The Distribution of ^{14}C-Labelled Lidocaine Injected Intravenously in the Rat

*Jordan Katz, M.D.**

The physiologic distribution of ^{14}C-labelled lidocaine after intravenous injection was studied in the rat. Plasma levels decreased rapidly, with only 6.8 per cent of the injected dose remaining by one minute. The vessel-rich (highly perfused) organs and plasma showed similar decay curves. An increasing amount of radioactivity in the liver indicated that an active process, probably metabolism, was occurring there. Muscle, although it contained as much as 23.6 per cent of the injected drug at one time, had a low affinity for the drug and was important in redistribution only because of its large mass.

THERE has been a revival of the use of lidocaine (Xylocaine) intravenously for anesthetic and medical purposes. These include isolated extremity anesthesia,[1,2] supplementation of general anesthesia,[3] treatment of cardiac arrhythmias,[4,5] and treatment of epilepsy.[6] Knowledge of the distribution of the local anesthetic when given intravenously is limited, however. The purpose of this report is to define further the early distribution of intravenously-administered lidocaine in the rat.

Methods

Sprague-Dawley rats weighing 230 to 560 Gm. were anesthetized with pentobarbital (50 mg./kg.) intraperitoneally. The femoral vein was exposed and 2 mg./kg. lidocaine HCl containing 8.0×10^6 to 9.6×10^6 counts/minute of the ^{14}C-labelled drug were injected intravenously within a 10-second period. The lidocaine molecule was labelled on the carbonyl carbon (fig. 1). At one, three, five and 15 minutes, the animals were sacrificed rapidly by thoracotomy and clamping of the major vessels at the base of the heart.

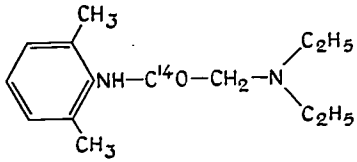

FIG. 1. Lidocaine with the carbonyl carbon labelled.

A blood sample was taken from the left ventricle and tissue specimens for biopsy were obtained from heart, lung, muscle, liver, spleen, kidney, small intestine, fat, and brain. Muscle was obtained from the quadriceps group of the leg opposite the site of injection, fat from the mesentery, brain from the cortex; small intestine was assumed to be representative of the entire bowel.

The samples were weighed in tared glass scintillation vials. Two ml. of NCS † were added and the tissue was homogenized and dissolved at a temperature of 70–80° C. After cooling, the pH was adjusted to 6.0–7.0 with 20 per cent H_2SO_4 in methanol (w./v.) to minimize the amount of chemi-luminescence caused by the reaction of tissue protein with the NCS. Gentle shaking at this time usually produced a clear solution. If not, NCS in small amounts was added until clarity occurred. Ten ml. of a toluene solution ‡ were then added to each sample. Samples were counted in a Beckman Liquid Scintillation Counter, Model #1650.§ Controls of non-radioactive tissue and NCS-toluene mixtures also were counted, to establish background activity. Since background activity varies with tissue, an indi-

* Assistant Professor, Department of Anesthesia, Stanford University School of Medicine, Palo Alto, California.

Accepted for publication September 8, 1967.
Supported in part by USPHS Program Project No. GM 12527-03.

† NCS—Nuclear Chicago Liquid Scintillation Solubilizer, Nuclear-Chicago, Des Plaines, Ill.

‡ Toluene 1 liter (Baker reagent) + 5 Gm. 2,5-diphenyloxazole (PPO); the PPO is available from Beckman Instruments, Inc., Fullerton, Calif.

§ Beckman Instruments, Inc., Fullerton, Calif.

vidual background count was determined for each. Ordinary blank tissues should not emit more than 70–80 counts/minute. Radioactive samples were counted several times until consistent values were acquired. After correction for quenching factors (which impede efficiency of counting), the following calculations were done:

$$(1)\ \text{Counts/min./mg. tissue} = \frac{\text{gross counts/min.} - \text{control counts/min.}}{\%\ \text{Efficiency} \times \text{tissue weight in mg.}}$$

$$(2)\ \text{Per cent dose} = \frac{\text{counts/min./mg. tissue} \times \text{weight of organ}\P\ \text{(in mg.)}}{\text{Total counts injected}}$$

The blood sample was treated slightly differently. Plasma was separated from red cells by centrifugation. One tenth ml. of plasma was mixed with 10 ml. Dioxane solution.** Because there is no quenching phenomenon in counting of plasma it is preferable to whole blood for counting samples which remain highly chemi-luminescent. If one assumes that plasma is 5 per cent of body weight, the following calculations may be made:

$$(1)\ \text{Counts/min./0.1 ml. plasma} = \text{gross counts/min.} - \text{control counts/min.}$$

$$(2)\ \text{Per cent dose} = \frac{\text{counts/min./0.1 ml. plasma} \times 10 \times 5\%\ \text{body weight (mg.)}}{\text{Total counts injected}}$$

Means, standard deviations and F ratios were determined using computer program BMD04.††

Results

The results are tabulated in tables 1 and 2, and presented in figures 2, 3, and 4. Each figure represents the mean of four to six observations. In table 2 the results have been calculated to show counts/min./mg. of tissue in a 500 Gm. rat which received 8.0×10^6 counts.

Plasma—The plasma decay curve is represented graphically in figure 2. At the end of one minute, only 6.8 per cent of the injected dose remained in plasma. Lidocaine is distributed equally to cells and plasma and, therefore, whole blood concentrations are the equivalent of plasma concentrations. There is no increased absorption of the drug in or onto red cells.††

Muscle—Muscle and liver appeared to be the major sites of concentration. Within five minutes, muscle accounted for 23.6 per cent of the injected dose; however, in the rat, muscle comprises 45 per cent of body weight. It is apparent from the counts/min./mg. of tissue that muscle plays a rather small role in the drug distribution, compared with the other organs sampled, and is significant only because of its larger mass.

Liver—Distribution to the liver is shown in figure 3. Liver comprises 4.8 per cent of body mass. By three minutes, it accounted for 23.4 per cent, and by 15 minutes for about one third, of the injected dose, indicating major concentration in the liver and supporting the evidence that the liver is the site of metabolism of lidocaine.[7]

Fat—Although there were no significant changes in fat concentration, the data definitely showed no increased deposition in fat with time.

Heart, Lung, Spleen, Brain, Bowel—The decay curves of radioactivity are shown in figure

¶ Per cent of body weight of organs sampled: plasma 5%; liver 4.8%; muscle 45.4%; spleen 0.3%; kidney 0.8%; bowel 2.4%; brain 0.8%; heart 0.4%; lung 0.6%; fat 5.7%.

** Dioxane 1 liter (Baker reagent) + 100 Gm. naphthalene (Baker reagent) + 5 Gm. 2,5-diphenyloxazole (PPO).

†† Analysis of Variance of One-Way Design; Version of January 8, 1964. Health Sciences Computing Facility, UCLA.

†† Unpublished data.

TABLE 1. Physiologic Disposition of Lidocaine in a 500-Gm. Rat (% Recovery/organ)

Organ	Time (min.)	% Recovered (±1 SD)
Plasma	1	6.8 ± 1.6
	3	3.1 ± 0.8*
	5	2.5 ± 1.1
	15	2.1 ± 0.3**
Heart	1	3.2 ± 1.0
	3	0.99 ± 0.25*
	5	0.58 ± 0.09
	15	0.27 ± 0.05**
Lung	1	7.6 ± 1.4
	3	3.9 ± 0.9*
	5	2.9 ± 0.9
	15	1.2 ± 0.2**
Liver	1	15.5 ± 2.4
	3	23.4 ± 4.0*
	5	25.7 ± 5.3
	15	32.6 ± 4.2**
Gut	1	12.0 ± 4.1
	3	7.7 ± 1.7 NS
	5	8.1 ± 2.5
	15	3.0 ± 0.8**
Brain	1	2.5 ± 0.6
	3	2.1 ± 0.4 NS
	5	2.1 ± 0.8
	15	1.1 ± 0.3**
Spleen	1	2.9 ± 1.5
	3	1.7 ± 0.7 NS
	5	1.5 ± 0.6
	15	0.9 ± 0.3 NS
Kidney	1	11.5 ± 5.9
	3	6.4 ± 0.9 NS
	5	5.5 ± 1.5
	15	7.2 ± 2.9 NS
Fat	1	7.3 ± 2.8
	3	5.4 ± 3.3 NS
	5	4.0 ± 2.4
	15	3.4 ± 1.7 NS
Muscle	1	8.9 ± 4.4
	3	19.7 ± 2.3*
	5	23.6 ± 8.1
	15	16.2 ± 3.7 NS

* Significant ($P < 0.05$) change between 1- and 3-minute samples.
** Significant ($P < 0.05$) change between 1- and 15-minute samples.
NS = No significant change between 1- and 3-minute samples and/or 1- and 15-minute samples.

TABLE 2. Physiologic Disposition of Lidocaine in a 500-Gm. Rat (Counts/minute/mg. tissue)

Organ	Time (min.)	Counts/min./mg. (±1 SD)
Plasma (cts/min./0.1 cc.)	1	21,082 ± 5,960
	3	9,457 ± 1,833*
	5	7,827 ± 3,436
	15	6,639 ± 903**
Heart	1	124 ± 44
	3	38 ± 11*
	5	22 ± 3
	15	11 ± 2**
Lung	1	196 ± 45
	3	103 ± 14*
	5	73 ± 16
	15	32 ± 4**
Liver	1	50 ± 10
	3	74 ± 9*
	5	81 ± 14
	15	126 ± 17**
Gut	1	77 ± 28
	3	49 ± 9 NS
	5	45 ± 7
	15	20 ± 5**
Brain	1	48 ± 10
	3	40 ± 6 NS
	5	39 ± 10
	15	21 ± 5**
Spleen	1	134 ± 82
	3	70 ± 16 NS
	5	75 ± 30
	15	47 ± 14 NS
Kidney	1	187 ± 104
	3	127 ± 19 NS
	5	103 ± 21
	15	118 ± 69 NS
Fat	1	20 ± 8
	3	14 ± 7 NS
	5	11 ± 7
	15	10 ± 5 NS
Muscle	1	3.7 ± 0.8
	3	6.9 ± 0.9*
	5	8.0 ± 3.3
	15	5.7 ± 1.3 NS

* Significant ($P < 0.05$) change between 1- and 3-minute samples.
** Significant ($P < 0.05$) change between 1- and 15-minute samples.
NS No significant change between 1- and 3-minute samples and/or 1- and 15-minute samples.

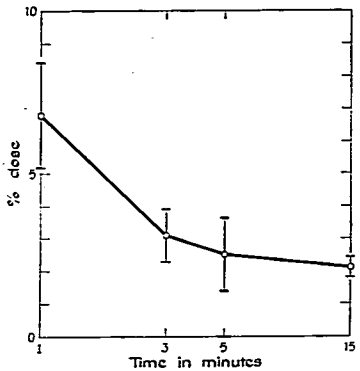

FIG. 2. Concentrations of lidocaine in the plasma.

4. It is apparent that they follow the general pattern of decay observed in plasma.

Kidney—No statistically valid trend for concentration in the kidney was observed. There are two possible explanations: the more obvious is that the rather large standard deviations of the one-minute samples obviate what could be "real" decreases in mean concentrations with time; second, there is the possibility that the kidney participates in the metabolism of the drug.

Discussion

It must be pointed out that we measured radioactivity and not specific lidocaine levels. We assume that significant redistribution of the metabolites produced had not occurred because of the short duration of the experiments. The radioactivity in liver, the major site of metabolism, was probably due in part to metabolites.

The nature of the metabolism was not investigated in this study. Hollunger[8] showed that lidocaine (diethylglycine xylidide) is oxidized to monoethyl xylidide, this process occurring in the rabbit liver as the result of an enzymatic system localized in hepatic microsomes.[9] Oxygen and triphosphopyridine nucleotide (TPN) were necessary accompaniments. Geddes[11] has shown diethylglycine, a hydrolytic product of lidocaine, to be another metabolite. In addition, in autoradiographic studies of the metabolic products of ^{14}C-labelled prilocaine (Citanest), a congener of lidocaine, several areas of radioactivity were noted in rat urine,[10] indicating that more than one metabolite was excreted.

Incubation of rat tissue with the ^{14}C prilocaine indicated that the liver was the prime site for production of these unidentified metabolites.[10] The kidney also produced a second spot on the autoradiogram, indicating still another metabolite. Whether metabolism occurs in the kidney *in vivo* remains to be answered.

It is compatible with the aforementioned observations that some radioactivity measured could be from metabolites. The short duration of these experiments compared with the *in vitro* experiments, which lasted from 45 minutes[10] to five hours,[11] suggests, however, that the majority of the radioactivity present in tissues other than liver indeed indicated unaltered lidocaine.

A general scheme of disposition of intravenously-injected lidocaine, in this species at least, can be postulated. The drug rapidly leaves the vascular compartment and comes into equilibrium with the tissues of the body. At one minute, organs with high blood flow per unit volume of tissue, the so-called vessel-rich group—heart, lung, liver, brain, kidney, spleen and bowel—contained most of the lidocaine. Approximately 70 per cent of the recovered lidocaine was present in these tissues.

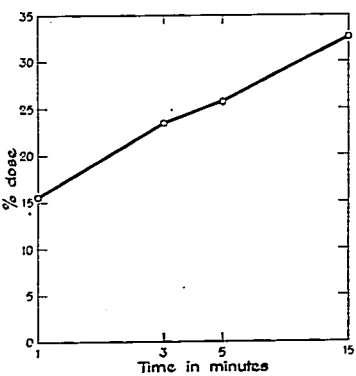

FIG. 3. Concentrations of radioactivity in the liver.

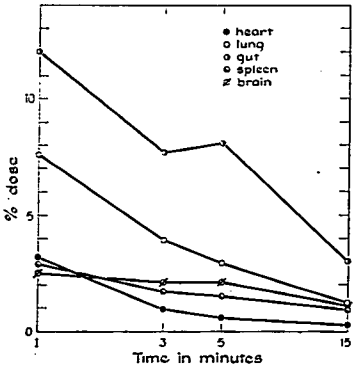

FIG. 4. Concentrations of lidocaine in five organs.

The muscle and fat compartments, with their lesser blood flows, accounted for 20.7 per cent of recovered drug.

By three minutes, larger quantities of the lidocaine appeared in muscle. This trend continued at the five-minute sampling. At 15 minutes, muscle levels began to fall. The vessel-rich tissues showed rapid decay, with the exception, of course, of liver (and possibly kidney), where metabolism probably was taking place. The paths of excretion of the drug have not been studied in the rat, but in five hours 25–40 per cent of the radioactivity appeared in dog urine, less than 3 per cent in bile.§§ In addition, it has been shown, with ^{14}C-labelled prilocaine, that in 24 hours 23 per cent of activity appeared in rat urine and 5 per cent in the expired air. Most of this radioactivity, however, was probably of metabolic origin.

Summary

The distribution of ^{14}C-labelled lidocaine after intravenous injection was studied in the rat. Rapid uptake by all tissues of the body was noted. After one minute, only 6.8 per cent of the injected dose remained in plasma. By 15 minutes, this was further reduced to 2.1 per cent. There was a similar pattern in highly-perfused organs. The muscle mass, although it accounted for almost 25 per cent of the drug by five minutes, showed no particular affinity for the drug when the absolute counts per mg. tissue were considered. Liver, the major organ of metabolism, had a constantly increasing concentration for the duration of the experiment.

The author wishes to thank Miss Nancy Hood for technical assistance.

References

1. Holmes, C. M.: Intravenous regional analgesia. A useful method of producing analgesia of the limbs, Lancet 1: 245, 1963.
2. Adams, J. P., Dealy, E. J., and Kenmore, P. I.: Intravenous regional anesthesia in hand surgery, J. Bone Joint Surg. 46A: 81, 1964.
3. Steinhaus, J. E., and Gaskin, L.: A study of intravenous lidocaine as a suppressant of cough reflex, ANESTHESIOLOGY 24: 285, 1963.
4. Harrison, D. C., Sprouse, J. H., and Morrow, A. G.: The antiarrhythmic properties of lidocaine and procaine amide, Circulation 28: 486, 1963.
5. Frieden, J.: Antiarrhythmic Drugs. Part VII. Lidocaine as an antiarrhythmic agent, Amer. Heart J. 70: 713, 1965.
6. Bohm, E., Flodmark, S., and Petersen, I.: Effect of lidocaine (Xylocaine) on seizure and interseizure electroencephalograms in epileptics, A.M.A. Arch. Neurol. Psych. 81: 550, 1959.
7. Sung, C., and Truant, A. P.: The physiological disposition of lidocaine and its comparison in some respects with procaine, J. Pharmacol. Exp. Therap. 112: 432, 1954.
8. Hollunger, G.: On the metabolism of lidocaine. II. The biotransformation of lidocaine, Acta Pharmacol. Toxicol. 17: 365, 1960.
9. Hollunger, G.: On the metabolism of lidocaine. I. The properties of the enzyme system responsible for the oxidative metabolism of lidocaine, Acta Pharmacol. Toxicol. 17: 358, 1960.
10. Geddes, I. C.: Studies of the metabolism of Citanest C^{14}, Acta Anaesth. Scandinav. Suppl. XVI: 37, 1965.
11. Geddes, I. C.: La méthode de detoxication de la Xylocaine au moyen de l'isotope C^{14}, Anesth. Analg. Réanim. 15: 908, 1958.

§§ Unpublished data.