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Report

Prediction of the Distribution Volumes of Cefazolin and Tobramycin in Obese Children Based on Physiological Pharmacokinetic Concepts

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So as to estimate the appropriate dose of antibacterial drugs in obese children, prediction of the volume of distribution in these children was attempted based on physiological pharmacokinetic concepts which had been constructed from results in normal-weight children. Serum concentration–time data after intravenous drip infusions of tobramycin and cefazolin were analyzed using noncompartmental analysis of obese children in whom the degree of obesity ranged from 30 to 80%. Volume of distribution at steady state (V_{ss}) per total body weight of tobramycin was significantly less than that for normal-weight children ($P < 0.05$), whereas the value of cefazolin was almost equal to that for normal-weight children. The equation to express the difference of V_{ss} between cefazolin and tobramycin obtained in normal-weight children failed in obese children, suggesting that there is a large decrease in the extracellular space in obese children exceeding the interindividual variations in normal-weight children. The V_{ss} value (liter) for tobramycin was predicted by using the equation 0.261 · {ideal body weight (kg) + 0.4 · [total body weight (kg) − ideal body weight (kg)]}. The V_{ss} value of cefazolin was predicted to be 0.3 · (predicted V_{ss} of tobramycin) + 0.052 · total body weight (kg). A good correlation between the predicted and the observed V_{ss} values was obtained.

KEY WORDS: cefazolin; tobramycin; volume of distribution; pharmacokinetics; intravenous administration; obese children.

INTRODUCTION

Relatively little information regarding pharmacotherapy in the obese patient is available (1). Changes in pharmacokinetic behavior caused by obesity may result from distributional changes of drug partitioning into the various body compartments. Since there are great fluctuations in drug content in body compartments in children during growth (2), it is difficult to estimate the volume of distribution of drugs in obese children.

To predict the distribution volume of drugs, it is important to analyze the physicochemical and physiological bases of the volume of distribution. Following a physiologically based pharmacokinetic approach to the distribution and elimination of β-lactam antibiotics, we reported that the volume of distribution at steady state (V_{ss}) of cefazolin in animals can be expressed mathematically in terms of distribution into the extracellular water space and disposing organs (3–5). On the basis of these studies (3–5), we analyzed the comparative distribution kinetics of cefazolin and tobramycin in children and presented equations to predict the V_{ss} of cefazolin and tobramycin (6).

Many reports suggest that aminoglycoside dosages in adult obese subjects should be determined on the basis of ideal body weight (IBW) or a hybrid body weight between the IBW and the total body weight (BW) rather than only on BW (7–10). Such an adjustment is necessary because the volume of distribution per body weight (V_{ss}/BW) of aminoglycoside decreases in relation to an increase in adipose tissue, in which the extracellular water volume is smaller than in other tissues (11).

Both cefazolin and tobramycin are distributed in the extracellular water space in the body. Therefore, it might be expected that fluctuations in extracellular water content, as in obesity (11), during growth (2), or due to various other interindividual differences, may produce changes in the distribution of the drugs. Although the prediction of V_{ss} for β-lactam antibiotics has been reported with reference to physiologically based pharmacokinetics (12), prediction of V_{ss} for cefazolin and tobramycin in obese children has not yet been addressed.

To achieve optimal antimicrobial therapy, the initial dose must be determined to obtain the most effective con-

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centration in the target organ with minimal risk of unwanted side effects. In this paper we attempt to apply our equations, which were elucidated to predict V_{ss} for cefazolin and tobramycin in normal-weight children (6), to the prediction of V_{ss} for cefazolin and tobramycin in obese children.

MATERIALS AND METHODS

Subjects. Four boys ranging from 1 to 9 years were hospitalized for closer examination of their morbid obesity, and one girl (6 years old) was admitted with a coronary aneurysm due to Kawasaki disease. Prior to study, informed consent was obtained from the parents of each patient. Individual patient characteristics are given in Table I. Patients 1, 2, 3, and 4 were diagnosed as simple obesity. Patient 5, with a diagnosis of familial growth hormone deficiency, was relatively obese due to his short stature. Patients 3 and 4 were twins, and patient 4 had received treatment for diabetes mellitus. However, none had clinical or laboratory evidence of renal or hepatic disorders or a history of allergy to cephalosporins.

The degree of obesity was estimated from the BW and height of each patient using the nomogram of Kato *et al.* (13). Ideal body weight was estimated using the same nomogram. Our subjects ranged in degree of obesity from +30 to +78% (mean = +63%, SD = 18%).

All had normal laboratory screening results including white and red blood-cell counts, hematocrit, platelet count, serum creatinine, blood urea nitrogen, total serum protein, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase.

Drug Administration Protocol. Each patient received a single 25-mg/kg dose of cefazolin (Cefamezin, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan) by intravenous infusion over 30 min. Subsequently, after an interval of 10 min, tobramycin (Tobracin, Shionogi Pharmaceutical Co., Ltd., Osaka, Japan), 2.0 mg/kg, was given over 30 min in an identical manner. Each dose of cefazolin and tobramycin was based on the mean body weight of the measured total body weight (BW) and the calculated ideal body weight (IBW) of each patient and was diluted in 20 ml of sterile water and administered through an indwelling venous needle placed in a vein of the dorsal manus. The infusion rate was controlled using a constant-flow pump (STC-521; Terumo Co., Ltd., Tokyo). Any remaining drug in the infusion line was washed out with several milliliters of saline at the end of administration.

Sampling. A second indwelling venous needle was placed in a vein of the opposite dorsal manus, and blood samples (2 ml) were drawn through the needle at the following times: 30, 50, 70, 90, 110, 130, 160, 190, 220, and 280 min after the start of the cefazolin infusion, which corresponded to 10, 30, 50, 70, 90, 120, 150, 180, and 240 min after the start of the tobramycin infusion. Serum samples were separated and assayed on the same day or frozen at −20°C until analyzed. Glass instruments were not used to avoid the adhesion of tobramycin to glass surfaces.

Cefazolin Assay. Serum concentrations of cefazolin were determined by high-performance liquid chromatography (HPLC). Serum samples (50 μl) were mixed for 30 sec by vortex mixer with an equal volume of isotonic phosphate buffer (pH 7.4) and 100 μl of methanol in a polyethylene centrifuge tube (1 ml). The contents were allowed to stand in a 4°C ice bath for 30 min and centrifuged (MR-15A; Tomy Seiko Co., Ltd., Tokyo) at 12,000 rpm for 30 min at 4°C. The supernatant was filtered through a membrane filter (TM-2; Toyo Roshi Co., Ltd., Tokyo). Samples for analysis (15 μl) were injected onto a reverse-phase column μ-Bondapak C18 column (30 cm × 4.0-mm i.d., Waters Associates, Milford, Mass.) of the HPLC system (TRI-ROTER; Japan Spectroscopic Co., Ltd., Tokyo) utilizing 10% acetonitrile in 0.01 *M* ammonium acetate mobile phase at a flow rate of 1.5 ml/min. A variable-wavelength UV detector (UVIDEC-100-VI; Japan Spectroscopic Co., Ltd.) was set at 270 nm, with a range of 0.08 AFS, and the peak area was recorded (DS-L300; Japan Spectroscopic Co., Ltd.).

To prepare standard curves, 50 μl of pooled blank human serum was added to 50 μl of various concentrations of cefazolin and tested in triplicate. Serum cefazolin concentrations ranging from 5 to 200 μg/ml yielded a linear correlation with peak areas (r = 0.999).

Tobramycin Assay. Tobramycin concentrations in serum were assayed by fluorescence polarization immunoassay (TDX; Dinabot Co., Ltd., Tokyo). All samples were assayed in duplicate or triplicate, and the mean concentrations were used for pharmacokinetic analysis.

Table I. Characteristics of the Study Population

Patient No.	Age[a]	Sex	Height (cm)	Weight (kg)	IBW (kg)	Degree of obesity (%)	CL_{cr}/BW (ml/min/kg)
Obese children							
1	1 y 10 m	M	91	22.4	13.0	61	2.93
2	6 y 4 m	F	117	27.2	20.7	30	1.20
3	8 y 4 m	M	143	60.6	35.5	71	2.00
4	8 y 4 m	M	142	63.0	35.0	78	2.25
5	9 y 4 m	M	117	37.8	21.0	75	1.49
Mean	6 y 10 m		122	42.2	25.0	63	1.97
SD			20	16.8	9.9	18	0.68
Normal-weight children[b] (N = 6)							
Mean	6 y 10 m		114	19.6	19.2	−7	1.75
SD			20	7.3	6.9	7	0.19

[a] y, years; m, months.
[b] From Ref. 6.

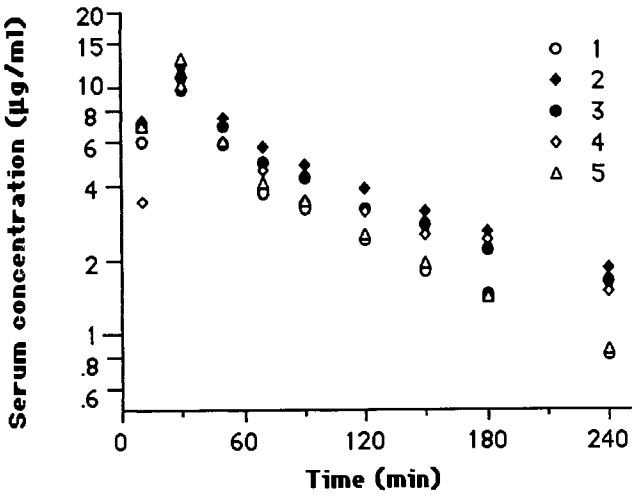

Fig. 1. Semilogarithmic serum concentration–time profiles following 2-mg/kg tobramycin administration as 30-min intravenous drip infusions in five obese children. Numbers to the right of the symbols are patient numbers. Detailed pharmacokinetic parameters are listed in Table II.

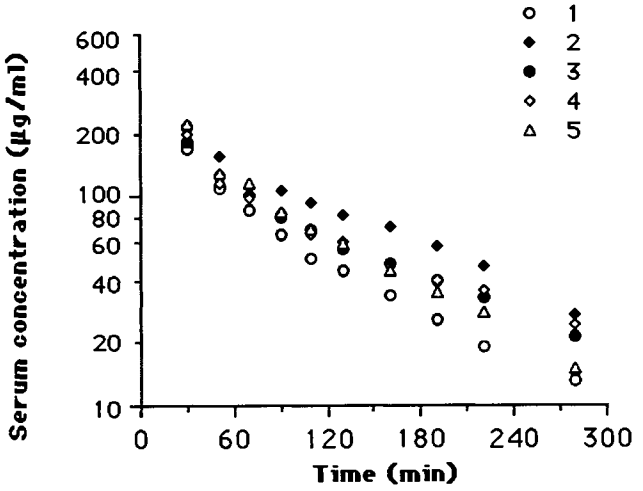

Fig. 2. Semilogarithmic serum concentration–time profiles following 25-mg/kg cefazolin administration as 30-min intravenous drip infusions in five obese children. Numbers to the right of the symbols are patient numbers. Detailed pharmacokinetic parameters are listed in Table III.

Serum Protein Binding. To investigate the binding of cefazolin to serum protein, an ultrafiltration technique using disposable Centrifree MPS devices (Amicon Co., Danvers, Mass.) was adopted. A part (0.5–1.0 ml) of the sample withdrawn at appropriate intervals after the administration of cefazolin was added to the sample reservoir. The ultrafiltrate was obtained by centrifugation at 37°C for 7 min (2400 rpm), using a KR-702 centrifuge equipped with a 45° angle rotor (Type RA-360 Kubota Co., Ltd., Tokyo). The percentage of bound cefazolin to serum protein was calculated with reference to the initial sample concentration.

Data Analysis. Serum concentration data in the subjects were analyzed utilizing noncompartmental analysis. The area under the serum concentration versus time curve was estimated by means of the trapezoidal rule using the terminal slope of the log serum concentration–time curve. The volume of distribution at steady state per total body weight (V_{ss}/BW) and total body clearance per total body weight (CL_{tot}/BW) were estimated as described by Benet and Galeazzi (14). Since drug was given by a constant-rate intravenous infusion for 30 min, the mean residence time was corrected by subtracting the mean infusion time (15 min) from the calculated mean residence time.

RESULTS

Figure 1 represents the serum concentration versus time profile of tobramycin administered as an intravenous drip infusion to five obese children. Table II lists the noncompartmental pharmacokinetic parameters of $t_{1/2}$, V_{ss}/BW, V_{ss}/IBW, and CL_{tot}/BW for tobramycin compared with values for normal-weight children (6). The values of $t_{1/2}$ ranged from 74 to 125 min and did not differ from those of normal-weight children. The mean CL_{tot}/BW value in obese children was slightly smaller than that in normal children, but the difference was not significant. However, there was a significant difference between the mean V_{ss}/BW value in obese children and that in normal-weight children ($P < 0.05$) (Table II).

The time courses of the serum levels of cefazolin after

Table II. Pharmacokinetic Parameters of Tobramycin in Obese Children

Patient No.	$t_{1/2}$ (min)	V_{ss}/BW (ml/kg)	V_{ss}/IBW (ml/kg)	CL_{tot}/BW (ml/min/kg)
Obese children				
1	74	192	334	1.83
2	125	226	299	1.38
3	120	196	335	1.25
4	101	214	386	1.43
5	81	159	286	1.55
Mean	100	197*	328	1.49
SD	23	26	39	0.22
Normal-weight children[a] ($N = 6$)				
Mean	113	263	241	1.82
SD	29	40	27	0.29

[a] From Ref. 6.

* Significantly different ($P < 0.05$) from the mean value for the normal-weight children.

Table III. Pharmacokinetic Parameters of Cefazolin in Obese Children

Patient No.	$t_{1/2}$ (min)	V_{ss}/BW (ml/kg)	V_{ss}/IBW (ml/kg)	CL_{tot}/BW (ml/min/kg)	Protein binding(%)
Obese children					
1	97	153	266	1.2	—
2	95	135	179	0.915	—
3	103	138	235	0.927	80
4	127	145	261	0.847	83
5	76	105	189	0.906	79
Mean	100	135	226	0.959	
SD	18	18	40	0.138	
Normal-weight children[a] (N = 6)					
Mean	92	133	122	1.02	78
SD	25	15	9	0.14	3

[a] From Ref. 6.

intravenous drip infusion are illustrated in Fig. 2. Table III lists the noncompartmental pharmacokinetic parameters of $t_{1/2}$, V_{ss}/BW, V_{ss}/IBW, and CL_{tot}/BW for cefazolin. For comparison, the values determined for normal-weight children (6) are also cited. The $t_{1/2}$ value ranged from 76 to 127 min and did not differ from that of normal-weight children. The percentages of cefazolin binding with serum protein for three obese children ranged from 79 to 83% and are listed in Table III. No significant difference in the serum protein binding of cefazolin was observed between obese and normal-weight children. The mean V_{ss}/BW value of obese children was not significantly different from that of normal-weight children. The mean CL_{tot}/BW value of obese children was also in accord with that of normal-weight children.

As seen in Table I, CL_{cr}/BW was slightly larger in obese children than CL_{cr}/BW in normal-weight children. Although the mean CL_{tot}/BW value of tobramycin in obese children tended to decrease about 20% compared with that of normal-weight children (Table II), the CL_{tot}/BW value of cefazolin almost coincided for obese and normal-weight children (Table III).

DISCUSSION

The mean V_{ss}/BW value of tobramycin in obese children was 25% lower than that of normal-weight children (Table II), whereas the mean V_{ss}/BW value of cefazolin was almost the same as that of normal-weight children (Table III). We have previously confirmed that (i) change in extracellular space is a major factor determining interindividual differences in V_{ss}/BW for tobramycin and cefazolin in normal-weight children and (ii) the plot of the differences in V_{ss}/BW

Table IV. Relationship Between Predicted and Observed Values of Volume of Distribution in Obese Children

		Volume of distribution (liters)			
			Predicted based on		
Drug	Patient No.	Observed	BW[a]	IBW[b]	Eq. (1) or (2)[c]
Tobramycin	1	4.30	5.85 (35.9)[d]	3.39 (21.1)	4.37 (1.7)
	2	6.15	7.10 (15.5)	5.40 (12.1)	6.08 (1.1)
	3	11.88	5.82 (33.2)	9.27 (22.0)	11.89 (0.1)
	4	13.48	16.44 (22.0)	9.14 (32.2)	12.06 (10.6)
	5	6.01	9.87 (64.2)	5.48 (8.8)	7.23 (20.4)
	Mean		(34.1)	(19.3)	(6.8)
				$P < 0.02$[e]	
Cefazolin	1	3.43	2.46 (28.4)	1.97 (42.6)	2.49 (27.4)
	2	3.67	3.26 (11.3)	2.92 (20.5)	3.25 (11.4)
	3	8.36	6.71 (19.7)	5.41 (35.3)	6.74 (19.4)
	4	9.14	7.32 (19.9)	5.86 (35.8)	6.92 (24.2)
	5	3.97	3.77 (5.0)	2.90 (27.1)	4.15 (4.6)
	Mean		(16.8)	(32.3)	(17.4)
			$P < 0.001$[e]	$P < 0.01$[e]	

[a] Predicted V_{ss} of cefazolin = 0.3 · (observed V_{ss} of tobramycin) + 0.052 · BW. Predicted V_{ss} of tobramycin = 0.261 · BW.
[b] Predicted V_{ss} of cefazolin = 0.3 · (observed V_{ss} of tobramycin) + 0.052 · IBW. Predicted V_{ss} of tobramycin = 0.261 · IBW.
[c] Predicted V_{ss} of cefazolin by Eq. (2); see the text. Predicted V_{ss} of tobramycin by Eq. (1); see the text.
[d] Percentage difference between observed and predicted values in parentheses.
[e] Paired t test.

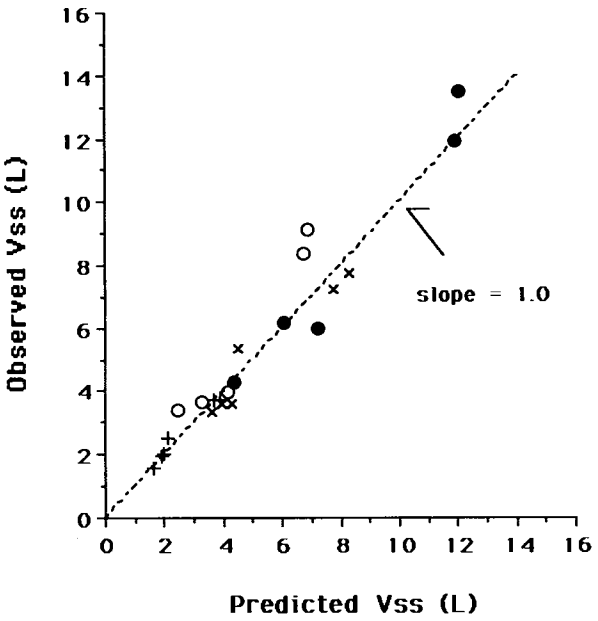

Fig. 3. Correlation between the predicted and the observed volume of distribution at steady state of tobramycin and cefazolin in obese children: (●) tobramycin; (○) cefazolin. The correlation is significant ($r = 0.956$, $P < 0.001$). The dashed line is drawn with slope equal to 1. The reported values in normal-weight children are also presented: (×) tobramycin; (+) cefazolin.

of tobramycin and cefazolin in the same children against the V_{ss}/BW of tobramycin showed a linear relationship in normal-weight children. However, this relationship could not be applicable in obese children. A significant difference in the V_{ss}/BW between obese and normal-weight children was detected in the case of tobramycin (Table II). This discrepancy between normal-weight and obese children may be due to the extreme decrease in extracellular space in obese children exceeding the interindividual variations in normal-weight children.

Hull and Sarubbi (15) showed an improved correlation between measured and predicted serum levels of gentamicin when IBW is used in place of BW. They suggested that drug dosage in all patients, regardless of degree of obesity, should be calculated on IBW basis. However, in our study, V_{ss}/IBW of tobramycin did not agree with that of normal-weight children (6). As seen in Tables II and III, V_{ss}/IBW was higher than V_{ss}/BW of normal-weight children for both tobramycin (Table II) and cefazolin (Table III).

Schwartz *et al.* (16) concluded that the volume of distribution in adult obese patients closely approximated that in normal subjects when IBW plus 40% of the adipose mass was used to calculate an estimate of the volume of distribution. Since our data for tobramycin in children tended to be in general agreement with those of Blouin *et al.* (8) and Schwartz *et al.* (16), the following analysis was made.

It has been reported that the extracellular water content in adipose tissue is about 40% of that in other tissues (11). By considering this value, the equations, which we have presented for the prediction of V_{ss} of tobramycin and cefazolin in normal-weight children (6), can be modified to apply to obese children as follows:

for tobramycin,

$$V_{ss}\ (\text{liters}) = 0.261 \times \{\text{IBW (kg)} + 0.4 \times [\text{BW (kg)} - \text{IBW (kg)}]\} \quad (1)$$

for cefazolin,

$$V_{ss}\ (\text{liters}) = 0.3 \times [\text{predicted } V_{ss} \text{ of tobramycin (liters)}] + 0.052 \times \text{BW (kg)} \quad (2)$$

where the values 0.261, 0.3, and 0.052 refer to the extracellular water content (liters/kg) in IBW, the distribution ratio of cefazolin to tobramycin in extracellular water space (6), and the volume of distribution of cefazolin into the space where the distribution of tobramycin is limited (liters/kg). Table IV lists the relationship between the observed and the predicted values of V_{ss} including predicted values from a previous method (6). For the sake of comparison, the predicted values based on IBW for both extracellular water space and the disposing organs are also listed. Interestingly, the prediction of V_{ss} gave the largest errors when the estimates were based on IBW for cefazolin and BW for tobramycin, respectively. These erroneous predictions are statistically different from the estimates obtained with Eq. (1) or (2), which produced small errors in many cases.

Figure 3 illustrates the relationship between the observed V_{ss} values of the drugs and the values predicted from Eqs. (1) and (2) including the reported values of normal-weight children. In this simulation, we assumed that the volume of distribution of cefazolin into the space where the distribution of tobramycin is limited increased in relation to the increase in BW. When it was assumed that the volume of distribution of cefazolin into that space was proportional to IBW instead of BW, the predicted V_{ss} values for cefazolin tended to be about 20% less than the observed values.

From this study, we can predict differences in the volume of distribution between tobramycin and cefazolin in obese children compared with normal-weight children. For example, the value of V_{ss}/BW in an obese child, whose IBW and BW are 25 and 40 kg, could be calculated to be 204 ml/kg for tobramycin and 113 ml/kg for cefazolin. The degree of difference between obese and normal-weight children is 22% for tobramycin and 14% for cefazolin.

In conclusion, V_{ss} for tobramycin is greatly influenced by the change in extracellular water space; therefore the loading dose in obese children should be determined based on IBW and the corrected extracellular water space in adipose tissue. However, V_{ss} for cefazolin is almost proportional to BW, with the same correction factor as that for normal-weight children; thus the loading dose of cefazolin in obese children should be determined based on BW rather than IBW.

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REFERENCES

1. D. R. Abernethy and D. J. Greenblatt. *Clin. Pharmacokin.* 7:108–124 (1982).

2. B. Friis-Hansen. *Pediatrics* 28:169–181 (1961).
3. A. Tsuji, T. Yoshikawa, K. Nishide, H. Minami, M. Kimura, E. Nakashima, T. Terasaki, E. Miyamoto, C. H. Nightingale, and T. Yamana. *J. Pharm. Sci.* 72:1239–1252 (1983).
4. A. Tsuji, K. Nishide, H. Minami, E. Nakashima, T. Terasaki, and T. Yamana. *Drug Metab. Dispos.* 13:729–739 (1985).
5. A. Tsuji, T. Terasaki, N. Imaeda, K. Nishide, and E. Nakashima. *J. Pharmacobio-Dyn.* 8:167–174 (1985).
6. R. Koshida, E. Nakashima, F. Ichimura, O. Nakano, R. Watanabe, N. Taniguchi, and A. Tsuji. *J. Pharmacobio-Dyn.* 10:436–442 (1987).
7. F. A. Sarubbi and J. H. Hull. *Ann. Intern. Med.* 89:612–618 (1978).
8. R. A. Blouin, H. J. Mann, W. O. Griffen, L. A. Bauer, and K. E. Record. *Clin. Pharmacol. Ther.* 26:508–512 (1979).
9. G. W. Counts, A. D. Blair, K. F. Wagner, and M. Turck. *Clin. Pharmacol. Ther.* 31:662–668 (1982).
10. L. A. Bauer, W. A. Drew Edwards, E. P. Dellinger, and D. A. Simmonowitz. *Eur. J. Clin. Pharmacol.* 24:643–647 (1983).
11. W. I. Morse and J. S. Soeldner. *Metabolism* 12:99–107 (1963).
12. Y. Sawada, M. Hanano, Y. Sugiyama, and T. Iga. *J. Pharmacokin. Biopharm.* 12:241–261 (1984).
13. S. Kato, S. Nakahara, K. Adachi, Y. Sai, G. Tsuji, and H. Yabuuchi. *Shonika Rinsho (Japan)* 31:689–692 (1978) (Japanese).
14. L. Z. Benet and R. L. Galeazzi. *J. Pharm. Sci.* 68:1071–1074 (1979).
15. J. H. Hull and F. A. Sarubbi. *Ann. Intern. Med.* 85:183–189 (1976).
16. S. N. Schwartz, G. J. Pazin, J. A. Lyon, M. Ho, and A. W. Pasculle. *J. Infect. Dis.* 138:499–505 (1978).