Table I—Values of Observed Concentrations Compared to Values Predicted Using Single-Dose Data and Values Predicted Using the Self-Induction Model

Day	Hour	Concentration Predicted from Single-Dose Data, μg/ml	Observed Serum Concentration, μg/ml	Concentration Predicted Using Self-Induction Model, μg/ml
8	0	10.2	5.3	5.4
	2	13.4	8.9	9.3
	4	13.9	9.6	9.8
	6	13.5	9.0	9.6
	8	13.2	8.9	8.9
	12	12.5	7.8	8.3
	24	10.4	5.2	5.4
15	0	10.6	4.3	4.5
	2	13.6	7.8	8.2
	4	14.2	8.2	9.1
	6	13.6	7.6	8.2
	8	13.4	7.7	7.5
	12	13.0	6.5	6.5
	24	10.6	4.4	4.5
22	0	10.6	3.8	4.4
	2	13.6	7.1	8.0
	4	14.2	8.3	9.1
	6	13.6	8.0	8.6
	8	13.4	7.1	7.6
	12	13.0	6.3	6.5
	24	10.6	3.8	4.4
	48	6.4	1.8	1.9
	72	4.0	1.0	0.9

an increasing elimination rate constant, thus yielding more efficacious epilepsy therapy.

(1) H. Meinardi, in "Antiepileptic Drugs," D. M. Woodbury, J. K. Penry, and R. P. Schmidt, Eds., Raven, New York, N.Y., pp. 407–496.

(2) P. L. Morselli, M. Gerna, D. DeMaio, G. Zandra, F. Viani, and S. Garattini, presented at the Workshop on the Determination of Antiepileptic Drugs in Body Fluids II, Bethel, Federal Republic of Germany, May 1974.

(3) A. S. Troupin, J. R. Green, and R. H. Levy, *Neurology*, **24**, 863(1974).

(4) P. L. Morselli, P. Biandrate, A. Frigerio, and S. Garattini, *Eur. J. Clin. Invest.*, **2**, 297(1972).

(5) O. Penttila, P. J. Neuvonen, K. Aho, and R. Lehtovaara, *Brit. Med. J.*, **2**, 470(1974).

(6) J. Hansen, K. Siersbaek-Nielsen, and L. Skovsted, *Clin. Pharmacol. Ther.*, **12**, 539(1973).

(7) R. Ronfeld and L. Z. Benet, presented at the APhA Academy of Pharmaceutical Sciences, Chicago meeting, 1974.

(8) R. H. Levy, W. H. Pitlick, A. S. Troupin, J. R. Green, and J. M. Neal, *Clin. Pharmacol. Ther.*, **17**, 657(1975).

(9) M. Eichelbaum, K. Ekbom, L. Bertilsson, V. A. Ringberger, and A. Rane, *Eur. J. Clin. Pharmacol.*, **8**, 337(1975).

William H. Pitlick *
René H. Levy ˣ
Departments of Pharmaceutical Sciences and Neurological Surgery
School of Pharmacy and School of Medicine
University of Washington
Seattle, WA 98195

Allan S. Troupin
John R. Green †
Department of Neurological Surgery
School of Medicine
University of Washington
Seattle, WA 98195

Received May 27, 1975.
Accepted for publication November 21, 1975.
Supported in part by National Institutes of Health Grant RR-37 and by a research grant from Ciba-Geigy Corp.
Part of this research was performed at the Clinical Research Center of the University of Washington.

* Present address: School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261
† Deceased.
ˣ To whom inquiries should be directed.

Pharmacokinetic Analysis of Renal Handling of Sulfamethizole

Keyphrases □ Sulfamethizole—renal excretion mechanisms, pharmacokinetic analysis □ Excretion, renal—sulfamethizole, pharmacokinetic analysis □ Pharmacokinetic analysis—renal excretion mechanisms, sulfamethizole

To the Editor:

It is important to clarify the renal excretion mechanisms of drugs when considering their effectiveness and safety. Weiner and Mudge (1) carried out extensive physiological studies of renal tubular excretion mechanisms, but studies have not been made on the quantitative relationship between secretion and reabsorption of drugs in the nephron. Previously, we elucidated the renal handling of sulfonamides by means of inhibitory experiments (2, 3); but since the conditions are harsh, there is a limitation in the application of this method to humans.

The present study was undertaken to establish an analytical method for renal excretion mechanisms of drugs under more suitable conditions to enable clinical applications to humans. For this purpose, renal handling of sulfamethizole was analyzed using an analog computer to determine the alteration of plasma concentration and clearance ratio after intravenous administration of a single dose of sulfamethizole.

Generally, the excretion of a drug from the kidney into urine is expressed by:

$$UV = (GFR)P_f + S - A \qquad \text{(Eq. 1)}$$

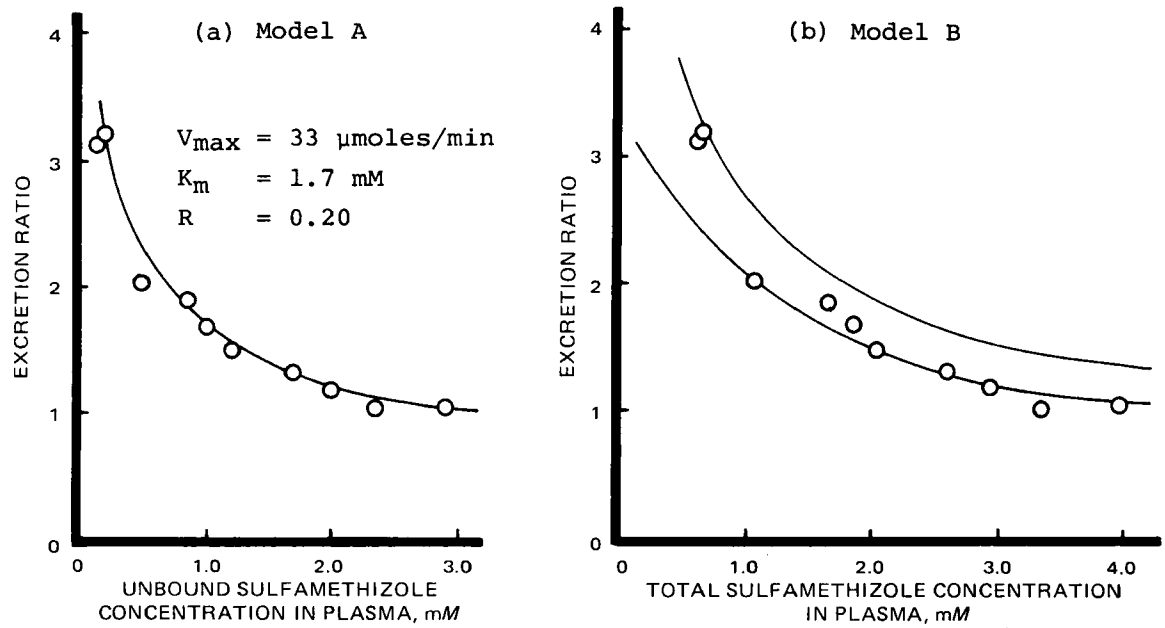

Figure 1—*Experimental data points and simulated computer curves. Each point represents renal clearance data. The solid line represents the computer-simulated curve. The upper solid line in Fig. 1b is the simulation curve for the data of a low plasma level and the lower curve is for the data of a high plasma level of sulfamethizole.*

where U is the drug concentration in urine, V is the urine flow rate, GFR is the glomerular filtration rate, P_f is the unbound drug concentration in plasma, S is the rate of secretion, and A is the rate of reabsorption. By assuming that a drug is reabsorbed by nonionic diffusion and that the rate of active secretion of a drug conforms to the Michaelis–Menten equation and is dependent upon the protein-free drug concentration in plasma, A and S can be expressed as:

$$A = (R)[(GFR)P_f + S] \quad \text{(Eq. 2)}$$

$$S = \frac{V_{max}P_f}{K_m + P_f} \quad \text{(Eq. 3)}$$

where R, V_{max}, and K_m indicate the reabsorption fraction, the maximum velocity of secretion, and the Michaelis constant, respectively. On the other hand, the clearance ratio corrected for plasma protein binding of the drug, ER (excretion ratio), is:

$$ER = \frac{UV}{(P_f)(GFR)} \quad \text{(Eq. 4)}$$

From Eqs. 1–4, ER can be expressed as:

$$ER = \left[1 + \frac{V_{max}}{(K_m + P_f)(GFR)}\right](1 - R) \quad \text{(Eq. 5)}$$

If the rate of active secretion is dependent upon the total concentration of the drug in plasma (P), Eq. 5 should be:

$$ER = \left[1 + \frac{V_{max}}{(K_m + P)(GFR)}\frac{P}{P_f}\right](1 - R) \quad \text{(Eq. 6)}$$

Equations 5 and 6 are programmed on the analog computer as model equations, Eq. 5 for Model A and Eq. 6 for Model B. In these equations, UV, P, P_f, and GFR are determined by the clearance method after administration of a single dose and V_{max}, K_m, and R are parameters.

Renal clearance experiments were performed by the single-injection technique using male New Zealand albino rabbits. Urine samples were collected at 5- and 10-min intervals, and blood samples were taken at 1 min before the midpoint of the urine collection periods. This 1 min indicates the delay time required for phenolsulfonphthalein to appear in the urine after intravenous injection in rabbits based on the experiment in humans (4). Experiments with the combination of the standard renal clearance and the secretory inhibition using iodopyracet (2) were also performed.

Inulin was used to determine the glomerular filtration rate. The plasma and urine samples were treated with Somogyi deproteinizing reagents (5) and then analyzed as follows: (*a*) sulfamethizole by the procedure of Bratton and Marshall (6), using 2-diethylaminoethyl-1-naphthylamine as the coupling agent (7); and (*b*) inulin by a modification of the Dische and Borenfreund method (8). Binding of sulfamethi-

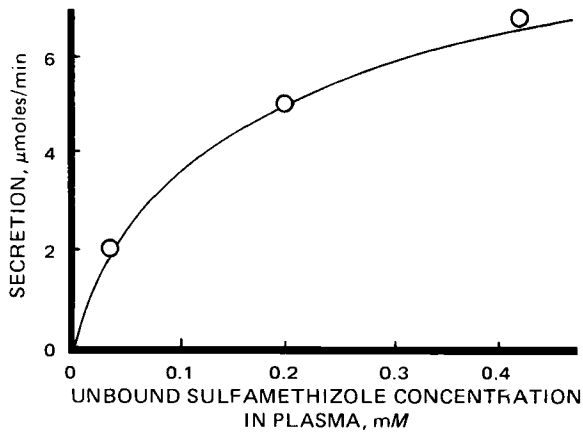

Figure 2—*Relationship between plasma concentration and renal tubular secretion of sulfamethizole. Each point represents the experimental data obtained by inhibitory experiments. The solid line represents the calculated curve of Model A.*

zole to rabbit plasma protein was determined by the membrane ultrafiltration technique (9). Analysis of the clearance data was performed using the analog computer.

The results are shown in Fig. 1. The simulation curve of Model A fitted well with the experimental data. However, in Model B, a fitting curve could not be obtained with any of the various parameters available. When the parameters were selected at the values given in Fig. 1*a*, the calculated curve of Model A agreed well with the experimental data obtained by inhibitory experiments (2, 3) (Fig. 2). From these results, it is considered that the tubular reabsorption of sulfamethizole can be explained by nonionic diffusion, while the tubular secretion can be explained by active transport that conforms to the Michaelis–Menten equation.

In addition, since Model A fits the experimental data, it can be presumed that the tubular secretion of sulfamethizole is dependent upon the unbound sulfamethizole concentration in plasma. Details of pharmacokinetic analyses of some sulfonamides and phenolsulfonphthalein using Model A will be described in a subsequent paper.

In conclusion, this analytical method permits analysis of a limited amount of experimental data on the renal excretion of sulfamethizole in a dynamic condition where the concentration in plasma varies with time after administration of a single dose. It also can be used to clarify the renal handling of sulfamethizole within a short period. This method is presently being applied to humans.

(1) I. M. Weiner and H. Mudge, *Amer. J. Med.*, **36**, 743(1964).
(2) T. Arita, R. Hori, E. Owada, and K. Takahashi, *Chem. Pharm. Bull.*, **17**, 2526(1969).
(3) E. Owada, K. Takahashi, R. Hori, and T. Arita, *ibid.*, **22**, 594(1974).
(4) H. W. Smith, W. Goldring, and H. Chasis, *J. Clin. Invest.*, **17**, 263(1937).
(5) M. Somogyi, *J. Biol. Chem.*, **86**, 655(1930).
(6) A. C. Bratton and E. K. Marshall, Jr., *ibid.*, **128**, 537(1939).
(7) T. Koizumi, T. Arita, and K. Kakemi, *Chem. Pharm. Bull.*, **12**, 413(1964).
(8) Z. Dische and E. Borenfreund, *J. Biol. Chem.*, **192**, 583(1951).
(9) E. Owada, R. Hori, and T. Arita, *Yakuzaigaku*, **33**, 125(1973).

Ryohei Hori [x]
Kosaku Sunayashiki
Akira Kamiya
Institute of Pharmaceutical Sciences
Hiroshima University School of Medicine
Kasumi 1-2-3, Hiroshima, Japan

Received August 27, 1975.
Accepted for publication December 1, 1975.
Supported in part by Grant 847093 from the Ministry of Education of Japan.
[x] To whom inquiries should be directed.

BOOKS

REVIEWS

A Textbook of Pharmaceutical Analysis, Second Edition. By KENNETH A. CONNORS. Wiley, 605 Third Avenue, New York, NY 10016, 1975. 15.5 × 23.5 cm. Price $18.95.

Many changes have been incorporated into the second edition of this classic textbook. A new chapter on analytical toxicology has been included which adds immeasurably to the topics covered. The analysis of drugs in blood and/or urine samples is fast becoming an important area of interest and responsibility for the clinical pharmacist. In a community pharmacy, knowledge of preferred qualitative screening methods for drugs allows the pharmacist to function better as a drug expert in his or her locality. Another addition to the book is a chapter that provides basic information on volumetric techniques. This is of tremendous value to those pharmacy schools where a separate course in quantitative analysis is no longer required due to changing curricula. New sections dealing with such topics as ion-selective electrodes, ORD and CD, NMR and ESR, mass spectrometry, and high-pressure liquid chromatography have also been added.

The material is presented in six sections, which are entitled Titrimetric Analysis, Physical and Instrumental Methods, Separation Techniques, Elemental Analysis, Functional Group Analysis, and General Topics. These sections are further divided into chapters where the various techniques and/or subjects are discussed. A theoretical treatment is presented initially followed by practical application of the methodology in drug identification and/or quantification.

At the end of each chapter, the author has included laboratory exercises and questions dealing with the application of the subject matter in that segment. Several experiments have been added to those chapters where none existed in the first edition and other existing experiments have been updated and/or changed. The book therefore functions suitably as a source of sound laboratory exercises which can be performed either totally or in part during the customary 3-hr lab period.

The book is effective in its scope, variety of experiments and problems, and presentation style. It is a must for any student interested in pharmaceutical analysis. The researcher may find the book to be a helpful source of information on almost any analytical technique. The second edition of this textbook is truly an exciting adventure.

Reviewed by J. T. Stewart
School of Pharmacy
University of Georgia
Athens, GA 30602