants calculated by the computer for each subject. Provided the assumptions inherent in the model are correct, it also shows the amount of lignocaine passing through each pathway of metabolism.

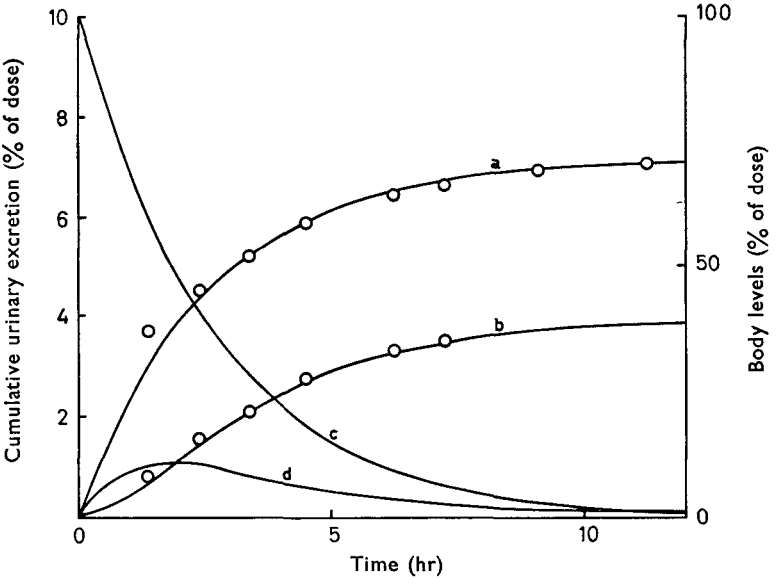

FIG. 4. Agreement between computer calculated and experimental cumulative excretion data for lignocaine (a) and MEGX (b) after a dose of lignocaine. Curves (c) and (d) are calculated body level - time plots for the same compounds. Continuous lines: analogue computer curves; open circles: experimental excretion data. Subject P.A.

Discussion

The use of an analogue computer to develop model systems which can simulate drug distribution is an established procedure (see Garrett, Thomas, Wallach & Alway, 1960; Taylor & Wiegand, 1962).

In the present study, accurate experimental data for the urinary excretion of lignocaine and its metabolite, MEGX, have been obtained under conditions of constant acid urinary pH (see Fig. 3). In the computer simulation each of the rate constants in the model has a distinct influence on the solution of the differential equations involved. With the exception of the ratio of k_{m_1} to k_{m_2}, approximations of all of the constants can easily be obtained from the experimental data by classical means. The constants presented in Table 2 were those which resulted in the best agreement between the empirical data and that calculated by the computer (see Fig. 4, curves a and b). Thus the proposed model may be used initially as a reasonable approximation of the metabolism and excretion of lignocaine in man and

the calculated results for the other compartments in the model accepted as satisfactory approximations.

The low recovery of unchanged lignocaine in the urine (see Table 1) indicates substantial metabolism of the drug in man. Since 3–5% of the lignocaine dose was excreted as MEGX, and only about 12% of a dose of MEGX is excreted unchanged (see Table 1), it may be concluded that dealkylation is probably a major pathway in the metabolism of lignocaine. As shown in Table 2, the computer indicates approximately 42% of the dose was metabolised by this pathway. Such substantial dealkylation in man is in agreement with Hollunger's (1960a, b) findings in rat and rabbit liver microsomes. The fact that glycinexylidide was not detected in any of the urine samples analysed suggests that if the dealkylation of the secondary amine MEGX occurs in man, it is a slow process.

Table 2 shows that there are differences between the sum of k_u and k_{m3} for MEGX when given as an intravenous dose and when present as a metabolite of lignocaine. Differences in the volumes of distribution of MEGX, when given intravenously and when formed as a metabolite, may explain the changes in the sum of the constants under these separate conditions: similar results have also been obtained for ephedrine and its metabolite norephedrine (Wilkinson, 1966). It has also been suggested (Portmann, McChesney, Stander & Moore, 1966) that there may be a difference in the volume of distribution for hydroxynalidixic acid when given orally and when formed as a metabolite of nalidixic acid.

The very low blood levels of lignocaine 45 min after an intravenous injection indicated a high extravascular concentration of this compound. The body levels of lignocaine and MEGX predicted by the computer (Fig. 3, curves c and d) show that, after 2 hr, 45% of the administered dose of lignocaine remains unchanged in the body and 12% is present as MEGX; the presence of MEGX in the body may contribute to the toxicity of lignocaine on prolonged administration.

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