Pharmacokinetic Aspects of Intravenous Regional Anesthesia

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The kinetics of disposition of lidocaine after intravenous regional anesthesia of the arm and direct intravenous infusion were studied in volunteers. Plasma levels of the drug in blood samples from a contralateral artery and in some cases also from the pulmonary artery and a contralateral vein were determined by gas chromatography. Peak plasma levels of lidocaine after cuff release (iv regional anesthesia) were 20 to 80 per cent lower than those found when the same dose was given directly into a vein over three minutes. Peak levels after cuff release were inversely proportional to tourniquet-application time; they also tended to be lower (by about 40 per cent) when the same dose was given in 0.5 per cent instead of 1.0 per cent solution. During the first few minutes after cuff release, distribution of lidocaine within the pulmonary system buffers the vital organs against high blood levels of the drug. Computer analysis of the data afforded estimates of the amount of drug remaining in the arm as a function of time after cuff release. Release of drug into the systemic circulation was found to be biphasic, an initial fast release of about 30 per cent of the dose, followed by a gradual washout of the remainder. Calculations indicated that even 30 minutes after cuff release about 50 per cent of the dose still remained in the arm. If anesthesia is to be re-established following cuff release this may be possible 10 to 30 minutes after initial release by injection of about half of the original dose following reinflation of the cuff. (Key words: Intravenous regional anesthesia; Lidocaine—intravenous infusion, pharmacokinetics, lung uptake.)

ALTHOUGH the technique of intravenous regional anesthesia was the subject of a recent symposium,[1] it is clear that many questions relating to pharmacologic and clinical aspects remain unanswered. For example, how is the local and systemic disposition of the local anesthetic agent influenced by the tourniquet-application time ‡ and by the volume of injected solution?

In considering these variables, we undertook a pharmacokinetic analysis of plasma levels of lidocaine (Xylocaine) following cuff release after iv regional anesthesia of the arm and following direct iv infusion of the drug. From these two sets of plasma-level data we hoped to be able to quantify the rate of drug release from the tissues of the arm following deflation of the cuff. With this information, further suggestions could then be made concerning, for example, the manner of cuff release and the dosage of a refill injection necessary to re-establish anesthesia in the limb.

Methods

Healthy, unmedicated male volunteers were used. Subjects were Caucasian and their ages ranged from 21 to 39 years. The study was fully explained to each man and signed informed consent obtained.

Catheters were inserted percutaneously to measure arterial and central venous pressures, cardiac output, stroke volume, and total peripheral resistance, and to obtain blood samples for drug and blood-gas analysis. Continuous ECG recordings were obtained throughout the experiments.

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‡ Referred to throughout as "cuff time."

Intravenous Infusions

Lidocaine HCl, 3 mg/kg, was given to each of five subjects via constant-rate infusion through a needle placed in a forearm vein. Infusion time was three minutes. On a separate occasion, one of these subjects also received the same dose over a period of 31 minutes. An additional subject received the dose over a 19-minute period. Arterial blood samples (5 ml) from the opposite arm were collected in heparinized tubes at appropriate intervals for three hours (see table 1).

Intravenous Regional Anesthesia

In each of 26 subjects, a needle was inserted into a vein on the dorsum of one hand and a single pneumatic tourniquet placed on the upper arm. The limb was exsanguinated by elevation for a minute before inflation of the cuff (250 mm Hg pressure). Lidocaine HCl, 3 mg/kg, was then injected through the needle.

Subjects were divided into five groups receiving the drug in different concentrations and/or having different cuff times:

Group I (n = 6): 1 per cent solution; 10 min cuff time
Group II (n = 5): 1 per cent solution; 20 min cuff time
Group III (n = 5): 1 per cent solution; 30 min cuff time
Group IV (n = 5): 1 per cent solution; 45 min cuff time
Group V (n = 5): 0.5 per cent solution; a different cuff time was used for each subject (*viz.*, 10, 15, 20, 30, and 45 min)

Five minutes before releasing the cuff, a control blood sample was taken from the arterial catheter in the contralateral arm. After release, the cuff was kept deflated and the subject was instructed not to move his arm. Arterial blood samples (5 ml) from the contralateral arm were collected in heparinized tubes. Sampling was continued at appropriate intervals for 30 minutes after cuff release. Four of the subjects were instructed to exercise their arms 32 minutes after cuff release, and additional arterial blood samples were obtained at 35 minutes.

In Group V subjects, blood samples were also obtained through the central venous catheter, which in these subjects had been advanced into the pulmonary artery. The final location of the catheter tip was ascertained from the form of the blood-pressure recording. In one subject in this group, further blood samples were taken from the antecubital vein of the unanesthetized arm.

All subjects were asked to describe any subjective effects occurring after cuff release.

Analytical Methods

Plasma levels of lidocaine were determined by a procedure based upon gas chromatography.[2]

Pharmacokinetic Calculations

Individual and mean plasma drug levels observed post-three-minute infusion of lidocaine were fitted by a triexponential equation. The parameters of this equation were then used to simulate the complete iv infusion data and for the calculation of the systemic absorption of lidocaine after cuff release in iv regional anesthesia. Details of these calculations are given in the Appendix.

Assumption implicit in the mathematical treatment include: 1) The kinetics of elimination of the drug from the plasma are independent of the mode and rate of administration and the dosage; 2) there is negligible leakage of lidocaine prior to cuff release, either directly through the main venous drainage of the arm or via vessels in the bone marrow; 3) metabolism of drug within the arm does not occur.

It was not possible to perform a crossover study with each subject receiving direct iv injection and iv regional anesthesia; therefore, we have had to rely on an analysis using mean sets of data.

Results

Intravenous Infusion

Plasma Levels

Intravenous infusion of lidocaine over three minutes produced peak arterial plasma levels of about 13 μg/ml (range: 9–16 μg/ml) (table 1). Postinfusion levels were fitted by a triexponential equation (fig. 1; table 2). The effect of varying the infusion rate on plasma drug levels is illustrated in figure 2. Levels

TABLE 1. Plasma Lidocaine Data (All Doses Were 3 mg/kg Lidocaine HCl)

	Subject	Weight (kg)	Sample Site	μg Lidocaine Base/ml Plasma															
				¼ min	½ min	1 min	1½ min	2 min	2½ min	3 min	4 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min	120 min	180 min
Constant intravenous infusion Infusion time 3 min	1*	67	Peripheral artery	0.34	—	3.02	5.93	7.99	9.36	11.51	—	4.82	2.33	1.62	1.17	0.81	0.59	0.51	0.31	0.20
	2	71	Peripheral artery	1.66	—	5.99	7.69	11.10	13.34	15.54	10.61	6.36	3.89	3.01	2.57	1.94	1.48	1.21	0.70	0.48
	3*	60	Peripheral artery	—	0.93	2.99	4.70	7.15	8.84	9.32	7.10	4.12	2.57	1.85	1.44	1.17	0.76	0.61	0.39	0.25
	4*	77	Peripheral artery	0.98	—	3.36	6.52	9.19	9.90	14.56	10.49	6.83	3.17	2.23	1.81	1.28	0.90	0.77	0.49	0.31
	5*	70	Peripheral artery	1.22	—	4.00	6.00	8.03	9.01	14.00	8.70	5.00	2.01	1.90	1.50	1.16	0.83	0.64	0.42	0.27
	Mean	69	Peripheral artery	0.83	0.93	4.02	6.27	8.61	10.23	13.09	9.23	5.43	2.01	2.12	1.72	1.27	0.93	0.75	0.46	0.30
	SD	6.2		0.74	—	1.14	1.06	1.58	1.84	2.45	1.06	1.27	0.45	0.54	0.53	0.42	0.35	0.27	0.14	0.10
	SEM			0.37	—	0.51	0.48	0.71	0.82	1.10	0.83	0.57	0.20	0.24	0.24	0.19	0.16	0.12	0.06	0.04
				2 min	4 min	6 min	8 min	10 min	15 min	19 min	20 min	22 min	25 min	30 min	31 min	32 min	35 min	40 min	50 min	60 min
Infusion time 10 min	6	75	Peripheral artery	0.60	2.06	2.05	2.36	2.48	2.91	3.11	—	2.00	1.56	1.17	—	—	0.89	0.82	—	—
Infusion time 31 min	3	60	Peripheral artery	—	0.91	1.21	1.31	1.33	1.65	—	1.83	—	1.07	—	2.18	2.02	1.56	1.03	0.80	0.60
				¼ min†	1 min	2 min	4 min	8 min	15 min	30 min	35 min (post exercise)									
Intravenous regional anesthesia	7*	73	Peripheral artery	—	4.52	3.18	2.20	1.88	1.30	0.70										
	8	101	Peripheral artery	21.65	7.05	3.88	2.58	1.80	1.36	0.91										
Group I	9*	90	Peripheral artery	6.08	4.10	3.36	2.83	2.18	1.51	1.09										
1 per cent solution; cuff time 10 min	10	74	Peripheral artery	7.80	5.80	4.37	2.93	1.98	1.32	0.74	1.18									
	11	60	Peripheral artery	7.30	6.24	3.77	2.48	1.80	1.22	0.86										
	12*	81	Peripheral artery	8.51	6.19	4.23	3.44	2.20	1.45	0.84										
	Mean	81	Peripheral artery	10.29	5.67	3.80	2.75	2.00	1.36	0.84										
	SD	12.1		6.42	1.10	0.47	0.41	0.19	0.12	0.11										
	SEM			2.87	0.45	0.19	0.17	0.08	0.05	0.05										
Group II	13*	77	Peripheral artery	—	3.95	3.75	3.09	2.59	1.62	0.83										
1 per cent solution; cuff time 20 min	14*	63	Peripheral artery	—	5.60	4.51	4.10	2.86	1.73	0.95										
	15	80	Peripheral artery	—	5.92	5.28	3.10	2.25	1.54	1.03										
	16	81	Peripheral artery	11.79	4.82	3.00	3.26	2.01	1.28	0.76										
	17*	70	Peripheral artery	7.38	4.03	2.30	2.04	1.43	1.23	0.82										
	Mean	77	Peripheral artery	9.58	4.66	3.97	3.20	2.17	1.48	0.88										
	SD	7.2		3.11	0.77	1.08	0.84	0.66	0.22	0.11										
	SEM			2.20	0.34	0.48	0.37	0.30	0.10	0.05										

TABLE 1. (*continued*)

	Subject	Weight (kg)	Sample Site	μg Lidocaine Base/ml Plasma															
				½ min†	1 min	2 min	4 min	8 min	15 min	30 min	35 min (post exercise)								
Group III 1 per cent solution; cuff time 30 min	18	60	Peripheral artery	—	3.52	3.25	2.18	1.41	1.05	0.75									
	19*	87	Peripheral artery	—	4.25	3.40	3.28	2.80	2.32	1.25									
	20*	66	Peripheral artery	—	4.28	3.85	2.86	1.88	1.58	0.86									
	21*	62	Peripheral artery	—	3.75	3.15	3.00	2.33	1.58	1.13									
	22*	69	Peripheral artery	0.03	3.57	2.50	2.12	1.41	0.91	0.60									
	Mean	69	Peripheral artery	0.03	3.87	3.23	2.69	1.97	1.49	0.92									
	SD	0.6		—	0.37	0.40	0.51	0.60	0.56	0.27									
	SEM			—	0.16	0.22	0.23	0.27	0.25	0.12									
Group IV 1 per cent solution; cuff time 45 min	23	65	Peripheral artery	1.06	2.00	2.30	1.96	1.45	0.98	0.69	0.81								
	24*	62	Peripheral artery	3.29	3.93	3.82	3.34	2.08	1.33	0.73	0.84								
	25*	69	Peripheral artery	4.10	5.04	3.07	2.83	1.75	1.14	0.73	0.90								
	26	74	Peripheral artery	2.05	2.38	2.60	2.95	1.74	1.22	0.71									
	27	67	Peripheral artery	0.82	2.40	2.90	2.83	2.32	1.42	0.77									
	Mean	67	Peripheral artery	2.28	3.15	3.08	2.73	1.87	1.22	0.73									
	SD	4.5		1.44	1.20	0.66	0.51	0.31	0.17	0.03									
	SEM			0.65	0.58	0.30	0.23	0.15	0.08	0.01									

	Subject	¼ min†	½ min	¾ min	1 min	1½ min	2 min	2½ min	4 min	4½ min	6 min	8 min	8½ min	10 min	15 min	15½ min	30 min
Group V 0.5 per cent solution; cuff time 10 min	28	Peripheral artery	—	4.62	5.60	5.20	—	3.77	—	2.32	—	—	1.60	—	—	1.17	—	0.70
		Pulmonary artery	10.74	7.55	6.32	5.82	—	3.11	—	2.17	—	—	1.49	—	—	1.04	—	0.75
Cuff time 15 min	29*	Peripheral artery	0.05	2.47	2.73	2.82	—	2.71	—	2.32	—	1.68	1.48	—	1.37	1.02	—	0.73
		Pulmonary artery	4.72	3.37	3.41	3.25	—	2.80	—	1.95	—	1.67	1.45	—	1.35	1.01	—	0.73
Cuff time 20 min	32	Peripheral artery	1.58	4.61	3.95	3.41	—	2.86	—	2.33	—	1.84	1.62	—	1.31	1.01	—	0.66
		Pulmonary artery	0.88	4.17	3.13	3.00	—	2.35	—	1.59	—	1.36	1.36	—	1.20	0.89	—	0.64
Cuff time 30 min	31	Peripheral artery	—	0.27	—	2.36	—	2.75	—	2.09	—	1.78	1.45	—	1.32	0.97	—	0.66
		Pulmonary artery	—	4.06	—	4.52	—	2.77	—	1.87	—	1.55	1.36	—	1.21	0.93	—	0.63
Cuff time 45 min	32	Peripheral artery	0.05	1.21	1.93	2.33	—	2.73	—	2.52	—	2.20	1.88	—	1.55	1.07	—	0.60
		Pulmonary artery	0.30	4.02	3.72	2.43	—	3.05	—	2.43	—	1.96	1.53	—	1.30	0.99	—	0.55
		Peripheral vein	—	—	—	—	0.47	—	0.07	—	1.02	—	—	0.03	—	—	0.85	0.60

* Subjects who reported subjective effects.
† Times after cuff release.

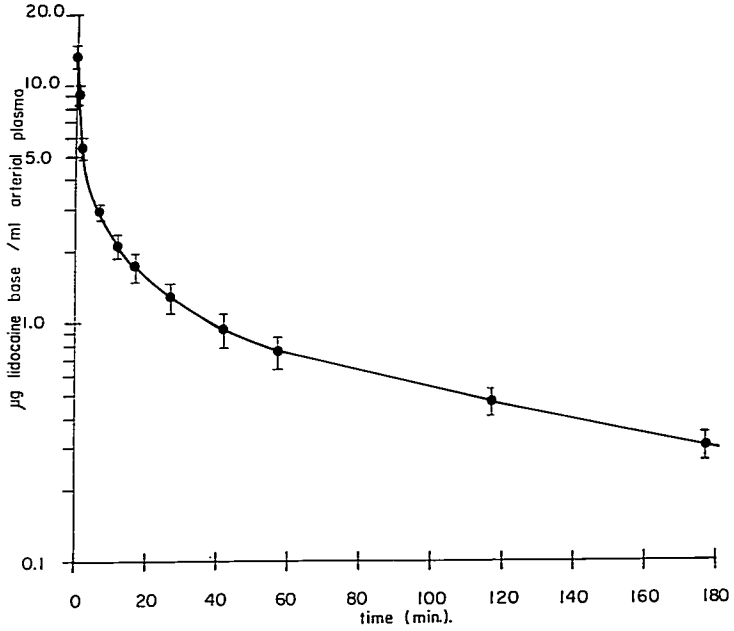


FIG. 1. Mean concentrations of lidocaine (±SEM) in arterial plasma post-intravenous infusion. of 3 mg/kg lidocaine HCl at a constant rate over 3 minutes (five subjects).

calculated using the analog computer program (fig. 7, section *a*) are indicated by the curves. In simulating the experimental data for the 19- and 31-minute infusions, the kinetic constants calculated from the three-minute infusion data of subject 3 (table 2) were used. Only the setting on the potentiometer controlling the rate of infusion (k_0) was altered.

Subjective Effects

Four of the volunteers receiving the drug over three minutes reported mild and transient signs of CNS irritability (dizziness, lightheadedness, apprehension, tinnitus) corresponding with the peak plasma level, but there were no complications requiring treatment.

Intravenous Regional Anesthesia

All subjects developed full anesthesia to pinprick in the extremity.

Plasma Levels

In all cases analysis of control blood samples taken before cuff release indicated negligible drug leakage (<0.05 μg/ml).

Studies with 1 Per Cent Solution (Groups I–IV). An inverse relationship between cuff time and peak lidocaine levels after cuff release was observed (table 1). At one minute, differences between data for 10- and 30-minute and 10- and 45-minute cuff times were significant at $P < 0.01$; for 20- and 30-minute and 20- and 45-minute cuff times at $P < 0.05$ (*t* test) (see fig. 3). Comparison of the mean plasma levels for 10- and 45-minute cuff times (fig. 4 and 5) demonstrate the extreme initial differences, but for each of the groups the mean lidocaine levels were statistically indistinguishable after the two-minute sample. In four subjects whose lidocaine levels were mea-

TABLE 2. Parameters of the Triexponential Equation Describing the Post-3-minute Intravenous Infusion Plasma Level Curves of Lidocaine*

	A_1'	A_2'	A_3'	α_1	α_2	α_3	CD†	Cp‡	Vp§
Subject 1	63.2	30.1	6.7	51.81	6.742	0.469	1.0000	25.2	7.97
Subject 2	72.6	15.3	12.1	40.77	3.211	0.529	0.9976	30.9	6.89
Subject 3	58.0	32.0	10.0	62.61	5.421	0.466	0.9940	22.0	8.17
Subject 4	74.0	19.7	6.3	31.68	4.068	0.396	0.9986	25.5	9.07
Subject 5	78.3	16.3	5.4	46.38	3.625	0.402	0.9990	32.8	6.40
Mean data	67.4	24.0	8.6	50.61	4.949	0.454	0.9969	28.9	7.16

* A_1', A_2', and A_3' are expressed as percentages of $(A_1' + A_2' + A_3')$; α values are in hr^{-1}.

† CD = coefficient of determination = $(\sum obs^2 - \sum dev^2)/\sum obs^2)$; where obs and dev refer to observed plasma drug levels and deviations of same from calculated levels, respectively.

‡ Cp_0 = extrapolated concentration of drug in plasma at zero time after an iv bolus injection (mg/l).

§ Vp = an apparent volume of distribution (in liters) = dose (mg)/Cp_0 (mg/l).

sured after arm exercise, a mean rise in the arterial level of about 25 per cent occurred (table 1).

Studies with 0.5 Per Cent Solution (Group V). For corresponding cuff times, peak arterial plasma levels of lidocaine observed with the 0.5 per cent solution were generally lower and later than those found using the 1 per cent solution (see table 1 and fig. 3). Initially, levels of lidocaine in the pulmonary artery after

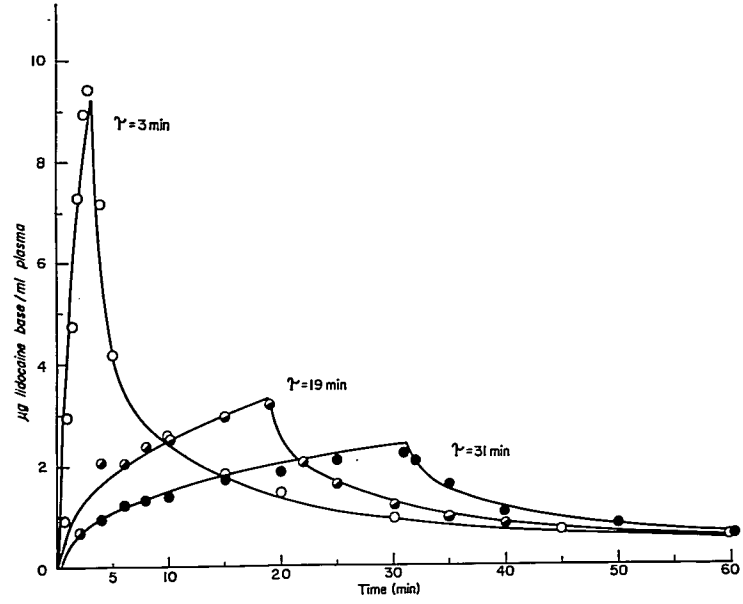


FIG. 2. Arterial plasma levels of lidocaine after constant-rate intravenous infusion in man. Circles = subject 3, infusion time = 3 min; half dot = subject 6, infusion time = 19 min; dot = subject 3, infusion time = 31 min. Computer-calculated levels are indicated by continuous lines.

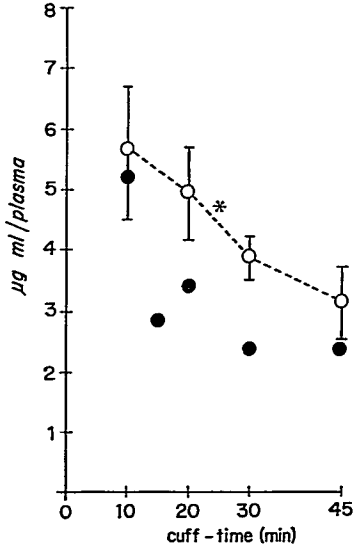


FIG. 3. Relationship between cuff time (iv regional anesthesia) and arterial plasma level of lidocaine at a minute after cuff release. Open circles = mean data ±SD, 1 per cent solution; * = difference significant at $P < 0.05$; closed circles = individual data; 0.5 per cent solution.

cuff release (table 1) were significantly higher than simultaneous peripheral arterial levels, but rapidly approached the latter between ¼ and 2 minutes. Levels of lidocaine in a vein of the contralateral arm in subject 32 (45-minute cuff time) were markedly lower than levels in the corresponding artery, but achieved approximately the same value about 30 minutes after cuff release. Figure 6 shows the levels of lidocaine at the three sampling sites after cuff release in subject 32.

"Arm" Levels §

Calculations indicated that after a 10-minute cuff time (1 per cent solution), release of drug from the arm followed a biphasic pattern (fig. 4). There was a fast release of about 30 per cent of the dose, followed by a much slower release of the remainder. After 30 minutes about 45 per cent of the dose still remained in the arm. (The small dip in the arm-level curve just after two minutes probably results from a slight difference in the mean systemic elimination rate of the drug in Group I subjects compared with that assumed from the direct iv injection data.)

The pattern after a 45-minute cuff time (fig. 5) was significantly different from that after a 10-minute cuff time, in that the initial release was much slower and about 55 per cent of the dose was estimated to remain in the arm after 30 minutes. For both cuff times, drug release could not be described accurately by simple combinations of well-defined rate processes (zero- and first-order). This would probably be true for individual as well as mean data.

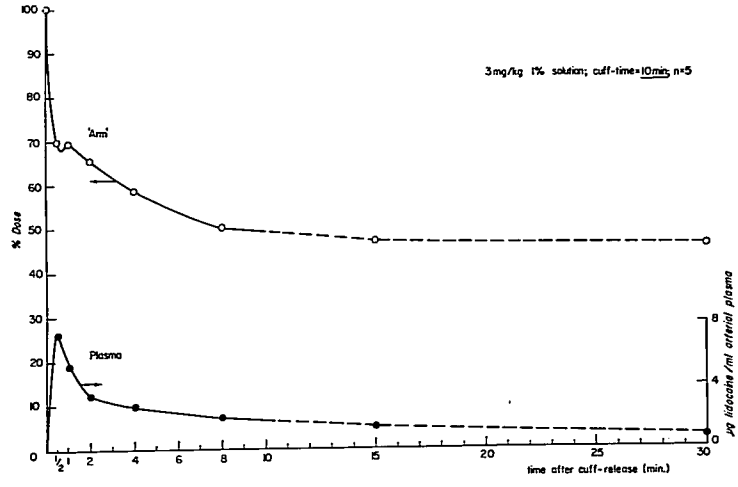
Subjective Effects

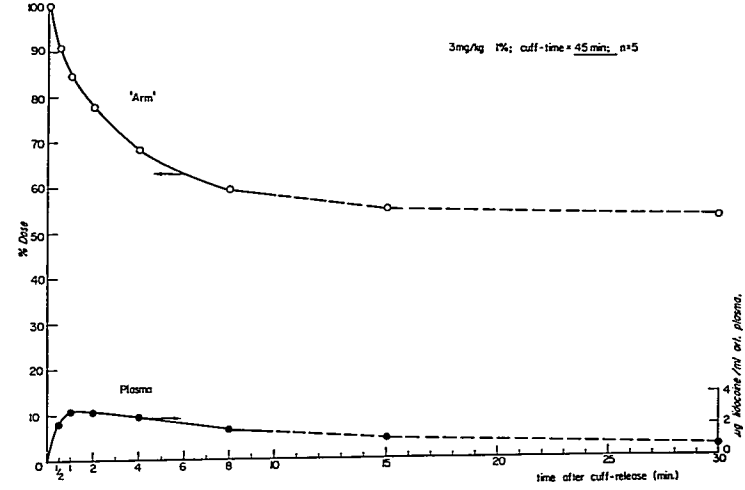
Thirteen subjects reported mild subjective effects lasting as long as three minutes after cuff release. There was no significant differ-

§ In analyzing Group I data it was assumed that peak plasma drug levels did not occur before ½ minute after cuff release. Also, the arterial drug level was assumed to increase immediately after cuff release. Since the kinetic analysis depends upon a comparison of direct iv and iv regional data, we considered that the small lag time representing arm-to-arm circulation time would be common to both and its effect would essentially be cancelled out. The mean of results from only five of the six subjects in Group I was used. Data for subject 8 were omitted because the plasma drug level at ½ minute was atypically high (see table 1). Results from Groups II and III were not analyzed either, owing to insufficient data ½ minute after cuff release.

FIG. 4 (*above*). Mean arterial plasma levels of lidocaine after iv regional anesthesia (3 mg/kg 1 per cent lidocaine HCl; cuff time = *10 min;* n = 5), and calculated arm levels of drug following cuff release. "Arm" data: solid line = calculated by method A—analog computer; circles = points calculated by method B—numerical. Plasma data: dots = experimental points; solid line = simulation with function generator.

FIG. 5 (*below*). Mean arterial plasma levels of lidocaine after iv regional anesthesia (3 mg/kg 1 per cent lidocaine HCl; cuff time = *45 min;* n = 5), and calculated arm levels of drug following cuff release (key as in fig. 4).





ence between the incidences in the groups (see table 1).

Cardiovascular Effects

Details of these were reported elsewhere.[9] They were mostly of a mild stimulatory nature but did show consistent trends from group to group.

Discussion

Systemic Disposition of Lidocaine

Confirming the results of others,[10] peak plasma levels of local anesthetic after fairly rapid iv infusion were significantly higher than corresponding levels after cuff release in iv regional anesthesia using the same dosage. Close prediction of lidocaine levels after slower rates of iv infusion from data obtained after a three-minute infusion (see fig. 2) suggests that the kinetics of lidocaine disposition are independent of maximum drug level in the range studied.

Clearly, prolonging the cuff time for iv regional anesthesia will reduce peak arterial plasma levels after cuff release; exercise of the limb after cuff release, as also shown by Hargrove *et al.*,[10] will increase plasma drug levels; using a larger volume of lower-concentration solution will tend to decrease peak levels. Since prolonging the injection–release interval lowers drug levels on release, there may be some virtue in applying the cuff for an extended period of time prior to injection of the local anesthetic agent, as recommended by Harris.[11] For operations requiring shorter cuff times we agree with others[1, 12] that periodic deflation and reinflation of the cuff would only help to reduce significant drug release from the limb if carried out within a short time (less than 30 seconds—see "arm"-level profile in fig. 4). However, with longer cuff times of the order of 45 minutes or more, a wider tolerance in the deflation–reinflation interval seems warranted (see "arm"-level profile in fig. 5).

Drug released from the blocked arm must first pass through the lungs before delivery to the arterial side of the circulation. The lungs, therefore, are in a strategic position for clear-

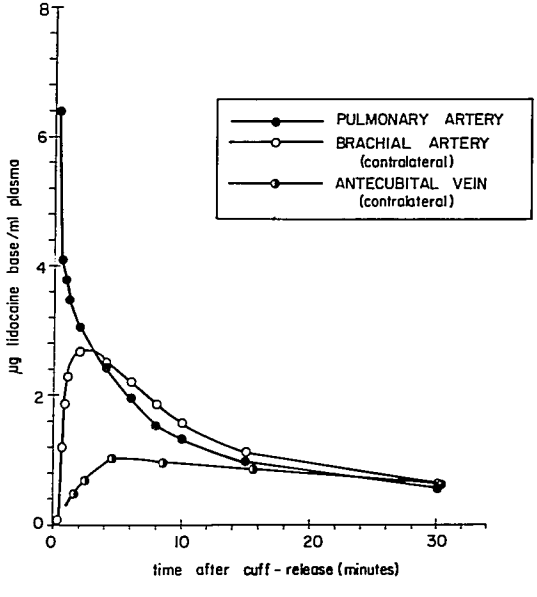


FIG. 6. Plasma lidocaine levels in a subject following cuff release after iv regional anesthesia with 3 mg/kg lidocaine HCl (0.5 per cent solution; 45 min cuff time).

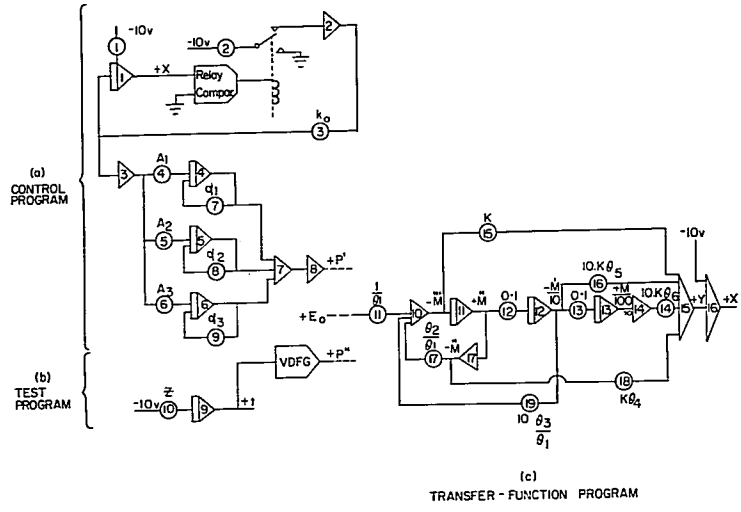


FIG. 7. Analog computer programs for simulation of lidocaine disposition kinetics (see text of Appendix for explanation of symbols).

ing the blood of drug, thereby protecting the CNS and other vulnerable organs from high (and possibly toxic) levels. Crawford [13] discussed the theoretical aspects of this phenomenon, and animal studies invariably show high concentrations of basic drugs, including local anesthetics, in the lung, compared with plasma and other organs.[14, 15] This study indicates the uptake and distribution of lidocaine in the human lung as evidenced by the differences between pulmonary arterial and peripheral arterial levels (fig. 6; table 1). It follows, therefore, that any clinical condition involving a severe compromise of pulmonary perfusion might reduce removal of drug by the lung and tend to increase the risk of intoxication.

Persistence of systemic blood levels of local anesthetic will depend mainly upon redistribution in peripheral tissues and metabolism in the liver. Considerable peripheral uptake of local anesthetic makes measurement of arterial drug levels, rather than peripheral venous levels, preferable in considering CNS and cardiovascular toxicity limits (fig. 6). Also, since venous levels are damped compared with arterial levels, relationships between cuff time, volume of drug solution, and disposition of local anesthetic would tend to be obscured if only venous samples were analyzed. Higher blood levels are to be anticipated in patients with low cardiac output and/or low hepatic blood flow, in whom distribution and metabolism of lidocaine may be severely modified.[16]

Lack of a clear correlation between incidence of subjective symptoms and arterial drug levels in this study suggests a need for caution in relying solely on blood-level data to predict local anesthetic toxicity. On the other hand, subjective reports are likely to be imprecise measures of CNS effects. Our results, therefore, do not allow us to make any definite safety recommendations about the optimum cuff time and solution concentration to be used in iv regional anesthesia.

Local (Arm) Disposition of Lidocaine

The effect of volume of solution on systemic drug levels after cuff release presumably results from an enhanced spread of the drug in the limb with the 0.5 per cent as opposed to

the 1 per cent solution. Also, the initial bolus from the vascular space will be at a lower concentration in the former case.

Observation of lower peak blood drug levels after cuff release when a longer cuff time is used must be related largely to a progressive change in drug distribution within the limb. In part, this may be a function of the time taken to establish diffusion and "binding" equilibria *per se*. However, these equilibria may in turn be profoundly influenced by the marked acid–base and metabolic changes occurring in the limb as ischemia is prolonged.[17] Prior exsanguination of the arm followed by shifts of fluid between spaces may also be important. Differences in blood levels may also reflect a relationship between cuff time and blood flow in the arm immediately after cuff release.

Others[12, 15] have noticed a secondary peaking of lidocaine concentrations in axillary venous blood draining the blocked arm and in the contralateral artery after cuff release. Explanations of this included an effect of reactive hyperemia or differential washout from the tissues. In contrast, we did not observe any nonmonotonous changes in arterial drug levels in any of our subjects for 30 minutes after cuff release, and we suggest that the secondary peaks observed by others may have resulted from movement of the arm.

Successful re-establishment of iv regional anesthesia after cuff release is reported by Brown,[19] who allows ten minutes of tourniquet release and then injects half the initial dose for the succeeding anesthetic. Inspection of the "arm" anesthetic curves in figures 4 and 5 indicates clearly that halving the dose on a second injection could indeed re-establish an anesthetizing level of local anesthetic without producing a greater peak in systemic level with the subsequent release. It is evident also that this might be used successfully for at least 30 minutes after cuff release.

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References

1. D'Amato H, Wiedling S (Editor): Intravenous Regional Anaesthesia, An International Conference, Worcester, Mass., Sept. 1966. Acta Anaesth Scand suppl 36, 1969
2. Tucker GT: Determination of bupivacaine (Marcaine) and other anilide-type local anesthetics in human blood and plasma by gas chromatography. ANESTHESIOLOGY 32:255–260, 1970
3. Rescigno A, Segre G: Drug and Tracer Kinetics. New York, Blaisdell, 1966, pp 20
4. Marquardt DW: Least squares estimation of non-linear parameters. IBM Share Program Library No. 3094, 1966
5. Silverman M, Burgen ASV: Application of analogue computer to measurement of intestinal absorption rates with tracers. J Appl Physiol 16:911–913, 1961
6. Loo JCK, Riegelman S: Assessment of pharmacokinetic constants from postinfusion blood curves obtained after iv infusion. J Pharm Sci 59:53–55, 1970
7. Loo JCK, Riegelman S: New method for calculating the intrinsic absorption rate of drugs. J Pharm Sci 57:918–928, 1968
8. Rescigno A, Segre G: *op cit*, pp 91–95
9. Boas RA, Tucker GT, Everett GB: Cardiovascular effects and arterial lidocaine levels associated with intravenous regional anesthesia. Proc 3rd Eur Congr Anaesth, Prague, Aug–Sept 1970 (in press)
10. Hargrove RL, Hoyle JR, Boyes RN, *et al.*: Blood levels of local anesthetics following intravenous regional anesthesia. Acta Anaesth Scand suppl 36:115–120, 1969
11. Harris WH: Choice of anesthetic agents for intravenous regional anesthesia. Acta Anaesth Scand suppl 36:47–52, 1969
12. Thorn-Alquist AM: Blood concentrations of local anaesthetics after intravenous regional anaesthesia. Acta Anaesth Scand 13:229–239, 1969
13. Crawford JS: Speculation: The significance of varying the mode of injection of a drug, with special reference to the brain and the placenta. Brit J Anaesth 38:628–640, 1966
14. Akerman B, Aström A, Ross S, *et al.*: Studies on the absorption, distribution and metabolism of labelled prilocaine and lidocaine in some animal species. Acta Pharm Toxicol 24:389–403, 1966
15. Hansen D, Ohnesorge FK, Palisaar R: Die verteilung von ^{14}C-markiertem lidocaine und prilocaine nach intravenoser applikation beim meerschweinchen. Der Anaesthesist 17:168–173, 1968
16. Stenson RE, Constantino RT, Harrison DC: Interrelationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. Circulation 43:205–211, 1971
17. Déry R, Pelletier J, Jacques A, *et al.*: Metabolic changes induced in the limb during tourniquet ischaemia. Canad Anaesth Soc J 12:367–378, 1965
18. Cotev S, Robin CG: Experimental studies on intravenous regional anaesthesia using radio-

active lignocaine. Brit J Anaesth 38:936–940, 1966

19. Brown EM: Continuous intravenous regional anesthesia. Acta Anaesth Scand suppl 36: 39–45, 1969

Appendix

Pharmacokinetic Calculations

Simulation of IV Infusion Data

Preliminary graphical analysis by the method of residuals[3] indicated that the individual and mean post-three-minute infusion data declined in a triexponential manner, as described by equation (1):

$$P_{post}(t') = A_1' \cdot e^{-\alpha_1 t'} + A_2' \cdot e^{-\alpha_2 t'} + A_3' \cdot e^{-\alpha_3 t'} \quad (1)$$

where: P_{post} equals fraction of arterial plasma level at three minutes, and P_{post} A_1', A_2', and A_3' are expressed as fractions of $(A_1' + A_2' + A_3')$. α_1, α_2, and α_3 are expressed in reciprocal hours and t' is the time after the end of infusion in hours.

Nonlinear least-squares fits of equation (1) to the data were obtained using the "NLIN" program of Marquardt[4] and a CDC 6400 digital computer.

After we had obtained best values for A_i' and α_i (see table 2), the A_i' values were corrected for an iv *bolus* injection of lidocaine using equation (2)[6]:

$$A_i = \frac{\alpha_i \tau}{1 - e^{-\alpha_i \tau}} \cdot A_i' \quad (2)$$

where: A_i values are the intercepts on the y axis at zero time and τ is the experimental infusion time.

The "pure" elimination of lidocaine from arterial plasma was then described by equation (3):

$$P(t) = A_1 \cdot e^{-\alpha_1 t} + A_2 \cdot e^{-\alpha_2 t} + A_3 \cdot e^{-\alpha_3 t} \quad (3)$$

where: P equals the fraction of a hypothetical plasma level at zero time after an iv bolus injection of the drug. Values of α_i are as in equation (1).

Values of the parameters of equation (3) were then used to simulate the complete iv infusion data. This was done using an E.A.I. TR 20 analog computer programmed with the circuit shown in section *a* of figure 7. By setting the infusion time, τ, (3, 19, or 31 min), computer-calculated lidocaine levels were compared with appropriate experimental values.

Calculation of Systemic Absorption of Lidocaine Following Cuff Release after iv Regional Anesthesia

Two methods were used, both of which have the advantage that no *a priori* assumptions about the form of the absorption function (*e.g.*, zero or first-order rate) are made.

Method A

This method is based upon that described by Silverman and Burgen,[5] and involves a function generator and an analog computer to deconvolute the iv regional data relative to the direct iv injection data.

Applying this procedure to a triexponential curve produces the following pair of equations:

$$E_0(t) - \theta_1 \dddot{M} - \theta_2 \ddot{M} - \theta_3 \dot{M} = 0 \quad (4)$$

$$E_i(t) = K\dddot{M} + K\theta_4 \ddot{M} + K\theta_5 \dot{M} + K\theta_6 M \quad (5)$$

where:

$E_0(t)$ = output function, *i.e.*, plasma level curve.
$E_i(t)$ = input function (when $E_i(t)$ is a step-function, $E_0(t)$ becomes the iv bolus plasma curve; when $E_i(t)$ is the "arm" response, $E_0(t)$ becomes the iv regional plasma curve.)
K = total dose
M = an operator
$\theta_1 = (A_1 + A_2 + A_3)$
$\theta_2 = A_1(\alpha_2 + \alpha_3) + A_2(\alpha_1 + \alpha_3) + A_3(\alpha_1 + \alpha_2)$
$\theta_3 = A_1\alpha_2\alpha_3 + A_2\alpha_1\alpha_3 + A_3\alpha_1\alpha_2$
$\theta_4 = \alpha_1 + \alpha_2 + \alpha_3$
$\theta_5 = \alpha_1\alpha_2 + \alpha_2\alpha_3 + \alpha_1\alpha_3$
$\theta_6 = \alpha_1\alpha_2\alpha_3$

The analog computer program corresponding to equations (4) and (5) is shown in figure 7 *c*. This figure also shows two different inputs to the transfer-function circuit:

Control Program (zero-order infusion into a triexponential system). The output of this circuit as a function of time $[E_0(t) = P'(t)]$* fed into the transfer-function circuit allows recovery of $X(t)$, the amount of drug (expressed as a fraction of the dose) remaining to be injected as a function of time. The output of integrator 1 of the control circuit should be identical to the output of amplifier 16. Thus, the former circuit functions as a check on the system.

Test Program. The output here consists of the iv regional plasma level curve $[E_0(t) = P''(t)]$* simulated with a variable-diode function generator (VDFG). When this output is fed into the transfer-function circuit the output gives the integral absorption function $[E_i(t) = Y(t)]$; subtracting this from the dosage yields $X(t)$, the fraction of the dose remaining in the "arm" as a function of time. Intravenous regional data for the first ten minutes after cuff release only were analyzed, owing to a limitation on breakpoint setting on the VDFG to intervals > 0.25 v.

Method B

The numerical method of Loo and Reigelman[7] was adapted for a four-compartment mammillary model. Values for the rate constants were obtained as described by Resigno and Segre.[8] Calculations were facilitated by the use of a programmable electronic desk calculator (Monroe Model 1655).

* *Nb.* $P'(t)$ and $P''(t)$ represent the plasma concentrations of drug at time t expressed as fractions of the plasma concentration at zero time (Cp_0) following an iv bolus injection.