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Pharmacokinetic study in a phase I trial with an alkylating agent, diacetyldianhydrogalactitol (DADAG)*

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Summary. Diacetyldianhydrogalactitol (DADAG), a new alkylating hexitol derivative, was given in 30-min infusions for 5 consecutive days or as a single high-dose administration. The parent drug was eliminated in a biphasic manner, with a terminal half-life of 30–40 h. Dianhydrogalactitol (DAG), the main, pharmacologically active metabolite, appeared after a lag time of about 0.2–0.6 h. Its peak concentration was reached 1–2 h after termination of the infusion. The terminal elimination of DAG followed that of the parent compound. During the 5-day schedule slight accumulation was observed, and the plasma concentrations of both compounds approached the steady state. Over a dose range of 75–1050 mg/m^2 the daily mean plasma concentrations of DADAG increased by only about 3–4 times. Dose-dependent expansions of the distribution volumes of the drug (V_c, V_{λ_1}, V_{ss}) were observed. The behavior of DADAG and DAG in the body could be adequately described by a three-compartment open model. After equilibration the plasma levels of the parent compound and its metabolite were determined by the rate of return of DADAG from the peripheral compartment and its conversion to DAG.

Introduction

1,2:5,6-Dianhydro-3,4-diacetyl-galactitol (DADAG) (Fig. 1), synthesized by Ötvös et al. [14], is a new alkylating sugar alcohol derivative developed in Hungary. The compound is amphiphilic, like the clinically quite effective dibromdulcitol (DBD), but DADAG is more soluble in water, permitting IV administration. DBD is converted to the highly hydrophilic dianhydrogalactitol (DAG), which is the ultimate alkylating agent [1, 6, 7]. Unfortunately, DAG has proved to be more toxic and less effective than DBD in clinical practice [2, 4, 10, 13]. The amphiphilic nature is advantageous for penetration of cell membranes, and is thought to be partly responsible for the higher effectiveness of DBD and DADAG than of DAG against model solid tumours [8, 9, 16]. It is assumed further that it might be clinically advantagous to administer the less toxic DBD or DADAG, which slowly produce the more active compounds.

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The present study was undertaken to describe the pharmacokinetic behavior of DADAG and its suspected main active metabolite DAG in patients.

Materials and methods

Treatment of patients and blood sampling. Patients with disseminated cancer but having normal kidney and liver functions were selected for the investigation. During the study no other antineoplastic treatment was given. Drugs for supportive therapy were administered as needed.

In the human tolerance study two administration schedules were used [11]. First the drug was given for 5 consecutive days (qdx5) (trial no. 9901). The following doses were studied: 15, 30, 50, 75, 105, 135, 165–180, 240, 220–230, and 390 mg/m^2. In the second study, single-dose, intermittent administration (qld) was investigated with dose levels of 390, 525, 690, 915, 1050, and 1200 mg/m^2 (trial no. 9902). In both trials the patients could be treated at the same or higher dose levels after a pause of 4 weeks.

The lyophilized drug, kindly provided by the Chinoin Pharmaceutical and Chemical Works, was dissolved in 300 ml saline and was infused over 30 min by infusion pump (Infusiomat) for detailed pharmacokinetic studies. In the other cases the drip infusion method was used, keeping the infusion time constant within 5 min.

In four cases in each trial a complete pharmacokinetic profile was determined on the first day. Blood samples were taken immediately before the infusion, at its termination (zero time), and later at 15, 30, 45, 60, 90 min and 2, 3, 4, 5, 6, 8, 24, 48, and 72 h.

To relate the administered dose to plasma concentration, maximum and minimum plasma levels of DADAG

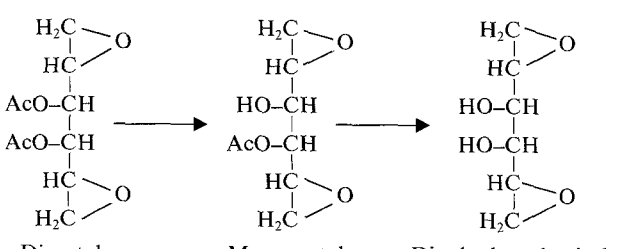

Fig. 1. Metabolic pathway of DADAG

were determined in many more patients. In the case of the qdx5 schedule this was done by taking blood samples each day immediately after the infusion and 24 h later, immediately before the next infusion. The maximum concentration of DAG is not reached until 1–2 h after the end of drug administration, and consequently the maximum plasma levels of DAG could not be analyzed routinely. For its determination a partial pharmacokinetic study was performed in some cases by collecting blood samples at 30-min intervals for 3 h after termination of the infusion on the 2 and 4th or on the 3rd and 5th days. After single-dose administration this strategy was applied in each subject. The maximum concentrations and those measured 24 h after the end of the infusion were used to calculate the daily mean plasma levels.

Analytical method. Blood samples (5 ml) were obtained through an indewelling cannula and were collected in tubes containing 50 µl heparin and 100 µl 100 mg% Eserin (physostigmine/Fluka) to inhibit the deacetylation of DADAG by plasma enzymes. From 1 ml plasma, separated by centrifugation at 3000 rpm, DADAG and DAG were trapped on Amberlite XAD-2 resin (SERVA). The compounds absorbed onto the resin were eluted with 3 × 10 ml ethyl acetate and 10 ml methanol. The combined solutions were evaporated to dryness and the residue was dissolved in 100 µl acetone containing 250 µg *n*-butane-boronic acid for the derivation of DAG [12] and 5 µg *n*-hexadecane, which served as external standard (ES).

GLC was carried out with a CHROM 42 (KOVO) gas chromatograph equipped with FID. A glass column (1220 × 4 mm i.d.) packed with 5% SE-30 on GAS Chrom Q (80–100 mesh was maintained for isothermal chromatography at 128 °C, with the injector at 140 °C and the detector at 140 °C. The retention gas flow rate was 25 ml/min. Hydrogen and air flows were adjusted to obtain maximum efficiency as recommended by the manufacturer. The retention time (RT) was 393 s for DADAG, 512 s, for the derivatized DAG and 720 s for the ES. The detection limit, calculated from a signal corresponding to twice the noise level under normal operating conditions, was 0.5 µg/ml for DADAG and 0.8–1 µg/ml for DAG.

Within-run precision of the assay was determined by processing aliquots of pooled plasma in the same way during a single day. The coefficients of variation were found to be 5% at 3 µg/ml ($n=6$) and 3% at 30 µg/ml $n=6$).

Data analysis. Sums of exponentials were fitted to the DADAG and DAG plasma concentration-versus-time data using nonlinear regression program BMD85. The function used for DADAG had the following form:

$$c_1(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} \quad (1)$$

Where $c_1(t)$ is the DADAG plasma concentration and t is time after completion of the infusion.

From the estimated values of the parameters A_1, A_2, λ_1 and λ_2 the zero-time intercepts (A and B) following IV injection were recalculated from the formulae:

$$A = \frac{A_1 \lambda_1 T}{1 - e^{-\lambda_1 T}}, \qquad B = \frac{A_2 \lambda_2 T}{1 - e^{-\lambda_2 T}}, \quad (2)$$

where T is the duration of the zero-order infusion [5].

When the infusion rate (k_0) and the parameters of A, B, λ_1, λ_2, and T are known the different apparent volumes of distribution (V_c, V_2 and V_{ss}), the total body clearance (Cl), and the mean residence time (F) can be obtained by the model-independent method of Tozer [17].

Assuming a linear two-compartment open model, the transport coefficients between the central and peripheral compartments (k_{12} and k_{21}) and the elimination constant from the central volume (k_{10}) can be calculated [5].

The time course of the plasma concentration for the metabolite DAG follows a three-exponential curve with a lag time of τ:

$$c_2(t) = B_1 e^{-\lambda 1(t-\tau)} + B_2 e^{-\lambda 2(t-\tau)} - B_3 e^{-\lambda 3(t-\tau)}. \quad (3)$$

Since a similarly good fit was obtained by assuming the $B_1 + B_2 = B_3$ relation, to decrease the number of the parameters B_3 was substituted as the sum of B_1 and B_2.

The areas under the curves for DADAG (AUC_1) and DAG (AUC_2) were calculated from the end of the infusion to 24 h.

For interpretation of the concentration-versus-time data for DADAG and DAG in the same system, the simplest compartment model compatible with the mathematical forms of (1) and (3) is shown in Fig. 2. The model neglects the transport of DAG between the central and the peripheral compartments. By fitting of the functions (1) and (3) simultaneously to the data for DADAG and DAG the parameters k_{10}, k_{13} and $k_{30} = \lambda_3$ can be obtained. As a consequence of the small number of data points in the ascending phase of the curve for DAG, the errors in the estimated parameters k_{13} are mostly higher than 30%.

Results

DADAG concentration measured up to 72 h after single dosing exhibited a biphasic curve (Fig. 3). The distribution (λ_1) and disposition (λ_2) rate constants were 2.63 ± 1.35 and $0.040 \pm 0.018\ h^{-1}$, giving half-lives of 0.33 ± 0.15 and 21 ± 17 h, respectively (Table 1). The disposition phase was longer in subsequent cycles of the same patients, the half-

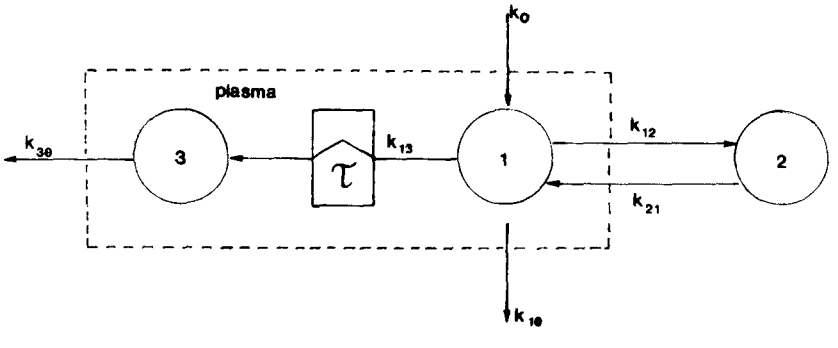

Fig. 2. Three-compartment open-model pharmacokinetic system for DADAG and DAG, where τ is lag time, *1* is the central compartment, *3* is the DAG compartment in the plasma, and *2* is the peripheral compartment of DADAG

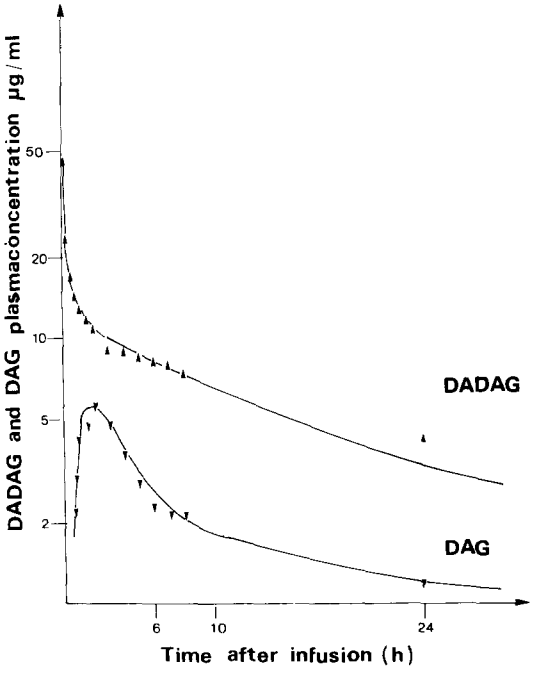

Fig. 3. Plasma level curves of DADAG and DAG in a patient after the administration of 915 mg/m² DADAG. Patient's trial number: 990220109

life increasing up to 32 ± 16 h (Table 2). This difference did not reach the level of significance according to the paired Student's *t*-test.

The pharmacokinetic parameters for DAG could be calculated with reasonable accuracy only if a detailed study was performed (Table 3). DAG became measurable with a lag time of 0.40 h, and the peak value was reached between 1 and 2 h. The two disposition constants and the formation rate constant were 1.73 ± 0.95, 0.024 ± 0.07, and 2.64 ± 1.53 h^{-1}, corresponding to half-lives of 0.52 ± 0.33, 32 ± 11, and 0.37 ± 0.28 h. The terminal elimination of DAG followed that of DADAG closely.

The AUC of both DADAG and DAG measured between 0 and 24 h following drug administration showed wide individual variation. It increased with dose elevation, but its rate lagged behind that of dose escalation (Tables 1–3).

The plasma concentration curves of DADAG and DAG measured during the 5-day schedule are shown in Fig. 4. The accumulation observed for both compounds is in accordance with the half-lives determined, 30–40 h (Tables 4, 5). Usually about one-fifth of the maximum levels of DADAG and DAG were still present in the plasma when the next injection was given. The degree of accumulation varied in different individuals, but was usually slight. The presence of a large exudate was seen, to prolong excretion considerably however, leading to significant accumulation. At the 5th day of the course the plasma levels of both compounds came close to reaching a plateau.

The maximum DADAG and DAG values and those measured 24 h after the end of the infusion were averaged, and the resulting daily mean plasma levels were used to acquire further insight into the relation between parent compound and metabolite. Although DAG concentrations became higher with increasing DADAG concentrations, their correlation was only around 0.2 over the wide dose range studied (Fig. 5).

When daily mean plasma concentrations of DADAG were plotted as a function of the doses administered the points clearly delineated two slopes in spite of the individual scatter (Fig. 6). In the first stage of dose escalation, up to about 300–400 mg/m², the plasma levels followed the rate of dose elevation quite closely. At higher doses the rate of plasma concentration increase fell rapidly behind that of dose escalation. On the other hand, total-body clearance exhibited a marked dose-dependent increase (Fig. 7). While the elimination rate constants did not demonstrate corresponding changes, the expansion of the volume of the central compartment (V_c) showed a close correlation with dose increase (Fig. 8). The correlation coefficient was 0.907 in the eight cases concerned, in which detailed pharmacokinetic measurements permitted accurate estimation of the V_c. In pharmacokinetic studies with few points the correlation coefficient fell to 0.33. Similarly, V_{t2} and V_{ss} also increased with dose elevation.

Table 1. Pharmacokinetic profile of DADAG in man following DADAG infusion during the first course of single-dose administration

Kinetic parameters	Trial no. 9902 201-01[a]	-03[a]	-04	-05	-07	-08	-09[a]	-12	-10[a]	-11	-14
Age (years)	49	45	34	48	39	57	55	51	30	34	45
Dose (mg/m²)	525	690	690	690	915	915	915	915	1050	1050	1050
A_1 (µg/ml)	58.2	38.1	24.4	55.3	17.9	35.2	34.7	38.5	62.8	48.4	43.8
A_2 (µg/ml)	6.1	13.8	7.7	11.6	12.4	5.3	11.7	15.5	11.8	12.3	12.9
λ_1 (h^{-1})	2.89	1.93	1.44	4.33	1.69	1.12	4.08	>7	2.04	1.82	4.95
λ_2 (h^{-1})	0.063	0.041	0.036	0.053	0.010	<0.007	0.046	0.043	0.041	0.007	0.058
V_c (l)	7.2	14.1	30.4	8.8	32.9	28.2	16.7	9.5	19.5	20.1	14.4
V_{λ_2} (l)	87.7	66.1	148	90.9	102	258	122	89.2	152	137	131
V_{ss} (l)	71.0	60.9	134	80.5	101	245	113	84.6	131	134	118
Cl_T (l h^{-1})	6.2	2.7	5.3	4.8	1.0	1.8	5.6	3.8	6.2	0.96	7.6
t (h)	11.5	22.5	25.1	16.7	98.8	136	20.2	22.1	21.1	140	15.6
k_{21} (h^{-1})	0.21	0.41	0.30	0.42	0.55	0.12	0.56	0.75	0.26	0.27	0.55
$k_{10} + k_{13}$ (h^{-1})	0.85	0.19	0.18	0.55	0.031	0.064	0.34	0.40	0.32	0.048	0.53
k_{12} (h^{-1})	1.89	1.37	1.00	3.42	1.12	0.94	3.23	5.89	1.50	1.51	3.94
AUC_1 (µg ml^{-1} h^{-1})	97	230	139	172	275	157	178	123	209	298	169

[a] Detailed pharmacokinetic study

Table 2. Pharmacokinetic profile of DADAG in man following DADAG infusion during the second, third, and fourth courses of single dose administration

Kinetic parameters	Trial No. 9902 201-03	–03	–03	–04	–05	–07	–08	–09	–11
Course no.	2	3	4	2	2	2	2	2	2
Dose (mg/m^2)	690	690	915	915	690	915	915	1050	1050
A_1 (μg/ml)	48.6	35.5	41.4	48.5	50.5	15.1	17.7	58.2	51.5
A_2 (μg/ml)	13.5	15.5	19.3	11.5	13.1	16.9	17.2	15.8	10.6
λ_1 (h^{-1})	1.78	1.78	2.67	3.47	5.78	>7	2.17	2.31	1.73
λ_2 (h^{-1})	0.014	0.019	0.019	0.053	0.023	0.053	0.041	0.011	< 0.007
V_c (l)	10.8	14.5	14.0	15.7	7.2	17.9	31.2	15.7	19.8
$V_{\lambda 2}$ (l)	70.6	62.0	66.6	129	87.6	73.0	80.7	109	158
V_{ss} (l)	67.5	59.8	64.8	115	83.7	71.3	78.2	106	154
Cl (l h^{-1})	0.99	1.2	1.3	6.8	2.0	3.9	3.3	1.2	1.1
t (h)	68.3	50.8	51.2	16.8	41.6	18.4	23.7	88.3	13.9
AUC_1 (μg ml^{-1} h^{-1})	303	318	392	168	251	230	271	359	267

Table 3. Pharmacokinetic profile of DAG in man following the first DADAG infusion of single-dose administration

Kinetic parameters	Trial no. 9902 201-01	–03	–09	–10
Age (years)	49	45	55	30
Dose (mg/m^2)	525	690	915	1050
B_1 (μg/ml)	23	28	42	32
B_2 (μg/ml)	1.2	1.6	2.4	1.5
λ_1 (h^{-1})	3.01	1.61	0.70	1.61
λ_2 (h^{-1})	0.015	0.030	0.030	0.020
λ_3 (h^{-1})	4.62	2.57	0.90	2.48
τ (h)	0.70	0.55	0.30	0.35
AUC_2 (μg ml^{-1} h^{-1})	22	30	45	35

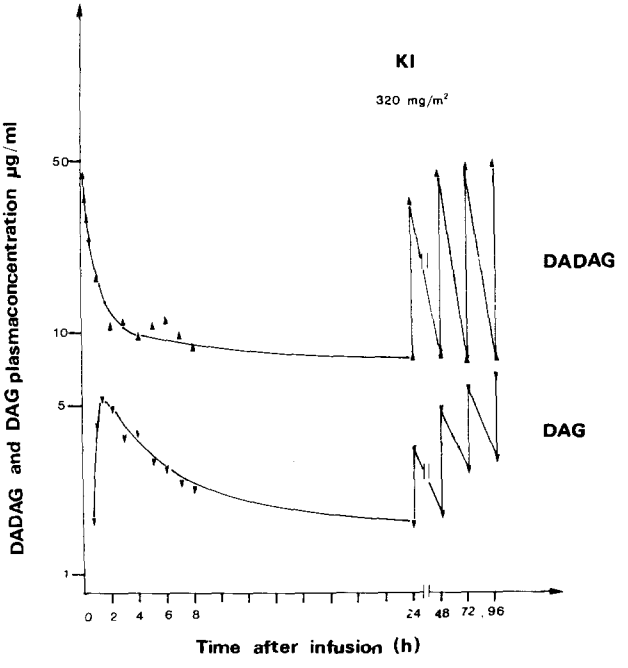

Fig. 4. Plasma level curves of DADAG and DAG in a patient following the administration of 320 mg/m^2 DADAG for 5 consecutive days. Patient's trial number: 9901 201 09

Table 4. Pharmacokinetic profile of DADAG in man following the first DADAG infusion of daily administration

Kinetic parameters	Trial no. 9901 201-07	–25	–19	–23
Age (years)	45	62	48	34
Dose (mg/m^2)	75	300	320	390
A_1 (μg/ml)	20.1	31.0	36.3	27.0
A_2 (μg/ml)	4.5	9.7	10.4	5.7
λ_1 (h^{-1})	1.06	4.62	1.87	1.98
λ_2 (h^{-1})	0.0151	0.0240	0.0154	0.030
V_c (l)	4.8	5.9	9.4	8.1
V_{λ_2} (l)	29.9	51.6	57.2	60.4
V_{ss} (l)	27.7	49.5	54.9	53.9
Cl (l h^{-1})	0.45	1.2	0.88	2.0
t (h)	61.3	40.0	62.2	27.0
k_{21} (h^{-1})	0.17	0.53	0.31	0.26
$k_{10} + k_{13}$ (h^{-1})	0.094	0.21	0.094	0.25
k_{12} (h^{-1})	0.81	3.90	1.48	1.50
AUC_1 (μg ml^{-1}h)	109	184	228	107

Table 5. Pharmacokinetic profile of DAG in man following the first DADAG infusion of daily administration

Kinetic parameters	Trial no. 9901 201-07	–25	–19	–23
Age (years)	45	62	48	34
Dose (mg/m^2)	75	300	320	390
B_1 (μg/ml)	24	33	13	30
B_2 (μg/ml)	1.4	1.0	3.0	2.5
λ_1 (h^{-1})	1.10	1.31	0.69	1.39
λ_2 (h^{-1})	0.018	0.020	0.025	0.014
λ_3 (h^{-1})	1.51	3.47	1.31	1.78
τ (h)	0.45	0.30	0.30	0.50
Maximum concentration (μg/ml)	3.79	2.16	5.27	4.89
AUC_2 (μg ml^{-1} h^{-1})	33	23	57	52

The model developed (Fig. 2) consists of a central (no. 1) and a peripheral compartment (no. 2), and a third one for the metabolite DAG (no. 3). The rate constants k_{12} and k_{21} reflect the rate of entry of DADAG into and out of the peripheral compartment, the former being about 3–4

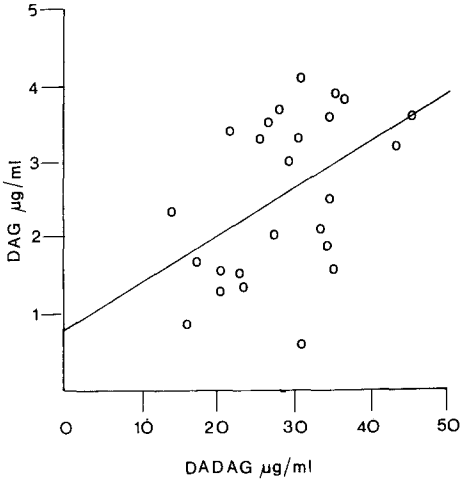

Fig. 5. Plot of the daily mean plasma levels of DADAG versus those of DAG in patients treated at various dose levels. Correlation coefficient is 0.2

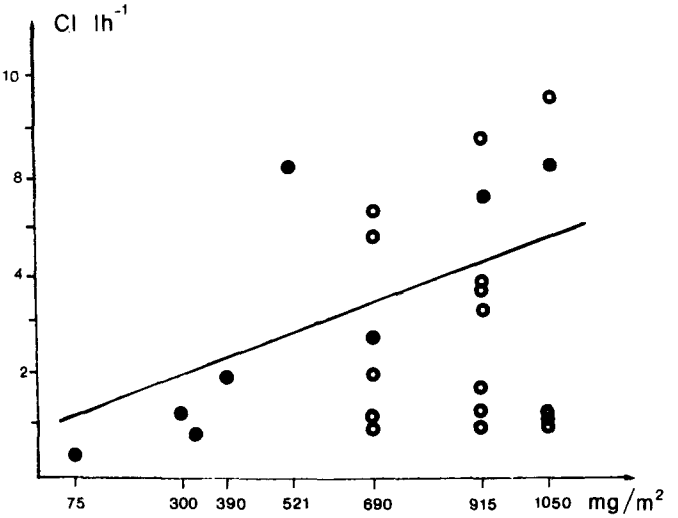

Fig. 7. Change in total-body clearance (Cl) with increasing doses. *Filled circles* represent those patients in whom detailed pharmacokinetic study was performed. In the other patients DADAG levels were measured every 30 min only for 3 h only, and then at 24 h. The Correlation coefficient for all the patients shown was 0.3, while it was 0.7 when only values obtained in detailed pharmacokinetic evaluations were used.

times higher (Table 6). The rate constant k_{13} representing DAG formation is much smaller than the two above constants. A lag time (τ) of DAG formation was also incorporated into the model to account for the later appearance of DAG. DADAG is thought to disappear from the central compartment both through conversion to DAG (k_{13}) and by some other, still unknown, route of elimination (k_{10}). The actual concentrations of DADAG and DAG found in the plasma and those predicted by the compartment model are shown in Fig. 9. The simulated curves corresponded reasonably well with those for the experimentally determined DADAG and DAG concentrations.

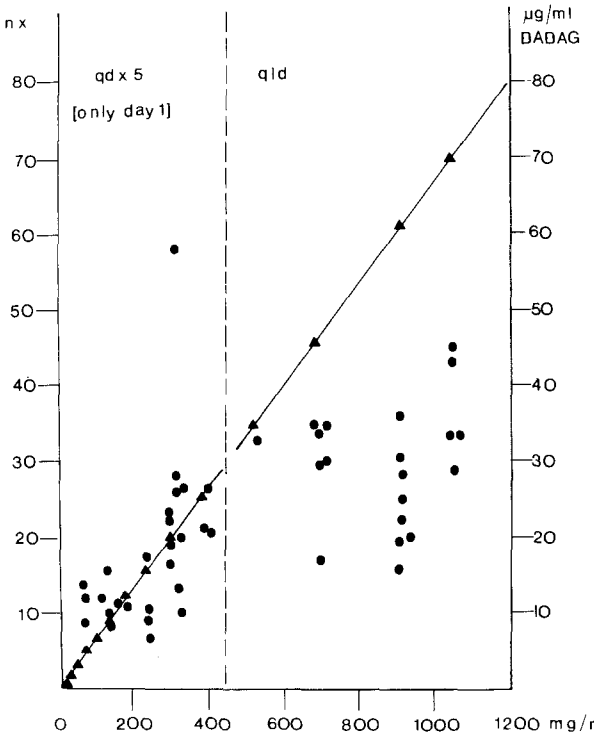

Fig. 6. Daily mean plasma levels of DADAG measured in patients treated at various dose levels. Up to 390 mg/m^2 patients were treated for 5 consecutive days, and above that, only once in every 4 weeks. For all patients the mean plasma level measured after the 1st day of drug administration is shown. The *straight line* represents the modified Fibonacci dose escalation scheme used; *triangles* denote the dose levels applied. On the *left ordinate* the multiples of the initial dose ($n=15$; mg/m^2) are given

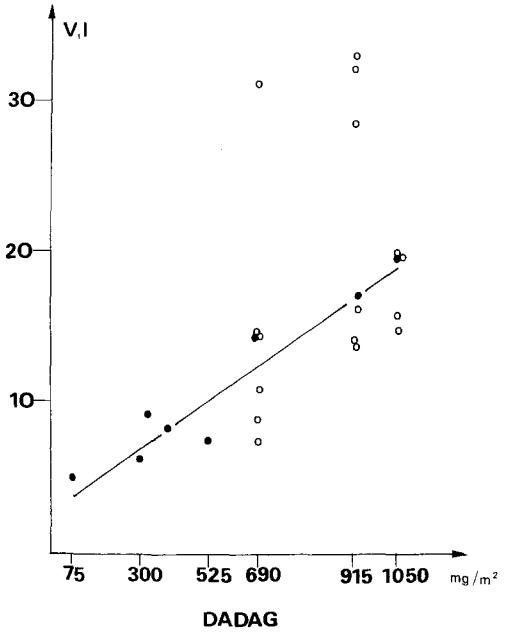

Fig. 8. Dose-dependent change in the volume of the central compartment (V_c). The *symbols* are as described for Fig. 7. The correlation coefficient for all patients shown was 0.3; if only values derived from detailed pharmacokinetic studies were used it increased to 0.9

Table 6. Pharmacokinetic parameters for DADAG and DAG calculated according to the three-compartment open model

Trial no.	Kinetic parameters	k_{30} h^{-1}	k_{21} h^{-1}	k_{12} h^{-1}	k_{13} h^{-1}	k_{10} h^{-1}	τ (h)
9901 201 07		1.06	0.232	0.801	0.022	0.063	0.42
9901 201 25		4.56	1.13	3.45	0.020	0.083	0.43
9901 201 19		0.929	0.446	1.38	0.022	0.055	0.45
9901 201 23		0.508	0.323	1.40	0.078	0.062	0.48
9902 201 01		1.340	0.219	2.35	0.44	0.059	0.44
9902 201 03		>5.0	0.254	0.60	0.014	0.112	0.40
9902 201 09		1.21	0.968	2.64	0.111	0.098	0.34
9902 201 10		2.14	0.348	1.46	0.245	0.050	0.33

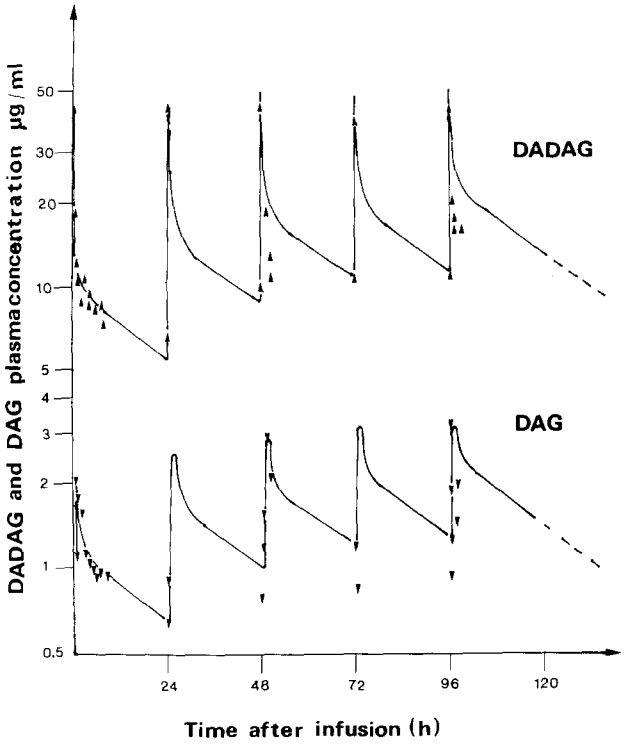

Fig. 9. Simulated compartmental DADAG and DAG level profiles following the administration of 300 mg/m^2 DADAG for 5 consecutive days. Patient's trial number: 9901 201 25. *Symbols* indicate measured values.

Discussion

In patients suffering from a disease causing metabolic alterations even in organs not directly involved, great individual differences were expected. Nevertheless, characteristic pharmacokinetic trends became discernable, primarily due to the large number of cases and the wide dose range covered.

Following the IV administration of DADAG its predicted main metabolite DAG was readily detected in the plasma. Its peak concentration of 3–5 µg/ml, measured after the administration of 690–1050 mg/m^2 DADAG, was found to be close to that observed by Eagen et al. [3] after the injection of 120–150 mg/m^2 DAG. The DAG level was maintained for a prolonged period by continuous conversion of DADAG, so that the terminal half-life of DAG was 60 times longer than that of IV-injected DAG. The cause of the poor correlation between the average mean plasma concentrations of DADAG and DAG observed only over a large dose range is not yet clear. At higher doses both compounds appear in the urine in increasing amounts. In addition, the individual variability in the metabolism of the drug may play an important role.

On the basis of the pharmacokinetic model it was estimated that the majority of DADAG first entered the peripheral compartment and only a small fraction was converted directly to DAG in the plasma. The lag time might be due to the fact that DADAG is converted to DAG through monoacetyl-DAG (Fig. 1), which could not be detected by our method, however.

The amount of drug in the peripheral compartment could be calculated to be about 3–5 times higher than that in the central compartment due to the k_{12}/k_{21} ratio. On the other hand, the DAG compartment was 15 times less than the central DADAG compartment considering the low k_{13}/k_{30} ratio. After 10 h the plasma levels of both DADAG and DAG were essentially determined by the rate constants for the return of DADAG from the periphery (k_{21}), since these two constants are smaller than those describing the elimination of DAG (k_{30}).

The dose-concentration plot (Fig. 6) exhibited a disproportionately slow plasma level increase above 300–500 mg/m^2. Whether such phenomenon occurs in case of other alkylating agents is not known, since in dose escalation studies plasma concentrations have generally not been followed over a wide range. Only Eagen and coworkers [3] have mentioned that no correlation was found between plasma level and the DAG dose administered over the range of 120–150 mg/m^2 total dose given as two split injections 1 h apart. This finding, together with the dose-related increase in the apparent volumes of distribution (V_c, V_{t2}, V_{ss}) and of the total-body clearance (Cl) suggests dose-dependent pharmacokinetics of DADAG.

The observation is similar to that found in the case of prednisone and prednisolone, which are bound extensively to plasma albumin and transcortin. Rose et al. reported [15] that the plasma clearance of IV-administered prednisolone increased from 111 to 194 ml/min over a dose range of 5–40 mg. The steady-state volume of distribution of prednisone increased, but there was no change in plasma half-life with increasing doses. It was suggested that protein binding and possibly other factors might contribute to the dose-dependent pharmacokinetics of prednisolone and prednisone. Our preliminary results also indicate a dose-dependent increase of the protein binding of DADAG.

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