(2) A. D. Reynolds, *Mfg. Chem. Aerosol News*, **41**, 40(1970).
(3) H. J. Malinowski, M.S. thesis, Philadelphia College of Pharmacy and Science, Philadelphia, Pa., 1971.
(4) D. C. Fox, M. D. Richman, G. E. Reier, and R. F. Shangraw, *Drug Cosmet. Ind.*, **92**, 161(1963).
(5) G. E. Reier and R. F. Shangraw, *J. Pharm. Sci.*, **55**, 510 (1966).

ACKNOWLEDGMENTS AND ADDRESSES

Received January 31, 1972, from the *Department of Pharmacy, Philadelphia College of Pharmacy and Science, Philadelphia, PA 19104*

Accepted for publication May 12, 1972.

▲ To whom inquiries should be directed.

Circuit for Simulation of Multiple-Dosing Kinetics

EDWARD B. KIRSTEN*▲ and SAMUEL M. ROSS

Abstract □ An electronic circuit is described which simulates the theoretical curves associated with multiple-dosing kinetics. The output is an analog voltage which generates plasma concentration *versus* time curves consistent with the assumptions in a one-compartment open model with rapid intravenous injection. Potentiometer settings offer wide variations in dosing schedules, distribution volumes, and elimination rate constants. Also, once steady-state levels are achieved, a second circuit can be used to produce sudden changes in the elimination rate constant. Both circuits use commercially available electronic components and have been used in student lecture/demonstrations to display multiple-dosing kinetics graphically.

Keyphrases □ Multiple-dosing kinetics—simulation, electrical circuits □ Electrical circuits—simulation of multiple-dosing kinetics □ Simulation of multiple-dosing kinetics—electrical circuits

An understanding of drug accumulation through repeated administration is an important aspect in the teaching of pharmacology. Concepts such as dosing interval, volume of distribution, and half-life can be made more meaningful if time–concentration curves are generated to illustrate significant points. Both analog and digital computers can simulate models of multiple-dosing kinetics (1–3). Likewise, hydrolic analogies have been employed in discussions of one- and two-compartment systems (4, 5). These models, however, are often expensive or inconvenient to use during a lecture/demonstration. The purpose of this report is to present a simple and inexpensive electrical circuit which can be used to simulate the theoretical curves associated with multiple-dosing kinetics. The device can be used in both the training of research scientists and the teaching of medical students.

DISCUSSION

The model discussed in this paper is an analog device which was constructed from standard electronic components to simulate the theoretical plasma concentration *versus* time curves associated with repetitive dosing. This simple analog consists of two independent circuits. The first, or multiple-dosing circuit, generates an output voltage proportional to the time-varying drug concentration. The time–concentration curves are consistent with the multiple-dosing conditions set on four potentiometers representing dosing interval, volume of distribution, dose magnitude, and elimination half-life. Plasma concentration falls exponentially between individual administrations, with drug accumulation from sequential administrations following equations given by Goldstein *et al.* (6) and Wagner (7).

A second, or level-change circuit, employs a level controller to alter automatically the elimination half-life when a certain preset voltage, *i.e.*, drug concentration, is reached. The multiple-dosing circuit functions independently of the level-change circuit.

The multiple-dosing circuit is shown in Fig. 1. The circuitry consists of an oscillator to control pulse rate, a monostable multivibrator to regulate pulse duration, and a constant-current source to charge rapidly capacitor C of the RC network. These active components control drug injection parameters, while the RC network is analogous to the "patient." A ±5-v. power supply[1] drives all of the circuitry with the exception of the battery supply[2] to the operational amplifier in the constant-current circuit.

The first component, a unijunction oscillator, produces a pulse train output. Each pulse is analogous to a single dose. The pulse frequency is variable, with a rate determined by potentiometer R_1 in the oscillator circuit. In the parameters of pharmacokinetics, altering R_1 would be analogous to varying the dosing interval. The output pulse rate can be accurately monitored by an oscilloscope as indicated in Fig. 1 and is variable from 3 to 60 pulses/sec.

The oscillator output drives a monostable multivibrator[3]. The multivibrator provides a pulse at the oscillator rate but with a duration that is a function of potentiometer R_2. Altering R_2 is equivalent to changing the volume of distribution on a multiple-dosing time–concentration curve. The exact electrical analogy of varying the volume of distribution consists of a change in capacitor C, *i.e.*, a change in the distribution volume of the patient. This, however, is technically difficult to accomplish without also changing the time constant of the RC network and, consequently, the drug half-life. To simplify the circuitry in this particular model, pulse duration is used as the electrical parameter corresponding to distribution volume. For pragmatic reasons the volume of drug distribution is controlled by the electronic circuit involved with drug injection rather than the circuit components of the patient.

The multivibrator is coupled to a constant-current source by a photoisolator[4]. A constant-current circuit is employed to accomplish rapid buildup of charge across the passive RC network, thereby adequately describing instantaneous drug absorption. Constant current is achieved by using an operational amplifier[5]. The output

[1] 2.6.100, Semiconductor Circuits, Inc.
[2] TRII5R-6.75 V, Mallory, Inc.
[3] 9601, Fairchild, Inc.
[4] MCT2, Monsanto Corp.
[5] UC-4250C, Solitron Devices, Inc.

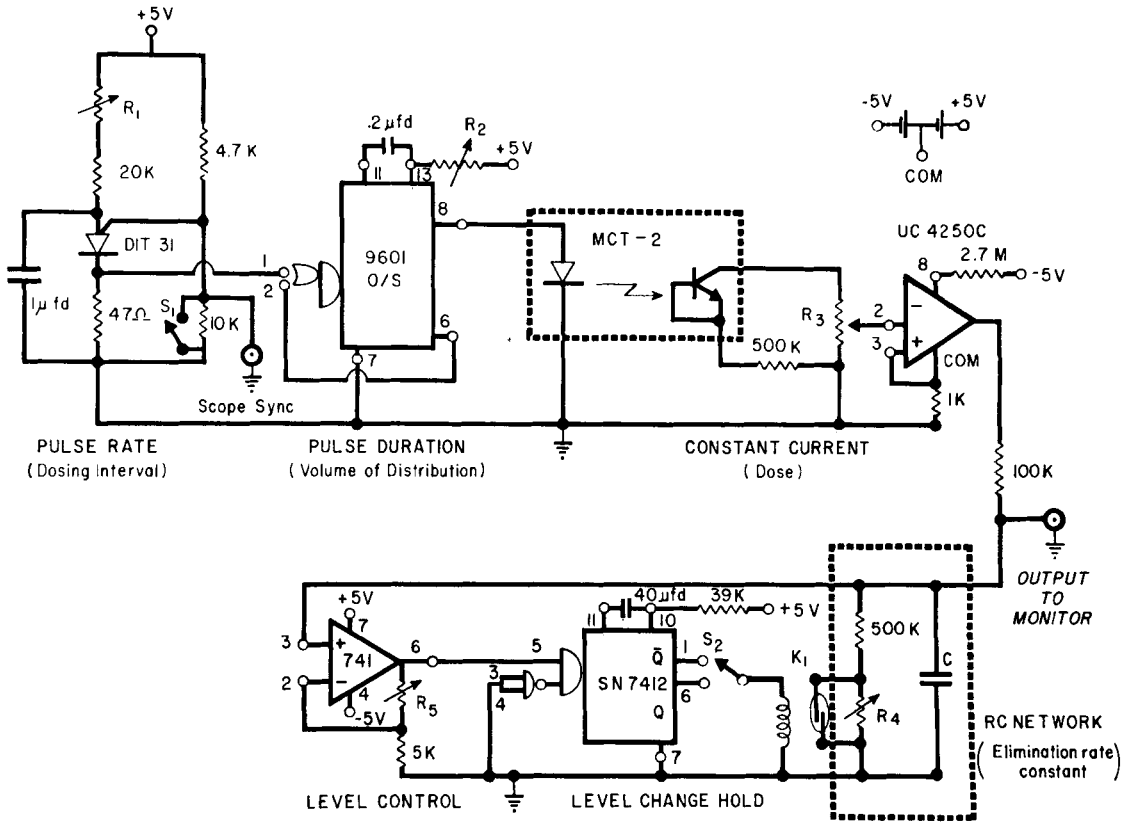

Figure 1—*Diagram of multiple-dose circuitry (upper) and level-change circuitry. Potentiometer R_1 is 250 kΩ, R_2 and R_5 are 100 kΩ, R_3 is 10 kΩ, and R_4 is 2.5 MΩ. Both R_2 and R_3 are 10-turn potentiometers. The electrical function of each circuit is given with its pharmacokinetic analogy given in parentheses. Capacitor C is a 3 μf., 200-v. unit. K_1 is a reed relay (model PRB3009HI, Clare Co.). S_1 is a single-pole, single-throw switch; S_2 is a single-pole, double-throw switch.*

current level, equivalent to the magnitude of a single dose, is regulated by the 10-turn potentiometer R_3[6]. Since the distribution volume is determined by R_2 and the dose magnitude is controlled by R_3, the resulting drug plasma level in the patient is determined by the active network.

The constant-current output pulses are fed into a passive RC network simulating first-order elimination between individual doses. The setting on potentiometer R_4 determines the half-life or elimination rate constant of the drug. The analog voltage output measured across the RC network is proportional to the charge on capacitor C and, hence, to the instantaneous drug levels in the patient.

The accumulation of charge on capacitor C proceeds in the following manner. After the circuit is activated by closing S_1, the first current pulse across the RC network charges capacitor C to some value determined by R_2 and R_3, *i.e.*, the predetermined plasma drug concentration for the patient. Exponential discharge of the capacitor starts immediately and follows the equation:

$$Q_t = Q_0 e^{-t/RC} \qquad \text{(Eq. 1)}$$

where Q_t, the charge on the capacitor, is proportional to the plasma drug concentration at time t; and Q_0 is the drug concentration just after the first dose. The elimination rate constant is given by the time constant $(RC)^{-1}$ of the RC network, where $R = 500\ k\Omega + R_4$. The second pulse, *i.e.*, second administration, arrives after an interval determined by potentiometer R_1. This current pulse adds further charge (Q_0) to the exponentially discharging capacitor, resulting in an instantaneous buildup to a new level. The succeeding pulses continue to add charge to the discharging capacitor, resulting in an accumulation of charge given by:

$$Q_{nt}^* = Q_0 \frac{(1 - e^{-nt^*/RC})}{(1 - e^{-t^*/RC})} \qquad \text{(Eq. 2)}$$

where n is the number of current pulses across the RC network, and t^* is the interval between pulses. This process continues until a steady state is reached when the charge delivered to capacitor C during a current pulse is equal to the charge discharged through R.

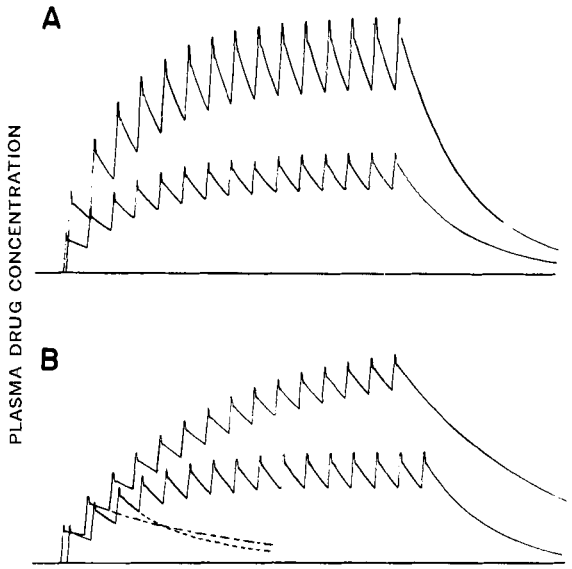

Figure 2—*Graphical display of curves generated by the multiple-dose circuit. (A) The volume of distribution is decreased (upper curve) compared with the control. The notch on the initial segment of the exponentially decaying curve is due to a mechanical overshoot of the x–y recorder. (B) The elimination rate constant is decreased (upper curve) compared with the control. The curves were started at different points to avoid partial overlap. The dashed lines illustrate the differences in elimination rate constant.*

[6] 62JA-10K, Clarostat Corp.

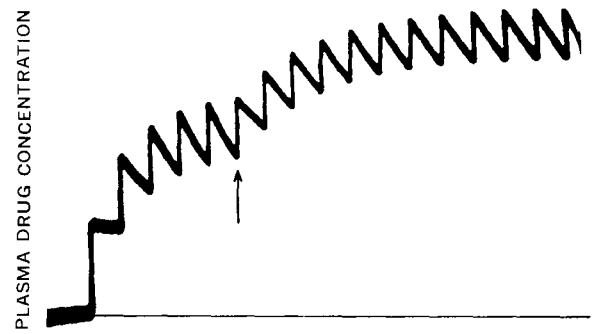

Figure 3—*Alteration of multiple-dosing curve when level-change circuitry is triggered (arrow). A longer half-life is obtained by setting S_2 at the appropriate position.*

The pharmacokinetic equations analogous to Eqs. 1 and 2 were given by Goldstein *et al.* (6) and Wagner (7).

The second, or level-change circuit, incorporates a level controller and holder to alter automatically the time constant of the RC network when a certain charge level is reached on capacitor C (Fig. 1). The trigger level of the 741 operational amplifier[7] is set by potentiometer R_5 so that the level-change hold circuit[8] opens or closes relay K_1, depending upon the position of switch S_2. For example, with S_2 in the No. 1 position (as shown in Fig. 1), K_1 is open and the time constant of the RC network is determined by the product (R_4 + 500 KΩ)C. When a certain predetermined charge has built up across C, S_2 changes to the No. 6 position, thereby closing K_1 and effectively removing R_4 from the circuit. The new time constant given by (500 kΩ)C results in a shorter exponential discharge time, *i.e.*, higher elimination rate constant.

RESULTS AND CONCLUSIONS

The assumptions consistent with a one-compartment open model of drug distribution were employed in designing this multiple-dosing analog (7). The pharmacokinetic parameters (dose, dosing interval, volume of distribution, and elimination half-life) can all be altered by simple potentiometric controls as described. Furthermore, a second circuit can be used to alter automatically (or manually) the half-life at some point during the exponential voltage buildup generated by the multiple-dosing circuit. The "new" half-life might be consistent with some physiological or pharmacological procedure done on the patient, thereby shifting the plasma drug concentration to a new level.

Typical time–concentration curves displayed on an *x–y* recorder[9] are shown in Fig. 2. In Fig. 2A the volume of distribution was changed by varying the R_2 potentiometer on the pulse duration circuitry. In a similar manner, the elimination rate constant can be altered by increasing or decreasing the R_4 potentiometer in the RC network (Fig. 2B). In both figures the maximum along the curve of accumulation lies on a curve which is identical with the curve of disappearance (8). Neither of the curves was generated using the level-change circuitry described.

Figure 3 shows a curve where the half-life was changed upon reaching a predetermined drug concentration (arrow). The level-change circuitry can either increase or decrease the half-life, depending on the position of switch S_2. In this figure the output was displayed directly on a TV monitor, using one channel of an eight-channel multiplexer[10] and a scan converter[11].

Simple electronic teaching devices such as these are often sufficient to convey a reasonable understanding of the pharmacokinetic concepts of multiple dosing. Moreover, the basic relationships illustrated empirically by this device can be easily expanded into a more rigorous theoretical treatment.

REFERENCES

(1) E. R. Garrett and H. J. Lambert, *J. Pharm. Sci.*, **55**, 626(1966).

(2) R. Bellman, in "Advances in Biosciences," vol. 5, G. Raspe, Ed., Pergamon, New York, N. Y., 1970, pp. 79–88.

(3) M. Gibaldi and H. Weintraub, *J. Pharm. Sci.*, **60**, 624(1971).

(4) E. Rowe and W. Morozowich, *ibid.*, **58**, 1375(1969).

(5) E. R. Garrett, in "Advances in Biosciences," vol. 5, G. Raspe, Ed., Pergamon, New York, N. Y., 1970, pp. 7–20.

(6) A. Goldstein, L. Aronow, and S. Kalman, "Principles of Drug Action," Harper and Row, New York, N. Y., 1968, pp. 300–304.

(7) J. G. Wagner, "Biopharmaceutics and Relevant Pharmacokinetics," Drug Intelligence Publications, Hamilton, Ill., 1971, pp. 270–277.

(8) J. H. Gaddum, *Nature*, **153**, 494(1944).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 11, 1971, from the *Department of Pharmacology, College of Physicians & Surgeons, Columbia University, New York, NY 10032*

Accepted for publication May 22, 1972.

Supported in part by a grant-in-aid from Eli Lilly & Co.

* Fellow of the John Polacheck Foundation for Medical Research.

▲ To whom inquiries should be directed.

[7] Fairchild Instrument.
[8] SN7412, Texas Instrument Corp.
[9] 7004A, Hewlett Packard.
[10] 4701, Tektronix, Inc.
[11] 4501, Tektronix, Inc.