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The Clinical Pharmacology of VM26 and VP16-213

A Brief Overview

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Introduction

The purpose of this overview is to review briefly the pharmacology of the clinically used epipodophyllotoxins. The structure of the two drugs, VM26 (4′-demethylepipodophyllotoxin 9-(4,6-O-thenylidene-β-D-glucopyranoside, teniposide PTG) and VP16-213 (4′-demethylepipodophyllotoxin 9-(4,6-O-ethylidene-β-D-glucopyranoside, VP16-213, etoposide EPEG) is shown in Fig. 1 with the position of the tritium label of the radioactive materials used in the earlier studies. Several reviews have appeared of these drugs [6, 19, 20, 30, 31] and aspects of their chemistry and mode of action are covered in other parts of this Symposium. This brief overview will,

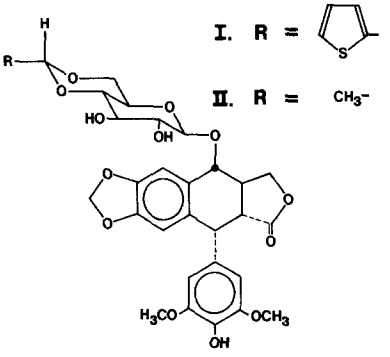

Fig. 1. The structure of VM26 (I) and VP16-213 (II). The position of the tritium label in the drug used in the radioisotopic studies is shown by (●)

Table 1. Approximate weekly dose of VP16-213 to produce moderate hematologic toxicity

Dosage form	Dose[a]	Comments	Authors	References
Lipophilic capsules	> 700	Mainly gastrointestinal toxicity. Leucopenia 39%	Falkson et al.	[17]
	> 750	Leukopenia 42%. Hematologic toxicity not dose dependent	Nissen et al.	[27]
	> 600	3/21 courses gave W.B.C.[b] < 4,000/cu · mm	Brunner et al.	[9]
Oral solution	600		Brunner et al.	[9]
	500	Hematologic toxicity somewhat more than with 250 mg/m^2 intravenously	Cavalli et al.	[10]
	300		Nissen et al.	[26]
Hydrophilic soft gelatin capsule	300		Lau et al.	[22]
Intravenous	172		Nissen et al.	[28]
	290		Creaven et al.	[14]
	250		Cavalli et al.	[10]
	300		Brunner et al.	[9]

[a] Computed as the dose in mg/m^2 given per week
[b] W.B.C. – white blood count

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therefore, be limited largely to a consideration of the clinical pharmacology and pharmacokinetics of these agents.

Gastrointestinal Absorption

The early clinical studies with these agents were carried out with an intravenous preparation. Subsequently studies were initiated with oral preparations, initially a lipophilic capsule [9, 17, 27] followed by evaluation of an oral solution [9, 10, 26] and most recently of a hydrophilic soft gelatin capsule [22]. A rough comparison of the dose (computed as mg/m^2/week) of these dosage forms required to produce moderate hematologic toxicity, compared with the dose of the drug when given intravenously is shown in Table 1. From the data in this table it would appear that absorption from the lipophilic capsules is poor and erratic and that absorption from the oral solution and the hydrophilic capsule is much better, probably greater than 50% and may approach 100%. Table 2 shows some data on gastrointestinal absorption derived from recovery of radioactivity or by AUC (area under the plasma concentration curve) as measured by high performance liquid chromatography (HPLC). In general the data are in good agreement with the conclusions drawn from studies of the toxicity of the orally administered drug.

Distribution

The early studies of the distribution of the drug in man were carried out with radiolabelled drug (see Fig. 1) using differential extraction and paper and thin layer chromatography to distinguish between unchanged drug and metabolites [11, 12]. The plasma levels of unchanged drug were computer fitted by non-linear least-squares regression analysis using the programs NONLIN [24] and MLAB [21]. For VM26 the best fit was to Eq. 1:

$$Cp = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} \qquad \text{Eq. 1}$$

indicating a triexponential plasma decay.

Figure 2 shows the curves generated when plasma concentrations of drug in two patients were computer fitted to Eq. 1.

These studies indicate a terminal $t_{1/2}$ of 21.2 h in six patients who received a dose of 67 mg/m^2 [12].

For VP16-213 the best fit was to Eq. 2.

$$Cp = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{Eq. 2}$$

A terminal $t_{1/2}$ of 11.06 h in 20 patients receiving doses of 70–290 mg/m^2 was computed (there was no statistically significant difference in the half lives at the doses studied).

Figure 3 shows the curves generated when the plasma concentrations of drug in three patients who received 70, 130, and 290 mg/m^2 respectively were fitted to Eq. 2.

Table 2. Gastrointestinal absorption of VP16-213

Dosage form	Absorbed (% dose)	Author	References
Oral solution	73[a]	Sandoz Ltd. Basel, quoted by Nissen et al.	[26]
Capsule	51–90	Farina et al.	[18]
	50 (approx.)	Arnold et al.	[7]
	30–63	Farina et al.	[18]

[a] Based on urinary excretion after oral (^{3}H) VP16-213. Other values based on HPLC assay of plasma concentrations

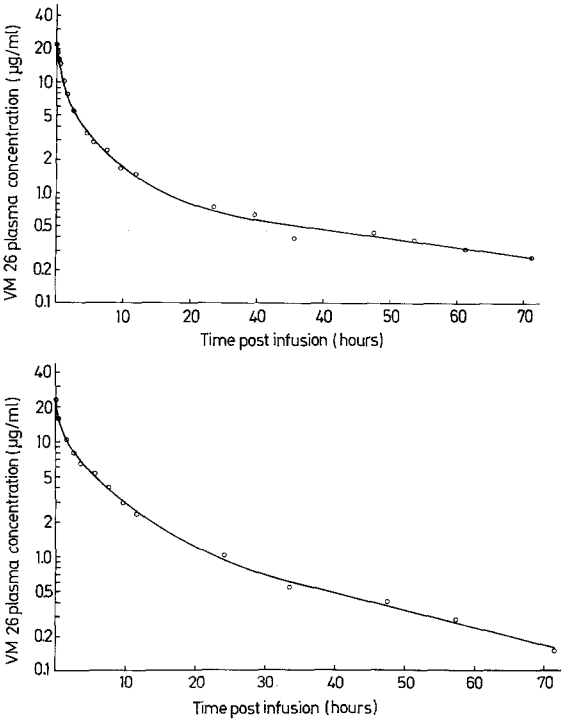

Fig. 2. The plasma decay of VM26 for two patients was fitted to Eq. 1 by non-linear least-squares regression analysis using the program NONLIN [24] on an IBM 370/165 digital computer. Observed data ○. Computer fitted line (———). (Reprinted with permission from Clinical Pharmacology and Therapeutics, Vol. 18: Creaven, P. J. and Allen, L. M., PTG, A New Antineoplastic Epipodophyllotoxin. Copyright 1975, The C. V. Mosby Company)

More recently a number of HPLC techniques for the analysis of these drugs have been described [3, 7, 16, 18, 34, 36] (Table 3). A comparison of the plasma $t_{1/2}$ data derived by using these techniques with the data obtained from the isotopic studies is given for VM26 in Table 4 and for VP16 in Table 5. Because of the considerable variability in the reported values of the half-lives and the lack of agreement on the appropriate model to describe the plasma decay of these two agents it is difficult to draw any firm conclusions from these data. It would seem reasonable to conclude, however, that VM26 has a longer terminal half-life than VP16 and that the half-life is shorter in children than in adults.

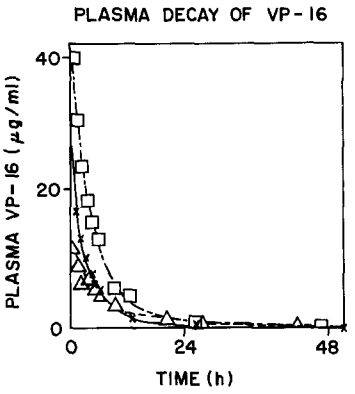

Fig. 3. The plasma decay of VP16-213 for one patient each at doses of 70 mg/m^2, 170 mg/m^2, and 290 mg/m^2 fitted to Eq. 2 by non-linear least-squares regression analysis using the program MLAB [21] on a DEC System-10 digital computer. Symbols are the observed data, lines are the computer fitted curves (△– – –△) 70 mg/m^2; (×———×) 170 mg/m^2; (□– – –□) 290 mg/m^2

Penetration of the Blood-Brain Barrier

VM26 and VP16-213 are both reported to have some activity against intracranial neoplasms though the experience reported with VP16-213 has been small. In 23 patients treated with VM26 in a number of studies summarized by Radice et al. [30] an overall partial response rate of 52% was noted, a level of activity not confirmed by others [8, 35]. Madajewicz et al. have, however, reported an impressive response rate to intracarotid VM26 in ten patients: two complete and five partial responses [23].

In studies on the cerebrospinal fluid (CSF) only low levels of the drug have been found. In three of

Table 3. HPLC assays for VM26 and VP16-213

Author	Drug	Column	Mobile phase	Detection	References
Strife et al.	VM26 VP16-213	Reversed phase C18	Methanol/water 60:40	U.V. absorption at 254 nm	[36]
Allen	VP16-213 VM26	Reversed phase Partisil-10 ODS	5 mM KH_2PO_4-NaOH buffer pH 7.8/Methanol 50:50 (25:75 for VM26)	U.V. absorption 252 nm	[3]
Snodgrass et al.	VP16-213	Reversed phase C18	Methanol/water 55:45 with 1% glacial acetic acid	U.V. absorption 293 nm	[34]
Arnold et al.	VP16-213		–[a]	–	[7]
Evans et al.	VM26 VP16-213		–	Electrochemical oxidation mode (AP = 0.7 V)	[16]
Farina et al.	VP16-213	Lichrosorb RP-8	Methanol/water 55:45	U.V. absorption 254 nm	[18]

[a] Indicates details not given in the publication

Table 4. Plasma decay kinetics of VM26

Dose (mg/m^2)	Kinetics of plasma decay	Terminal $t_{1/2}$ (h)	Assay technique	Author (References)
67	Triexponential	21.2 ± 9.9 (n = 6)	Radioisotopic[a]	Creaven and Allen [12]
165[b]	Biexponential	9.8 ± 1.6 (n = 3)	HPLC	Evans et al. [16]

[a] Parent drug separated from metabolites by extraction, paper and thin layer chromatography
[b] Studies in children

Table 5. Plasma decay kinetics of VP16-213

Dose (mg/m^2)	Kinetics of plasma decay	Terminal $t_{1/2}$ (h)	Assay technique	Author (References)
70–290	Biexponential	11.06 ± 6.0 ($n = 20$)	Radioisotopic[a]	Creaven and Allen [11]
200[b]	Biexponential	3–5	HPLC	Snodgrass et al. [34]
200	Triexponential	43.2 ($n = 6$)	HPLC	Arnold et al. [7]
200–500[b]	Biexponential	5.7 ± 1.3 ($n = 6$)	HPLC	Evans et al. [16]
100	Biexponential	4–5 ($n = 2$)[c]	HPLC	Farina et al. [18]

[a] Parent drug separated from metabolites by extraction, paper and thin layer chromatography
[b] Studies in children
[c] 4–9 h after oral drug (D'Incalci et al. [15])

Table 6. Levels of VP16-213 in cerebrospinal fluid and plasma after infusion with (^3H) VP16-213

Dose (mg/m^2)	Time post infusion (h)	Drug plasma level (μg/ml)	Drug CSF level	
			μg/ml	% plasma level
70	2.50	7.66	<0.01	–
70	4.00	3.59	0.02	0.6
100	4.25	4.25	0.05	1.2
	28.00	0.83	0.03	3.6
100	54.00	0.14	0.02	14.3
170	5.80	11.27	0.13	1.2
170	19.00	0.64	0.08	12.5
170	24.00	2.07	0.09	4.4
220	2.00	15.27	0.05	0.3
220	4.66	11.35	0.01	0.1
220	11.75	2.78	0.05	1.8
220	26.00	1.30	0.13	10.0
290	23.50	1.46	0.07	4.8

References: [11]
Creaven and Allen unpublished data

Table 7. Excretion of radioactivity after intravenous (^3H) VM26[a] and (^3H) VP16-213[a] in rats

	VM26 (% dose)	VP16-213 (% dose)	
		Intact rats	Bile fistula rats
Urine	14.5	28	33
Feces	54.1	60	10
Bile	–	–	50
Total	68.6	88	93

[a] Dose 5 mg/kg
References [32, 33]

four patients studied who rceived [^3H]VM26 levels of drug in the CSF were < 1% of the plasma levels at 24 h post drug infusion. The levels in the fourth patient were zero at 3.25 h post drug infusion but at 27 h were 27% of plasma levels [12]. This patient had had brain surgery and removal of the left frontal lobe

Table 8. Recovery of radioactivity in patients receiving intravenous (^3H) VP16-213

Dose (mg/m^2)	n	Radioactivity (% dose)	
		Urine	Feces
70	2	51.5, 38.4	–
100	1	54.4	
130	3	41.9 ± 9.5	0.2, 0.2, 12.8
170	5	67.3 ± 15.1	0, 6.0
220	3	43.3 ± 3.6	0
290	5	45.1 ± 7.7	1.2, 1.6, 16.3

References [11] Creaven and Allen, unpublished data

as well as extensive brain radiotherapy. The level of VP16-213 in the CSF of 12 patients treated with doses of 70–290 mg/m^2 at times from 2–54 h post drug infusion are shown in Table 6. Very low levels of drug were found in the CSF at all time points. No VP16-213 was detected by HPLC in the CSF of two patients given the drug intravenously and sampled at 4 and 17 h post drug administration respectively, in the study recently reported by D'Incalci et al. [15]. As we have previously discussed [11, 12], it is possible that the very poor water solubility of these drugs limits their presence in the CSF. However, the levels of the drugs in rat brain after intravenous administration are also very low [32, 33] so the reported activity of these agents against brain tumors is difficult to explain on a pharmacological basis.

Excretion

The drugs are excreted predominantly via the bile in rats [32, 33] (Table 7). In man, the urinary recovery of VM26 was 44.5 ± 8.2% in five patients receiving an intravenous dose of 67 mg/m^2. Fecal recovery in four of these patients was 0, 4.6, 9.8, and 10.1% of the dose. The recovery of radioactivity in the urine

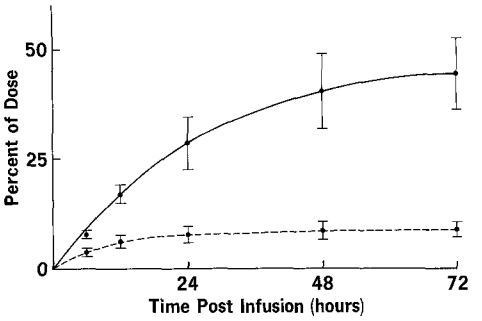

Fig. 4. Urinary excretion of VM26. Cumulative excretion of total radioactivity (O———O) and unchanged drug (O– – –O) by five patients who received 67 mg/m^2 of [^{3}H]VM26 (mean ± SD). (Reprinted with permission from Clinical Pharmacology and Therapeutics, Vol. 18: Creaven, P. J. and Allen, L. M., PTG, A New Antineoplastic Epipodophyllotoxin. Copyright 1975, The C. V. Mosby Company)

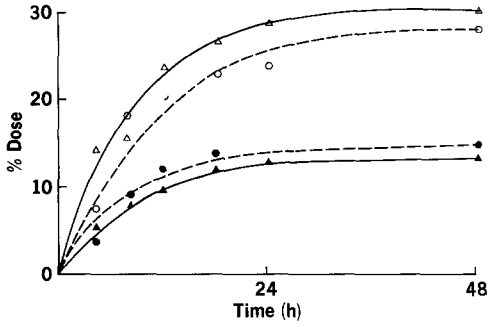

Fig. 5. Urinary excretion of VP16. Cumulative excretion of unchanged drug and of total metabolites by patients who received 220 mg/m^2 (n = 4) and 290 mg/m^2 (n = 5) of [^{3}H]VP16-213. Dose mg/m^2: 220 unchanged drug (O– – –O); total metabolites (●– – –●); 290 unchanged drug (△———△); total metabolites (▲———▲). (Reprinted with permission from Clinical Pharmacoloy and Therapeutics, Vol. 18: Creaven, P. J. and Allen, L. M., EPEG, A New Antineoplastic Epipodophyllotoxin. Copyright 1975, The C. V. Mosby Company)

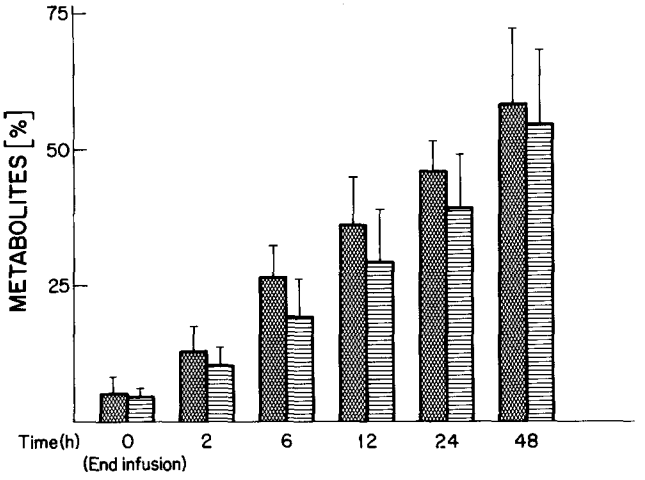

Fig. 6. Plasma radioactivity as metabolites after intravenous [^{3}H]VM26 and [^{3}H]VP16-213. Percentage of radioactivity presented as metabolites in the plasma of 6 patients who received [^{3}H]VM26 and 20 patients who received [^{3}H]VP16. Each bar represents mean ± SD. (▨) VM26 ± SD 67 mg/m^2, n =6. (▤) VP16-213 ± SD 100–290 mg/m^2, n = 20

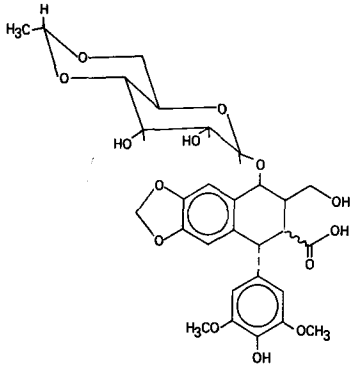

Fig. 7. Structure of 4′-demethylepipodophyllic acid-9-(4,6-O-ethylidene-β-D-glucopyranoside), the major urinary metabolite of VP16-213

and feces of 19 patients receiving intravenous VP16 at doses of 70–290 mg/m^2 is shown in Table 8. The cumulative excretion of total radioactivity and of unchanged drug obtained after the administration of intravenous [^{3}H]VM26 is shown in Fig. 4. In Fig. 5, similar data for studies on the two highest doses of VP16 are shown but here the data are presented as cumulative excretion of unchanged drug and of total metabolites. The recovery of radioactivity was in all cases incomplete, the best urinary recovery being at a dose of 170 mg/m^2 (mean 67.3%, range 51.0–87.5%). The recovery in the feces was variable, the maximum being 16.3%. Because of the technical difficulties associated with total recovery of fecal drug in patients with far advanced disease, values for recovery in the feces should be regarded as minimum values. The incomplete recovery of these agents is discussed below.

Metabolism

Of the radioactivity recovered in the urine after intravenous [^{3}H]VM26, only 21.3% was unchanged drug whereas after [^{3}H]VP16-213, 66.8% of the urinary radioactivity was in the form of unchanged drug (see Figs. 4 and 5) [11, 12]. These figures probably overestimate the difference in the extent of metabolism of the two drugs (see the discussion below of pharmacokinetic analysis). The plasma radioactivity at the end of the infusion was approximately 95% unchanged drug for both compounds. The percentage of plasma radioactivity as metabolite rose throughout the observation period exceeding 50% for both compounds by 48 h post infusion (Fig. 6) (Creaven and Allen, unpublished data).

The principal urinary metabolite of VP16-213 was identified by mass spectroscopic analysis of the

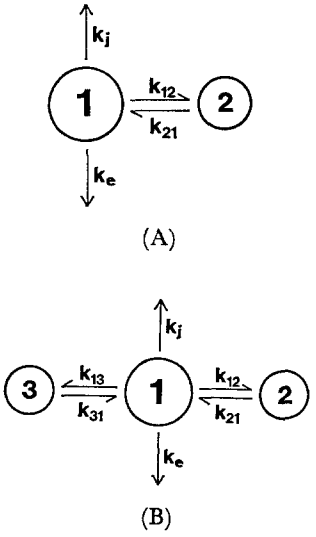

Fig. 8. Two-compartment open model for VP16-213 (A) and 3-compartment open model for VM26 (B). k_e and k_j represent excretion rate constants to urine and all other elimination processes respectively. $k_{el} = k_e + k_j$. (Reprinted with permission from the European Journal of Cancer, Vol 11: Allen, L. M. and Creaven, P. J., Comparison of the Human Pharmacokinetics of VM26 and VP16-213, Two Antineoplastic Epipodophyllotoxin Glucopyranoside Derivatives. Copyright 1975, Pergamon Press, Ltd.)

methylated derivative to be 4′-demethyl-epipodophyllic acid-9-(4,6-O-ethylidene-β-D-glucopyranoside) [5] (Fig. 7). Probable evidence that the corresponding acid of VM26 is the major human urinary metabolite of that compound was also adduced but could not be confirmed because of limitation of available human material [5]. Confirmation of this acid as the major human metabolite of VP16-213 and its further identification as probably the trans hydroxy acid have been made by Strife et al. using paired ion chromatography with tetrabutylammonium bromide and fluorescence detection [36]. These acids have also recently been noted as the principal urinary metabolites of VM26 and VP16-213 in children by Evans et al. [16] who also identified the picro-isomers of VM26 and VP16-213 in the plasma of patients treated with these drugs.

Pharmacokinetic Analysis

The data presented above of the plasma decay and urinary excretion of [^{3}H]VM26 and [^{3}H]VP16-213 were used to carry out pharmacokinetic analysis in an attempt to explain the substantial difference in maximum tolerated dose of weekly VM26 and VP16-213 (67 mg/m^2 for VM26 [25] vs 290 mg/m^2 for VP16-213 [14]) and the difference in their plasma decay kinetics [11, 12] (see Tables 4 and 5). A

Table 9. Selected pharmacokinetic model parameters for VM26 and VP16-213

Parameters	VM26	VP16-213
V_{DSS} (% B.W.)	28.450	28.860
k_{el} (h^{-1})	0.272	0.319
Cl_p ($ml \cdot min^{-1}$)	15.950	47.100
Cl_b ($ml \cdot min^{-1}$)	15.900	47.200
Cl_r ($ml \cdot min^{-1}$)	2.220	13.560
F_m	0.860	0.660

V_{DSS}: Volume of distribution at steady state.
B.W.: body weight; Cl_p: plasma clearance (Vc × kel); Cl_b: body clearance (Dose/$\int_0^\infty$ Cp dt)
Cl_r: renal clearance; F_m: fraction metabolized calculated from K_m/k_{el} where:

$$k_m = k_{el} - k_e \text{ and } k_e = Cl_r/V_c$$

Reference [4]

2-compartment open model for VP16-213 and a 3-compartment model for VM26 were constructed from data for 67–90 mg/m^2 of VM26 and for 130–290 mg/m^2 of VP16-213 (Fig. 8) [4]. Some of the model parameters are shown in Table 9. The volume of distribution at steady state is similar for the two compounds but VP16-213 showed a three-fold greater plasma clearance than VM26 and a six-fold greater renal clearance of the unchanged drug. It was felt that these differences could at least partly account for the difference in the toxic dose of the two drugs. There is a substantial difference in the degree of plasma protein binding of the two drugs (94% for VP16-213, 99.4% for VM26 [4]) which could account for the difference in plasma decay kinetics. The pharmacokinetic analysis gave values of 86% and 66% for the percentage of VM26 and VP16-213 metabolized respectively (Table 9). These values agree very well with the fraction of the administered dose not recovered as unchanged drug (89% and 71%, respectively) but markedly overestimate the percentage of administered drug recovered as metabolite (32% and 18%, respectively). This observation pointed to sequestration of metabolite as a possible explanation for the incomplete recovery of these agents. To evaluate this, the model for VP16-213 and its metabolite(s) shown in Fig. 9 was developed [29], using the patient data already discussed. The volume of the metabolite compartment (V_4) was found to be 27.51 ± 14.25 l. The renal clearance of the metabolite 31.27 ± 7.67 $ml \cdot min^{-1}$ and the body clearance 111.72 ± 41.86 $ml \cdot min^{-1}$ in seven patients. Computer fits of the model to the plasma and urine data for unchanged drug and metabolite are shown for two patients in Fig. 10.

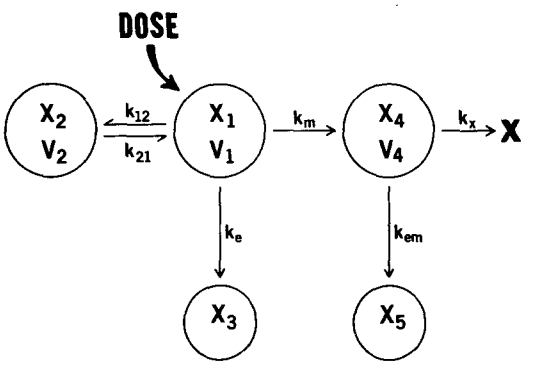

Fig. 9. Pharmacokinetic model for VP16-213 and its metabolites in which k_m is the first order rate constant for biotransformation, k_e and k_{em} are the excretion rate constants into urine of unchanged drug and metabolite respectively and k_x is the rate constant for irreversible loss from the metabolite compartment X_4. (Reprinted with permission from the Journal of Pharmaceutical Sciences, Vol. 67: Pelsor, F. R., Allen, L. M., and Creaven, P. J., Multicompartment Pharmacokinetic Model of 4′-demethylepipodophyllotoxin-9-(4,6-O-ethylidene-β-D-glucopyranoside) in humans. Copyright 1978, American Pharmaceutical Association)

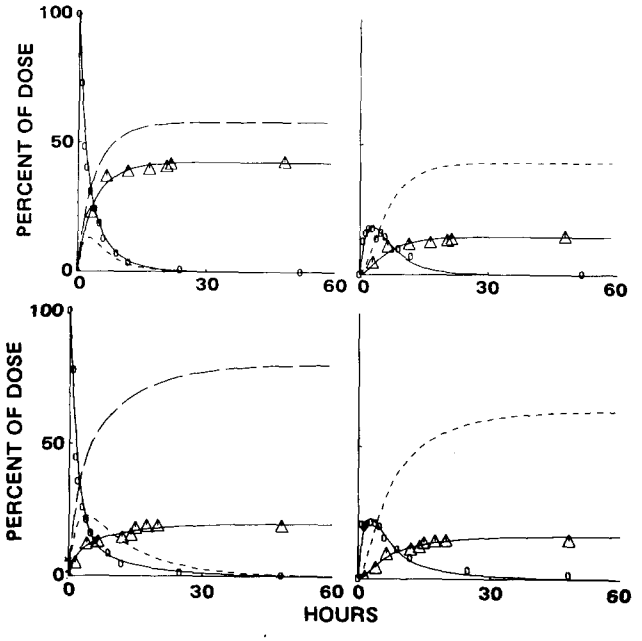

Fig. 10. The distribution excretion and metabolism of VP16-213 as a percent of dose as predicted by the model shown in Fig. 9 for two patients (*upper* and *lower* panels, respectively). Lines were generated by computer fitting and symbols are experimental data (serum ○, urine △). Left-hand panels are unchanged drug, right-hand panels are metabolite. The line (– – –) represents cumulative amount of drug metabolized. In the left-hand panels the line (- - - - -) represents theoretical amount of VP16-213 in compartment X_2 and in the right-hand panels the theoretical amount of depot of metabolite in body tissues, X. (Reprinted with permission from the Journal of Pharmaceutical Sciences, Vol. 67: Pelsor, F. R., Allen, L. M., and Creaven, P. J. Multicompartment Pharmacokinetic Model of 4′-demethylepipodophyllotoxin-9-(4,6-O-ethylidene-β-D-glucopyranoside) in Humans. Copyright 1978, American Pharmaceutical Association)

Pharmacokinetic analysis was taken a step further by Allen who used data from the pharmacokinetics of VM26 [4] and from studies of cellular uptake of the drug [2] to develop an integrated model of drug disposition and cellular pharmacokinetics [1]. Using computer simulation the concentration of free drug in the cell in both the nucleus and cytoplasm could be predicted on different schedules of administration giving the approach great theoretical appeal and potentially practical value.

The above summarizes very briefly some of the principal clinical pharmacology studies reported to date on VM26 and VP16-213. In the papers that follow, much of the data I have outlined will be expanded upon to bring us up to date on the pharmacology of these two very interesting and increasingly clinically important drugs.

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