An Analog Computer Simulation for the Distribution of d-Tubocurarine

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A nine compartment analog computer model was constructed to simulate and study the uptake and distribution of *d*-tubocurarine. By varying model parameters, six compartments were simulated using directly obtained experimental data. Drug distribution in the experimentally inaccessible compartments was obtained indirectly from the analog model. The model proved predictive and close agreement was observed with the experimentally observed data.

In 1953, Kalow [1] described a theoretical model for the uptake and distribution of *d*-tubocurarine using data obtained from urinary excretion. With limited experimental measurements available, much of this description rested on general mathematical principles of drug distribution previously set forth by Teorell.[2] Kalow conceived of the distribution of *d*-tubocurarine as occurring within four compartments: tissue, blood, excretion, and destruction. At that time he was unable to further extend his model because of difficulty in manipulating the complex mathematical equations and also by the lack of satisfactory analytic methods for the detection of *d*-tubocurarine in various body tissues. Availability of the analog computer and development of new analytic techniques [3] have made possible a comprehensive model for the uptake and distribution of *d*-tubocurarine (fig. 1).

Use of the analog computer for the purpose of developing model systems which can simulate drug distribution is an established procedure. Initial requirements include a precise definition of each parameter involved, *i.e.*, number of compartments, size of compartments, relationship between compartments, etc. From this beginning one may then progress to the mathematical testing of the distribution hypothesis. Subsequently, the model may be modified until it meets the experimental situation, fails to do so, or possibly suggests an alternative solution.

The model system developed for the distribution of *d*-tubocurarine initially was limited to six compartments. It soon became apparent that this number of compartments was inadequate, and other depots were needed for more accurate simulation. For example, an additional depot was required which would temporarily hold or indiscriminately bind the *d*-tubocurarine. Such a reservoir described by Cavillito [4] has been termed an 'acceptor tissue depot.' This depot represents areas wherein the drug may temporarily be stored and from which it exerts no local pharmacologic response. Additional experimental data on the plasma protein binding of *d*-tubocurarine indicated that protein binding played a significant role in its distribution. It was thus necessary to simulate this distribution with a separate compartment.

Kalow [5] has recently described the distribution of *d*-tubocurarine as occurring in three phases: an initial distribution from plasma into extracellular fluid, continued distribution from extracellular into intracellular fluid, and finally elimination by metabolism or excretion. To simulate these three stages, each tissue compartment could be most accurately represented by an intracellular and an extracellular division. Since such divisions add greatly to the complexity of the model we did not believe it advantageous to divide all tissue compartments. Muscle tissue, however, represents the largest body mass (45 per cent body weight)

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and two compartments were provided to describe its intra- and extracellular distribution phases.

Initially, we were concerned with the possible metabolism of *d*-tubocurarine since previous experiments accounted for only 30 per cent of the drug eliminated in the urine within a six-hour period.[8] Recently, studies have been extended to 24 hours and drug concentration in the urine measured using tritiated *d*-tubocurarine. With these techniques 60–70 per cent of the drug is recovered through renal elimination unchanged. Since additional studies also indicate elimination of *d*-tubocurarine in the bile, it appears unlikely that metabolism of *d*-tubocurarine plays a significant role.*

Model Theory

In an analog model which serves to simulate the uptake and distribution of a drug, the total amount of drug within a given compartment equals the integral of the net flow of the drug into the compartment.

$$C_B = \int (K_{AB}[C_A] - K_{BA}[C_B])\,dt \quad (1)$$

C_B = sum of material in compartment B. $[C_A]$ and $[C_B]$ = concentrations of the material in compartments A and B. K_{AB} = permeability coefficient from compartment A to compartment B. K_{BA} = reverse permeability coefficient from compartment B to compartment A.

With passive diffusion, rate constants are equal in both directions, *i.e.*, $K_{AB} = K_{BA}$. Net flow is then directly proportional to concentration gradient. In customary fashion, electronic integrators and summers may be used to perform these operations. The output of the integrator represents total amount of drug accumulated within the compartment. To obtain the concentrations which determine flow, the amount of drug in each compartment must be divided by its respective volume of distribution. If we assume passive diffusion, the amount of drug within a given compartment may be expressed as:

$$C_B = \int \frac{1}{R_{AB}}\left(\frac{C_A}{V_A} - \frac{C_B}{V_B}\right)^{dt} \quad (2)$$

* Unpublished observations.

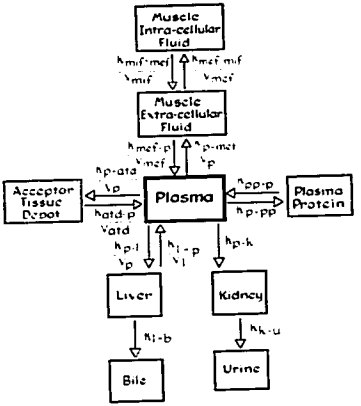

FIG. 1. A nine compartment representation for the distribution of *d*-tubocurarine. Initially, *d*-tubocurarine is present in the plasma compartment and arrows indicate further transport between compartments. Each transport rate constant is composed of a permeability constant ($K = 1/R$) and a concentration constant (V).

R_{AB} = resistance to flow between compartment A and compartment B. V_A and V_B = volumes of distribution for compartments A and B.

Since in many instances transport may be an active rather than a passive process, the apparent volumes of distribution obtained by formula (2) may be in error. Under such circumstances, and in the absence of more exact information, judgment of the operator becomes critical in assigning proper relationships. In our model the diffusion of *d*-tubocurarine appeared to closely simulate a passive process, but with certain compartments, this assumption proved invalid (table 1). In simulation of the uptake and distribution of *d*-tubocurarine the potentiometer settings were varied until a model was found which was best able to fit the empirical data. Although this approach to modelling does not necessarily always offer a unique solution a useful model system could be developed by these methods.

TABLE 1. Simulation Data for the Distribution of *d*-Tubocurarine

Potentiometer Number	Constant	Potentiometer Setting	Theoretical Volume* (percentage)	Compartment
1	$\frac{1}{R_{p-l}}$	1.0		
2	$\frac{1}{V_l}$	5.0	1.0	Liver
3	$\frac{1}{R_{l-b}}$	0.03	—	Bile
4	$\frac{1}{R_{p-pp}}$	1.0		
5	$\frac{1}{V_{pp}}$	3.2	1.7	Plasma protein
6	$\frac{1}{R_{p-k}}$	0.21		
7	$\frac{1}{V_k \cdot R_{k-u}}$	0.60	—	Kidney, urine
8	$\frac{1}{R_{p-atd}}$	0.85		
9	$\frac{1}{V_{atd}}$	0.24	21.2	Acceptor tissue depot
10	$\frac{1}{R_{p-mef}}$	1.41		
11	$\frac{1}{V_{mef}}$	0.72	7.0	Muscle extracellular fluid
12	$\frac{1}{R_{mef-mif}}$	0.15		
13	$\frac{1}{V_{mif}}$	0.1	35.0	Muscle intracellular fluid
14	0.1	—	—	
15	$\frac{1}{V_p}$	1.0	5.0	Plasma

* Theoretical volumes are calculated by assuming passive diffusion. Plasma volume is assumed to be 5% of body weight.

Circuit Description and Application

The electrical diagram for the model representing uptake and distribution of *d*-tubocurarine is shown in figure 2. Plasma *d*-tubocurarine (A19) is the sum of *d*-tubocurarine found free in plasma (A26) and that bound to plasma protein (A18). *d*-Tubocurarine present in the kidney is represented by the output of (A20), in the urine by (A21), in the liver by (A16), and in the bile by (A17). Total muscle *d*-tubocurarine (A25) represents the sum of *d*-tubocurarine in muscle extracellular fluid (A23), muscle intracellular fluid (A24), plus 10 per cent of that *d*-tubocurarine concentration existing in the plasma. Potentiometer (P14) applies a correction factor for free blood as present in the muscle tissue sample. Other potentiometers are used to determine flow between compartments. As an example, (P12) determines flow of *d*-tubocurarine between the muscle extracellular fluid compartment to the muscle intracellular compartment.

In developing the model, the output of the six experimentally known compartments (plasma, kidney, liver, urine, bile, and muscle) was displayed repetitively on an oscilloscope screen and the parameters adjusted to allow the model curves (fig. 3) to match those obtained from the experimental data (fig. 4). Experimentally inaccessible areas such as the acceptor tissue depot (A22) were also displayed. The acceptor tissue depot was derived by totalling all values to 100 per cent.

Adjustment of certain parameters was subject to restraint imposed by prior experimental data. The binding ratio of *d*-tubocurarine to plasma protein was thus fixed at 0.32. Since the volume of muscle extracellular fluid approximately equals that of plasma, we attempted to keep (P11) and (P15) equal. In order to simulate the high concentration of *d*-tubocurarine experimentally found in muscle tissue, it was necessary to adjust this ratio of 1.41:1. This may be interpreted to indicate that the volume of distribution of *d*-tubocurarine in muscle extracellular fluid is 1.41 times the plasma volume or, alternatively, that the process is not passive diffusion. Estimates of the ratio of muscle intracellular fluid volume to muscle extracellular fluid volume are variously given as 3:1 to 6:1. The ratio of (P11) to (P13) could be held within this range, and good fit was found with a ratio of 5:1.

Other parameters for which there was limited experimental data were adjusted without restraint. The best fit for the liver compartment was obtained with the ratio of potentiometer settings for liver volume (P2) and plasma volume (P15) at 5.0:1. Since the liver volume represents ap-

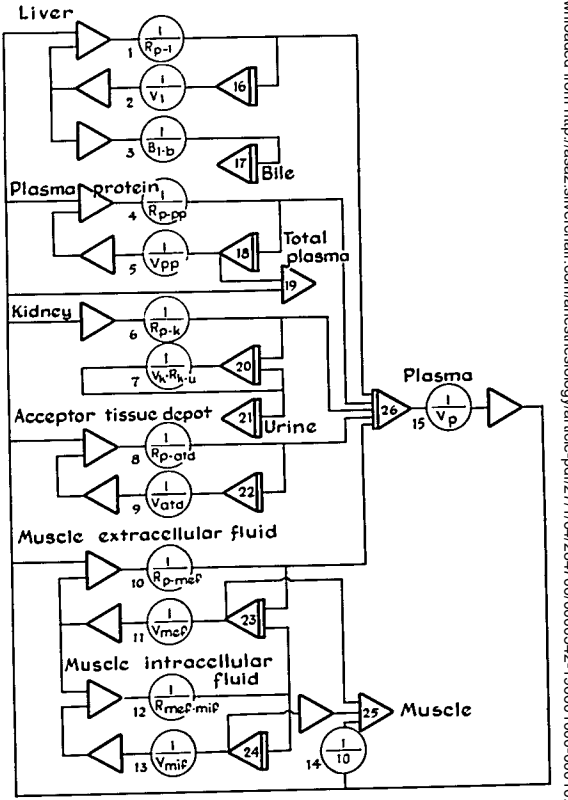

FIG. 2. Circuit diagram for the analog computer representation of the distribution of *d*-tubocurarine.

proximately two thirds of the plasma volume, this would indicate that *d*-tubocurarine does not distribute evenly throughout the liver tissue. The best fit for the combined curves was obtained by setting the ratio of acceptor tissue depot volume (P7) to plasma volume (P15) at 4.25:1. From this ratio one calculates the hypothetical volume of the acceptor tissue depot as 21.2 per cent of body weight (table 1).

Discussion

The analog computer model developed by the above procedure closely simulates the distribution of *d*-tubocurarine observed in the experimental animals. Furthermore, the model is linear and does not contradict any intuitive expectations. Thus, although such a model cannot in the true sense verify the experimental data, it does strengthen their reliability and also indicates that the experimental data can be subjected to precise mathematical treatment (as in a computer model). The close agreement between model curves (fig. 3) and experimental data curves (fig. 4) is apparent.

Other advantages may be derived from con-

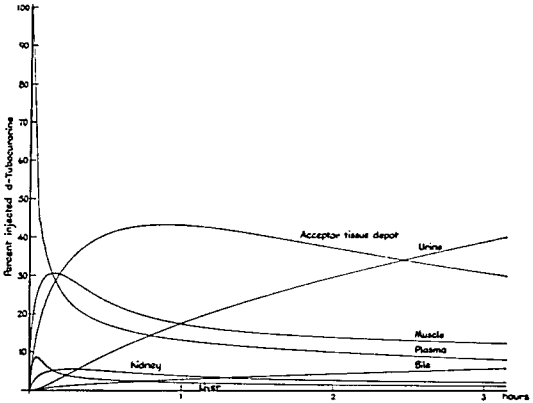

FIG. 3. Simulated distribution of *d*-tubocurarine as recorded on an X-Y plotter.

struction of such an analog model for the distribution of *d*-tubocurarine. In this situation analytic procedures did not permit sampling of all possible tissue depots. Since the mathematical model further requires that all values sum to 100 per cent it was necessary to add an additional depot (not experimentally found) to account for the remainder of the drug. The basis for such a compartment is met through use of an "acceptor tissue depot" as postulated by Cavillito.[4] This depot of indiscriminate binding may alternatively represent "sites of loss" or possibly "sites of detoxification." Studies by Chagas *et al.*[6] and by Ehrenpreis[7] suggest that acidic mucopolysaccharides are involved as primary binding sites. The speculative aspects of this depot must be emphasized.

Finally, the analog model proved useful in predictive experiments. We were thus able, for example, to eliminate the kidney compartment in the model, and the resulting distribution curves closely followed the experi-

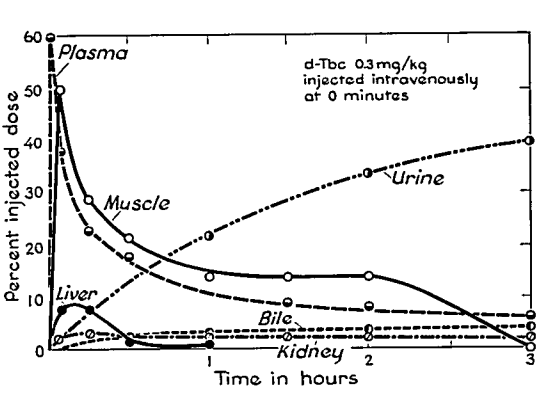

FIG. 4. Experimental data determined for the distribution of *d*-tubocurarine within six known compartments.

mental data observed in the nephrectomized animal. Other useful experiments indicated elevated plasma levels of *d*-tubocurarine present on repetitive injection and affirm the known cumulative action of this drug. This type of experiment could also be used to predict dosage requirements over prolonged use of the drug and also served to compare requirements for a single dose versus multiple or continuous injection techniques.

Since construction of the model was strictly linear, we were unable to simulate the effect of large injections of *d*-tubocurarine sufficient to produce saturation of certain body depots. In recent experiments with the dog, distribution curves at higher dose levels have proved radically different than those at lower levels.[8] Such studies suggest an initial saturation of the acceptor tissue depot. Further experimental data is needed to test this hypothesis.

Conclusion

An analog computer model has shown that the distribution of *d*-tubocurarine is consistent with the principles of linear compartment theory. With this model we have been able to closely simulate the experimentally obtained data, to postulate distribution in experimentally inaccessible compartments, to predict volumes of distribution of *d*-tubocurarine within various compartments, and to judge whether or not the distribution was passive. The model proved accurately predictive and provided additional insight into the process of distribution of *d*-tubocurarine.

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CHLOROFORM Chloroform was used in 110 operations on human beings and 45 experiments on dogs. Accurate dosage was secured by the use of a "Khlorotek." Phase 1 of surgical anesthesia was maintained by means of endotracheal intubation with semi-opened circuit and artificial ventilation. Sodium thiopental was used for induction, and relaxation was obtained by means of suxamethonium. Relative advantages and drawbacks of chloroform and halothane are discussed. Chloroform did not give rise to any serious myocardial, hepatic or renal complications. A transient disturbance of coronary circulation was noted in a woman with chronic coronary insufficiency; bradycardia occurred in 5 and slight jaundice in 3 cases. Chloroform anesthesia was followed by sustained postoperative analgesia which helped to maintain good ventilation. Nausea and vomiting were extremely rare in spite of the fact that many patients had been treated with antineoplastic agents whose side effects include vomiting. (*Smolnikov, V. P., and Narodnitskaya, N. A.: Modern Chloroform Anesthesia in Oncology (Russian), Ekper. Khir. Anesteziologiya 1: 748, 1965.*)