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Clinical pharmacokinetics of 3-deazaguanine

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Summary. 3-Deazaguanine (3DG), an antipurine antimetabolite, has recently completed a phase I clinical trial at this Institute. The drug was given on a daily × 5 schedule by i.v. infusion over 0.25–2.16 h. The pharmacokinetics of 3DG during 16 courses were studied in 12 patients at doses of 200–800 mg/m^2. 3DG in plasma was measured by an isocratic reverse-phase high-performance liquid chromatographic (HPLC) procedure carried out on IBM phenyl columns at 40°C using 10 mM phosphate buffer (pH 7) as the mobile phase and detection at 300 nm. Plasma decay of 3DG was biexponential in all patients. The AUC correlated linearly with dose at 200–600 mg/m^2 but deviated from linearity at doses >600 mg/m^2. The drug was cleared rapidly from plasma; at doses of 200–600 mg/m^2, the mean plasma clearance was 61.64±9.97 l/h and the mean terminal-phase elimination half-life was 1.6±0.6 h. The steady-state volume of distribution (98.9±29.1 l) and distribution coefficient (1.24±0.39 l/kg) indicated extensive tissue distribution for the drug. No statistically significant difference was observed between the pharmacokinetics of 3DG on day 1 and that on day 4 as evaluated in three patients for whom complete plasma data were available on both days.

Introduction

3-Deazaguanine [dezaguanine (USAN), CI-908, 3DG] is a purine antimetabolite that differs from guanine in the substitution of a carbon for the nitrogen in the 3 position. The free base is poorly water-soluble and the drug was formulated for clinical use as a methanesulfonic acid salt (Fig. 1) [9]. The compound is active against transplantable rodent leukemias [6, 7, 12]. However, of greater interest is its activity against a number of mammary adenocarcinomas [2, 6, 7, 12], which include slow- and fast-growing tumors, hormone-sensitive and -insensitive tumors, and a human breast cancer xenograft (MX-1) implanted in the subrenal capsule [2, 6, 7, 12]. 3DG is activated to the nucleotide form intracellularly [13, 14]. It is believed to act by incorporation into DNA [8, 11, 15, 16] and by inhibition of inosine 5′-monophosphate (IMP) dehydrogenase [17], a key enzyme in guanosine monophosphate (GMP) biosynthesis.

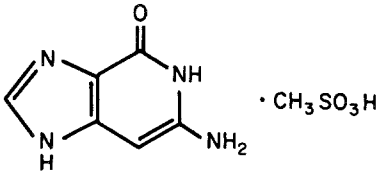

Fig. 1. Dezaguanine mesylate (3-deazaguanine methanesulfonic acid salt)

A phase I clinical trial of 3DG given daily for 5 days has been carried out at this Institute [4], and we studied the pharmacokinetics of the drug during that period. In this report we present the results of that study. Preliminary accounts of these data have been published elsewhere [4, 10].

Patients and methods

Patients and drug administration. The dose range used for the clinical study was 11–800 mg/m^2. Pharmacokinetic studies were carried out in 12 patients, who gave their informed consent to participate and collectively received a total of 16 courses at doses ranging from 200 to 800 mg/m^2 daily. The drug was given i.v. by constant-rate infusion. The infusion time varied from 0.25 h at a dose of 200 mg/m^2 up to ≥2 h for higher doses. This variation was attributable to an increase in the volume infused due to (a) limitations in the solubility of the drug and (b) the occurrence of phlebitis when relatively concentrated solutions were infused.

The pharmacokinetic study was generally carried out on day one; in three cases it was repeated on day 4. In an additional three patients, limited blood samples were obtained on day 5 after drug administration.

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Table 1. Demographic data of patients who were studied for 3DG pharmacokinetics

Patient	Age (years)	Sex	BSA (m^2)	Tumor type
A	65	M	2	Renal cell carcinoma
B	55	M	2.15	Renal cell carcinoma
C	61	F	1.9	Adenocarcinoma, colon
D	66	M	1.9	Adenocarcinoma, rectum
E	57	M	1.9	Renal cell carcinoma
F	57	M	1.67	Adenocarcinoma, esophagus
G	56	M	1.86	Renal cell carcinoma
H	74	M	1.92	Melanoma
I	64	F	2.5	Renal cell carcinoma
J	58	M	2.22	Adenocarcinoma, colon
K	51	M	1.85	Adenocarcinoma, rectum
L	65	F	1.86	Adenocarcinoma, rectum

BSA, Body surface area

The sampling times for blood (5 ml) were as follows: at time zero (pretreatment), during infusion (1–3 samples, depending on the duration of the infusion), and at 5, 10, 15, 20, 30, 45, 60, 75, and 90 min and 2, 3, 4, 6, 8, 12, and 24 h following the end of the infusion. In all cases the samples were processed and assayed within 24 h. Separation of protein from plasma was accomplished by centrifugal ultrafiltration using Amicon Centrifree micropartition systems (Danvers, Mass.). The plasma ultrafiltrate was analyzed for 3DG using a validated high-performance liquid chromatographic (HPLC) method [3].

Analytical methodology. The HPLC system consisted of a Waters Associates M590 pump, an M710B WISP, an M481 UV detector, and a model 4400 Nelson Analytical Chromatography data system. The separation was carried out by injecting plasma ultrafiltrate onto two 25-cm IBM phenyl columns (5 μm) joined in series, with a 5-cm IBM phenyl column (used as a guard column), using 10 mM phosphate buffer (pH 7.0) as the mobile phase at 40° C. 3DG was detected at 300 nm. The method was specific for 3DG, showing a detection limit of 0.1 μg/ml.

Data analysis. A two-compartment open model involving constant i. v. input and first-order output was fitted to the plasma concentration-time data using the nonlinear regression analysis program PCNONLIN (Statistical Consultants, Lexington Ky.). The data were weighted by the reciprocal of the observed plasma concentration and the following equation (Model 10, PCNONLIN) was fitted to the data:

$c(T) = A*[e^{(-\alpha*T)} - e^{(-\alpha*TSTAR)}] + B*[e^{(-\beta*T)} - e^{(-\beta*TSTAR)}]$,

where T represents time and TI, the length of the infusion; $TSTAR = T - TI$ for $T > TI$; and $TSTAR = 0$ for $T < TI$. The estimated parametes were R, S, α, and β, where R and S represent the coefficients obtained from stripping the postinfusion data and are related to A and B as follows:

$$A = \frac{R\,D\,\alpha}{K_0\,[1 - e^{(-\alpha*TI)}]} \quad \text{and}$$

$$B = \frac{S\,D\,\beta}{K_0\,[1 - e^{(-\beta*TI)}]} ,$$

where D represents the dose and K_0, the infusion rate. Using standard equations [5], pharmacokinetic parameters were calculated from A, α, B, and β as derived from curve fitting. In 10/16 cases, postinfusion data alone gave a better fit than all the data (during infusion + postinfusion) as based on an examination of the 95% confidence limits of the derived parameters, the general curve fit, and an examination of the residuals and the residual sum of squares. The pharmacokinetic data comparisons between day 1 and day 4 were carried out using paired t-test with the program EPISTAT on a Sperry PC.

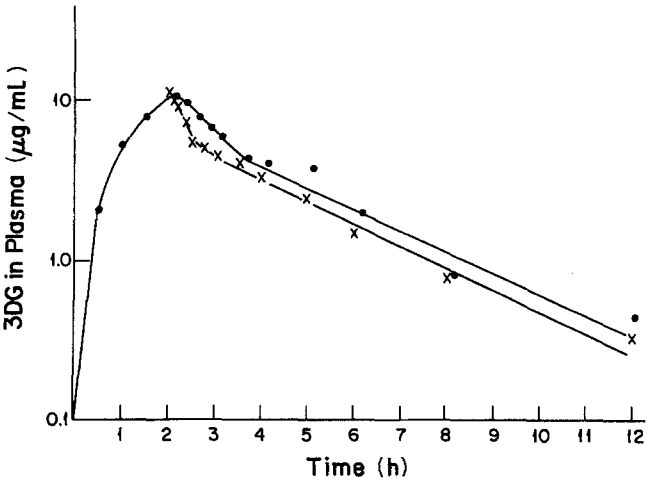

Fig. 2. Plasma decay of 3DG in a patient receiving a dose of 720 mg/m^2. —O—, Day 1; —X—, day 4

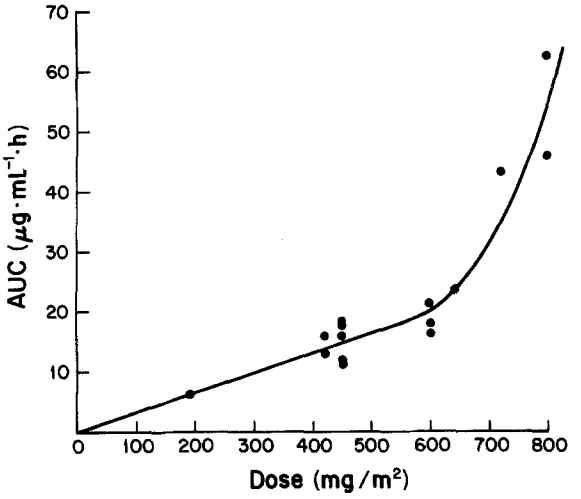

Fig. 3. AUC vs dose relationship found for 3DG in the patients studied

Results

The demographic data obtained prior to drug administration for the patients who were entered in the pharmacokinetics study are shown in Table 1. The plasma decay of 3DG was biexponential at all doses and fitted a two-compartment open model (Fig. 2). The calculated pharmacokinetic parameters are listed in Table 2.

The area under the concentration × time curve (AUC) plotted against dose (Fig. 3) indicates that the kinetics of 3DG were apparently linear with dose up to 600 mg/m^2, above which the AUC deviated significantly from linearity. In the dose range of 200–600 mg/m^2, the mean pharmacokinetic parameters were as follows: initial distribution phase half life ($t_{1/2\alpha}$), 0.17 ± 0.14 h; terminal elimination phase half life ($t_{1/2\beta}$), 1.61 ± 0.63 h; steady-state volume of distribution (V_{ss}), 98.9 ± 29.1 l; K_D (distribution coefficient, V_{ss}/total body weight), 1.24 ± 0.39 l/kg; CL, 61.64 ± 9.97 l/h.

In six patients 3DG pharmacokinetics was studied first on day 1 and then on day 4 or 5. In three of these subjects,

Table 2. Pharmacokinetic parameters for 3DG

Patient	Dose (mg/m^2)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	AUC ($\mu g\ ml^{-1}\ h$)	V_{ss} (l)	k_D (l/kg)	*CL* (l/h)
A	200	0.14	1.34	5.68	114.54	1.32	70.44
B	420	0.07	1.16	13.21	90.24	0.96	68.15
B	420	0.16	2.16	15.62	141.86	1.5	57.61
C	450	0.22	1.33	15.61	77.85	0.8	54.79
C	450	0.04	0.72	11.98	61.82	0.64	71.4
D	450	0.21	1.5	18.08	56.36	0.83	47.28
E	450	0.08	1.24	11.01	106.28	1.38	77.68
E	450	0.03	1.58	15.28	80.45	1.05	55.97
F	450	0.18	1.48	15.15	84.72	1.42	49.51
E	600	0.2	2.01	16.35	150.2	2	69.72
G	600	0.57	3.33	21.49	112.43	1.5	51.94
H	600	0.14	1.51	17.69	109.51	1.49	65.13
I	640	0.51	1.39	23.55	113.2	0.79	67.95
J	720	0.35	2.11	43.48	94.27	0.91	36.8
K	800	0.23	2.83	63.03	75.84	0.97	23.48
L	800	0.14	1.4	46.05	35.78	0.45	32.36

$t_{1/2\alpha}$, Initial distribution phase half-life; $t_{1/2\beta}$, terminal elimination phase half-life; V_{ss}, study-state volume of distribution; K_D, distribution coefficient, *CL*, plasma clearance; AUC, area under the concentration × time curve

Table 3. Comparison of pharmacokinetic parameters in three patients receiving a dose of 3DG on day 1 and day 4

Patient	Dose (mg/m^2)	Pharmacokinetic parameters							
		Day 1*				Day 4*			
		$t_{1/2\beta}$ (h)	AUC ($\mu g\ ml^{-1}\ h$)	V_{ss} (l)	*CL* (l/h)	$t_{1/2\beta}$ (h)	AUC ($\mu g\ ml^{-1}\ h$)	V_{ss} (l)	*CL* (l/h)
H	600	1.51	17.69	109.51	65.13	3.7	44.3	104.7	25.98
I	640	1.39	23.55	113.2	67.95	2.77	35.05	104.5	45.7
J	720	2.11	43.48	94.27	36.8	2.22	37.34	99.3	42.85

* Paired *t*-test indicated that the mean of the data set for each parameter from day 1 to day 4 was not significantly different

who received doses of 200 (patient A) or 450 mg/m^2 (patients C and D), the sampling on day 5 was limited and did not enable the generation of reliable pharmacokinetic parameters. A comparison of the plasma levels measured between day 1 and day 5 in these patients showed that they were generally similar. In three subjects who received the drug at 600 (patient H), 640 (patient I) and 720 mg/m^2 (patient J) on day 1 and again on day 4, sampling was complete. For these 3 patients we calculated a complete set of pharmacokinetic parameters for 3DG on both days of administration. Table 3 shows the comparisons of these data.

As seen in this table, patient H showed a considerable increase in AUC and a marked decrease in plasma clearance between day 1 and day 4. When data from all three patients were used in a paired *t*-test for the comparison of each pharmacokinetic parameter obtained on day 1 with that obtained on day 4, no significant difference was found ($t_{1/2\beta}$, P=0.18; AUC, P=0.38; V_{ss}, P=0.22; *CL*, P=0.31). The plasma decay data for one patient (J) who received the drug at a dose of 720 mg/m^2 on days 1 and 4 are shown in Fig. 2.

Discussion

Preliminary results of an ongoing phase I and pharmacokinetics study of 3DG were reported by Ardalan et al. [1]. In that study, 3DG was given in a 15-min i. v. infusion once every 3 weeks. The pharmacokinetic data obtained by these authors show that the drug is cleared from plasma biexponentially, exhibiting a $t_{1/2\beta}$ of 63 min, and that 4% of the drug was excreted unchanged in the urine within 24 h. The data reported in the present paper are in agreement with those of Ardalan et al. [1], in that the plasma decay of 3DG followed a biexponential pattern, exhibiting rapid clearance and an average half-life of 1.61 h. The calculated steady-state volume of distribution (98.9 ± 29.1 l) and the K_D value (1.24 ± 0.39 l/kg) clearly exceeded the total body water, indicating extensive tissue distribution for the drug. Although the pharmacokinetics of 3DG were apparently linear over the 200–600 mg/m^2 dose range, they were nonlinear at doses of >600 mg/m^2, indicating that the drug exhibits saturation kinetics.

A statistical analysis of the data on the three patients for whom complete sets of pharmacokinetic data were available for day 1 and for day 4 revealed no significant difference. This finding suggests that the drug disposition is not changed by the daily administration of drug under the daily

× 5 dosing schedule. However, further studies are needed to confirm this observation.

A major dose-limiting toxicity of the drug in the phase I clinical trial was reversible renal dysfunction. A possible correlation between (a) the maximal increase in the levels of serum creatinine or blood urea nitrogen (BUN) and the AUC values for the drug and (b) the maximum percentage increase in serum creatinine or BUN levels as compared with the patient's pretreatment values and the AUC for the drug was sought. No correlation was found for the absolute increases; however, when the increases relative to the patient's pretreatment values were used, a positive correlation was suggested [correlation coefficients were 0.502 and 0.595 for BUN ($P = 0.047$) and serum creatinine ($P = 0.015$), respectively]. Since this correlation was weak, it appears possible that the AUC of 3DG may only one of several factors contributing to the renal toxicity of the drug.

In conclusion, 3DG is a drug that displays rapid plasma clearance, a short elimination half-life, extensive tissue distribution, and apparently linear pharmacokinetics at doses of up to 600 mg/m^2 daily for 5 consecutive days, the recommended starting dose for phase II studies. Daily administration of the drug did not alter the pharmacokinetic parameters in the few patients studied. There was a suggestion that the observed renal toxicity may have been partly related to the AUC of the drug. However, more data are required before any definitive conclusions can be drawn.

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