

Intravascular Lidocaine Compartment:

Kinetics of Bolus Injection

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Using a large intravenous bolus of lidocaine and immediate and frequent sampling of arterial blood, the authors identified an initial rapidly-clearing lidocaine compartment in the cat. This first compartment has the volume characteristics of the cat's intravascular space. The three-compartment open model matches lidocaine kinetics better than the two-compartment model. (Key words: Kinetics; Three-compartment model; Lidocaine; Intravascular compartment; Drug distribution.)

LOCAL ANESTHETICS are given intravenously for a variety of clinical purposes. They are used, for instance, to anesthetize a tourniquet-occluded limb, to augment general anesthetics, and to correct cardiac arrhythmias. Calculating the proper dose of local anesthetic is difficult, however, for the therapeutic dose range is narrow. Pharmacokinetic models, such as the one described here, aid in predicting dosage schedules that will quickly yield therapeutic drug levels with minimal over- or undershoot.

Viewing the body as one large uniform compartment from which drug is removed only by excretion and biotransformation furnishes a model that, while simple, fails to account for events immediately following intravenous injection.¹ The two-compartment open model² overcomes this disadvantage, yielding substantial agreement between observed and predicted values of lidocaine.^{3,4} A three-compartment

lidocaine model that accounted better yet for lidocaine disposition was described recently.⁵

The predictive potential of such models would be strengthened if—as common sense would dictate—one could equate the initial drug distribution space with the intravascular compartment. But the latter is difficult to demonstrate in man, where slow injection is desirable to avoid potential harm. Thus, drug may be leaving the bloodstream while injection is still in progress, so yielding a falsely high estimate of the initial compartment.

To bypass the problem, we rapidly injected a lidocaine bolus in cats and sampled arterial blood at frequent intervals. We show here that lidocaine initially occupies the intravascular space in a three-compartment model.

Methods

Seventeen adult cats, weighing 3.7 kg on the average, were anesthetized with nitrous oxide and halothane. After cannulating a femoral artery and vein and placing extradural cortical electrodes, halothane was discontinued. Thereafter, the animals were ventilated with 70 per cent nitrous oxide and oxygen, with end-tidal CO₂, P_{iO₂}, and pH maintained at levels normal for the cat.⁶ Arterial blood pressure, urine output, and temperature likewise were held within near-normal limits by infusion of fluids and warming, respectively. Decamethonium was injected intermittently to maintain immobility.

A 16.8 mg/kg dose of lidocaine hydrochloride (lidocaine-HCl crystals dissolved in sterile saline solution and brought to pH 7 with NaOH) was injected intravenously in 10 seconds or less. One milliliter of arterial blood was drawn into a heparinized syringe 0.5, 1, 2.5, and 10 minutes after lidocaine injection, and less frequently thereafter for a 60 to 120

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minute period. Samples not immediately analyzed were frozen. (A 16.8 mg/kg dose was given because this is the median convulsant dose of lidocaine in diazepam-treated cats.⁷)

A gas chromatographic technique similar to that described by Tucker⁸ was used to measure lidocaine levels with an accuracy better than 5 per cent down to 0.05 μg lidocaine/ml blood. The assay yields a sharp lidocaine peak that excludes lidocaine metabolites and drugs used in animal preparation. Results

were fitted to bi- and tri-exponential curves with a nonlinear least-squares algorithm⁹ on a PDP-15 computer.

Assuming, and there is no sound evidence to the contrary, that lidocaine distribution and clearance are exponential rate processes,³⁻⁵ the lidocaine blood level $C(t)$ at time t can be represented by a multiexponential equation such as

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} \quad (1)$$

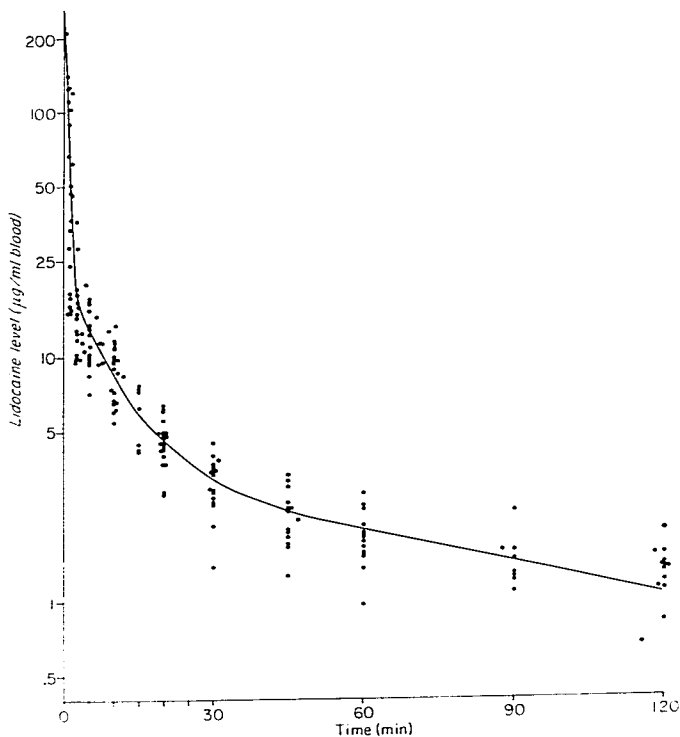


FIG. 1. Best-fitting tri-exponential curve, computer-fitted to 166 data points. Time (minutes) on the abscissa, logarithm of the lidocaine blood level ($\mu\text{g}/\text{ml}$) on the ordinate.

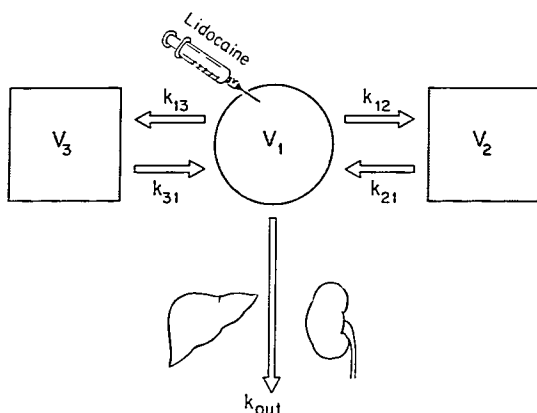


FIG. 2. Three-compartment open model describing kinetics of intravenously injected lidocaine. The drug is assumed to be eliminated from the initial (V_1) compartment.

In the above equation, e is the number (2.718) whose natural logarithm is 1, and A , B , C , α , β , γ are parameters of the best-fitting curve.

While suitable curves can be fitted by eye and the corresponding parameters obtained from a semilog plot, the procedure is inexact. A more rigorous approach is to minimize the sum of squared deviations of the observed points from a computed curve.¹⁰ The diffusion and elimination rate constants are then calculated from the parameters of equation 1 by solving the compartmental linear differential equations for the unknowns.¹¹ The initial distribution volume is obtained by dividing dose of drug administered by drug concentration at zero time (calculated by setting the variable t in equation 1 to zero).

Results

Eight of 174 samples had to be discarded because of clotting. The remaining 166 data pairs (μg lidocaine/ml blood versus time) were fitted to bi- and tri-exponential decay curves, representing the two- and three-compartment models proposed for lidocaine, respectively. The former yielded a visibly poor fit, missing entirely points beyond 90 minutes, as shown too by a reduced chi-

square χ^2 of 15.71. The tri-exponential curve, conversely, encompassed all data points (fig. 1), yielding a reduced chi-square value of 3.34.

In the resultant equation

$$C(t) = 241.61e^{-2.12t} + 16.04e^{-0.12t} + 3.65e^{-0.01t} \quad (2)$$

$C(t)$ is the lidocaine concentration in μg per ml blood at time t , and t is the time in minutes after injection. Fitting the data to an exponential equation with additional terms would have been meaningless, because the 101.5-minute time constant of the slowest-changing (third) term was of the same order of magnitude as the last sampling time, 120 minutes.¹²

LIDOCAINE MODEL

Equation 2, the sum of three exponential terms, describes the behavior of the dependent variable (concentration) in a three-compartment open system. The corresponding model is illustrated in figure 2, where V_1 , V_2 , and

χ^2 Closeness of fit is expressed by the chi-square statistic: the sum of squared deviations from the computed curve, divided by the expected value. To ease comparison, the sum is normalized by dividing it by the degrees of freedom to yield the reduced chi-square.¹⁰

TABLE 1. Pharmacokinetic Constants in the Cat,* Intravenous Bolus of Lidocaine;
Arterial Sampling

k_{12} (min^{-1})	k_{21} (min^{-1})	k_{13} (min^{-1})	k_{31} (min^{-1})	k_{out} (min^{-1})	C_0 ($\mu\text{g}/\text{ml}$)	V_1 (l/kg)
1.07	0.26	0.48	0.02	0.42	261.3	0.0643

* The subscripted "k's" are disposition rate constants corresponding to figure 1. C_0 is the calculated initial lidocaine concentration. V_1 is the initial lidocaine distribution volume.

V_3 represent the three compartments among which lidocaine is distributed.

Injected lidocaine leaves the central V_1 compartment by three paths. One path is irreversible, removing lidocaine exponentially with a rate constant of k_{out} by excretion and biotransformation. The other paths are reversible, with lidocaine diffusing into and out of peripheral compartments V_2 and V_3 with first-order rate constants k_{12} , k_{21} , k_{13} , and k_{31} , respectively. With the parameters of equation 2 known, one can now solve the compartmental rate equations for the unknown rate constants (table 1).¹¹

Note in the table the volume V_1 of the first compartment. Its 64.3 ml/kg falls inside the 62 to 69 ml/kg blood volume range described for normal cats.¹² Within the limitations of the model, then, lidocaine is distributed initially through the intravascular (blood) compartment. Soon thereafter, however, with half-times of only 0.65 and 1.44 minutes, lidocaine spreads to the other compartments.

Discussion

The three-compartment lidocaine disposition model demonstrated here supports a similar one proposed by Tucker and Boas.⁵ Their studies were done in man, using a 3 mg/kg dose of lidocaine given intravenously over a 3-minute period. Rapid injection allowed us to start sampling arterial blood almost immediately, thereby bringing out details of the earliest phases of drug distribution that may escape detection when venous blood is sampled.¹⁴ We further enhanced the resolution of the method by injecting a large quantity of lidocaine and found that the initial distribution volume was identical to the blood volume observed in cats.¹²

Linking a mathematical postulate to biologic reality requires consideration of the fundamental assumptions.¹² One premise as-

sumes sampling from a well-stirred compartment. With a 3-5-second circulation time (vein to artery) in cats¹⁵ and sampling delayed to 30 seconds after injection, we consider this condition adequately satisfied. Calculations further assume instantaneous injection. We believe that the 10-second injection time approached the theoretical "impulse" input about as closely as technically feasible.

Constancy of the distribution volumes, too, may be assumed with some assurance, as the hematocrit in cats injected with lidocaine varies little from control (unpublished results). Had large fluid shifts into or out of the vascular compartment been associated with lidocaine injection, the hematocrit would have fallen or risen, respectively. The assumption that solute transfer is an exponential (first-order) process likewise holds true for lidocaine.^{2-5, 16}

The premise that rate constants are independent of drug concentration, on the other hand, is generally assumed but rarely proven. The work by Boyes and associates,³ who administered lidocaine at various rates, tends to confirm the tenet. However, other than purely mathematical considerations enter. Stensen *et al.*,¹⁷ for instance, showed an inverse association between cardiac output and blood lidocaine level in man. Decreased tissue perfusion presumably impedes lidocaine extraction from the intravascular compartment, yielding a blood lidocaine level higher than that seen during normal perfusion. The relationships between the rate constants, cardiac output, and drug dose, and their effects on lidocaine disposition, clearly remain to be worked out.

Computation of the volumes of compartments V_2 and V_3 is premised on a steady-state system. This condition is not easily achieved in short-term experiments. Judging by the distribution time constants (and analogous to

(the model for inhalation anesthetics), we consider V_2 to represent rapidly perfused, and V_3 slowly perfused, tissue compartments.

Our three-compartment lidocaine disposition model is notable in that it actually encompasses a physiologic body space, namely the intravascular volume. In two-compartment models, initial lidocaine distribution volume V_1 was 0.435 l/kg in one study,⁴ 0.77 l/kg in another,¹⁶ and 0.66 l/kg in dogs.³ Tucker and Boas,⁵ in a three-compartment model, found a mean value of 0.10 l/kg for the first compartment in five subjects, still about 50 per cent greater than the blood volume in man.

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CNS Function

CEREBRAL EDEMA AND HEPATIC NECROSIS Unlike certain well-known sequelae of massive hepatic necrosis, cerebral edema has received little attention as a potential complication. In this retrospective study of 32 patients who died of hepatic necrosis, necropsies of 16 demonstrated cerebral edema. This incidence was much higher than that in a control series of necropsies. Compared with hepatic necrosis patients without cerebral edema, those with this complication were younger, had been in end-stage hepatic coma longer, and had had better renal function and

higher arterial-blood pH levels. An obvious cause of the edema was not found, nor did the application of vigorous treatment in several instances lead to relief of the cerebral swelling subsequently found at autopsy. In view of difficulties inherent in making the diagnosis of cerebral edema, a high index of suspicion when caring for the patient with hepatic necrosis is needed. Frequent neurologic examinations are recommended. (Warc, A. J., D'Agostino, A. N., and Combes, B.: *Cerebral Edema: A Major Complication of Massive Hepatic Necrosis. Gastroenterology* 61: 877-884, 1972.)