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A COMPARISON OF INTRAVENOUS AND SUBARACHNOID LIDOCAINE PHARMACOKINETICS IN THE RHESUS MONKEY

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ABSTRACT

A comparative study between intravenous and subarachnoid lidocaine in the rhesus monkey was conducted in an effort to compare the kinetics of lidocaine in the monkey with reported intravenous human data, and to determine the rate and extent of systemic absorption of lidocaine following subarachnoid injection. Each animal received an intravenous and subarachnoid treatment in an effort to determine the fraction of drug absorbed. Pharmacokinetic parameters were calculated for each animal based on arterial blood concentrations of lidocaine. In the case of the intravenous data, a standard two-compartment model was used. Subarachnoid injections were evaluated by fitting data to an extravascular one-compartment model and by analog computer fitting of the blood level data to an extravascular two-compartment model. Data for both intravenous and subarachnoid injection were also analysed independent of compartment model.

The intravascular parameters, α and β, were in excellent agreement with those reported for man.

KEY WORDS Lidocaine kinetics Intravenous Subarachnoid

INTRODUCTION

As the cardiocirculatory, renal and environmental risks and complications of the general anesthetic agents have been identified, interest in the scientific re-examination of spinal anesthesia has increased. There are several reports which suggest that anesthetic drugs may have pharmacologic and toxicologic effects well after the immediate anesthetic effect has worn off. The recent publication by Giasi, D'Agostino and Covino on the serum drug levels of lidocaine resulting from placement in the subarachnoid compared to the epidural space prompted an editorial by Greene, reflecting on the need to re-examine the mechanisms and physiologic responses from spinal anesthesia, as related to drug concentration and pharmacokinetics.[1,2]

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Although spinal anesthesia was first reported by August Bier 80 years ago and, since that time, untold millions of spinal anesthetics have been administered, there exists a paucity of objective data relating to the mechanisms, physiology and pharmacology associated with spinal anesthesia.[3]

The development of a non-human primate model for spinal anesthesia will aid in the determination of the efficacy associated with many new drugs and pain management techniques such as intrathecal narcotics and continuous epidural infusion of local anesthetics. The validity of extrapolating the data from such a model to the human situation hinges on both pharmacodynamic and pharmacokinetic responses. This paper compares the intravenous and subarachnoid lidocaine pharmacokinetics in the rhesus monkey. The study was designed to compare the intravenous kinetics in the monkey with reported human data and to determine the rate and extent of systemic absorption of lidocaine following subarachnoid injection.

METHODS

Adult rhesus monkeys ($N = 15$) weighing $6{\cdot}8 \pm 0{\cdot}4$ kg were used throughout this study. Our entire primate colony is under the care of a full time veterinary staff. The animals are housed individually in AAALAC approved squeeze cages and are on a diet of Purina Monkey Chow, fed once each day, and water *ad lib* from an automatic watering system. The primates are tested for TB by intradermal eyelid injection of PPD monthly and by chest X-ray each 90 days. The primates are housed in rooms which are on a 12 h light–dark cycle and have the temperature and humidity controlled.

After fasting overnight, the animals were sedated with ketamine ($10\,mg\,kg^{-1}$, IM). A 20 ga cannula was placed in a peripheral arm vein for administration of maintenance fluids (D5LR, $4{\cdot}5\,ml\,kg^{-1}\,h^{-1}$) via an infusion pump and for injection of lidocaine. Aortic and inferior vena cava (IVC) cannulae were placed and positioned at the L4–5 level via a femoral artery and vein. Positions were verified by radiography. For studies utilizing a peripheral venous line, a distal femoral vein cannula was placed contralateral to the arterial and venous cannulae. All cannulations were accomplished under light general anesthesia consisting of 60/40 nitrous oxide/oxygen supplemented with 0·5 per cent halothane as required. A 6 l total flow was maintained.

At the termination of the experiment, the animals were anesthetized with ketamine ($10\,mg\,kg^{-1}$, IM) supplemented with 60/40 nitrous oxide/oxygen. Femoral vein and arterial repairs were accomplished using 4–0 chromic suture. The wound was then sutured with 3–0 Dexon. One millimetre of broad spectrum antibiotic ($300{,}000\,\mu\,ml^{-1}$) was given prophylactically and the animals returned to their cages. Animals were allowed to rest for a minimum of five weeks between experiments.

Intravenous lidocaine studies were accomplished using 2 per cent Xylocaine Hydrochloride (Astra). Subarachnoid studies were accomplished using 5 per

cent xylocaine in 7·5 per cent dextrose (Astra). With the exception of one animal (RH130) who received 20 mg during the intravenous study, 30 mg of lidocaine was used throughout the study. Eight animals were used in the detailed pharmacokinetic crossover study. An additional seven animals received 30 mg of subarachnoid lidocaine for comparison of aortic, inferior vena cava and peripheral venous concentrations. Arterial blood sampling was done for both the intravenous and subarachnoid crossover experiments. Four millilitres samples were uniformly drawn throughout the study. For the comparison experiments, samples were drawn at 0, 5, 10, 15, 30, 60, 120, 180, 240, and 300 min. For the pharmacokinetic experiments, blood samples were drawn at 0, 4, 7, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, 240, and 300 min.

Blood was allowed to clot and centrifuged to obtain the serum for lidocaine determination. Lidocaine concentrations were determined as described previously.[4]

Intravenous injections

Following arterial cannulation described above, 2 per cent lidocaine was administered over 30 s through an antecubital vein cannula. All animals were restrained during the 5 h study using a primate restraining chair, maintaining the animals in the sitting position.

Subarachnoid injections

Following cannulation, the animals were placed in the right lateral decubitus position and a 22 ga, 1·5 in spinal needle was placed in the subarachnoid space at L5–6. Return of free-flowing, clear CSF was considered as evidence of subarachnoid placement. Lidocaine was administered and the spinal needle flushed with 0·1 ml of air. The spinal needle was removed and the animals were turned supine and restrained in this position for 1·5 min while breathing 100 per cent oxygen. The animals were then transferred to a primate restraining chair for the duration of the experiment.

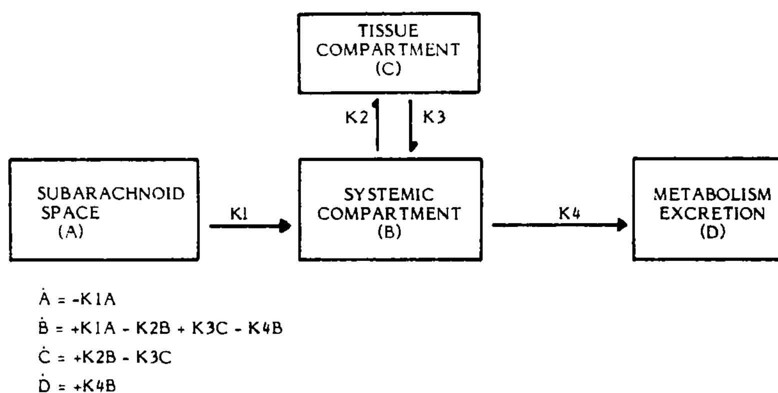
DATA ANALYSIS

Intravenous blood level data were analysed in two ways.

1. Data were fitted to an intravascular open two-compartment model using standard linear regression analysis programs and pharmacokinetic equations.
2. Parameters were calculated independent of compartment model using the area under the blood concentration curve. Area under the curve (AUC(0–∞)) were estimated using the linear trapezoidal rule.

Subarachnoid blood level data were analysed in three ways:

1. Data were fitted to an open one-compartment model for extravascular injection ($N = 6$) or an open two-compartment model for extravascular injection ($N = 2$) using standard linear regression analysis programs and pharmacokinetic equations.
2. Parameters were calculated independent of compartment model using the AUC(0–∞) for extravascular injection.
3. Data were analysed by analog computer fitting of the blood level data for extravascular injection and the microconstants ($k12, k21, k13$) obtained for intravascular injection. Analog computer was based on the following model:



Analog computer data were obtained using a Comdyna dose generator (Comdyna Inc., Barrington, Illinois). Statistical analysis was accomplished using either paired t or Student's t test. $p < 0.05$ were considered significant.

4. Solutions for the blood level equations using the above method were tested for 'goodness of fit' by determining F and R^2 values using standard equations.

RESULTS

Figure 1 is a representative concentration versus time plot of arterial, inferior vena cava (IVC) and peripheral venous obtained following subarachnoid injection. A representative plot is given since there was a wide interanimal variation in the time required to achieve peak serum concentrations (t_{max}). t_{max} ranged from 0·33–1 h. In all cases, inferior vena cava concentrations were significantly higher than arterial concentrations ($p < 0.05$). Peripheral venous concentrations were significantly lower than arterial ($p < 0.05$) and inferior vena cava ($p < 0.01$) concentrations. After 4 h, all blood concentrations had begun to converge.

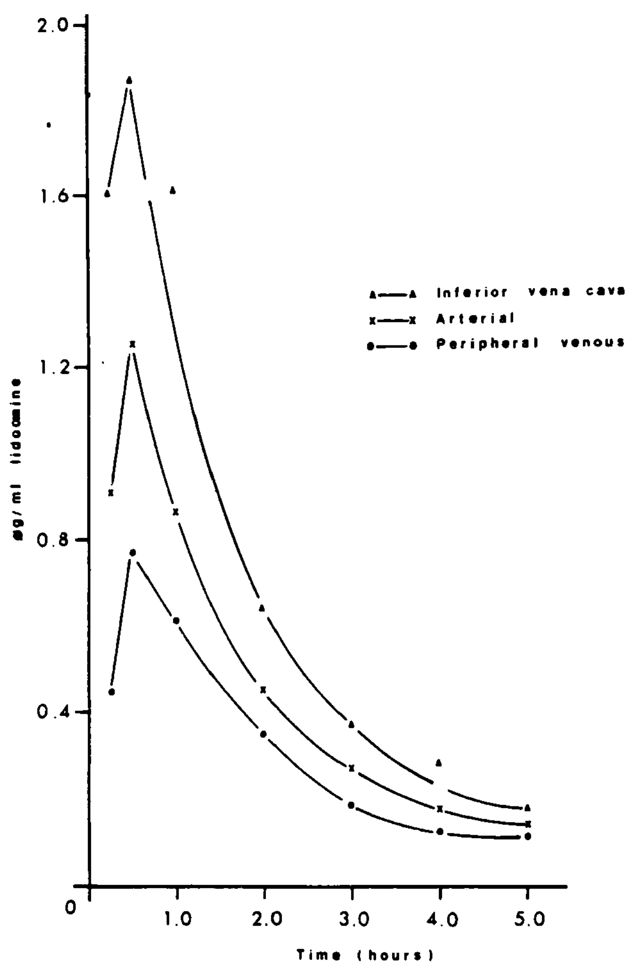


Figure 1. A representative concentration versus time plot for inferior vena cava, aortic and peripheral venous samples following subarachnoid injection of lidocaine

Figure 2 provides a detailed summary of data obtained for both intravenous and subarachnoid lidocaine for each of the eight animals used in the crossover experiments. Examination of the curves for intravenous injection suggest these data are best described by a two-compartment model. Table 1 is a summary of the pharmacokinetic parameters resulting from fitting the data to an intravenous two-compartment model. The excellent agreement for AUC($0 \rightarrow \infty$) calculated by $A/\alpha + B/\beta$ and by the trapezoidal rule suggest the two-compartment model is an accurate pharmacokinetic description of intravenous lidocaine. Table 2 provides a comparison between parameters obtained from an open two-compartment model and those calculated independent of compartment model. No significant differences were found.

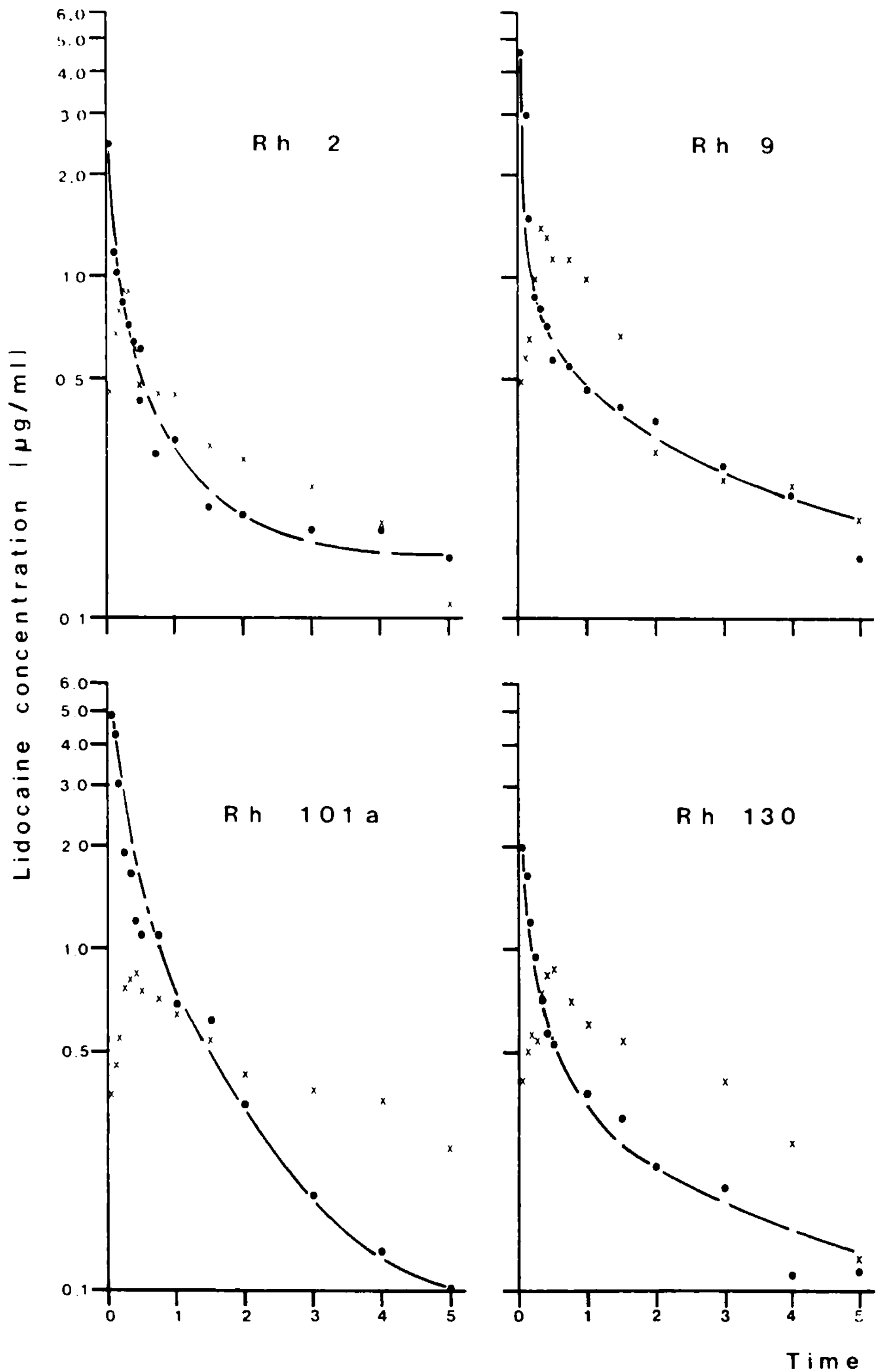
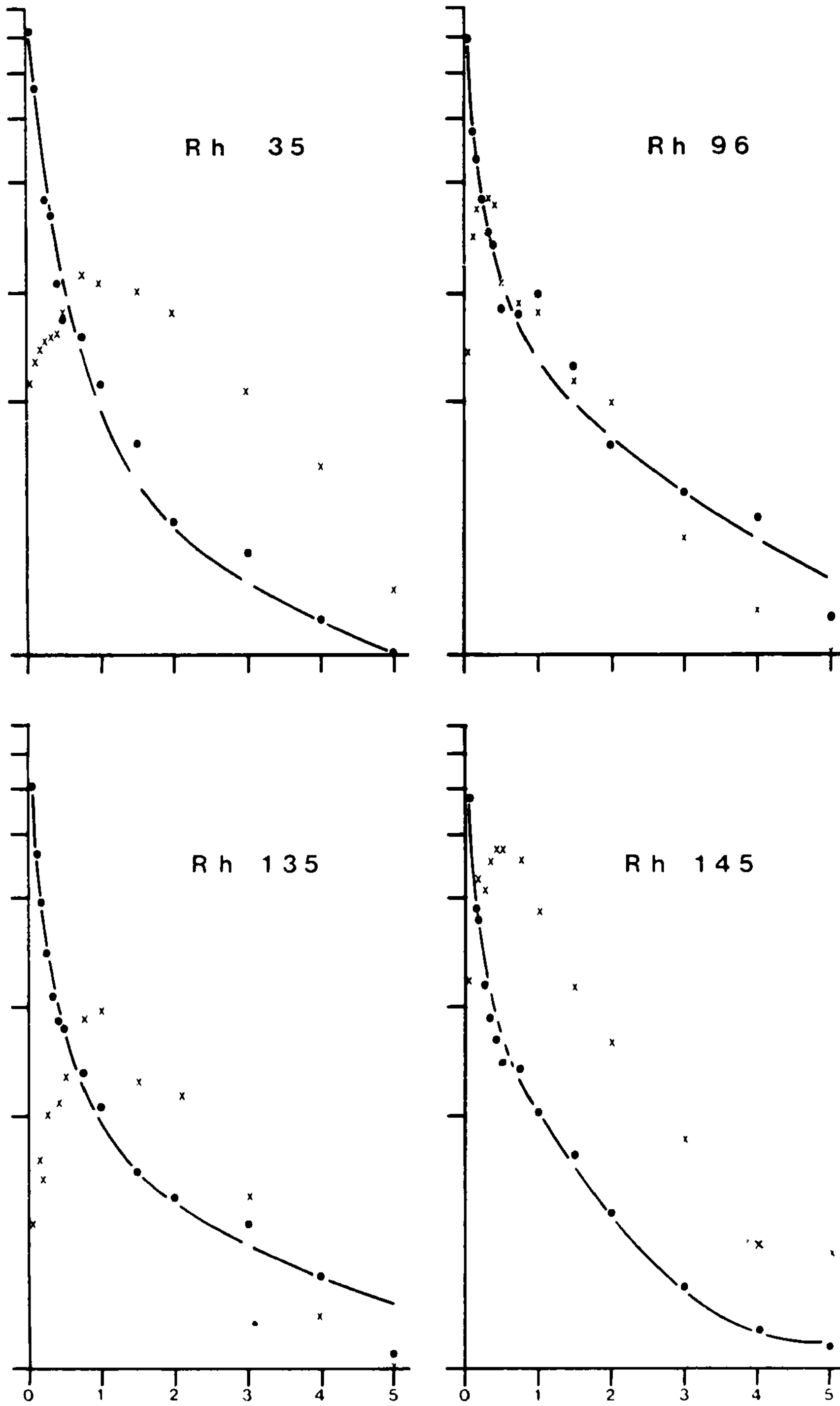


Figure 2. Individual semi-log plots of serum lidocaine concentrations versus time for both crossover



intravenous and subarachnoid injections for each of the eight monkeys used in the experiments

Table 1. Pharmacokinetic parameters obtained from an open two-compartment model for intravenous injection of lidocaine

	RH130	RH135	RH145	RH2	RH35	RH9	RH101a	RH96	Mean	S.E.M.	N
Weight (kg)	6·8	6·6	5·2	10·6	8·0	7·5	6·2	6·4	7·2	0·6	8
Dose (mg)	20·0	30·0	30·0	30·0	30·0	30·0	30·0	30·0	30·0	0	7
C(O) ($\mu g\, ml^{-1}$)	1·85	3·47	2·97	2·23	8·58	6·1	8·98	5·15	5·35	1·01	7
A ($\mu g\, ml^{-1}$)	1·4	2·94	2·4	1·82	6·83	5·3	7·6	4·04	4·42	0·84	7
B ($\mu g\, ml^{-1}$)	0·45	0·53	0·57	0·41	1·76	0·77	1·37	1·11	0·93	0·19	7
α (h^{-1})	3·86	3·94	4·34	5·03	8·84	9·49	8·99	5·94	6·30	0·86	8
β (h^{-1})	0·29	0·239	0·302	0·21	1·09	0·76	0·61	0·43	0·49	0·11	8
$k12$ (h^{-1})	2·02	2·21	2·35	3·17	3·64	4·52	4·80	3·16	3·23	0·37	8
$k21$ (h^{-1})	1·16	0·81	1·08	1·09	2·68	1·86	1·89	1·62	1·52	0·22	8
$k13$ (h^{-1})	0·98	1·16	1·22	0·97	3·61	3·87	2·9	1·59	2·04	0·43	8
V_{dc} (l)	10·8	8·6	10·1	13·5	3·5	4·9	3·3	5·8	7·3	1·2	8
V_{dss} (l)	29·5	32·2	32·1	52·4	8·2	16·9	11·8	17·2	25·0	5·1	8
$V_{d\beta}$ (l)	35·9	42·2	40·3	61·8	11·5	25·2	15·8	21·3	31·8	5·9	8
Cl_{tot} ($l\, h^{-1}$)	10·6	10·1	12·3	13·1	12·6	19·1	9·7	9·3	12·1	1·12	8
V_{dc} ($ml\, g^{-1}$)	1·6	1·3	1·9	1·3	0·44	0·66	0·54	0·91	1·08	0·19	8
V_{dss} ($ml\, g^{-1}$)	4·3	4·9	6·2	4·95	1·03	2·25	1·9	2·7	3·53	0·64	8
$V_{d\beta}$ ($ml\, g^{-1}$)	5·3	6·4	7·8	5·8	1·44	3·4	2·6	3·33	4·5	0·76	8
$t_{\frac{1}{2}\alpha}$ (h)	0·18	0·18	0·16	0·14	0·07	0·07	0·07	0·12	0·124	0·02	8
$t_{\frac{1}{2}\beta}$ (h)	2·4	2·9	2·3	3·3	0·63	0·91	1·13	1·59	1·9	0·3	8
r_α	0·96	0·95	0·95	0·93	0·93	0·94	0·99	0·95	—	—	—
r_β	0·94	0·89	0·92	0·94	0·99	0·95	0·99	0·98	—	—	—
AUC ($0 \rightarrow \infty$) ($\mu g\, h\, ml^{-1}$)											
$A/\alpha + B/\beta$	1·91	2·96	2·44	2·31	2·38	1·57	3·08	3·23	2·48	0·20	8
Trapezoidal	1·98	3·09	2·54	2·27	2·40	1·67	3·12	3·24	2·53	0·20	8

Table 2. Comparison of pharmacokinetic parameters for intravenous lidocaine in the rhesus monkey calculated for a two-compartment model and independent of compartment model

Parameter	Two compartment Mean ± S.E.M.	Independent Mean ± S.E.M.
β ($\mathrm{l\,h^{-1}}$)	0·49 ± 0·11	0·44 ± 0·09
AUC ($0 \rightarrow \infty$) ($\mu\mathrm{g\,h\,ml^{-1}}$)	2·53 ± 0·20	2·61 ± 0·16
Cl_{tot} ($\mathrm{ml\,min^{-1}}$)	200·0 ± 18·4	196·4 ± 12·4
$V_{d\beta}$ (l)	31·8 ± 5·9	34·1 ± 6·6
$V_{d\beta}$ ($\mathrm{ml\,g^{-1}}$)	4·5 ± 0·8	4·8 ± 0·8

Analysis of the data for subarachnoid injection was somewhat more difficult. First, in a number of animals, the lidocaine levels at 5 h were essentially zero (at the lower limit of detection). Thus, for practical reasons, we examined the possibility of using a truncated AUC for calculation of fraction of drug absorbed (F). Since the ratio of AUC($0 \rightarrow \infty$)/AUC(0–5) for intravascular injection was constant for the eight animals, the F was calculated from the following equation:

$$F = \frac{\mathrm{AUC\,(0\text{–}5)\ extravascular}\ \dfrac{\mathrm{D\ i.v.}}{\mathrm{BW\ i.v.}}}{\mathrm{AUC\,(0\text{–}5)\ i.v.}\ \dfrac{\mathrm{D\ extravascular}}{\mathrm{BW\ extravascular}}}$$

These data are summarized in Table 3.

Table 3. Calculation of fraction of drug absorbed (F) for subarachnoid injection of lidocaine

Animal No.	AUC(0–∞)	Intravenous AUC(0–5)	R*	Subarachnoid AUC(0–5)	F
RH130	1·98	1·57	1·26	1·74	0·59
RH135	3·09	2·33	1·32	2·07	0·67
RH145	2·54	2·04	1·24	4·62	1·80
RH35	2·40	2·25	1·06	3·20	1·30
RH2	2·27	1·56	1·45	1·53	0·62
RH9	1·67	1·62	1·02	2·43	1·44
RH101a	3·12	2·97	1·03	2·34	0·75
RH96	3·24	2·97	1·09	2·38	0·70
Mean	2·54	2·16	1·18	2·54	0·98
S.E.M.	+0·20	+0·21	+0·06	+0·34	+0·16

* AUC(0–∞)/AUC(0–5).

Secondly, from examination of the blood level-time curves following subarachnoid injection (Figure 2), six of the animals appear to fit an open one-compartment model for extravascular injection while two of the animals exhibit curves typical of an open two-compartment model. The overall disposition function is probably the same. The need for different compartment models may be related to differences in absorption rates relative to rates of initial disposition in different animals.

Table 4 summarizes the values obtained from a one compartment model analysis. Further, analysis for subarachnoid injection was accomplished independent of compartment model from the area under the curve for the blood level-time data.

Table 4. Pharmacokinetic parameters obtained for a one-compartment model for extravascular injection

Parameter	Mean	S.E.M.
k_a (h^{-1})	4·2	±0·7
$t_{\frac{1}{2}}\alpha$ (h)	0·26	±0·08
K_{el} (h^{-1})	0·50	±0·01
$t_{\frac{1}{2}el}$(h)	1·7	±0·3
V_{dc} (l)	18·9	±3·3
V_{dc} (ml g^{-1})	2·9	±0·6
Cl_{tot} (l h^{-1})	10·0	±1·3

Table 5 provides a summary of the data obtained using this approach for both intravascular and subarachnoid injection. Interestingly, no significant differences were found for any of the parameters. This suggested that the k_a calculated from fitting the data to an extravascular one-compartment model was in fact the hybrid constant α. An analog computer analysis of the blood level curve using the microconstants ($k12$, $k21$, $k13$) from the intravascular data gave the data presented in Table 6.

Table 5. Comparison of intravenous and subarachnoid pharmacokinetic parameters for lidocaine in the rhesus monkey independent of compartment model

Parameter	Intravenous Mean + S.E.M.	Subarachnoid Mean + S.E.M.
β (h^{-1})	0·44±0·09	0·46±0·05
AUC($0\rightarrow\infty$)(μg h ml^{-1})	2·61±0·16	03·00±0·30
Cl_{tot} (ml min^{-1})	196·40±12·40	181·80±19·00
$V_{d\beta}$(l)	34·10±6·60	25·70±4·00
$V_{d\beta}$(ml g^{-1})	4·80±0·80	3·69±0·50

Table 6. Comparison of analog computer fitting of a two-compartment model and a one-compartment model for subarachnoid lidocaine with a two-compartment model for intravenous lidocaine in the monkey*

Parameter	Subarachnoid One-compartment	Subarachnoid Analog FIT	Intravenous Two-compartment
β (h^{-1})	$0{\cdot}45 \pm 0{\cdot}06$	$0{\cdot}45 \pm 0{\cdot}06$	$0{\cdot}49 \pm 0{\cdot}11$
α (h^{-1})	N.A.	$6{\cdot}00 \pm 1{\cdot}60$	$6{\cdot}30 \pm 0{\cdot}86$
k (h^{-1})	$4{\cdot}15 \pm 0{\cdot}80$	$2{\cdot}25 \pm 0{\cdot}25$†	N.A.

* Mean + S.E.M.
† $p < 0{\cdot}05$ when compared to either subarachnoid one-compartment or intravenous two-compartment.

α for the analog computer fit was calculated from the following equation: $\alpha + \beta = k12 + k21 + k13$. Statistical analysis of the data presented in Table 6 revealed two important results.

1. The calculated α from the analog computer analysis was identical to the k_a from the one-compartment analysis of the subarachnoid injection. Further, there was no statistical difference between k_a, α from the analog computer analysis or α for the intravascular data.
2. The k_a derived from the analog computer analysis was significantly different from the k_a obtained from the one-compartment analysis.

These findings suggest that the absorption and distribution phases following subarachnoid injection are approximately the same in duration and overlap significantly during the early sampling times, making separation of the two phases extremely difficult.

3. All data were evaluated for goodness of fit using fifteen concentration-time points for each animal. The reported solutions gave F values ranging from 0·0690–0·4630 and R^2 values ranged from 0·8859–0·9745.

Figures 3 and 4 are analog computer generated curves for arterial concentrations (measured), tissue accumulation, subarachnoid disappearance, and urinary excretion. Figure 3 is for the leanest animal and Figure 4 is for the fattest one. These curves demonstrate that disappearance from the subarachnoid space is independent of lean body mass whereas tissue uptake, arterial blood concentration and excretion by metabolism are highly dependent on lean body mass. These results are to be expected since lidocaine is highly lipid soluble with an apparent partition coefficient of 44.[5]

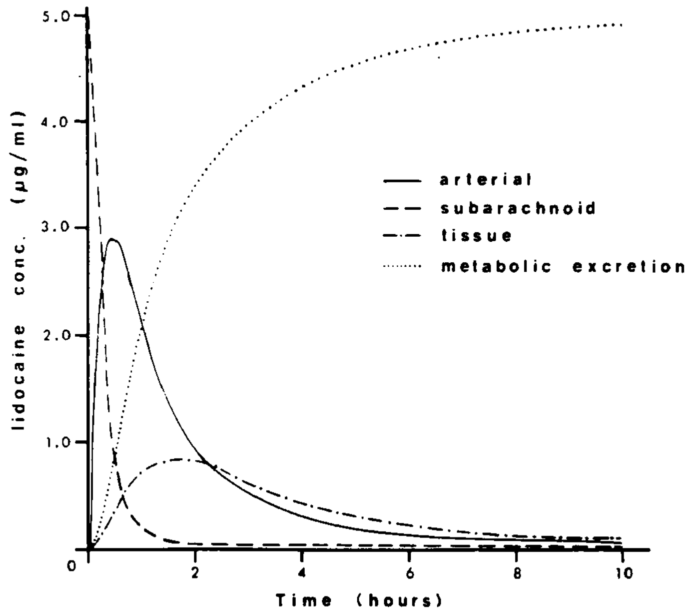


Figure 3. Analog computer generated curves for subarachnoid disappearance, tissue uptake, and urinary excretion (metabolism) based on curve fitting of actual blood level data for the leanest animal used in the study

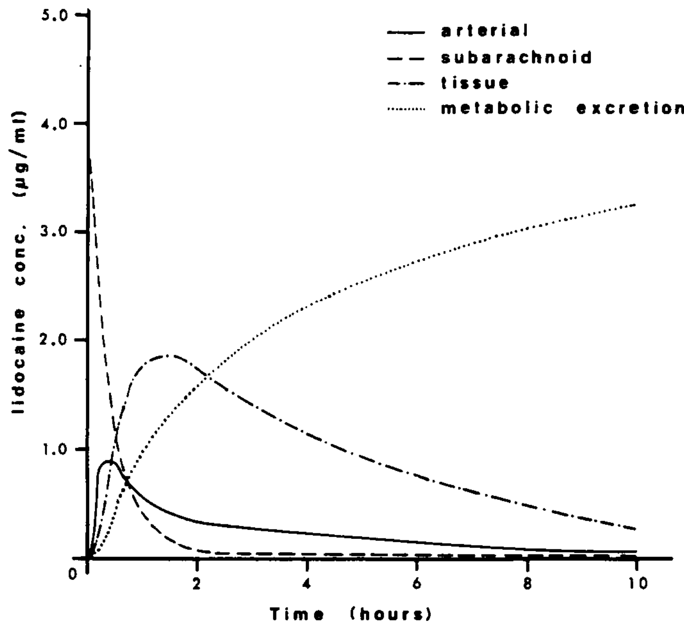


Figure 4. Analog computer generated curves for subarachnoid disappearance, tissue uptake, and urinary excretion (metabolism) on curve fitting of actual blood level data for the fattest animal used in the study

DISCUSSION

Table 7 provides a summary of the pharmacokinetic parameters obtained for intravenous and subarachnoid lidocaine in the monkey and compares these with data reported for intravenous lidocaine in rhesus monkey[6] and in man.[7] It is apparent from this table that the distribution and elimination half-lives for lidocaine determined in this study are statistically equivalent in both man and rhesus monkey. The significantly shorter half-lives for both the α and β phase reported by Benowitz *et al.* are most likely due to the sampling times used.[6] Benowitz *et al.* only sampled to 1·5 h before beginning a lidocaine infusion.[6] In fact, 1·5 h is in the early portion of the β phase. Significantly smaller V_{dc} and V_{dss} are also a result of this shorter sampling format. Interestingly, the total clearance in ml h^{-1} are identical for our study and that of Benowitz *et al.*[6] The difference in total clearance in ml kg^{-1} min^{-1} reflects the much smaller (and we suspect much younger) primates used by Benowitz *et al.*[6] Further, the age differences may well add to the shorter half-lives and lower volumes of distribution. The much higher clearance observed in the monkey may be a result of the baseline heart rate of ~200 beats min^{-1}. The differences seen in volumes of distribution are expected in terms of inter-species differences.

Table 7. Comparison of Pharmacokinetic Parameters from intravenous injections in man and intravenous and subarachnoid injections in rhesus monkeys

Pharmacokinetic parameter	Rhesus IV[6]	Man IV[7]	Rhesus IV	Rhesus SA
$t_{\frac{1}{2}\alpha}$ (h)	0·03	0·14	0·12	0·12
$t_{\frac{1}{2}\beta}$ (h)	0·25	1·8	1·9	1·7
V_{dc} (l)	1·92	37·0	7·3	·18·9
V_{dss} (l)	4·51	92·8	25·0	23·6
Cl_{tot}				
(ml min^{-1})	269·0	703·0	202·0	167·0
(ml kg^{-1} min^{-1})	64·0	10·0	28·0	24·2

Since $k12 > 2 \cdot k21$, extensive tissue distribution and a short α-phase is expected. This explains why, on subarachnoid injection, the distribution phase is masked by the absorption phase. In multiple dosing, a rapid equilibrium between central and peripheral compartments will be obtained. There is no linearity between changes in $k13$ and β.

As seen from the analog computer generated curves (Figures 3 and 4), a second or booster injection would result in a large increase in tissue levels in obese subjects. Although the low blood levels may suggest additional dosing, the curving of action may be disproportionately prolonged, a hypothesis which needs further clarification.

The absorption of 2·4 ± 0·3 per cent of the administered dose at t_{max} is in good agreement with the human data reported by Giasi, D'Agostino and Covino.[1] The intravenous pharmacokinetic data are consistent with α and β half-lives suggested by Tucker and Mather for man.[8] Our findings that IVC concentrations were higher than aortic levels support the hypothesis proposed by Tucker and Mather that systemic absorption from the subarachnoid space occurs prior to entering the hepatic circulation.[8]

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