Drug Absorption from the Rectum II

Rates of Absorption and Elimination from the Blood for Various Suppository Bases

By JOSEPH F. BORZELLECA and WERNER LOWENTHAL

To facilitate the calculations involved in Teorell's equation No. 25, a program in Fortran with Format was used in the IBM 1410 digital computer system. Using plasma salicylate levels, the rates of drug absorption and elimination from the blood and the specific apparent body volumes were determined for salicylic acid and sodium salicylate administered in 4 different suppository bases. The rate of absorption for sodium salicylate was found to be greater than that for salicylic acid except for polyoxyethylene sorbitan monostearate base. The rates of elimination from the blood for the 2 drug forms do not vary significantly. The specific apparent volumes for salicylic acid were less than that for the sodium salt, suggesting a lesser degree of storage for the acid form. Since Teorell's equation assumes apparent first-order rates of absorption and elimination from the blood, and this equation describes the data presented, this suggests that salicylic acid and its sodium salt are absorbed into the blood from the 4 bases tested and eliminated from the blood by apparent first-order kinetics. Two sets of data from the literature were also analyzed, and constants for 2 other sets could not be computed because of limitations on the computer.

GARRETT *et al.* (1) used an analog computer to solve a four-factor linear homogeneous equation of exponentials to explain the disappearance of ^{47}Ca from the blood. These authors (2) then programmed a distributive model on the analog computer to determine rate constants.

Riegelman and Crowell (3) using a mathematical solution for radial diffusion, derived equations to explain the absorption of radioactive compounds from the rectum. From the data collected on rats using solutions of ^{131}I compounds (NaI, CHI_3, and triiodophenol), the authors derived an equation which in its simplified form is:

$$\log N - N_f/N_0 - N_f = -kt \qquad \text{(Eq. 1)}$$

where

N = the dose detected at time t,
N_f = the dose detected at the end of the experiment,
N_0 = the total dose administered, and k was characterized as a pseudo first-order constant which included the diffusion coefficient, absorption constant, and any differences due to formulation.

No rate constants to characterize absorption through the rectal membrane, drug disappearance rate from the blood, or rates of elimination were determined.

Teorell (4) originally derived a general equation (equation No. 25) on a theoretical basis to describe the absorption and elimination of drugs administered by routes other than the intravenous. This equation involves 5 variables, 2 of which can be determined experimentally, and 3 are unknown. Because of the difficulty in solving this equation, it has been used only rarely. This could explain why much of the recent work concerned with the kinetics of drug absorption, distribution, and excretion has resulted in derivation of specific equations with limited application. However, the availability of computers makes solving the equation of Teorell a less formidable task.

Recently, Wiegand and Sanders (5), using blood levels determined for 2 drugs given orally as solutions to dogs, or aspirin tablets administered to humans, solved Teorell's equation with a digital computer. A program in Fortran without Format was written to solve the equation for absorption rate constant, drug elimination rate constant from the blood, and specific apparent body volume.

It is the purpose of this paper to apply the equation and a modification of the program presented by Wiegand and Sanders (5) to suppository dosage form, and to show that Teorell's equation combined with computer technology has wide application.

RESULTS AND DISCUSSION

In the work reported here, the program in Fortran without Format was modified to Fortran with Format for use in the IBM 1410 digital computer system. The explanation of the various steps were discussed by Wiegand and Sanders (5). By

Received October 29, 1965, from the School of Pharmacy, Medical College of Virginia, Richmond.
Accepted for publication November 30, 1965.
The authors acknowledge the assistance of members of the Department of Biometry, Medical College of Virginia, Richmond, and Mr. Paul Sanders of Abbott Laboratories, North Chicago, Ill.
This research was supported in part by grant GM-12684-01 from the National Institutes of Health, U.S. Public Health Service, Bethesda, Md.
Previous paper: Lowenthal, W., and Borzelleca, J. F., *J. Pharm. Sci.*, **54**, 1790(1965).

TABLE I.—COMPUTER CALCULATED CONSTANTS FOR DATA PRESENTED BY LOWENTHAL AND BORZELLECA (6)

Suppository Base and Drug[a]	$k_a \pm$ (S.E.)[b]	$k_d \pm$ (S.E.)	$V_d \pm$ (S.E.)
Cocoa butter SA	1.275 (0.487)	0.0293 (0.0531)	0.542 (0.108)
Cocoa butter NaS	2.199 (0.377)	−0.0368 (0.0115)	0.814 (0.052)
PEG SA	1.045 (0.105)	−0.0080 (0.0132)	0.697 (0.038)
PEG NaS	1.970 (0.376)	0.0340 (0.0172)	3.342 (0.269)
S-55 SA	0.812 (0.166)	0.0564 (0.0341)	0.359 (0.047)
S-55 NaS	1.245 (0.195)	0.0318 (0.0160)	0.851 (0.067)
PSMS SA	0.927 (0.324)	0.0607 (0.0585)	0.484 (0.103)
PSMS NaS	0.352 (0.530)	0.210 (0.351)	1.211 (1.653)

[a] PEG is polyethylene glycol mixture; S-55 is a synthetic mixture of glycerides; PSMS is polyoxyethylene sorbitan monostearate. SA is salicylic acid and NaS is sodium salicylate. *Reference 6* gives a complete description of the bases. [b] S.E., standard error.

use of the computer program, plasma, serum, or blood drug levels can be used to determine absorption rate constants, drug disappearance rate constants from the blood, and specific apparent body volumes.

The equation to be fitted to the plasma concentration data is:

$$C = \frac{k_a}{V_d(k_a - k_d)} a_0 (e^{-k_d t} - e^{-k_a t}) \quad \text{(Eq. 2)}$$

where

a_0 = the drug dose in mg./Kg.,
C = the plasma, serum, or blood drug concentration in mcg./ml.,
t = time in hours,
k_a = the apparent first-order absorption rate constant in hr.$^{-1}$,
k_d = the apparent first-order drug disappearance rate constant from the blood in hr.$^{-1}$, and
V_d = the specific apparent volume of drug distribution in L./Kg.

The plasma salicylate levels presented in our previous communication (6) were averaged and used to determine k_a, k_d, and V_d. The use of averages has been shown to be an acceptable procedure (5). The initial estimates for k_a, k_d, and V_d, required as input data, were those determined by Wiegand and Sanders (5) for aspirin tablets, and were 1.55, 0.209, and 0.144, respectively. For sodium salicylate in PSMS base, using the data averaged for the 6 dogs, constants could not be calculated even after several attempts using various estimates of k_a, k_d, and V_d. The plasma levels of

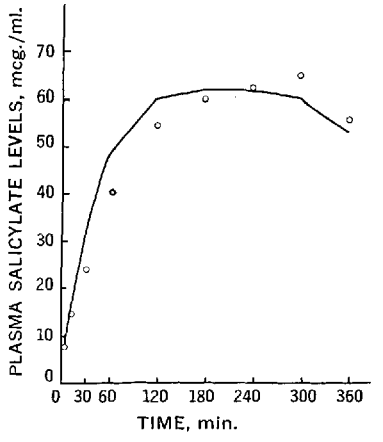

Fig. 1.—Plasma salicylate levels from salicylic acid in cocoa butter suppository base. Key: O, experimental points; —, theoretical curve.

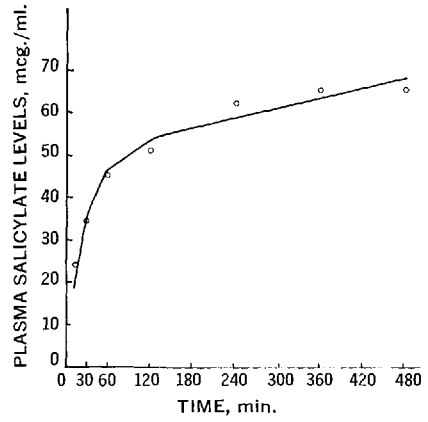

Fig. 2.—Plasma salicylate levels from sodium salicylate in cocoa butter suppository base. Key: O, experimental points; —, theoretical curve.

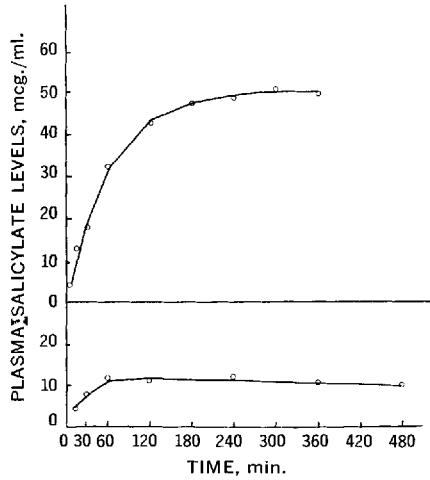

Fig. 3.—Plasma salicylate levels from sodium salicylate in PEG suppository base (bottom) and from salicylic acid in PEG suppository base (top). Key: O, experimental points; —, theoretical curves.

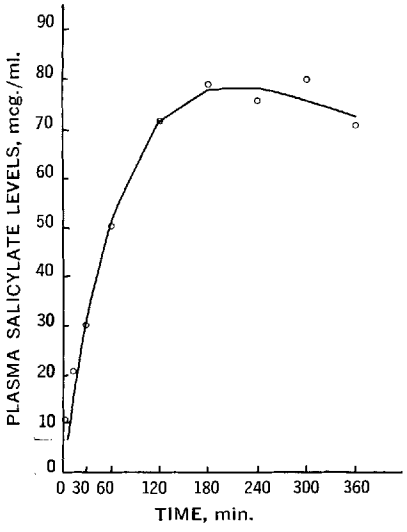

Fig. 4.—Plasma salicylate levels from salicylic acid in S-55 suppository base. Key: O, experimental points; —, theoretical curve.

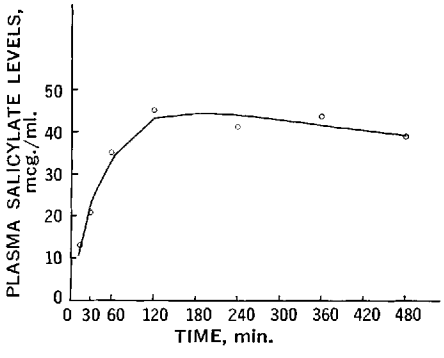

Fig. 5.—Plasma salicylate levels from sodium salicylate in S-55 suppository base. Key: O, experimental points; —, theoretical curve.

1 of the dogs were abnormally high when compared to the other 5 dogs. Constants were readily obtained using the averages obtained from 5 dogs. The calculated constants are given in Table I. Figures 1–6 show the curves for the calculated equation and the experimental data used.

Very few communications give 6 or more blood level concentrations with time data, so that demonstration of the usefulness of this equation and program is made more difficult. Blume and Nohara

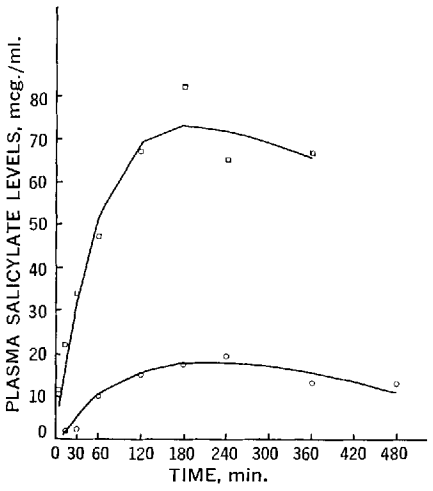

Fig. 6.—Plasma salicylate levels from salicylic acid (□) and sodium salicylate (O) in PSMS suppository base. Key: —, theoretical curves.

(7) gave sodium salicylate solutions orally and rectally to rabbits and determined plasma salicylate levels. From their data the constants were calculated and are shown in Table II; equation and data are plotted in Fig. 7. The same estimates for k_a, k_d, and V_d as listed above were used. Fincher *et al.* (8) administered orally to dogs capsules containing 3 different particle size distributions of sulfisoxazole. The drug in experiment *A* had an average diameter of 1.7 μ; in experiment *B*, 37 μ, and experiment *C*, 95 μ. The constants calculated from these data are shown in Table II and the equations and data plotted in Fig. 8. The estimates of k_a, k_d, and V_d used were 2.30, 0.254, and 3.74, respectively. The data from Swintosky *et al.* (9), and Walkenstein *et al.* (10) had sufficient number of observations and appear to follow Eq. 2. The computer was not able to calculate the constants because it was unable to handle power functions greater than 99. In the power function e^{-kt}, when t becomes large, k does not have to be very large for e to be raised to the 99th power.

In the previous communication (6), it was reported that salicylic acid resulted in higher plasma levels than the sodium salt, but it can be seen from the constants listed in Table I that the salicylic acid is absorbed at a slower rate, except in the case of PSMS base. The rates of elimination from the blood for the 2 forms do not vary significantly. The specific apparent volume for salicylic acid was less than that for the sodium salt, suggesting a

Table II.—Computer Calculated Constants for Data Presented in the Literature

Source and Ref.	$k_a \pm$ (S.E.)[a]	$k_d \pm$ (S.E.)	$V_d \pm$ (S.E.)
(7), Oral	5.930 (2.371)	0.0965 (0.0307)	134.004 (10.972)
(7), Rectal	2.767 (0.741)	0.179 (0.044)	101.643 (10.234)
(8), Expt. *A*	0.709 (0.143)	0.262 (0.048)	0.598 (0.086)
(8), Expt. *B*	0.686 (0.209)	0.165 (0.046)	0.879 (0.172)
(8), Expt. *C*	0.673 (0.203)	0.0493 (0.0249)	1.483 (0.250)

[a] S.E., standard error.

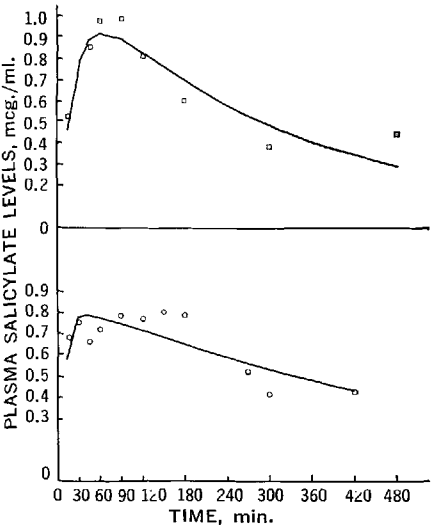

Fig. 7.—Plasma salicylate levels from sodium salicylate solutions (7). Key: ○, oral administration; □, rectal administration; —, theoretical curve.

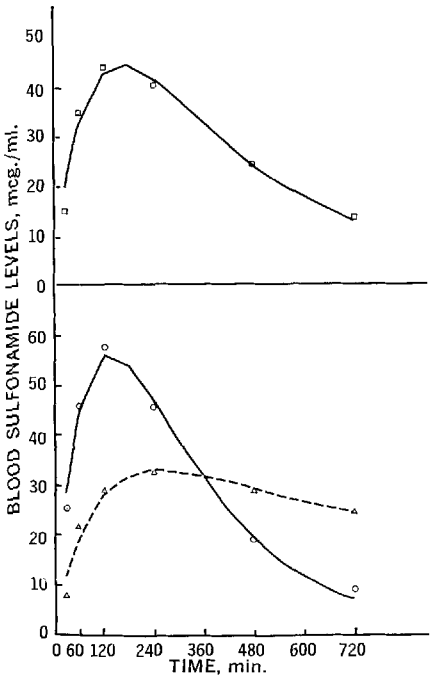

Fig. 8.—Plasma sulfonamide levels from oral administration of sulfisoxazole capsules (8). Key: ○, capsule *A*; □, capsule *B*; △, capsule *C*; — and - - -, theoretical curves.

lesser degree of storage for the acid form. This may be due to the slower rate of absorption resulting in less time for storage before excretion. The negative elimination rates obtained with sodium salicylate in cocoa butter and salicylic acid in PEG base indicate that the plasma levels were still rising at the time the experiment was stopped.

Equation 2 assumes apparent first-order rates of drug absorption and elimination from the blood. This equation describes the data presented, suggesting that salicylic acid and the sodium salt are absorbed into the blood from the 4 bases tested and eliminated from the blood by apparent first-order kinetics.

The constants presented in Table II indicate that sodium salicylate was absorbed at a faster rate orally than rectally, and eliminated from the blood at a slower rate. The large V_d indicates a large amount of the drug is stored in tissue. The constants calculated from the data of Fincher *et al.* (8) show that as average particle diameter increases there is a slight and probably nonsignificant decrease in rate of absorption, a decrease in rate of elimination from the blood, and an increase in specific apparent body volume.

REFERENCES

(1) Garrett, E. R., Johnston, R. L., and Collins, E. J., *J. Pharm. Sci.*, **51**, 1050(1962).
(2) *Ibid.*, **52**, 668(1963).
(3) Riegelman, S., and Crowell, W. J., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 115(1958).
(4) Teorell, T., *Arch. Intern. Pharmacodyn.*, **57**, 205(1937).
(5) Wiegand, R. G., and Sanders, P. G., *J. Pharmacol. Exptl. Therap.*, **146**, 271(1964).
(6) Lowenthal, W., and Borzelleca, J. F., *J. Pharm. Sci.*, **54**, 1790(1965).
(7) Blume, W., and Nohara, F. S., *Arch. Exptl. Pathol. Pharmakol.*, **173**, 413(1933).
(8) Fincher, J. H., Adams, J. G., and Beal, H. M., *J. Pharm. Sci.*, **54**, 704(1965).
(9) Swintosky, J. V., Foltz, E. L., Bondi, A., Jr., and Robinson, M. J., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 136 (1958).
(10) Walkenstein, S. S., Wiser, R., Gudmundsen, C. H., Kimmel, H. B., and Corradino, R. A., *J. Pharm. Sci.*, **53**, 1181(1964).