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The Pharmacokinetics and Metabolism of the Anilide Local Anaesthetics in Neonates

I. Lignocaine

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Summary. The pharmacokinetics and metabolism of lignocaine in premature neonates was studied after subcutaneous administration. The collection of serial urine together with a limited number of blood samples from neonates enabled simultaneous computer fitting of data to a pharmacokinetic model. The disposition kinetics of lignocaine in four neonates were compared with similar data reported for adults. Neonates had prolonged $t_{1/2}$ (neonate mean: 3.16 h; adult mean: 1.80 h), and an increased total volume of distribution (neonate mean: 2.75 l/kg; adult mean: 1.11 l/kg) compared with adults. Total plasma clearance (Cl_{tp}) normalised on body weight showed no significant difference between neonates (mean: 0.610 l/h/kg) and adults (mean: 0.550 l/h/kg). The urinary excretion of lignocaine and several of its metabolites was studied in 8 neonates and 11 adults. Neonates were shown to excrete much more unchanged lignocaine (mean: 19.67%) compared with adults (mean: 4.27%) and the proportion of the dose excreted as 4-hydroxyxylidine is considerably reduced in neonates (neonate mean: 8.89%; adult mean: 63.78%). The use of the two pharmacokinetic parameters, $t_{1/2}$ and Cl_{tp}, as indices of drug elimination ability are discussed.

Key words: Lignocaine, pharmacokinetics, neonates, metabolism, renal excretion, plasma concentrations.

Recent reviews (Yaffe and Juchau, 1974; Morselli, 1976) have indicated that information about neonatal metabolism and pharmacokinetics is limited. The objective of this investigation was the study of the disposition of lignocaine in the newborn. There were two reasons for using lignocaine: firstly, a clinical situation was available in which lignocaine was being used as a local anaesthetic in neonates, and secondly, the disposition of lignocaine in adults is well known (Keenaghan and Boyes, 1972; Rowland et al., 1971). Therefore, the contribution of several important drug detoxification mechanisms in the elimination of lignocaine could be compared quantitatively between neonates and adults.

An inherent problem with pharmacokinetic studies in neonates is the limited number of blood samples which may be obtained. The collection of serial urine along with blood samples offsets this problem considerably. The simultaneous computer fitting of the data on the urinary excretion and plasma concentration of lignocaine increases the reliability of the computed estimates of pharmacokinetic parameters.

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Materials and Methods

Lignocaine hydrochloride and monoethylglycinexylidide hydrochloride (MEGX) were obtained from Astra Chemicals Pty. Ltd., Australia. Xylidine hydrochloride (2,6-dimethylaniline hydrochloride) (xylidine purchased from Merck Chemicals) and 4-hydroxyxylidine (4-hydroxy-2,6-dimethylaniline) (Rowe et al., 1930) had been previously prepared by standard methods in this department. The three internal standards used were 1-naphthylamine (Koch-Light Laboratories Ltd., England), benzhexol hydrochloride (Cyanamide Australia Pty. Ltd.) and chlormethiazole ethane-disulphonate (Astra Chemicals Pty. Ltd., Australia). Diethyl ether was of anaesthetic grade B.P. and was distilled immediately before use.

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Subjects, Dosing and Sample Collection

Adults: Eleven healthy adult male subjects (age: 24–47 years, weight: 65–80 kg) were included in this study. They were each allocated to one of two groups. Group I (Subjects A1 to A7) had urinary pH controlled at 5.2±0.2 by administration of enteric coated ammonium chloride tablets (2.0 g taken 2 h prior to dosing with lignocaine and 500 mg three times daily thereafter until completion of the study). The remaining four subjects constituted Group II (A8 to A11) and had uncontrolled urinary pH. Urine was collected from all subjects for the 24 hour prior to the administration of 50 mg of lignocaine hydrochloride (Xylocaine® 0.5% Plain) as a constant rate intravenous infusion over 5 min via the antecubital vein. A bulk urine sample was collected from each subject for 48 h after dosing.

Neonates: Eight male neonates in the late stage of recovery from respiratory ailments (respiratory distress syndrome and hyaline membrane disease), but still in the intensive care nursery, were included in the study. Informed consent was obtained from the parents prior to inclusion of their neonates in this study. The eight neonates were born prematurely, with gestational ages from 26 to 38 weeks, and their post-natal ages varied from 5 to 42 days. These neonates routinely received small subcutaneous doses of local anaesthetic in the forearm to facilitate collection of radial arterial blood samples which were then analysed for blood gases and pH. On one such occasion, each neonate received lignocaine. Four of the eight neonates (Group I; neonates N1 to N4) required further monitoring of blood gases and pH. When subsequent sampling was necessary procaine was used as the local anaesthetic and additional blood (0.8–1.0 ml) was withdrawn for lignocaine and MEGX determinations. These neonates had urine collected in a serial manner for 48 h using a paediatric urine collector fitted with an in-dwelling polythene tube. The presence of the in-dwelling tube minimised the number of changes of the urine collector. The volume and pH of each urine sample was recorded as was the time of each micturition. For the remaining four neonates (Group II; neonates N5 to N8), further monitoring of blood gases and pH was not required after the initial dosing with lignocaine and consequently the plasma concentration-time profile of lignocaine was not determined for these neonates. Urine was collected as in Group I, but was pooled to form bulk 48 h collections. Creatinine clearance was determined on the day after dosing for the four Group I neonates. Blank samples of urine and blood were obtained from all neonates prior to the administration of lignocaine.

Assay Procedures

Lignocaine and MEGX: The assay procedure as described by Nation et al. (1976) was used for the quantitation of lignocaine and MEGX in urine and plasma.

4-Hydroxyxylidine (free and conjugated): The method of Thomas et al. (1976) was used for the determination of free and conjugated 4-hydroxyxylidine with the modification that the ethereal extraction at pH 14 was excluded.

Xylidine (total): Urine samples (2.0 ml) plus HCl (1.0 ml, 8.5 M) were placed in 15 ml stoppered centrifuge tubes and maintained at 100° for 1 h. The tubes were cooled and internal standard added (100 µl of chlormethiazole ethanedisulphonate, 5 µg/100 µl). This mixture was basified (2.0 ml, 10M NaOH) and extracted with diethyl ether (2 × 5 ml) for 1 min using a vortex mixer. The combined ethereal solutions were extracted with HCl (1 ml, 1M) for 1 min and the ethereal layer discarded. The aqueous phase was basified (0.5 ml, 10M NaOH) and extracted as before with diethyl ether (2 × 5 ml). The ether was concentrated to 10 µl in an evaporation tube (15 ml fitted with a 50 µl capacity capillary tip). The total ethereal residue was injected into the gas-liquid chromatograph (GLC) equipped with a glass column (2 m × 3 mm I.D.) packed with 3% OV-17 on Gaschrom Q (100/120 mesh) at 150° C.

Gas-liquid Chromatography and Calibration Data: All assays were performed using a Hewlett Packard model 5710A GLC fitted with a flame ionization detector. Flow rates were maintained at 50, 60 and 240 ml/min for N_2, H_2 and air, respectively. Column inlet temperature was 200° C and the detector was 250° C. Linear calibration curves, passing through the origin, were obtained for lignocaine and MEGX (50 ng to 50 µg); 4-hydroxyxylidine (200 ng to 20 µg) and xylidine (100 ng to 5 µg). Each curve was prepared by assaying blank samples of urine or plasma to which known amounts of lignocaine or metabolite were added. 4-Hydroxyxylidine was shown to be stable during the acid treatment necessary to effect hydrolysis of its conjugates. All samples of blank plasma and urine were found to be free of chromatographically interfering constituents.

Kinetic Analysis

The nonlinear least squares regression program, NONLIN (Metzler, 1969), was used to compute data. An attempt was first made to describe the phar-

macokinetics of lignocaine in neonates using a one compartment open model with first order absorption and elimination processes. Since early plasma time points were consistently underestimated, a model assuming intravenous dosage was employed (Fig. 1). The use of this model assumes that the subcutaneous dose of lignocaine is fully available. The relationship describing the drug concentrations (C) in the body with time (t) is given in Equation (1).

$$C = \frac{D}{V_d} \cdot e^{-k_{el} \cdot t} \quad (1)$$

V_d is the volume of distribution, D is the very rapidly absorbed subcutaneous dose and k_{el} the rate constant of elimination (equals the sum of k_{ren} and k_m, the rate constant for renal excretion of unchanged drug and combined rate constant for metabolism, respectively). The rate of urinary excretion of unchanged lignocaine $\frac{\Delta Xu}{\Delta t}$ is related to time (t) in Equation (2).

$$\frac{\Delta Xu}{\Delta t} = D \cdot k_{ren} \cdot e^{-k_{el} \cdot t} \quad (2)$$

The simultaneous solution of Equations (1) and (2) was obtained for k_{ren}, k_{el} and $1/V_d$ by iteration about graphically determined initial estimates of these parameters. Both plasma concentration and urinary excretion rate data were weighted (Boxenbaum et al., 1974) using Equation (3).

$$W_i = N \cdot \frac{1/Y_i^2}{\sum_{i=1}^{N} 1/Y_i^2} \quad (3)$$

Where W_i is the weight of the ith observation, N is the number of points for each observation (plasma or urine) and Y_i is either the ith plasma concentration or rate of urinary excretion value.

Statistical Analysis

Non parametric tests were used for statistical analysis. Comparisons of groups of data were done using the Mann-Whitney U Test (Goldstein, 1964) and linear correlation coefficients were determined using a Rank-Correlation test (Dixon and Massey, 1969).

Results

The semilogarithmic plots of both the experimentally determined and model predicted values of lignocaine's plasma concentration and urinary excretion rate against time for neonates N1, N2, N3 and N4 are contained in Figure 2. Also presented are linear

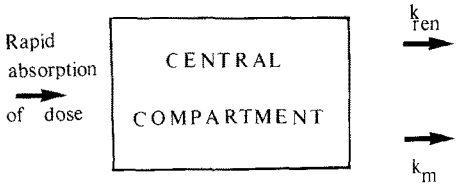


Fig. 1. One compartment open model describing the disposition of lignocaine in neonates receiving a rapidly absorbed subcutaneous dose. k_e is the rate constant for the renal excretion of unchanged lignocaine and k_m is the combined rate constant for metabolism

plots of urine flow rate and cumulative urinary excretion of lignocaine versus time. Excessive scatter in the data was observed during the latter stages of the urinary excretion rate plots because of the very small amounts of drug being excreted by this time.

These later points were considered unrepresentative of the drug's kinetics and were excluded in the fitting of the data. At least 97% of the amount of lignocaine ultimately eliminated unchanged had been excreted before any data was excluded from the calculations. The urinary excretion rate data of N1 was excluded from computer treatment since the highly variable urine flow rate precluded any meaningful interpretation of urinary excretion rate (Fig. 2 a). Experimental details of the four neonates (N1, N2, N3 and N4) and computer estimates of model parameters are contained in Table 1. A comparison of lignocaine's disposition kinetics between neonates and adults is presented in Table 2. In this table the estimates of pharmacokinetic parameters from plasma concentration-time data in adults were calculated from those reported by Rowland et al. (1971). The metabolic excretion profiles of lignocaine determined for adults in this study are given in Table 3. Group I consists of subjects that had urine pH controlled at 5.2±0.2, whilst Group II had uncontrolled urine pH.

Urinary metabolite profiles for all eight neonates are also contained in this table. All values are expressed as a percentage of the dose administered. The adequacy of a 48 h urine collection was demonstrated by the presence of only trace amounts of lignocaine and metabolite in urine collected later than 36 h after dosing. The metabolic excretion profile of lignocaine in neonates was compared with profiles obtained for adult groups I and II. This comparison is summarised in Table 4.

Discussion

A problem encountered in making comparisons between the pharmacokinetics of lignocaine in neonates and adults was that a single compartment model ade-

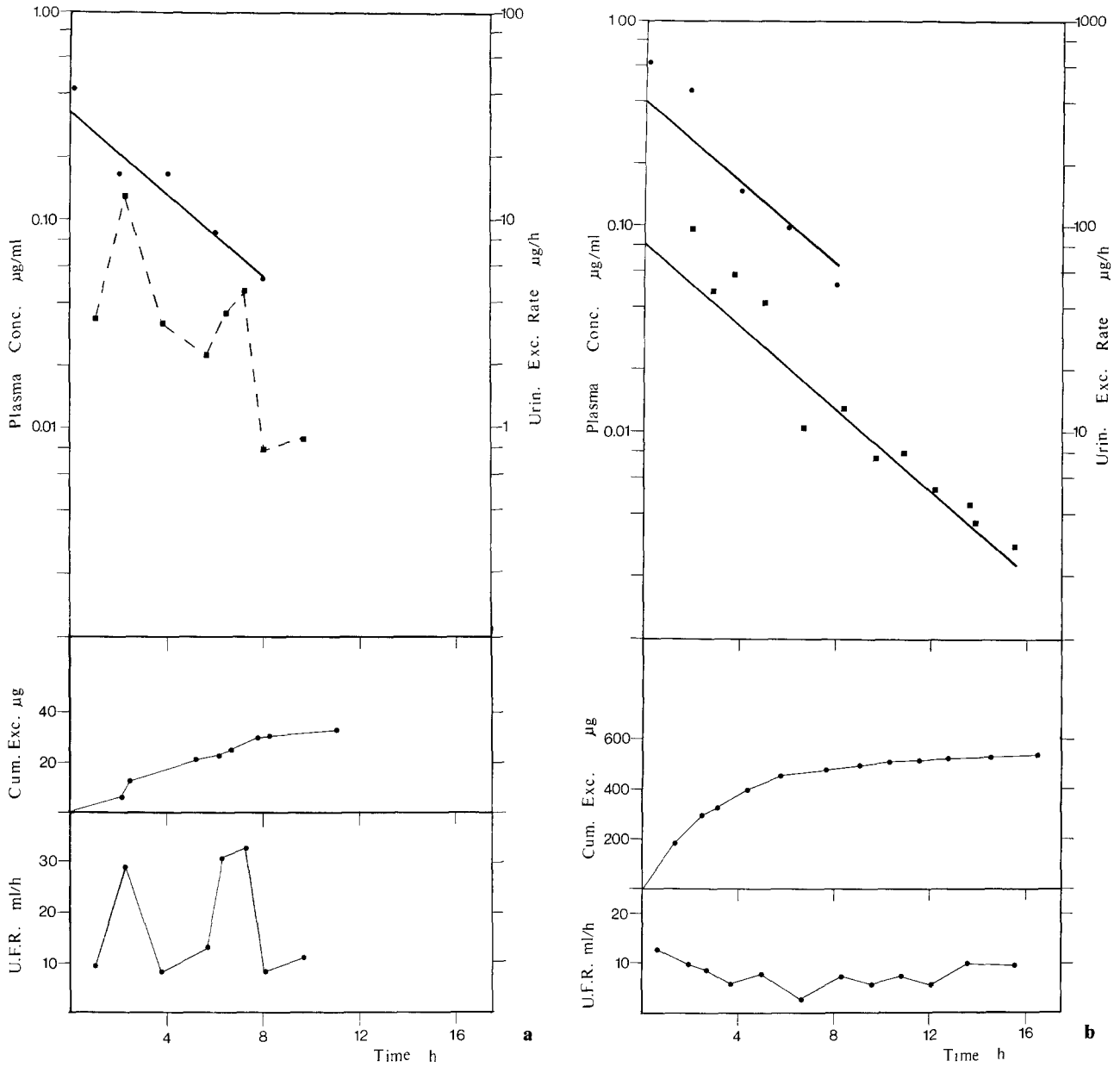


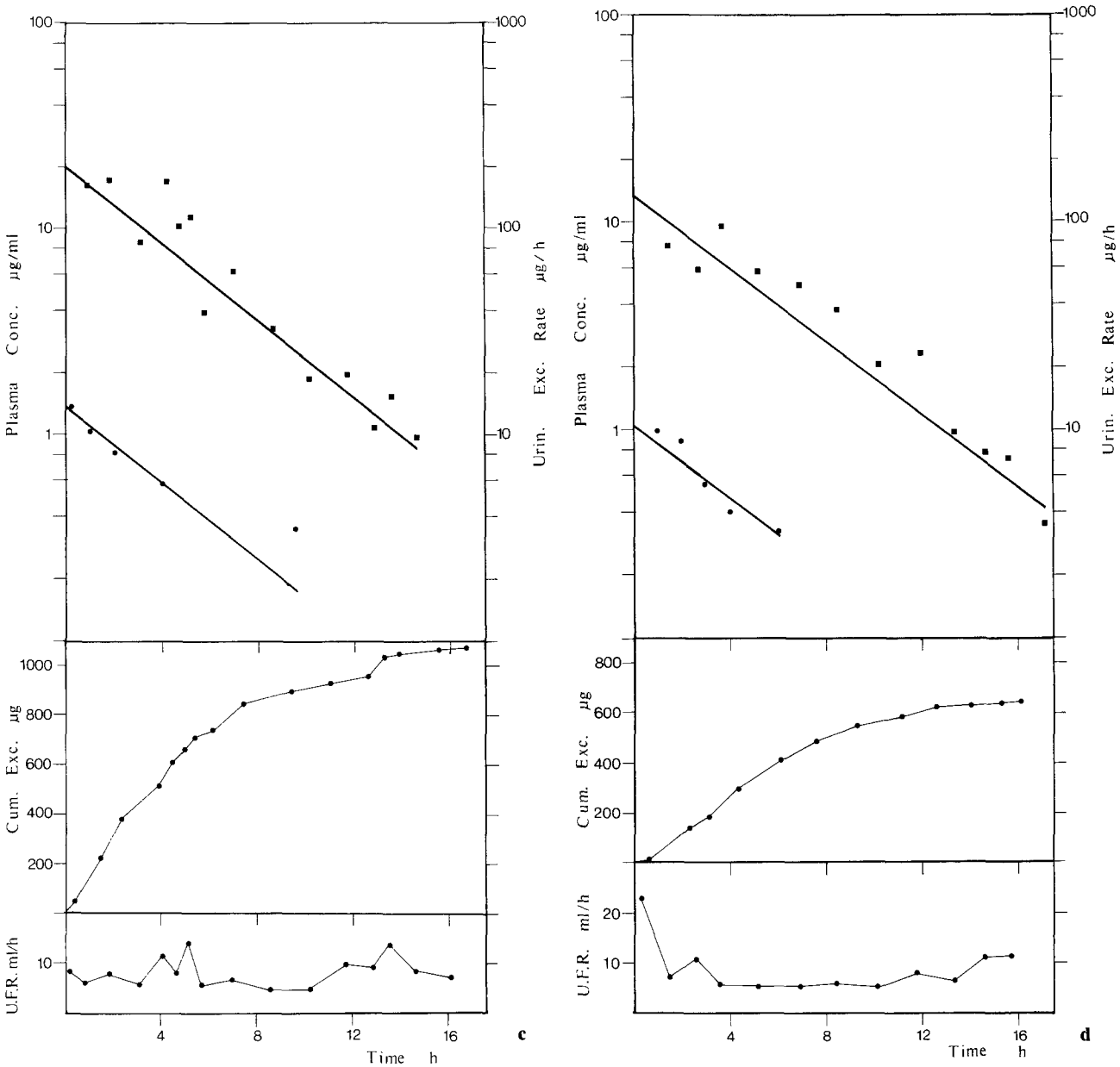
Fig. 2. The following data for N 2–N 4 (a, b, c, d) have been plotted against time after subcutaneous dosing of the neonate with lignocaine: the logarithm of urinary excretion rate (Urin. Exc. Rate ■ data points are experimental line is model predicted); the logarithm of the plasma concentration of lignocaine (Plasma Conc., ● data points are experimental, line is model predicted); cumulative urinary excretion of lignocaine (Cum. Exc.); urine flow rate (U. F. R.)

quately described the neonatal data whereas a two compartment model was necessary for the adult data. The reasons for this difference are not clear. They may either be due to limitations of methods used or truly reflect a basic difference in lignocaine's disposition between neonates and adults.

It may well be that the limited number of plasma samples which were available from neonates, due to ethical and practical constraints, masked a rapid α distribution phase. Alternatively, neonates may fundamentally handle lignocaine differently from adults. This would not be surprising in light of the significant difference in the pattern of tissue distribution in neonates as compared with adults.

Because of this problem more reliance is placed on estimates of model independent pharmacokinetic parameters such as terminal half-life and clearance in the following discussion. Model dependent parameters such as V_d, V_c and V_{ss}, while they have been computed, are limited in providing information with which neonates and adults may be compared.

The comparison of lignocaine's pharmacokinetics



in adults and neonates is presented by consideration of the three stages; absorption, distribution, and elimination.

Absorption

It was not the purpose of this study to characterise the absorption kinetics of lignocaine following subcutaneous administration. It is, however, pertinent to note that drug absorption was very rapid as indicated by the early attainment of peak plasma levels (Fig. 2).

Distribution

The volume of distribution of the compartment from which elimination occurs is much greater in neonates (mean V_d: 2.75 l/kg) than in adults (mean V_c: 0.44 l/kg) (Table 2). This difference may be in part due to drug disposition in the adult being of necessity described by a two compartment open model whereas disposition in the neonate is adequately described with a one compartment open model. Therefore, it appears in neonates that lignocaine readily distributes into the peripheral tissue that comprises

Table 1. Experimental details and computer estimates of pharmacokinetic parameters[a] for neonates N1, N2, N3 and N4

Detail or parameter	Neonates			
	N1	N2	N3	N4
Gestational \ Post Partum Age (Weeks) \ Age (Days)	36/10	29/9	26/42	34/14
Weight (kg)	3.2	1.2	1.5	2.2
Dose (mg)	3.0	2.4	3.0	4.0
Terminal Phase $t_{1/2}$ (h)	3.06	3.03	3.25	3.30
Fraction Excreted unchanged (F)	0.015[b]	0.144[c]	0.313[c]	0.167[c]
k_{el} (h^{-1})	0.227	0.229	0.213	0.203
k_{ren} (h^{-1})	0.003	0.033	0.067	0.034
V_d (l/kg)	2.83	4.99	1.44	1.72
Cl_{tp} (l/h/kg)[d]	0.642	1.141	0.307	0.350
Cl_{rp} (l/h/kg)[e]	0.010	0.165	0.096	0.058
Cl_{hp} (l/h/kg)[f]	0.632	0.976	0.211	0.291
Creatinine Clearance (l/h/kg)	0.096	0.064	0.052	0.112
Urine Flow Rate (l/h/kg)	0.0041	0.0062	0.0054	0.0042
Urine pH Range	6.8–7.5	5.0–5.5	5.4–6.0	5.0–5.5
Renal Concentration Factor[g]	23.5	10.2	9.6	26.5

[a] Plasma and urine data were computer fitted
[b] Experimentally determined value of F
[c] Computer estimate of F ($= {}^{k}e/k_{el}$)
[d] $Cl_{tp} = k_{el} \times V_d$
[e] $Cl_{rp} = k_{ren} \times V_d$
[f] $Cl_{hp} = Cl_{tp} - Cl_{rp}$
[g] Renal Concentration factor $= \frac{\text{Creatinine Clearance}}{\text{Urine Flow Rate}}$

V_p (volume of distribution of the peripheral compartment) in adults. A comparison of the total volume of distribution in adults, V_{ss} (mean: 1.11 l/kg) with the total volume of distribution in neonates, V_d (mean: 2.75 l/kg) indicates that neonatal total volume of distribution of lignocaine is still greater than adults (two and a half fold). The diminished binding of lignocaine to plasma proteins in neonates may contribute to this. Tucker et al. (1970 a, b) reported that 70% of plasma lignocaine was bound to adult plasma protein whereas in neonates only 20% of lignocaine was plasma protein bound. For the majority of drugs whose distribution has been studied in neonates and adults (Morselli, 1976), the apparent volume of distribution has been found to be greater in neonates.

Elimination

The value of the terminal phase half life ($t_{1/2}$) in adults (mean: 1.80 h^{-1}) is significantly less than that value obtained in neonates (mean: 3.16 h^{-1}). Our estimates of terminal phase half life in neonates are in agreement with estimates by Brown et al. (1975). The narrow range of values of $t_{1/2}$ in neonates (3.03 to 3.30 h) suggests a uniformity in the ability of neonates to eliminate lignocaine. The parameter, $t_{1/2}$, however, is not a good index for comparing elimination when distributional changes occur since it is a hybrid of both distribution and elimination in multi-compartment systems (Perrier and Gibaldi, 1974). The considerable alteration for lignocaine in the apparent volume of distribution parameters with age, compromises the usefulness of $t_{1/2}$ for comparing adult and neonatal elimination. Total plasma clearance, Cl_{tp}, is another index with which to compare the elimination of lignocaine between neonates and adults. The direct contribution of a change in volume of distribution can be observed using this parameter. The value of Cl_{tp} in neonates (mean: 0.610 l/h/kg) is not significantly different from that value obtained in adults (mean: 0.550 l/h/kg) (Table 2). From this comparison it can be seen that neonates eliminate lignocaine as effectively as adults when the data is normalised on body weight. Further insight into the elimination of lignocaine by neonates compared to adults can be gained by examining the separate contribution of renal (Cl_{rp}) and hepatic (Cl_{hp}) clearance.

Renal clearance: The mean estimate of Cl_{rp} in neonates (0.082 l/h/kg) is significantly greater than that in adults (0.011 l/h/kg). There is, however, a significant inverse correlation between Cl_{rp} and age (gestational + postnatal) for these four neonates and the estimate of Cl_{rp} (0.010 l/h/kg) for the oldest newborn N1, is similar to the mean (0.011 l/h/kg) for the adults. A brief consideration of the developmental

Table 2. Comparison of pharmacokinetic parameters for neonates and adults (mean and range)

Parameter	Adults[a] (10 subjects)	Neonates (4 subjects)	Test for significant[f] difference
V_c (l/kg)[b]	0.44 (0.28–1.03)		
V_d (l/kg)[c]		2.75 (1.44–4.99)	+[h]
V_{ss} (l/kg)[c]	1.11 (0.58–1.91)		
V_d (l/kg)[c]		2.75 (1.44–4.99)	+[h]
Terminal Phase Half-life $t_{1/2}$ (h)	1.80 (1.22–2.23)	3.16 (3.03–3.30)	+[h]
Fraction Excreted Unchanged (F)	0.019[d] (0.006–0.047)	0.160 (0.015–0.313)	+[h]
Elimination Rate Constant k_{el} (h^{-1})	1.450 (0.660–2.220)	0.218 (0.015–0.313)	+[g]
Renal Excretion Rate Constant k_{ren} (h^{-1})	0.028 (0.013–0.043)	0.034 (0.003–0.067)	–
Total Plasma Clearance Cl_{tp} (l/h/kg)	0.550 (0.318–0.726)	0.610 (0.307–1.141)	–
Renal Plasma Clearance Cl_{rp} (l/h/kg)	0.011 (0.006–0.014)	0.082 (0.010–0.165)	+[h]
Hepatic Plasma Clearance Cl_{hp} (l/h/kg)	0.539 (0.312–0.712)	0.528 (0.211–0.976)	–
Urinary Flow Rate (l/h/kg)	0.0006[d] (0.0005–0.0007)	0.0050 (0.0041–0.0062)	+[h]
Renal Concentration Factor	100[e]	17.5 (19.6–26.5)	+[g]

[a] Adult data calculated from Rowland et al. (1971)
[b] V_c (Volume of distribution of the central compartment)
[c] V_{ss} (Total volume of distribution) V_d (volume of distribution)
[d] Adult data (Group II)
[e] Renal Concentration factor calculated from Gibaldi and Perrier (1975)
[f] Test for significant differences using the Mann-Whitney U Test
[g] Neonates < Adults ($P = 0.025$)
[h] Neonates > Adults ($P = 0.025$)

changes in renal physiology may clarify the differences in Cl_{rp} and metabolic profile with age (Tables 3 and 4). The lower neonatal glomerular filtration rate (Loggie et al., 1975) which acts to decrease the renal excretion of lignocaine, appears to be offset by – (a) an increase in the fraction of unbound lignocaine in neonatal plasma (Tucker et al., 1970 a, b), (b) a decrease in tubular reabsorption due to a reduced ability of neonates to concentrate urine (Table 2), (c) a lower urinary pH in neonates (Table 3). The balance of these factors together with an increase in the volume of distribution of lignocaine in neonates results in an increased Cl_{rp} in neonates relative to adults.

Hepatic Clearance: Elimination, other than renal, was assumed to be hepatic elimination. The mean value of Cl_{hp} for adults (0.539 l/h/kg) was not statistically different to that of neonates (0.528 l/h/kg). Since the hepatic blood flow to the neonatal liver is unknown it is not possible, using the estimates for neonatal Cl_{hp}, to calculate the hepatic extraction ratio (E) for lignocaine. An estimate of E for each of these newborns would provide a better index of the

Table 3. Experimental details and metabolic profiles for adults (Group I and II) and neonates

Subject	Age (y)	wt. (kg)	Dose (mg)	Mean Urine pH	% of Dose 48 h collection					
					Lignocaine	MEGX	Total Xylidine	Total 40H Xylidine	Unconjugated 40H Xylidine	Total Recovery
A1	21	64	50	5.2	2.81	6.65	2.97	52.46	0.05	64.94
A2	21	75	50	5.2	1.16	2.49	2.50	74.00	0.00	80.15
A3	24	65	50	5.4	10.73	5.08	2.02	68.87	0.00	86.70
A4	21	65	50	5.3	4.88	8.62	2.82	63.65	0.05	80.47
A5	25	70	50	5.3	2.74	4.77	3.44	64.79	0.00	75.74
A6	46	82	50	5.3	5.18	2.24	1.34	59.91	0.00	68.67
A7	29	75	50	5.3	2.40	5.00	2.38	62.78	0.00	72.56
Mean ±S.D.					4.27 ±3.18	4.98 ±2.23	2.50 ±0.68	63.78 ±6.78	–	75.60 ±7.51
A8	22	67	50	6.2	1.40	4.82	2.94	63.74	0.45	73.35
A9	24	75	50	5.8	4.74	2.11	1.99	74.38	0.00	83.22
A10	25	75	50	6.8	0.56	2.54	2.21	53.15	0.00	58.46
A11	26	72	50	6.2	1.07	0.95	1.57	69.18	0.14	72.77
Mean ±S.D.					1.94 ±1.90	2.61 ±1.62	2.18 ±0.57	65.11 ±9.08	–	71.95 ±10.19
	[a]									
N1	36/10	3.2	3.0	7.1	1.48	4.20	1.85	15.21	0.00	22.74
N2	29/9	1.2	2.4	5.2	22.51	18.08	2.58	0.00	0.00	43.17
N3	26/42	1.5	3.0	5.5	36.73	16.87	2.62	4.44	0.00	60.66
N4	34/14	2.1	4.0	5.0	16.52	48.94	4.05	3.83	0.00	73.34
N5	38/8	3.0	3.0	5.1	15.67	14.11	2.21	15.29	0.00	47.28
N6	28/39	1.9	2.0	5.5	24.31	7.10	1.15	22.25	0.00	54.81
N7	34/5	3.0	6.0	5.5	19.05	29.87	4.26	4.29	0.00	57.47
N8	33/5	1.8	3.6	5.0	21.07	18.59	2.98	5.78	0.00	48.42
Mean ±S.D.					19.67 ±9.85	19.72 ±14.15	2.71 ±1.05	8.89 ±7.70	–	50.99 ±14.78

[a] Gestational age in weeks/Postnatal age in days.

Table 4. Comparison of metabolic urinary excretion profiles expressed as % of dose (mean and range) for adults and neonates

Metabolite	Neonates % of dose	Adults			
		Group I		Group II	
		% of dose	significant[a] difference	% of dose	significant[b] difference
Lignocaine	19.67 (1.48–36.73)	4.27 (1.16–10.73)	+[d]	1.94 (0.56–4.74)	+[d]
MEGX	19.72 (4.20–48.94)	4.98 (2.24–8.62)	+[d]	2.61 (0.95–4.82)	+[d]
Xylidine (total)	2.71 (1.15–4.26)	2.50 (1.34–3.44)	–	2.18 (1.57–2.94)	–
40H Xylidine (total)	8.89 (0.00–22.25)	63.78 (59.91–74.00)	+[c]	65.11 (53.15–74.58)	+[c]
40H Xylidine	0.00	0.27 (0.00–0.50)	–	0.29 (0.00–0.45)	–

[a] Test for significant difference between neonates and group I adults using the Mann-Whitney U test ($P = 0.025$).
[b] Test for significant difference between neonates and group II adults using the Mann-Whitney U test ($P = 0.025$).
[c] Neonates < Adults ($P = 0.025$)
[d] Neonates > Adults ($P = 0.025$)

maturity of their intrinsic hepatic function. It appears likely from the metabolic urinary excretion profiles presented in Table 4 that some of the metabolic pathways responsible for the elimination of lignocaine in adults are less developed in these neonates. The large degree of inter-neonatal variation in metabolic profiles (Table 3) suggests different degrees of maturation of the hepatic processes responsible for drug elimination in these premature newborns. Attempts to correlate age with the excretion of individual metabolites for the neonates was unsuccessful. There is, however, an inverse correlation between the proportion of lignocaine excreted unchanged, and age (gestational plus post-natal, Table 3).

The major metabolic pathways for lignocaine elimination in adults and neonates are N-dealkylation, amide bond cleavage, aromatic hydroxylation and conjugation.

N-dealkylation: Neonatal excretion of the N-dealkylated metabolite, MEGX, (mean: 19.72%) is significantly higher than that in adults (mean: 4.98%) (Table 4). It is possible, that the high neonatal levels of MEGX are more the result of a reduced degree of subsequent metabolism of MEGX than to a greater ability of neonates to N-dealkylate. The ability of premature neonates to N-dealkylate diazepam has been reported (Morselli et al., 1973).

Amide Bound Cleavage: The ability to cleave the amide bond to form the metabolite xylidine appears to be the same in both adults and neonates, since there was no significant difference in the proportion of the dose excreted as this metabolite between adults (mean: 2.50%) and neonates (mean: 2.71%).

4-Hydroxyxylidine: Whether 4-hydroxyxylidine is formed as a product of the hydroxylation of xylidine or as a result of amide bond cleavage of 4-hydroxylignocaine is unknown. This latter compound is a minor metabolite in man and assays for this metabolite were not performed in this study. Whichever pathway is involved, a reduced enzymic capacity in the neonate appears evident since 4-hydroxyxylidine, which constitutes the major urinary excretion product in adults (mean: 63.78%), is only a minor urinary excretion product in neonates (mean: 8.89%). A similar finding has been reported for the aromatic hydroxylation of mepivacaine (Meffin et al., 1973).

Conjugation: As for adults, the 4-hydroxyxylidine is excreted in urine of newborns as a conjugate, probably a glucuronide or sulphate conjugate. Both these important conjugation processes have been reported to be active in newborns for eliminating paracetamol (Levy et al., 1975; Miller et al., 1976) and salicylate (Garrettson et al., 1975).

Conclusions

Neonates appear to be as efficient as adults in eliminating lignocaine when the comparison is made using Cl_{tp} normalised on body weight as an index. The prolonged terminal phase half-life in neonates may not simply reflect diminished intrinsic hepatic function because there is a considerable increase in both the volume of distribution and renal clearance of lignocaine in neonates. Neonates were found to excrete a greater fraction of the dose unchanged in urine and the urinary metabolites, which accounted for more than 70% of the dose in adults, accounted for less than 30% of the dose in neonates.

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