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Short communication

Pharmacokinetics of thio-TEPA at two different doses*

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Summary. Thio-TEPA pharmacokinetics were studied at doses of 20 mg and 30 mg in six patients treated for ovarian cancer. Considerable interindividual variation was encountered in its pharmacokinetics, which were dose-independent within the dose range studied and similar to those reported at far higher doses. Interindividual dosing of thio-TEPA based on an initial AUC estimation is suggested.

Introduction

Thio-TEPA was first used clinically in 1952 and thus dates from the very first years of cancer chemotherapy. For some years this drug was the standard alkylating agent used against a broad spectrum of malignancies before it was replaced to a large extent by newer drugs. It has retained its position as the standard drug for the local treatment of superficial bladder cancer [13] and has been used to some extent against ovarian cancer, breast cancer and meningeal carcinomatosis [6, 10, 12]. However, a renewed interest in thio-TEPA has secent in recent years from a recognition that this drug's potential may not have been fully exploited [7]. The use of high-dose thio-TEPA combined with cyclophosphamide and autologous bone marrow transplantation (ABMT) has been reported [11], and several other studies using ABMT with high-dose thio-TEPA both as a single drug and in combination therapy are under way [1, 3, 8]. Only recently have pharmacokinetic data from human patients been reported [2]. We have reported its pharmacokinetics in ovarian cancer patients after IV or IM single-drug therapy at a fixed dose. After a fast initial distribution, a first-order elimination process with an elimination half-life of ~ 1.5 h was demonstrated. Repeated dosing after 24 h or the continuation of treatment up to 7 months did not alter the pharmacokinetics [5]. However, to clarify further the impact of the dose on the pharmacokinetics, we examined patients at two different low-dose levels usually applied when dividing the loading dose.

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Materials and methods

Six patients with epithelial ovarian carcinoma were included in the study. Their mean age was 74 years (range, 71–84). All patients had adequate haematological status (leucocyte count $\geq 3500/\mu l$, platelet count $\geq 150000/\mu l$), normal hepatic function (bilirubin $\leq 20\mu mol/l$) and normal renal function (creatinine $\leq 120\mu mol/l$). All patients underwent laparotomy prior to chemotherapy. The distribution of clinical stages (FIGO) was: two with stage I, one with stage II, two with stage III and one with stage IV. The patient characteristics are given in Table 1. No patient had received any chemotherapy prior to thio-TEPA treatment.

The serum pharmacokinetics of thio-TEPA were studied during two conventional 60-mg loading courses. Half of the patients (group *A*) started with 20 mg for 3 consecutive days and the other half, with 30 mg for 2 consecutive days. A cross-over was carried out after a wash-out of 2 weeks. Thio-TEPA (Lederle Laboratories) was dissolved in sterile water to a concentration of 1 mg/ml and given by IV bolus injection. No correction of the dose based on body surface was made. Blood samples were taken from a Venflon cannula before and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 h after the injection of thio-TEPA on days 1 and 3 when the dose was divided into three and on days 1 and 2 when it was divided into two.

Blood was allowed to coagulate at 4° C for 30 min and serum was separated by centrifugation at 1,100 *g* for 10 min and stored at −20° C until analysis. Unchanged thio-TEPA was assayed in serum by a gas chromatographic method that has previously been described [4], in which thio-TEPA was extracted into ethylacetate. The

Table 1. Patient characteristics

Individual	Group*	Age (years)	Body surface (m^2)	Clinical stage (FIGO)	Serum creatinine (μmol/l)	Serum bilirubin (μmol/l)
AaS	A	71	1.60	IV	57	12
SL	A	72	1.40	III	66	9
AA	A	71	1.90	Ia	89	6
KK	B	71	1.65	III	86	6
MS	B	84	1.70	IIb	81	8
RH	B	79	1.80	Ia	89	5

* A, First course 20 mg × 3; B, first course 30 mg × 2

retention times for thio-TEPA and the internal standard diphenylamine were 1.9 min and 2.5 min respectively, and the detection limit for thio-TEPA was 5 ng/ml. Each sample was analysed in duplicate.

Model-independent pharmacokinetic parameters were calculated. The elimination rate constant (K_e) was calculated by least-square regression from the linear slope of the semilogarithmic serum concentration – time plot. The elimination half-life was derived from the equation $t½ = \ln 2/K_e$.

The area under the serum concentration – time curve (AUC) was calculated from zero to infinity by the trapezoid rule:

$$AUC = \sum_{i=0}^{n-1} (t_{i+1} - t_i) \frac{C_{i+1} + C_i}{2} + \frac{C_n}{K_e},$$

where C_i represents the serum concentration measured at time t_i and C_n denotes the last measurable serum concentration at time t_n.

The apparent volume of distribution (V_d) was calculated from the equation $V_d = D/AUC \times K_e$, where D is the IV administered dose. The V_d obtained was subsequently divided by the body wt. and is also presented in *Results* as l/kg.

Total body clearance (Cl_t) was derived from the relation $Cl_t = V_d \times K_e$.

Differences between groups of observations were evaluated statistically by the Wilcoxon rank-sum test.

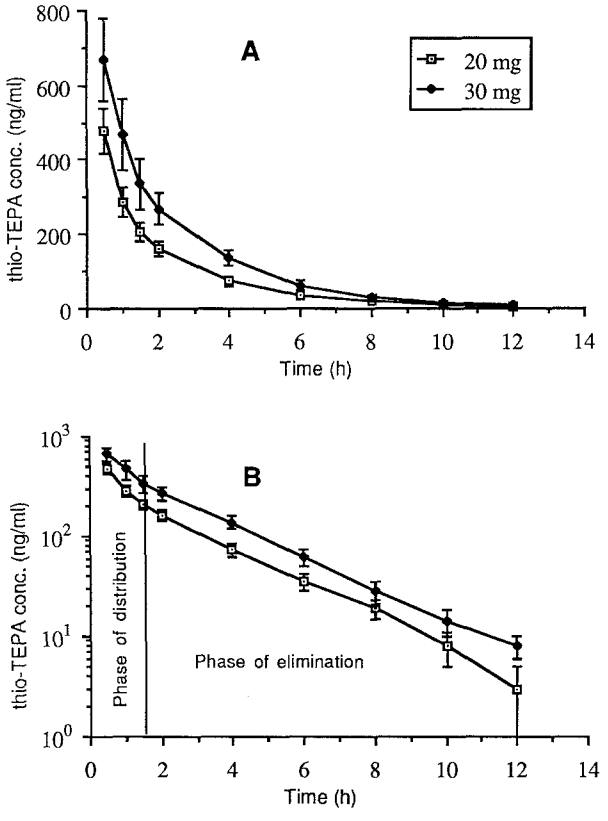

Fig. 1. The serum concentration – time relationship of thio-TEPA in six patients after IV bolus injections of 20 mg and 30 mg; linear (*A*) and semilogarithmic plot (*B*). Points and bars represent means ± SEM

Results

No nausea or vomiting, allergic manifestations, or any other complaint were observed among the patients. No systematic difference in pharmacokinetics was demonstrated between days 1 and 3 or days 1 and 2 at the 20 mg or 30 mg daily dose regimens respectively. Therefore, individual pharmacokinetic data are given as the mean of two courses at each dose level.

Figure 1 shows the average serum concentration – time curves obtained at the two dose levels. The semilogarithmic plot indicates that the phase of distribution was terminated within the first 1.5 h after administration of the drug at both dosage regimens. The pharmacokinetic data are given in Table 2. Considerable interindividual variations were encountered at both dose levels, with the AUC ranging from 595 to 1548 and from 1117 to 3117 ng/ml h for the 20 and 30 mg dosage regimens respectively. However, an unaltered elimination half-life, volume of distribution and AUC/dose ratio indicate that the pharmacokinetics of thio-TEPA are dose-independent in this dose range.

Table 2. Pharmacokinetic paramteters of thio-TEPA in six patients after single bolus injections of 20 and 30 mg

Individual	Group*	Elimination rate constant		Elimination half-life		Volume of distribution				Total body clearance		AUC			
		(h^{-1})		(h)		(l)		(l/kg)		(ml/min)		(ng/ml × h)			
		20 mg	30 mg	20 mg	30 mg	20 mg	30 mg	20 mg	30 mg	20 mg	30 mg	20 mg	30 mg	AUC20/20	AUC30/30
AaS	A	0.32	0.39	2.17	1.78	40	41	0.7	0.7	251	264	1548	1891	77	63
SL	A	0.45	0.38	1.54	1.82	31	25	0.7	0.5	235	160	1420	3117	71	104
AA	A	0.42	0.54	1.65	1.28	66	50	0.8	0.6	459	448	726	1117	36	37
KK	B	0.42	0.36	1.65	1.93	39	47	0.6	0.7	274	284	1216	1758	61	59
MS	B	0.26	0.29	2.67	2.39	68	55	1.0	0.8	293	269	1138	1871	57	62
RH	B	0.41	0.38	1.69	1.82	82	69	1.2	1.0	560	437	595	1144	30	38
Mean ± SEM		0.38± 0.03	0.39± 0.03	1.90± 0.18	1.84± 0.15	54±8	48±6	0.8± 0.1	0.7± 0.1	339± 57	310± 46	1107± 154	1816± 297	55±8	60±10
Significance (*P*)		0.38		0.30		0.09		0.08		0.12		0.01		0.23	

* A, First course 20 mg × 3; B, first course 30 mg × 2

Discussion

The thio-TEPA pharmacokinetics encountered in the present trial were comparable with those of our previous trial [5] and those reported by Cohen et al. [2], with a first-order elimination process after a fast initial phase of distribution and an apparent volume of distribution of approximately 0.7 l/kg. However, some interindividual variations were observed.

Part of the wide variation in the AUC between patients can be explained by the neglection of dose correction for body surface area. In fact, the three individuals with the lowest AUCs had the highest body surface areas (Tables 1 and 2). However, a real interindividual difference in pharmacokinetics was encountered and is highlighted by comparing patients RH and AaS: a nearly three fold higher AUC for AaS than for RH at the 20 mg dose level, and a nearly 50% reduction in both the volume of distribution and the total body clearance. The same differences were observed at the 30 mg dose level, although to a smaller degree. Great interindividual variation was also encountered in our previous trial with thio-TEPA pharmacokinetics [5].

In this study, with a 33% dose escalation within the conventional dose range, dose-independent pharmacokinetics were demonstrated. As this represents a relatively minor dose escalation, we recognize the limitations of this study in proving a general independence of dose on the pharmacokinetics of thio-TEPA. However, two reports have recently emerged, describing the pharmacokinetics of high-dose thio-TEPA with ABMT. Brown et al [1] treated patients with doses ranging from 180–1125 mg/m^2 and reported thio-TEPA pharmacokinetics that parallel those for conventional dosing. Henner et al. [8] reported AUCs linearly related to the dose after treating patients with continous infusions of thio-TEPA in the dose range of 180–900 mg/m^2. These reports are in abstract form and detailed data are not given; however, they represent a strong indication that our results on dose independence also apply to very high-dose levels.

As the pharmacokinetics of thio-TEPA are almost unknown, the only guideline to the dosing of this drug has been myelotoxicity. The dose recommendations have remained largely unchanged since the drug was introduced: loading doses in the range of 0.5–1.0 mg/kg are used, and the standard dose is reduced when myelotoxicity occurs. However, a corresponding increase in the dose given to patients not showing myelotoxicity is not standard practice. Although detailed knowledge about anti-cancer drug pharmacodynamics are scanty, the AUC is thought too be a useful parameter for the prediction of response [9]. We demonstrated a considerable variation in the AUC between comparable patients, and we therefore believe that obtaining individual pharmacokinetic data at the initiation of thio-TEPA therapy, so as to use the AUC as a dosing guide for subsequent courses, could be appropriate for a more rational use of the drug. The demonstration of dose-independent pharmacokinetics in this and other studies applying to thio-TEPA, using a wider range of doses, would be valuable.

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