A Pharmacokinetic Model for Intraperitoneal Administration of Drugs: Application to Teniposide in Humans

P. CANAL*, Y. PLUSQUELLEC‡, E. CHATELUT*, R. BUGAT*§, J. DE BIASI‡, AND G. HOUIN¶§x

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Abstract □ A pharmacokinetic study of teniposide after ip administration with a 4-h dwell time was performed in patients suffering from abdominal malignant ascites. A three-compartment open model was developed to fit together the data obtained in plasma and peritoneum. The pharmacokinetic parameters obtained by the model agreed with those obtained by model-independent analysis, and the fitting correctly depicted the plasma and peritoneal concentration decays. According to the results, such a model could be applied to ip administration of anticancerous drugs.

Intraperitoneal (ip) administration of anticancerous drugs has become more and more popular in the treatment of the disease when it is confined in the peritoneal cavity, such as in the case of ovarian carcinoma. Until now, the disposition of an ip administered drug has been described by an open two-compartment model including peritoneum as the input compartment.[1]

We have recently studied the ip administration of teniposide (4′-demethylepipodophyllotoxin-9-[4,6-*O*-(*R*)-2-thenylidene-β-D-glucopyranoside]; VM26), a semisynthetic derivative of podophyllin, in patients suffering from malignant ascites.[2] During this study, we noticed that the plasma concentrations decreased biexponentially. In order to describe these results, it was therefore necessary to develop a new pharmacokinetic model. This model, displayed in Figure 1, assumed that the drug, after administration into the peritoneal cavity (A), entered the circulation (compartment 1) and then diffused in a peripheral compartment (2) according to first-order kinetics. This model has been applied to the study of teniposide kinetics after different ip doses.

Experimental Section

Design of the Study—Eight fully informed adult subjects, suffering from abdominal malignant ascites, consented to enter the study. They received a total dose of teniposide ranging from 495 to 700 mg (Sandoz, Paris, France, lot no. 032). The drug was infused into the peritonal cavity via a Tenckhoff catheter in 2 L of 0.9% NaCl solution within 10 to 15 min. The teniposide was allowed to dwell in the peritoneal cavity for 4 h. After the completion of the 4-h dwell time, the cavity was drained as completely as possible.

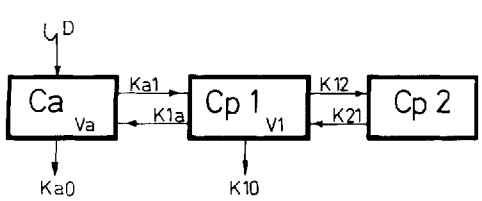

Figure 1—*Pharmacokinetic model for ip administration of teniposide.*

Pharmacokinetic Protocol—To determine teniposide concentrations, peritoneal fluid was sampled at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, and 4 h after the end of the peritoneal infusion. Plasma samples were obtained at the same time and then 5, 15, and 30 min, and 1, 2, 4, 6, 12, and 24 h after the dwell time. Peritoneal fluid and blood samples were collected in dry glass tubes and immediately centrifuged at 4 °C. The supernatant was frozen and stored at −20 °C until analysis. Teniposide concentrations were determined by HPLC using etoposide as an internal standard as described elsewhere.[3]

Calculations—*Model-Independent Analysis*—The apparent peritoneum disappearance half-life of teniposide was determined by the least-squares, log-linear regression method. The area under the peritoneal concentration–time curve (AUC) was calculated using the trapezoïdal rule from 0 to 4 h. For plasma pharmacokinetics, the terminal half-life was calculated from the terminal part of the plasma concentrations. The plasma AUC was also determined by the trapezoïdal rule, but extrapolated to infinity (by dividing the last measurable concentration by the terminal slope).

General Model Analysis—The pharmacokinetic parameters of the drug were obtained with the catenary model displayed in Figure 1. The drug injected in the peritoneal compartment (A) entered the circulation (compartment 1) and diffused in the peripheral compartment (2) following first-order kinetics. Elimination could take place from compartments A and 1. After 4 h, the drug was removed from compartment A and the main exchange between compartments A and 1 concerned the diffusion of drug from compartment 1 to A (k_{1a}).

Let us denote by D the injected dose and by $X_a(t)$, $X_1(t)$, and $X_2(t)$ the amounts of the drug at time t in compartments A, 1, and 2, respectively. The differential system connected with the model is described by eqs 1–4 if $0 \leq t \leq 4$ h:

$$\frac{dX_a}{dt} = -(k_{a1} + k_{a0})X_a + k_{1a}X_1 \quad (1)$$

$$\frac{dX_1}{dt} = k_{a1}X_a - (k_{1a} + k_{10} + k_{12})X_1 + k_{21}X_2 \quad (2)$$

$$\frac{dX_2}{dt} = k_{12}X_1 - k_{21}X_2 \quad (3)$$

$$X_a(0) = D, \qquad X_1(0) = X_2(0) = 0 \quad (4)$$

If $t \geq 4$ h, however, then the model is described by eqs 5 and 6:

$$\frac{dX_1}{dt} = -(k_{10} + k_{12} + k_{1a})X_1 + k_{21}X_2 \quad (5)$$

$$\frac{dX_2}{dt} = k_{12}X_1 - k_{21}X_2 \quad (6)$$

where the X_1 and X_2 functions are continuous at the time $t = 4$ h.

The apparent volumes of distribution in compartments A and 1 are denoted V_a and V_1; the concentrations in these compartments are $C_{a(t)} = X_{a(t)}/V_a$ and $C_{1(t)} = X_{1(t)}/V_1$, respectively.

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Profiles of Drug Concentrations—Using the Laplace transform Z(s) of $X_{(t)}$ (see *Appendix*), the expressions of $X_{(t)}$ at any time (t) were obtained using Cardan's method for solving the third degree equation which gives the eigen values $-\alpha$, $-\beta$, and $-\gamma$ of the system. Thus, if $0 \leq t \leq 4$h, then eqs 7 and 8 apply:

$$C_{a(t)} = \frac{D}{V_a}\left[\frac{P(-\alpha)e^{-\alpha t}}{(\beta-\alpha)(\gamma-\alpha)} + \frac{P(-\beta)e^{-\beta t}}{(\alpha-\beta)(\gamma-\beta)} + \frac{P(-\gamma)e^{-\gamma t}}{(\alpha-\gamma)(\beta-\gamma)}\right] \quad (7)$$

where $P(s) = s^2 + s(k_{10} + k_{1a} + k_{12} + k_{21}) + k_{21}(k_{10} + k_{1a})$.

$$C_{1(t)} = \frac{Dk_{a1}}{V_1}\left[\frac{(k_{21}-\alpha)e^{-\alpha t}}{(\beta-\alpha)(\gamma-\alpha)} + \frac{(k_{21}-\beta)e^{-\beta t}}{(\alpha-\beta)(\gamma-\beta)} + \frac{(k_{21}-\gamma)e^{-\gamma t}}{(\alpha-\gamma)(\beta-\gamma)}\right] \quad (8)$$

If $t > 4$ h, then eq 9 applies:

$$C_{1(t)} = \frac{1}{V_1(\mu-\lambda)}[R(-\lambda)e^{-\lambda(t-4)} - R(-\mu)e^{-\mu(t-4)}] \quad (9)$$

where $r_1 = X_{1(4)}$, $r_2 = X_{2(4)}$, $R(s) = (s + k_{21})r_1 + k_{21}r_2$ and $-\lambda$ and $-\mu$ are the roots of $s^2 + s(k_{21} + k_{10} + k_{1a} + k_{12}) + k_{21}(k_{10} + k_{1a}) = 0$.

Areas Under the Concentration Curves—The areas under the concentration curves for the peritoneal compartment and compartment 1 were derived from eqs 7 and 8, respectively, for time 0 to 4 h (see *Appendix* for time 4 to ∞). In compartment A, the AUC is defined as follows:

$$AUC_{(0-4)} = \frac{D}{V_a}\left[\frac{P(-\alpha)(1-e^{-4\alpha})}{\alpha(\beta-\alpha)(\gamma-\alpha)} + \frac{P(-\beta)(1-e^{-4\beta})}{\beta(\alpha-\beta)(\gamma-\beta)} + \frac{P(-\gamma)(1-e^{-4\gamma})}{\gamma(\alpha-\gamma)(\beta-\gamma)}\right] \quad (10)$$

In compartment 1, AUC is defined as follows:

$$AUC_{(0-\infty)} = AUC_{(0-4)} + AUC_{(4-\infty)} =$$

$$\frac{Dk_{a1}}{V_1}\left[\frac{(k_{21}-\alpha)(1-e^{-4\alpha})}{\alpha(\beta-\alpha)(\gamma-\alpha)} + \frac{(k_{21}-\beta)(1-e^{-4\beta})}{\beta(\alpha-\beta)(\gamma-\beta)} + \frac{(k_{21}-\gamma)(1-e^{-4\gamma})}{\gamma(\alpha-\gamma)(\beta-\gamma)}\right] + \frac{r_1+r_2}{V_1(k_{10}+k_{1a})} \quad (11)$$

Restricted Model Analysis—In each patient, the peritoneal and plasma concentrations were fitted together according to the general model from the analytical expressions of $C_{a(t)}$ and $C_{1(t)}$, using the nonlinear regression method of Marquardt[4] and a computer program (in Basic or Fortran for Multics DPS8 Honeywell-Bull, available from the authors upon request). As optimized values for k_{a0} and k_{1a} were near zero for the considered drug, we have built up a simplified model with $k_{1a} = k_{a0} = 0$. Then, eq 7 must be replaced by:

$$C_{a(t)} = \frac{D}{V_a}e^{-k_{a1}t} \quad (12)$$

In eq 8, α must be replaced by k_{a1}, while β and γ are the roots of $s^2 + s(k_{10} + k_{12} + k_{21}) + k_{10}k_{21} = 0$.

Equation 9 was replaced by:

$$C_{1(t)} = \frac{1}{V_1(\gamma-\beta)}[R(-\beta)e^{-\beta(t-4)} - R(-\gamma)e^{-\gamma(t-4)}] \quad (13)$$

Furthermore, with this model, in compartment A:

$$AUC_{(0-4)} = \frac{D}{V_a k_{a1}}(1 - e^{-4k_{a1}}) \quad (14)$$

In compartment 1, $AUC_{(0-\infty)}$ can be expressed as follows:

$$AUC = \frac{Dk_{a1}}{V_1}\left[\frac{(k_{21}-k_{a1})(1-e^{-4k_{a1}})}{k_{a1}(\beta-k_{a1})(\gamma-k_{a1})} + \frac{(k_{21}-\beta)(1-e^{4\beta})}{\beta(k_{a1}-\beta)(\gamma-\beta)} + \frac{(k_{21}-\gamma)(1-e^{-4\gamma})}{\gamma(k_{a1}-\gamma)(\beta-\gamma)}\right] + \frac{r_1+r_2}{V_1k_{10}} \quad (15)$$

Results

Model-Independent Analysis—The pharmacokinetic parameters of teniposide in the peritoneal fluid and ascites are summarized in Table I. The observed C_{max} ratio between peritoneal fluid and plasma ranged from 18.1 to 39.4 (mean 28.3 ± 8.8), and the AUC ratio averaged 9.4. The mean apparent peritoneal and plasma half-lives were, respectively, 6.9 ± 2.5 and 7.5 ± 3.1 h.

Model-Dependent Analysis—The different constants of the established model are summarized in Table II with mean ± SD. The corresponding pharmacokinetic parameters are displayed in Table III. When comparing the pharmacokinetic parameters obtained by the independent or dependent model analysis, no significant difference was found between peritoneal or plasma AUC, half-lives, or peak concentrations. On the other hand, the observed T_{max} in plasma was close to the calculated t_{max} (Table III).

An example of fitting is shown in Figure 2 which describes the pharmacokinetics of teniposide after ip administration of 570 mg to patient E.

Table I—Pharmacokinetic Parameters of the Different Patients Calculated by Model-Independent Analysis

Patient	Dose, mg	Peritoneal Fluid			Plasma			
		Peak, mg/L	AUC, (mg/L)h	$t_{1/2}$, h	Peak, mg/L	AUC, (mg/L)h	$t_{1/2}$, h	t_{max}, h
P	495	162	589.1	4.1	8.09	159.7	12.0	4
E	570	203	696.2	8.8	5.71	43.2	4.1	4
P	550	221	723.5	5.7	6.06	49.1	5.0	4
L	585	250	789.0	5.6	12.36	185.0	10.0	4
S1	700	283	1012.3	11.2	8.5	65.8	4.0	4.08
S2	700	280	892.4	6.9	7.1	76.3	7.2	4
B	700	319	1156.0	8.7	13.65	180.0	7.2	4.08
H	700	287	833.7	3.9	15.85	291.7	11.0	4.08

Table II—Different Constants Calculated by the Model

Patient	Dose, mg	k_{a1}, h^{-1}	k_{10}, h^{-1}	k_{12}, h^{-1}	k_{21}, h^{-1}
P	495	0.165	0.250	1.61	0.45
E	570	0.111	0.840	8.40	1.98
P	550	0.080	0.328	6.10	1.96
L	585	0.119	0.378	2.19	0.37
S1	700	0.058	0.498	3.44	2.90
S2	700	0.108	0.544	7.24	1.58
B	700	0.124	0.548	2.43	0.59
H	700	0.091	0.229	2.40	1.04
	Mean	0.107	0.452	4.23	1.36
	SD	0.030	0.187	2.45	0.84

Discussion

The primary pharmacokinetic interpretation according to the general model for ip administration of teniposide showed that the constant rate k_{a0} (rate of elimination from the peritoneal cavity) was very weak, approaching zero. This elimination could correspond to lymphatic drainage which Myers and Collins[5] described as one of the three elimination routes of a drug from the peritoneal cavity. This elimination route being negligible, almost all the drug left the peritoneal compartment for the central compartment 1. The return from the central compartment to the peritoneal one (k_{1a}) was also very low. The high concentration difference observed between the two compartments was in agreement with this fact, confirming the mass transfer rate. According to these calculations, a simplified model was used to describe the data which gave results close to those obtained with the general model. For all patients, the simplified model enabled us to obtain a satisfactory fitting of the data. This was confirmed since no difference was found between the independent and dependent model pharmacokinetic parameters.

The entry of the drug from compartment 1 into compartment 2 was very large (k_{12} = 4.22 ± 2.62 h^{-1}), showing a large tissue diffusion that is probably linked to the lipophilic pattern of the drug.[6] This was in agreement with the volume of distribution (Vd_β = 29.8 ± 9.6 L/m^2) previously estimated after iv injection of teniposide.[7]

The volumes of distribution calculated by the model showed that the volume V_a was almost 2 L (2.56 ± 0.28 L), which closely reflected the volume injected into the peritoneum. In addition, the volume of the central compartment 1, which was 4.5 ± 1.2 L, corresponded to the plasmatic volume. This result was in agreement with the volume of the central compartment found by Sinkule et al.[8] after iv administration of teniposide in children (V_c = 3.13 ± 2.9 L/m^2).

This model has also been used for predicting the maximum tolerated dose (MTD) of teniposide when administered by the ip route in a phase I clinical trial.[2] Taking into account that a plasma concentration of 10 mg/L was associated with hematologic toxicity,[9] and considering the data obtained from the first eligible patients, we calculated the potent MTD with the help of the model. The required dose was 700 mg, which corresponded approximately to the MTD established during the phase I study (450 mg/m^2).[2]

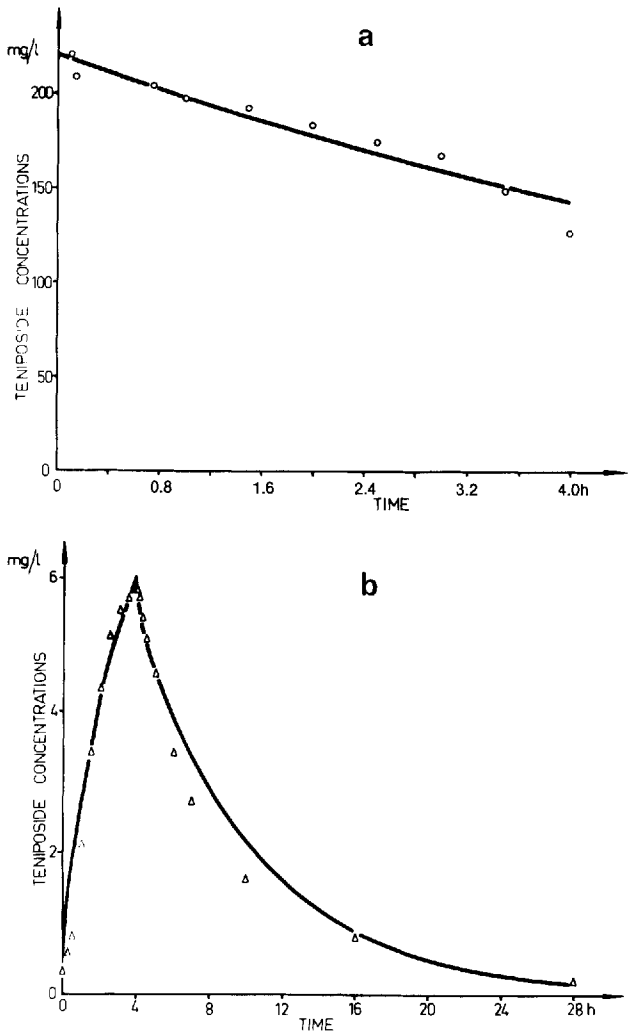

Figure 2—*Peritoneal fluid* (a) *and plasma* (b) *concentrations of teniposide as a function of time after ip administration of 570 mg of teniposide in patient E. Key:* (○) *peritoneal fluid measured concentrations;* (△) *plasma measured concentrations;* (—) *model fitting.*

Table III—Model-Dependent Pharmacokinetic Parameters of Different Patients

Patient	Dose, mg	Peritoneal Fluid				Plasma				
		Peak, mg/L	AUC, (mg/L)h	$t_{1/2}$, h	V_a, L[a]	Peak, mg/L	AUC, (mg/L)h	$t_{1/2}$, h	t_{max}, h	V_1, L[a]
P	495	161	460.0	4.2	3.15	8.26	149.7	12.9	4	6.50
E	570	222	716.4	6.2	2.57	5.76	49.6	6.2	4	4.90
P	550	204	696.1	8.6	2.70	5.98	84.0	8.9	4	5.49
L	585	249	792.9	5.8	2.35	13.30	215.5	11.2	4	2.72
S1	700	290	1036.8	11.9	2.41	8.73	62.6	3.4	4	4.65
S2	700	275	895.1	6.4	2.54	6.99	84.5	7.4	4	5.34
B	700	330	1042.2	5.6	2.12	13.53	150.7	7.4	4	3.31
H	700	261	875.7	7.6	2.68	16.43	265.7	10.7	4	3.51

[a] V_a and V_1 are the volumes of distribution of compartments A and 1, respectively, as defined in the model.

Conclusions

We have created and applied an open three-compartment model to the ip administration of teniposide. For all patients, the model enabled us to obtain a satisfactory fitting of the data and could be used for other drugs. This model also allowed us to predict the MTD in a phase I clinical trial and contributed to a pharmacokinetic guide dose escalation in phase I clinical trials, as recommended by Collins et al.[10]

Appendix

For $0 \leq t \leq 4$ Hours—With $Zi(s) = \mathcal{L}(Xi_{(t)})$ for i = a, 1, and 2, eqs 1–3 become:

$$(s + k_{a1} + k_{a0})Z_a - k_{1a}Z_1 = D \quad \text{(A1)}$$

$$-k_{a1}Z_a + (s + k_{10} + k_{1a} + k_{12})Z_1 - k_{21}Z_2 = 0 \quad \text{(A2)}$$

$$-k_{12}Z_1 + (s + k_{21})Z_2 = 0 \quad \text{(A3)}$$

Thus,

$$Z_a(s) = \frac{DP(s)}{Q(s)} \quad \text{(A4)}$$

$$Z_1(s) = \frac{Dk_{a1}}{Q(s)}(s + k_{21}) \quad \text{(A5)}$$

and

$$Z_2(s) = \frac{Dk_{a1}k_{12}}{Q(s)} \quad \text{(A6)}$$

where $P(s) = s^2 + s(k_{10} + k_{1a} + k_{12} + k_{21}) + k_{21}(k_{10} + k_{1a})$, $Q(s) = s^3 + as^2 + bs + c = (s + \alpha)(s + \beta)(s + \gamma)$, and where $a = k_{a1} + k_{a0} + k_{10} + k_{1a} + k_{12} + k_{21}$, $b = k_{21}(k_{10} + k_{1a} + k_{a1} + k_{a0}) + k_{a1}(k_{10} + k_{12}) + k_{a0}(k_{10} + k_{1a} + k_{12})$, and $c = k_{21}[k_{10}(k_{a1} + k_{a0}) + k_{a0}k_{1a}]$.

The three roots $-\alpha$, $-\beta$, and $-\gamma$ of Q(s) have been expressed by the Cardan's method. Let: $p = b - a^2/3$, $q = c + (2a^3/27) - (ab/3)$, and $m = [-(27/2)q + 3i(\sqrt{3}/2)\sqrt{-4p^3 - 27q^2}]^{1/3}$, where the i complex number, $i^2 = -1$, then, $\alpha = a/3 - (2/3)$ Real (m), $\beta = a/3 - (2/3)$ Real (jm), and $\gamma = a/3 - (2/3)$ Real (j^2m) if $j \notin \mathbb{R}$ and $j^3 = 1$.

Then, using the Heaviside's formula for the inverse Laplace transform, we have expressed $X_{a(t)}$ and $X_{1(t)}$ [also, $X_{2(t)}$ to get $X_{2(4)}$ for the next system].

For $t > 4$ hours—Putting $Yi(t) = 0$ if $0 < t < 4$ and $Xi(t + 4)$ if $t > 4$, with $Y_{1(0)} = X_{1(4)} = r_1$ and $Y_{2(0)} = X_{2(4)} = r_2$, the following relationship results:

$$\mathcal{L}(Y_{1(t)}) = \frac{(s + k_{21})r_1 + r_2k_{21}}{s^2 + s(k_{10} + k_{12} + k_{21} + k_{1a}) + k_{21}(k_{10} + k_{1a})} \quad \text{(A7)}$$

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