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RESEARCH ARTICLES

Pharmacokinetics of Sustained Serum Methotrexate Concentrations Secondary to Gastrointestinal Obstruction

WILLIAM E. EVANS ˣ, ANASTASIOS TSIATIS, WILLIAM R. CROM, GARRETT M. BRODEUR, THOMAS C. COBURN, and CHARLES B. PRATT

Received October 14, 1980, from the *Clinical Pharmacokinetics Laboratory, Biostatistics Section, Department of Diagnostic Imaging*, and the *Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, TN 38101.*
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Abstract □ A physiological pharmacokinetic model for methotrexate was refined and used to simulate serum methotrexate concentrations after high dose (5000 mg/m^2) intravenous infusions with fixed normal values for all model parameters except the GI transit rate. There was good agreement between simulated and measured values when model simulations with the normal GI transit rate were compared to values measured following 109 doses administered to 27 patients with normal GI function. When model simulations were performed using GI transit rates representing 75, 50, and 10% of normal, there was a marked prolongation of the terminal serum methotrexate half-life, which was directly related to the reduction in the transit rate. When simulations were performed with GI transit reduced by 50%, the maximum amount of methotrexate in the GI lumen was 25% higher and occurred 4 hr later. Model simulations of serum methotrexate concentrations, using a GI transit rate reduced by 50%, were also in good agreement with serum concentrations measured in two patients with partial GI obstruction. These data establish a pharmacokinetic basis for previous clinical observations indicating sustained serum methotrexate concentrations in patients with GI obstructions and exemplify the utility of physiological pharmacokinetic models in assessing the potential effects of clinical variables on drug disposition.

Keyphrases □ Methotrexate—sustained serum concentrations in patients with GI obstruction, pharmacokinetics □ Pharmacokinetics—sustained serum methotrexate concentrations in patients with GI obstruction □ Model simulations—sustained serum methotrexate concentrations in patients with GI obstruction, pharmacokinetics

High dose methotrexate with leucovorin rescue is widely used as adjuvant therapy for osteosarcoma and in the treatment of acute leukemia, non-Hodgkin's lymphoma, head and neck carcinoma, and other solid tumors. However, the administration of high dose methotrexate leucovorin rescue carries with it the risk of severe toxicity, which may be fatal. A national survey (1) conducted prior to 1977 revealed a 6% incidence of mortality attributed to high dose methotrexate. For this reason, efforts have been made to identify factors that predispose to toxicity and to establish guidelines that reduce the risk of morbidity and mortality associated with high dose methotrexate therapy.

Previous studies indicated that certain clinical characteristics such as renal dysfunction, dehydration, pleural effusions, and ascites (2–7) are associated with a higher risk of toxicity following high dose methotrexate leucovorin rescue, presumably due to delayed methotrexate plasma clearance. One study (6) reported slower methotrexate elimination from plasma of two patients who had GI obstruction, in the absence of any previously described clinical features associated with delayed clearance. The present study was undertaken to establish the pharmacokinetic basis for sustained serum methotrexate concentrations in patients with GI obstruction.

EXPERIMENTAL

Pharmacokinetic Model—The flow-limited physiological pharmacokinetic model of Bischoff *et al.* (8) (Scheme I) was used to simulate methotrexate concentrations in serum and tissues following high dose methotrexate intravenous infusions. Volume terms, flow rates, distribution ratios, rate constants, and transit times (*Appendix*) were those previously described by Bischoff *et al.* (8), unless otherwise stated. The volume terms and plasma flow rates were scaled to patient weight or body surface area by the equations shown in the *Appendix*, which were derived from previously published data (8, 9).

Previously published human studies (10–13) characterizing the renal clearance of methotrexate in patients with normal renal function established that the net renal clearance of methotrexate is serum concentration dependent. Glomerular filtration, tubular secretion, and tubular reabsorption are all components of methotrexate renal clearance (12), establishing the basis for saturable processes at high serum concentrations with the resulting lower net renal clearance. Therefore, net clearance probably is determined by both first-order (filtration) and saturable (secretion, reabsorption) processes. However, the rate constants (V_{max} and K_M) for tubular secretion and reabsorption of methotrexate have not been established in humans. Therefore, net renal clearance of methotrexate was calculated from the least-squares linear regression of net renal clearance on log serum concentrations, using the published data summarized in Table I. The regression line was described by the equation Cl_R (milliliters per minute per meter^2) = 92.0 − (13.8)(ln C_p), where r^2 = 0.81.

Secretion of methotrexate into bile from the liver was modified to represent a saturable process with V_{max} = 1000 μg/min and K_M = 5 μg/ml. Therefore, the ratio of V_{max} to K_M (200) was the same as that used by Bischoff *et al.* (8), but the differential equation permitted saturation of biliary secretion at high serum concentrations. As described in the original model-development work by Bischoff *et al.* (8), the biliary ex-

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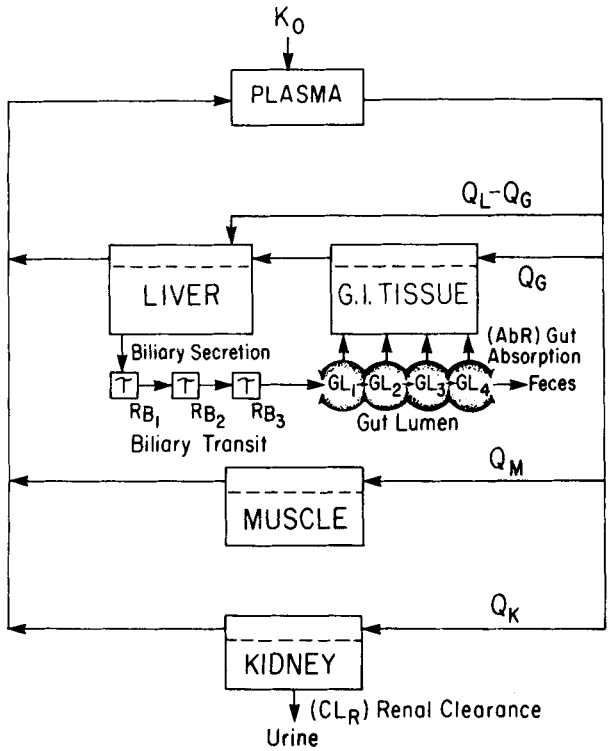

Scheme I—Scheme of physiological pharmacokinetic model for methotrexate simulations (modified from Ref. 8).

cretion parameter is a conjectural value to create the best fit to data from normal subjects. The assignment of V_{max} and K_M values in the present study represents a conservative approach by limiting the maximum velocity of drug entry into the GI compartment. GI blood flow (Q_G) was reduced from 82% of liver blood flow (as used by Bischoff) to 66% of liver blood flow. This value is more physiological since only ~80% of portal blood flow originates in the GI tract (14) and total portal blood flow is ~82% of hepatic blood flow (*i.e.*, 0.80 × 0.82 = 0.66). All other model parameters, including strong specific tissue binding constants, multicompartment models of biliary transit and gut lumen transit, and zero-order gut absorption, were the same as previously described (8).

A set of differential equations (*Appendix*) describing the mass balances of each model compartment was used to simulate the methotrexate concentration in each compartment as a function of time. These differential equations were simultaneously solved by a numerical method using the Runge–Kutta (15) algorithm.

Simulations of methotrexate serum and tissue concentrations were made using the previously described ("normal") values for all model parameters except GI transit time. To assess the influence of GI obstruction on serum disposition of methotrexate, model simulations were made using GI transit rates (K_f) of 0.001, 0.00075, 0.0005, and 0.0001 min^{-1}, representing 100, 75, 50, and 10% of the normal transit rate, respectively. All model simulations were for a 6-hr constant-rate intravenous infusion of 5000 mg of methotrexate/m^2.

For comparison, serum methotrexate concentrations measured following 109 infusions administered to 27 patients (6–30-hr concentrations) and 38 infusions administered to 21 of these patients (36–78-hr concentrations) are shown with model simulations. All of these patients had normal renal, hepatic, and GI function and had none of the previously described clinical features that predispose to toxicity. The clinical and laboratory evaluations of these patients were previously described in detail (6). Serum methotrexate concentrations measured in two patients with GI obstruction are also shown for comparison. The clinical and laboratory findings in these two patients were previously described (6). Both patients had partial small bowel obstructions secondary to tumor compression at the time of high dose methotrexate administration. Roentgenographic documentation of these GI obstructions is presented in Fig. 1.

Methotrexate serum concentrations for all of these patients were determined in duplicate by at least two methods: a radioenzymatic assay using dihydrofolate reductase (New England Enzyme) and an enzyme immunoassay (SYVA). These assays were shown to produce results comparable to a high-pressure liquid chromatographic assay and to cross-react <4% with the major methotrexate metabolite, 7-hydroxymethotrexate (16).

Table I—Net Renal Clearance of Methotrexate

Net Renal Clearance, ml/min/m^2	Mean Serum Concentration, μM
118	0.45[a]
103	~0.2[b]
78	~1.0[c]
65	10.0[a]
59	~10.0[d]
20–50	~100.0[e]

[a] Evans *et al.* (unpublished data). [b] Reference 12. [c] Reference 11. [d] Reference 13. [e] Reference 10.

RESULTS

As shown in Fig. 2, there was good agreement between simulated and measured serum methotrexate concentrations in patients with normal renal, hepatic, and GI function, using normal model parameters. Figure 2 also shows simulations with GI transit rates reduced by 25, 50, and 90%. These model simulations demonstrate a marked decrease in the rate of decline in serum concentrations beginning ~24–30-hr postinfusion. The prolongation of methotrexate half-life during this time interval was directly related to the reduction in the GI transit rate (Table II). These simulations also demonstrate that the GI transit rate has little influence on serum methotrexate half-life during the first 24 hr postinfusion. This finding is not surprising since most methotrexate is eliminated *via* renal clearance during this time interval and the amount of methotrexate undergoing enterohepatic circulation is relatively small.

There was good agreement between serum methotrexate concentrations measured in the two patients with GI obstruction and model simulations with the GI transit rate reduced by 50% (Fig. 3).

The simulated amounts (milligrams) of methotrexate in the GI lumen at selected times postinfusion, calculated as:

$$A_{MTX_{GL}} = \frac{(C_{GL_1} + C_{GL_2} + C_{GL_3} + C_{GL_4})}{4} V_{GL} \qquad \text{(Eq. 1)}$$

are summarized in Table III for model simulations using the normal GI transit rate and a transit rate reduced by 50%. As shown, the maximum amount of methotrexate in the GI lumen was ~25% higher and occurred 4 hr later when the GI transit rate was reduced by 50%. More importantly, the amount of methotrexate in the GI lumen declined more slowly when GI transit was reduced. By 48 hr, the amount of methotrexate was approximately four times higher when the GI transit was reduced 50% and more than 10-fold higher by 96 hr. Moreover, the amount of methotrexate in the GI lumen at 72 hr (with reduced transit) was comparable to conventional (25 mg/m^2) oral doses of methotrexate, although it represents <1% of the administered dose.

DISCUSSION

A previous study (6) suggested that GI obstruction could result in a prolonged serum methotrexate half-life following administration of high dose methotrexate. Since prolongation of methotrexate elimination places patients administered high dose methotrexate at increased risk for severe toxicity (6, 7, 17), it is important to establish the clinical variables that may alter methotrexate disposition. This has been done for clinical features such as renal dysfunction (11, 18), pleural effusion (2, 5), and ascites (5). Although an earlier report described (6) previous clinical observations of sustained serum methotrexate concentrations in patients with GI obstruction, the theoretical basis for these observations had not been established.

In the present study, a previously described physiological pharmacokinetic model (8) for methotrexate disposition was used to assess the effect of the GI transit rate on methotrexate disposition. The original model assumes that methotrexate is not metabolized. However, subsequent studies have established that methotrexate is metabolized to 7-hydroxymethotrexate and studies in this laboratory[1] indicate that nonrenal clearance of methotrexate in children is ~15 ml/min/m^2. Metabolic clearance was assumed to be negligible for the present study, and was the same for all model simulations (0 ml/min/m^2).

By using model parameters that were refined from the original model

[1] W. E. Evans *et al.*, unpublished data.

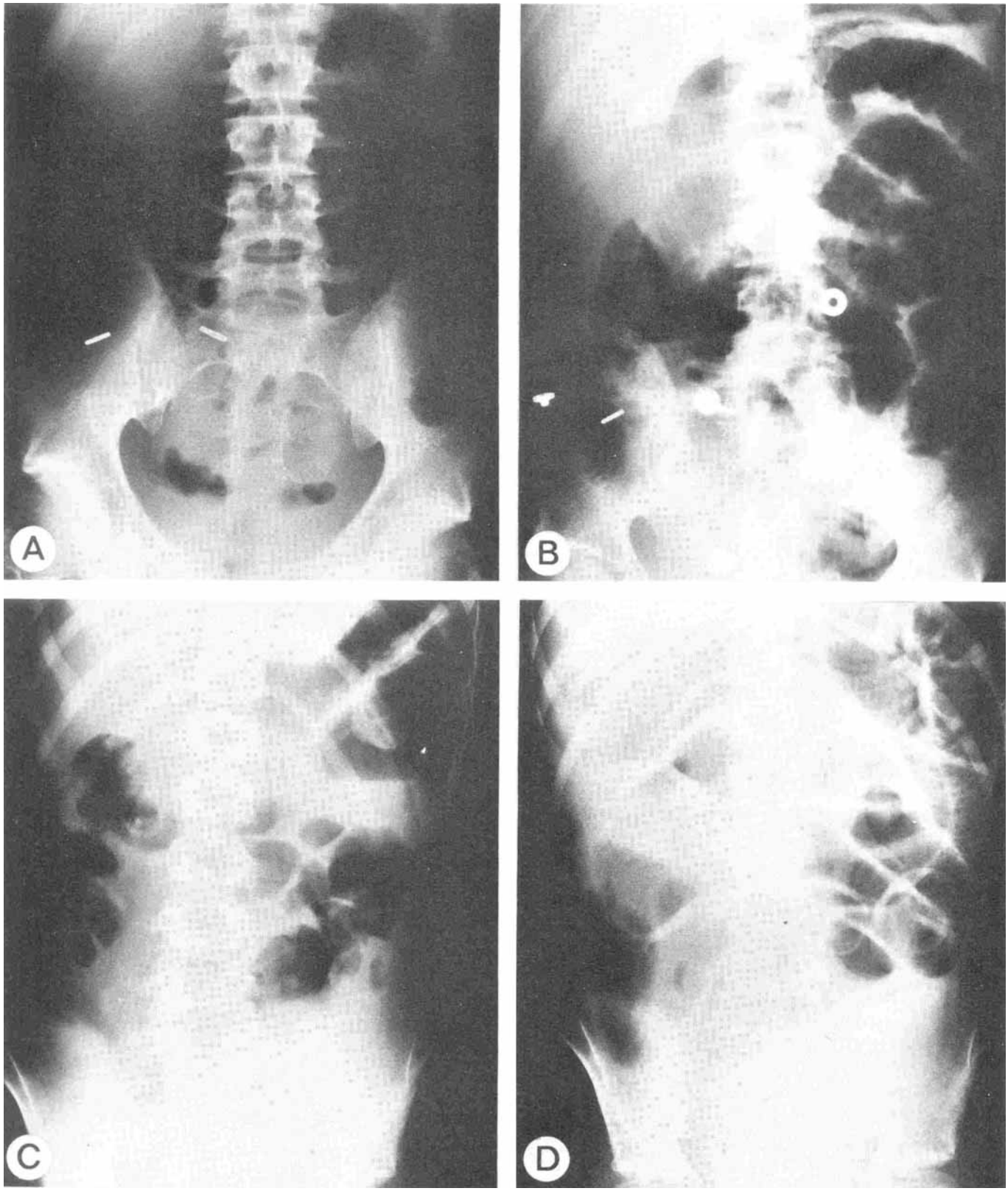

Figure 1—*Abdominal roentgenograms of the two patients with partial GI obstructions. Key: A, Patient 1, 9 days prior to high dose methotrexate; B, Patient 1, 6 days following methotrexate; C, Patient 2, 2 days prior to high dose methotrexate; and D, Patient 2, 19 days following methotrexate. Both sets of roentgenograms demonstrate partial GI obstruction during the evaluation period.*

(8), simulations were produced with all model parameters held constant except for the GI transit rate. These simulations demonstrated that greater amounts of methotrexate accumulate in the intestinal lumen when GI transit is reduced. The simulated amount of methotrexate in the GI lumen decreased more slowly when GI transit was reduced such that the amount in the lumen was more than 10-fold higher at 96 hr when transit was reduced by 50%. Moreover, the reduction of the GI transit rate and the resulting increased accumulation of methotrexate resulted in a prolongation of the terminal serum methotrexate half-life, which was directly related to the extent of reduction in GI transit. Model simulations

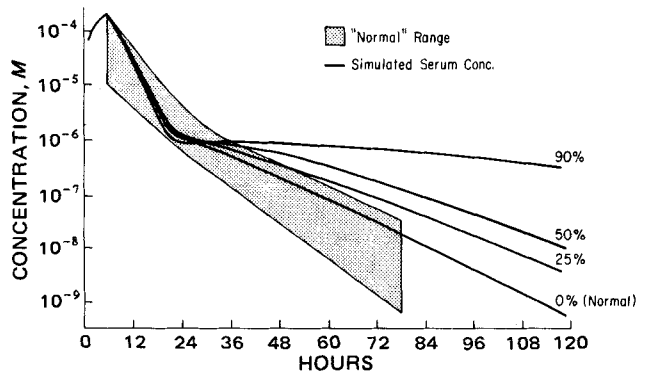

Figure 2—*Simulation of methotrexate serum concentrations* versus *time (solid line) by physiological pharmacokinetic model using normal GI transit rate and transit rate reduced by 25, 50, and 90% from normal. Shaded area represents range of serum concentrations measured following 109 doses administered to 27 patients (6–24-hr measurements) and 38 doses administered to 21 patients (25–78-hr measurements).*

with GI transit rate reduced by 50% were comparable to serum concentrations measured in two patients with partial GI obstructions.

These data indicate that the prolongation of serum methotrexate half-life produced by GI obstruction can result in serum methotrexate concentrations being sustained at cytotoxic levels beyond the period of conventional leucovorin rescue. These data also provide the theoretical basis for previously described (19) changes in methotrexate disposition in a patient with vincristine-induced ileus. The observed difference in simulated serum methotrexate concentrations when the GI transit rate was reduced 25% suggests that only a modest compromise in GI function could affect methotrexate disposition and provides a potential mechanism for other drug interactions.

The importance of altered GI function for a drug such as methotrexate, which is eliminated <5% in the feces, is related to the fact that the high dosage of methotrexate administered (*i.e.*, 5000 mg/m^2) produces serum concentrations (*i.e.*, 10^{-3} *M*) exceeding the minimum cytotoxic concentration (*i.e.*, $\sim 10^{-8}$ *M*) by ~100,000-fold. Thus, perturbation of an excretory pathway that eliminates only a small percentage of the administered dose becomes important. Moreover, reduction in GI transit would result in a more localized accumulation of methotrexate presented to the GI lumen, which produces more rapid saturation of the limited absorptive sites and thereby prolongs reabsorption. Thus, fecal elimination is retarded and reabsorption is delayed, resulting in sustained serum methotrexate concentrations.

The importance of the actual site of GI obstruction was not addressed in the present study, which assumed a consistent reduction in transit rate throughout the GI tract. It is conceivable that partial or complete obstruction in the upper portion of the small bowel might result in a greater localization of methotrexate (*versus* colonic obstruction), while complete obstruction at any site may lead to other clinical complications that could alter methotrexate disposition (*i.e.*, vomiting, malnutrition, *etc.*). These

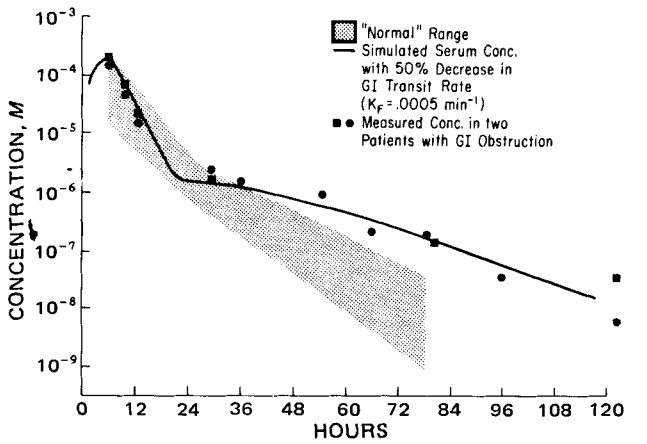

Figure 3—*Simulations of methotrexate serum concentrations* versus *time (solid line) by physiological pharmacokinetic model when GI transit rate is reduced by 50% from normal. Shaded area is as described in Fig. 2.*

Table II—Terminal Serum Half-Life of Methotrexate from Simulated Data

GI Transit, min^{-1} (Percent of Normal)	Half-Life, hr
0.001 (100%)	8.4
0.00075 (75%)	9.8
0.0005 (50%)	14.0
0.0001 (10%)	39.0

questions await further study, as does the clinical significance of potential drug-induced alterations in GI motility.

APPENDIX

The symbols used are:

AbR = absorption rate, micrograms per minute
aR = strong specific binding, micrograms per gram
C = concentration, micrograms per milliliter or micrograms per gram
Cl_R = renal clearance, milliliters per minute
K_f = transit rate in gut lumen, minute^{-1} (reciprocal of transit time)
K_M = Michaelis–Menten constant, micrograms per milliliter
$K_{0(t)}$ = drug infusion rate, micrograms per minute
Q = plasma flow rate, milliliters per minute
R = tissue-to-plasma equilibrium distribution ratio for linear binding
r = drug transport rate in bile, micrograms per minute
t = time, minutes
V = volume, milliliters
V_{max} = maximum rate of saturable process, micrograms per minute
Wt = body weight, kilograms
τ = nominal residence time in bile transit subcompartments, minutes

The subscripts used are:

G = GI tissue
GL = gut lumen
K = kidney
L = liver
M = muscle
P = plasma
1, 2, 3, 4 = gut lumen or bile subcompartments

The differential equations for the physiological model are as follows.

For plasma:

$$\frac{dC_P}{dt} = \frac{K_{0(t)} + Q_L\frac{C_L}{aR_L} + Q_K\frac{C_K}{aR_K} + Q_M\frac{C_M}{R_M} - (Q_L + Q_K + Q_M)C_P}{V_P} \quad \text{(Eq. A1)}$$

For kidneys:

$$\frac{dC_K}{dt} = \frac{Q_K\left(C_P - \frac{C_K}{aR_K}\right) - Cl_R\frac{C_K}{aR_K}}{V_K} \quad \text{(Eq. A2)}$$

For the liver:

$$\frac{dC_L}{dt} = \frac{(Q_L - Q_G)\left(C_P - \frac{C_L}{aR_L}\right) + Q_G\left(\frac{C_G}{aR_G} - \frac{C_L}{aR_L}\right) - \frac{V_{max_L}C_L/aR_L}{K_{M_L} + C_L/aR_L}}{V_L} \quad \text{(Eq. A3)}$$

For muscle:

$$\frac{dC_M}{dt} = \frac{Q_M\left(C_P - \frac{C_M}{R_M}\right)}{V_M} \quad \text{(Eq. A4)}$$

For GI tissue:

$$\frac{dC_G}{dt} = \frac{Q_G\left(C_P - \frac{C_G}{aR_G}\right) + AbR_{GL}}{V_G} \quad \text{(Eq. A5)}$$

Table III—Amount of Methotrexate Accumulated in GI Lumen from Simulated Data for 1.0-m² Patient

Hours	GI Transit Rate, min^{-1}: 0.001 (Normal), mg	0.0005 (50% Normal), mg
Peak[a]	444	553
24	319	496
48	37	148
72	5	36
96	0.7	8

[a] Sixteen hours for normal GI transit and 20 hr for 50% reduced GI transit.

For the gut lumen:

$$\frac{dC_{GL_1}}{dt} = \frac{4r_{B_3} - (4\,K_f V_{GL} C_{GL_1}) - AbR_{GL_1}}{V_{GL}} \quad \text{(Eq. A6}a\text{)}$$

$$\frac{dC_{GL_2}}{dt} = \frac{4K_f V_{GL}(C_{GL_1} - C_{GL_2}) - AbR_{GL_2}}{V_{GL}} \quad \text{(Eq. A6}b\text{)}$$

$$\frac{dC_{GL_3}}{dt} = \frac{4K_f V_{GL}(C_{GL_2} - C_{GL_3}) - AbR_{GL_3}}{V_{GL}} \quad \text{(Eq. A6}c\text{)}$$

$$\frac{dC_{GL_4}}{dt} = \frac{4K_f V_{GL}(C_{GL_3} - C_{GL_4}) - AbR_{GL_4}}{V_{GL}} \quad \text{(Eq. A6}d\text{)}$$

The gut absorption rate is given by

$$AbR_{GL_i} = \frac{V_{\max_{GL}} C_{GL_i}}{K_{M_{GL}} + C_{GL_i}} \qquad i = 1, \ldots, 4 \quad \text{(Eq. A7}a\text{)}$$

$$AbR_{GL} = \frac{AbR_{GL_1} + AbR_{GL_2} + AbR_{GL_3} + AbR_{GL_4}}{4} \quad \text{(Eq. A7}b\text{)}$$

The biliary transit rate is given by:

$$\frac{dr_{B_3}}{dt} = \frac{r_{B_2} - r_{B_3}}{\tau} \quad \text{(Eq. A8}a\text{)}$$

$$\frac{dr_{B_2}}{dt} = \frac{r_{B_1} - r_{B_2}}{\tau} \quad \text{(Eq. A8}b\text{)}$$

$$\frac{dr_{B_1}}{dt} = \frac{\dfrac{V_{\max_L} C_L / aR_L}{K_{M_L} + C_L / aR_L} - r_{B_1}}{\tau} \quad \text{(Eq. A8}c\text{)}$$

Renal clearance is given by:

$$Cl_R = BSA92.0 - (13.8)\,(\ln C_P) \quad \text{(Eq. A9)}$$

where:

$V_{\max_L} = 1000\ \mu g/min$
$K_{M_L} = 5\ \mu g/ml$
$V_{\max_{GL}} = 1900\ \mu g/min$
$K_{M_{GL}} = 200\ \mu g/ml$
$\tau = 10$
$R_K = 3.0$
$R_G = 1.0$
$R_L = 3.0$
$R_M = 0.15$

$$aR_K = R_K + \frac{0.3}{C_P}$$

$$aR_G = R_G + \frac{0.1}{C_P}$$

$$aR_L = R_L + \frac{0.4}{C_P}$$

$K_f = 0.001\ min^{-1}$ (normal value)

Volume equal:

$$V_P = 44 \cdot Wt^{0.99}\ \text{(plasma)} \quad \text{(Eq. A10}a\text{)}$$

$$V_K = 7.5 \cdot Wt^{0.85}\ \text{(kidneys)} \quad \text{(Eq. A10}b\text{)}$$

$$V_L = 34 \cdot Wt^{0.87}\ \text{(liver)} \quad \text{(Eq. A10}c\text{)}$$

$$V_G = 49 \cdot Wt^{0.94}\ \text{(GI)} \quad \text{(Eq. A10}d\text{)}$$

$$V_{GL} = 49 \cdot Wt^{0.94}\ \text{(GI lumen)} \quad \text{(Eq. A10}e\text{)}$$

$$V_M = 500 \cdot Wt\ \text{(muscle)} \quad \text{(Eq. A10}f\text{)}$$

where V is in milliliters and Wt is in kilograms.

Organ plasma flow equals:

$$Q_K = 24.5 \cdot Wt^{0.792}\ \text{(kidneys)} \quad \text{(Eq. A11}a\text{)}$$

$$Q_L = 29.96 \cdot Wt^{0.767}\ \text{(liver)} \quad \text{(Eq. A11}b\text{)}$$

$$Q_G = 0.66 \cdot Q_L\ \text{(GI)} \quad \text{(Eq. A11}c\text{)}$$

$$Q_M = 18.17 \cdot Wt^{0.738}\ \text{(muscle)} \quad \text{(Eq. A11}d\text{)}$$

where Q is in milliliters/minutes and Wt is in kilograms.

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