Cancer Chemother Pharmacol (1993) 32: 46–52

Cancer Chemotherapy and Pharmacology

Phase I pharmacokinetics study of high-dose fotemustine and its metabolite 2-chloroethanol in patients with high-grade gliomas

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Received 7 September 1992/Accepted 23 December 1992

Abstract. The pharmacokinetics of high-dose fotemustine followed by autologous bone-marrow transplantation during a phase I–II clinical trial in 24 patients with glioblastoma or astrocytoma (grade III–IV) was investigated. Plasma levels of fotemustine were determined by high-performance liquid chromatography (HPLC) and UV detection. The metabolite, 2-chloroethanol, was simultaneously followed in six patients by gag liquid chromatography and electron capture detection (GLC-ECD) assay. The drug was given as a 1-h infusion on 2 consecutive days. In all, 40 pharmacokinetic determinations of fotemustine were made at dose levels ranging from 2 × 300 to 2 × 500 mg/m^2. Plasma drug elimination was best described by a bi-exponential model, with short distribution and elimination half-lives of 4.15 ± 2.57 and 28.8 ± 12.1 min being observed, respectively. No significant difference in half-lives or clearance was seen between the first and the second administration. During dose escalation, the mean area under the concentrationtime curve (AUC) increased from 5.96 ± 2.89 to 12.22 ± 3.95 mg l^{-1} h. Drug clearance was independent of the dose given and equal to 109 ± 65 l/h, indicating no possible saturation of metabolism and elimination mechanisms at these high-dose levels. The metabolite 2-chloroethanol appeared very early in plasma samples. Its elimination was rapid and rate-limited by the kinetics of the parent compound, giving the same apparent terminal half-life. A close relationship between AUC and C_{45} values was evidenced ($r = 0.890$). Associated with the stability of fotemustine kinetic parameters, this could be used in future studies for individual dose adjustment, particularly for high-dose fractionated regimens.

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Introduction

Fotemustine (S10036), diethyl-1-[3-(2-chloroethyl)-3-nitrosoureido]ethyl phosphonate, is a nitrosourea compound originally synthesised by Servier Laboratories. It shows a broad spectrum of antitumoral activities both in vitro and in vivo [1, 2] by way of its alkylating property.

The therapeutic dose in man was established from a phase I study [7] at 100 mg/m^2 per week in a 3-consecutive-week induction treatment followed by a 4- to 5-week therapeutic rest. Subsequent phase II studies obtained a 24% objective response rate with the same administration schedule during the treatment of 153 melanoma patients receiving 100 mg/m^2 fotemustine [6]; interestingly, the cited study revealed significant activity (25%) against brain metastases in these patients.

After the administration of 100 mg/m^2 fotemustine as a 1-h infusion during the treatment of brain tumours, Lokiec et al. [9] described the plasma pharmacokinetics of the parent drug as following either a mono- or a bi-exponential pattern, with a short elimination half-life (20–25 min) and a large variability in clearance (8.96–83.49 l/h) being noted. Urinary metabolite excretion accounted for about 50%–60% of the delivered dose [5]. The chemical decomposition of fotemustine leads rapidly to the formation of the strongly reactive compound chloroethyl carbonium, its ultimate metabolite being 2-chloroethanol [8].

Given the demonstrated activity of the drug against cerebral metastases, a phase I study of high-dose fotemustine in primary malignant brain tumours was undertaken in our institution, the myelosuppressive effect of this procedure being counterbalanced by autologous bone-marrow transplantation. The present report describes the pharmacokinetic results we obtained at supra-conventional escalating doses of the drug given as a 1-h infusion on 2 consecutive days, the main aims of the study being (a) to determine the pharmacokinetic parameters of the parent drug and of its main plasma metabolite, (b) to follow the pharmacokinetic parameters' evolution during dose escalation and (c) to compare pharmacokinetic parameters between two consecutive similar administrations.

Table 1. Demographic and dosing details of patients

Patient	Sex	Age (years)	Body weight (kg)	Level (mg/m^2)	Dose (mg/day)	Days of infusion
ROI	M	26	50	2 × 300	480	(1,2)
VEY	M	62	76		550	(1,2)
GUI	M	60	55		450	(1,2)
CHA	M	38	85		600	(1,2)
HAK	M	38	65		540	(1,2)
FAY	M	33	80	2 × 350	630	(1,2)
PAR	M	60	66		600	(1,2)
GAR	M	55	82		700	(1,2)
DEL	M	60	63		600	(1,2)
SAR	F	51	57		550	(1,2)
JOU	F	37	53	2 × 400	640	(1,2)
PEL	M	38	62		680	(1,4)
CAN	F	49	68		660	(1,2)
BLA	M	25	95		800	(1,2)
BER.T	M	36	85	2 × 450	900	(1,5)
GUI.T	M	44	65		800	(1,5)
TOU	F	39	76		800	(1,2)
BER.N	F	52	46		650	(1,2)
COS	M	21	70		850	(1,3)
CHA.X	F	50	65		800	(1,2)
VIL	M	53	68	2 × 500	850	(1,3)
DEG	F	46	47		740	(1,2)
MAR	M	56	60		660	(1,2)
DUC	M	22	65		900	(1,3)

Patients and methods

This phase I study was a dose-escalation trial using an initial level of 600 mg/m^2 divided into two doses given on day 1 and day 2 (300 mg/m^2 daily); dose escalation in fixed increments of 100 mg/m^2 (50 mg/m^2 daily) was carried out in groups of at least three patients each.

Patients. A total of 24 patients (17 men, 7 women) aged between 21 and 62 years (mean, 44 ± 13 years) and newly diagnosed with high-grade glioblastomas were entered into this pharmacokinetics study. Their main demographic details are presented in Table 1. Written informed consent was obtained from each patient before treatment. The protocol was approved by the local ethical committee.

Treatment. At 1 day after the harvesting of bone marrow, the fotemustine treatment was initiated. Fotemustine (208 mg/vial) was supplied by Servier Laboratories, France. The drug was dissolved in the supplied solvent. Adequate volumes of the reconstituted solution (200 mg/4 ml), corresponding to the prescribed dose, were added to 250 ml 5% sterile glucose solution in an infusion vial.

The administration of fotemustine was similar to high-dose carmustine infusion: prior to dosing, the patient received a 20-min infusion of mannitol followed immediately by fotemustine given as a 1-h constant-rate intravenous infusion on 2 consecutive days. During drug reconstitution and administration, the infusion vial, tubing and room were kept protected from light. In cases of adverse events following the first injection, the second administration was delayed until up to day 5. Autologous bone marrow transplantation was performed 72 h after the second infusion; associated radiotherapy was performed 4 weeks after the chemotherapy regimen (50 Gy delivered as 2.5 Gy/fraction daily 5 days a week for 4 weeks).

Blood sampling. All blood samples (6 ml) for the pharmacokinetics study were drawn from the arm opposite to that receiving the infusion into light-protected ethylenediaminetetraacetic acid (EDTA)-containing tubes kept in ice. After a reference blood sample had been taken, fotemustine was infused using a constant-rate infusion pump. Blood samples were taken pre-dose and at 15, 45, 60 (just before the end of infusion), 65, 70, 75, 90 and 105 min as well as 2, 2.5, 3, 3.5 and 4 h after the start of infusion. Samples were immediately centrifuged at 2000 *g* at 0–4° C for 5 min in a refrigerated centrifuge, and the plasma was quickly frozen in liquid nitrogen. Plasma samples were stored at –20° C until the estimation of fotemustine and 2-chloroethanol levels. All operations were performed under light-protected conditions.

Sample analysis. Fotemustine was assayed according to a procedure previously described by Gordon et al. [4] using high-performance liquid chromatography (HPLC). Briefly, a solid-phase extraction of the drug in plasma samples was performed on CBA-bonded silica columns, with acidic methanol being used for the final elution. Separation of the eluted compounds was performed thereafter with a reverse-phase C18 precolumn connected to a Chromspher C18 5-µm, 3-mm inside diameter, 10-cm length glass cartridge. Elution was usually achieved at a flow rate of 0.8 ml/min with a mobile phase of acetonitrile: 0.05 *M* phosphoric acid (30 : 70, v/v), pH 3.5; UV detection of unchanged fotemustine and of the internal standard (S10338) was performed at the λ_{max} (230 nm).

The metabolite 2-chloroethanol was assayed by gas chromatography. Samples (1 ml) containing 100 µl chloropropanol (2 µg/ml) as the internal standard were extracted into methylterbutyl ether (2 ml), and the organic phase was treated with *N*-heptafluorbutyrlimidazole (HFBI). An aliquot (1 µl) of the extract was injected onto the gas chromatographic column (DB Wax 30 M) with a helium carrier flow of 7 ml/min. The injector was operated in the splitless mode (splitless off RT, 0.5 min) at 150° C. Separation was achieved using temperature gradients, with the oven temperature being held initially at 40° C for 0.5 min, then rising to 80° C at 5° C/min, followed immediately by an increase in temperature of up to 200° C at 30° C/min. This temperature was held until the end of the 45-min runtime. The detection of 2-chloroethanol and internal standard was performed by means of an electron-capture detector at 250° C.

Data analysis. Plasma concentrations of fotemustine and 2-chloroethanol were plotted versus time on a semilogarithmic scale. All curves obtained for drug and metabolite decay could best be fitted to a bi-exponential

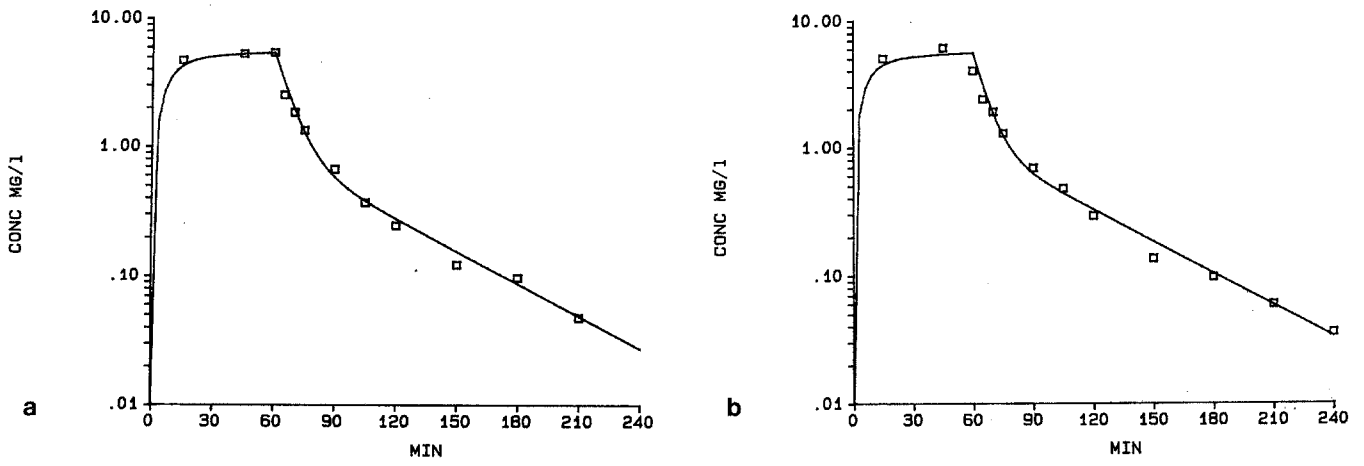

Fig. 1 a, b. Plasma-decay curves of unchanged fotemustine for patient GUI, treated at a dose level of 2 × 300 mg/m², on day 1 (**a**) and day 2 (**b**)

Table 2. Individual values obtained for C_{maxobs}, t_{max}, trapezoidal AUC, percentage of extrapolated AUC and Cl in patients

	t_{max} (min) Day		C_{maxobs} (mg/l) Day		AUC_{trap} (mg l^{-1} h) Day		$\%AUC_{trap}$ Day		Cl (l/h) Day	
	d_1	d_2	d_1	d_2	d_1	d_2	d_1	d_2	d_1	d_2
ROI	60	60	4.16	4.98	4.23	5.14	1.3	1.0	113	93
VEY	65	45	9.62	8.35	8.44	8.45	4.8	10.4	65	65
GUI	60	45	5.46	6.18	5.77	6.06	10.9	11.0	78	74
CHA	45	15	3.09	3.24	3.42	2.17	3.0	6.7	175	277
HAK[a]	–	–	–	–	–	–	–	–	–	–
FAY	45	45	3.29	5.63	3.19	5.19	0.1	0.1	197	121
PAR	59	44	5.48	7.71	4.60	7.05	3.4	1.1	130	85
GAR	45	60	12.37	7.92	10.77	9.03	0.4	0.7	65	78
DEL	45	45	9.16	8.40	8.18	8.25	0.4	0.2	68	73
SAR	65	60	5.46	6.67	6.43	6.36	0.3	0.1	86	87
JOU	45	62	9.22	8.31	7.42	7.67	0.2	0.2	86	83
PEL	45	45	4.78	7.05	4.98	6.57	2.5	2.6	137	104
CAN	30	65	5.68	4.64	[c]	4.69	[c]	2.0	[c]	141
BLA[a]	–	–	–	–	–	–	–	–	–	–
BER.T	45	45	3.20	3.70	2.92	2.82	0.4	0.6	308	320
GUI.T	60	[b]	6.91	[b]	6.12	[b]	0.5	[b]	131	[b]
TOU	15	55	11.12	13.85	10.74	14.59	1.1	0.6	74	55
BER.N	55	[c]	6.78	[c]	5.75	[c]	3.2	[c]	113	[c]
COS	55	[c]	8.77	[c]	6.51	[c]	2.7	[c]	131	[c]
CHA.X	15	45	9.10	14.76	8.76	16.05	1.4	1.5	91	50
VIL	55	55	10.12	10.80	9.41	11.09	1.9	7.8	90	77
DEG	45	45	8.36	10.54	7.98	7.95	1.5	0.9	93	93
MAR	45	15	15.88	21.10	13.54	19.20	8.2	6.4	56	34
DUC	54	54	11.40	11.72	9.28	11.72	0.4	0.3	97	77

[a] Interferences during drug assay
[b] Irregular infusion
[c] Sampling problems

function, taking into account the exact infusion time. The data were fitted using SIPHAR software [3] running on the Powell algorithm with a $1/y^2$ weighting of the plasma concentration values.

The parameters considered were:

1. Distribution and elimination half-lives ($t\alpha$ and $t\beta$, respectively, in minutes)
2. Observed t_{max} (in minutes) as well as observed C_{max} (C_{maxobs}, in milligrams per litre) and that computed from the equation of plasma-decay curves (C_{maxmod})
3. Areas under the concentration-time curve (AUC, in milligrams per litre times hours) trapezoidal from time 0 to infinity (AUC_{trap}), percentages of extrapolated AUCs (% AUC_{trap}) and AUCs computed from the model (AUC_{mod})
4. Clearance (Cl, in litres per hour) = Dose/AUC_{trap}
5. Volume of distribution at steady state (V_{dss}, in litres)

Validation of the model was performed by evaluation of the closeness between observed and computed values (C_{maxobs} versus C_{maxmod}), of % AUC_{trap}, and of the closeness between AUC_{trap} and AUC_{mod}. Comparisons between parameters determined on day 1 and day 2 were performed using Wilcoxon's signed-rank test for paired data.

Table 3. Individual pharmacokinetic parameters of fotemustine after fitting by a two-exponential model

	t_α (min) Day		t_β (min) Day		C_{maxmod} (mg/l) Day		AUC_{mod} (mg l^{-1} h) Day		V_{dss} (l) Day	
	d_1	d_2	d_1	d_2	d_1	d_2	d_1	d_2	d_1	d_2
ROI	5.6	9.5	25.0	55.8	4.16	4.79	4.35	5.19	31	36
VEY	6.1	3.3	41.5	23.0	8.03	8.13	11.39	8.72	17	17
GUI	5.2	4.6	36.0	36.4	5.46	5.66	5.86	6.14	22	22
CHA	5.8	2.7	33.6	28.6	3.54	3.01	3.71	2.33	55	76
HAK[a]	–	–	–	–	–	–	–	–	–	
FAY	0.8	2.1	16.3	17.6	3.26	5.26	3.36	5.41	30	18
PAR	9.3	3.2	63.8	24.7	4.71	6.87	5.11	7.22	50	17
GAR	2.7	6.2	33.3	37.0	10.74	7.02	11.36	9.54	15	29
DEL	2.5	3.9	30.0	23.6	9.48	8.55	9.28	8.44	13	19
SAR	10.2	5.6	23.7	21.1	6.91	6.60	7.13	6.99	32	30
JOU	2.3	6.5	17.2	23.0	8.71	9.48	8.54	9.20	8	14
PEL	2.8	1.3	21.7	20.1	4.90	7.20	5.18	7.57	31	18
CAN	–[c]	7.3	[c]	45.9	–c	4.99	–[c]	5.38	[c]	41
BLA[a]	–	–	–	–	–	–	–	–	–	–
BER.T	1.5	8.9	19.8	29.2	2.76	3.21	3.07	3.24	59	69
GUI.T	2.7	[b]	18.7	[b]	5.92	[b]	6.68	[b]	29	[b]
TOU	1.8	3.8	32.3	39.7	10.50	13.54	12.13	15.82	20	13
BER.N	3.1	[c]	21.5	[c]	6.20	[c]	6.25	[c]	71	[c]
COS	5.2	[c]	31.9	[c]	6.81	[c]	7.57	[c]	85	[c]
CHA.X	1.8	6.5	45.2	52.0	8.21	16.58	10.42	18.47	25	18
VIL	3.3	0.1	13.2	18.4	10.62	11.45	10.38	11.66	56	59
DEG	4.4	4.7	18.8	20.1	7.68	8.58	8.41	8.71	18	23
MAR	0.2	5.1	19.0	41.2	16.80	23.61	15.74	20.12	9	9
DUC	1.4	2.0	15.6	15.7	15.70	10.21	12.52	10.22	17	13

[a] Interferences during drug assay
[b] Irregular infusion
[c] Sampling problems

Results

Plasma pharmacokinetics of fotemustine

Plasma fotemustine was successfully assayed on day 1 and day 2 in 18 patients (36 kinetic profiles). Kinetics could be determined in 3 patients only on day 1 and in 1 patients only on day 2. Plasma concentrations of fotemustine could not be measured in 2 patients (HAK and BLA) due to strong interferences during the assay of the drug.

Figure 1 shows typical plasma-decay curves of fotemustine in a patient (GUI) treated at a dose level of 2×300 mg/m^2 on days 1 and 2 (total dose, 450 mg/day). In all cases, the plasma concentration of fotemustine increased during drug infusion, leading quickly to the steady state (in some cases the C_{maxobs} could be observed as early as 15 min after the start of infusion; Table 2). At the end of the infusion, fotemustine plasma concentrations fell rapidly, all plasma levels being less than 0.3 mg/l, the quantitative limit of the method, at 3 h after the termination of the infusion. In some patients, the baseline of the blank plasma chromatogram was noise- and interference-free. Hence, concentrations below the quantitative limit could be accurately evaluated; the numbers of observations were sufficient (each point being validated by the next ones), and residual values computed from the model (not taking into account these low points) were below 10%. Plasma-decay curves were very similar for the first and second administrations of fotemustine in a given patient.

In all cases, the pharmacokinetics could best be fitted to a two-compartment open model. Individual pharmacokinetic parameters are listed in Tables 2 and 3. Since the values for the percentage of extrapolated AUC (% AUC_{trap}) were less than 12% in all cases and less than 5% in 33 of 40 cases, we could consider trapezoidal values for AUC_{trap} from time 0 to infinity as valid. Moreover, a very strong correlation was observed between C_{maxobs} and C_{maxmod}, with the regression line lying very close to the identity line, as was the case for AUC_{trap} and AUC_{mod} ($C_{maxmod} = 1.083 \times C_{maxobs} - 0.77$, $r = 0.965$, $n = 40$; $AUC_{mod} = 1.092 \times AUC_{trap} + 0.047$, $r = 0.981$, $n = 40$). The model-dependent pharmacokinetic parameters presented in Table 3 were considered as valid.

Distribution and elimination half-lives (t_α, t_β) were short and showed high interpatient variability, ranging from 0.1 to 10.2 min and from 13.2 to 63.8 min, respectively.

The mean distribution and elimination half-lives obtained on day 1 (3.8 ± 2.6 and 27.5 ± 12.2 min, respectively) were similar to those observed on day 2 (4.6 ± 2.5 and 30.2 ± 12.1 min, respectively). No statistical difference was found between day 1 and day 2 (Wilcoxon-Mann-Whitney test) for any of the parameters presented in Table 3. Therefore, day-1 and day-2 data were joined, and

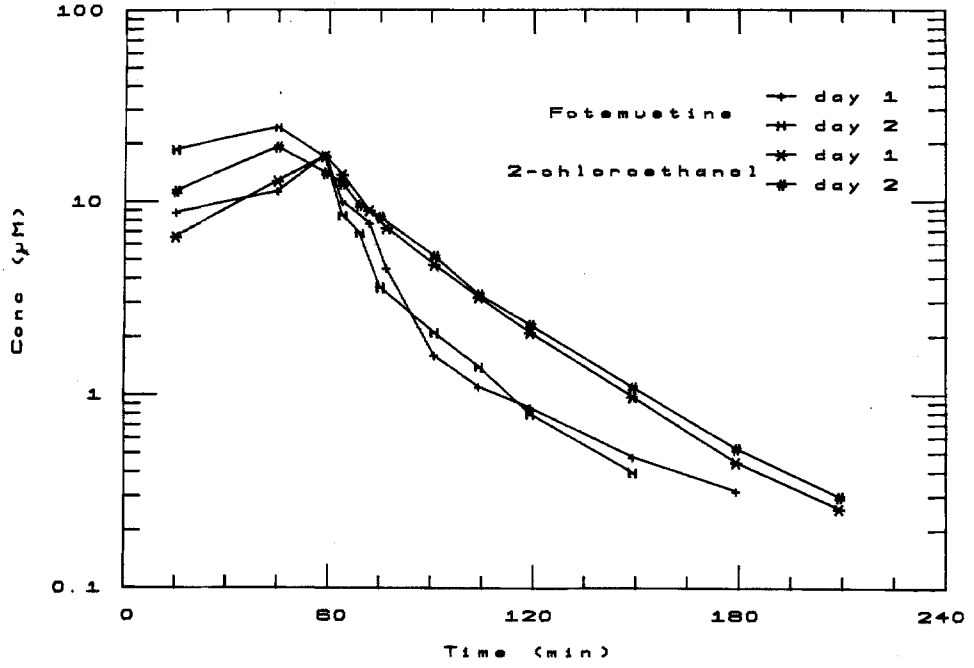

Fig. 2. Plasma-decay curves of fotemustine (+, –) and 2-chloroethanol (*, #) for patient PAR on day 1 and day 2

Table 4. Mean values obtained for pharmacokinetic parameters of fotemustine

Level (mg/m^2)		t_α (min)	t_β (min)	C_{maxmod} (mg/l)	AUC_{mod} (mg l^{-1} h)	Cl (l/h)	V_{dss} (l)
2 × 300	Mean	5.35	34.99	5.35	5.96	118	35
	SD	2.07	10.45	1.91	2.89	74	21
	n	8	8	8	8	8	8
2 × 350	Mean	4.65	29.11	6.94	7.38	99	25
	SD	3.13	13.84	2.23	2.37	41	11
	n	10	10	10	10	10	10
2 × 400	Mean	4.04	25.58	7.06	7.17	110	22
	SD	2.68	11.56	2.09	1.82	28	13
	n	5	5	5	5	5	5
2 × 450	Mean	3.92	32.26	8.19	9.29	141	43
	SD	2.50	11.60	4.61	5.37	102	28
	n	9	9	9	9	9	9
2 × 500	Mean	2.65	20.25	18.08	12.22	77	26
	SD	2.01	8.77	5.32	3.95	22	20
	n	8	8	8	8	8	8

the mean values are summarised in Table 4. Dose-dependent pharmacokinetics were demonstrated only for AUC_{mod} and C_{maxmod}. These two parameters increased from 5.96 ± 2.89 mg l^{-1} h and 5.35 ± 1.91 mg/l, respectively, at the lowest dose level (300 mg/m^2 daily) to 12.22 ± 3.95 mg l^{-1} h and 18.08 ± 5.32 mg/l, respectively, at 500 mg/m^2 daily. However, their increase was not directly proportional to the dose. A strong correlation was found between AUC_{mod} and C_{45} values ($AUC_{mod} = 0.940\ C_{45} + 1.565$; $r = 0.890$, $n = 40$).

Plasma pharmacokinetics of 2-chloroethanol

Gas-chromatography assay of 2-chloroethanol was linear from 2 to 300 ng/ml (from 2.5 to 3.7×10^{-5} μ*M*, with the quantitative limit being 4 ng/ml (5×10^{-5} μ*M*). The plasma kinetics of the main metabolite of fotemustine, 2-chloroethanol, was determined in 6 patients (11 kinetics). The plasma-decay curves of fotemustine and 2-chloroethanol at day 1 and day 2 are shown for patient PAR as an example (Fig. 2). In all cases, plasma-decay curves of the parent drug and its metabolite (all concentrations were expressed in micromolar values) were superimposable. The formation of 2-chloroethanol was extremely rapid, since plasma levels were measurable as early as at

Table 5. Pharmacokinetic parameters of fotemustine and 2-chloroethanol at day 1 and day 2

		t_α (min)		tβ (min)		C_{maxmod} (μM)		AUC_{mod} (μM h)	
		A	B	A	B	A	B	A	B
GAR	Day 1	2.7	3.9	33.3	32.6	34.0	19.9	36.0	22.1
	Day 2	6.2	5.0	37.0	30.0	22.2	16.3	30.2	23.0
PAR	Day 1	9.3	14.8	63.8	35.4	15.0	15.0	16.2	17.5
	Day 2	3.2	4.8	24.7	29.2	21.7	18.2	22.9	21.3
DEL	Day 1	2.5	3.5	30.0	31.4	30.0	20.7	29.4	21.9
	Day 2	3.9	4.8	23.6	28.8	27.1	20.6	26.7	22.3
JOU	Day 1	2.3	–	17.2	20.3	27.6	30.4	27.0	36.6
	Day 2	6.5	10.0	23.0	27.7	30.0	36.0	29.2	40.0
PEL	Day 1	2.8	2.4	21.7	26.7	15.6	20.3	16.5	26.3
	Day 2	1.3	9.0	20.1	47.0	22.8	27.5	23.9	37.7
CAN[a]	Day 1	–	–	–	–	–	–	–	–
	Day 2	7.3	4.5	45.9	21.5	15.8	12.0	17.0	13.1

A, Fotemustine; B, 2-chloroethanol
[a] Sampling problems

the first sampling time (15 min) after the start of the fotemustine infusion. Maximal observed levels were obtained at 45 min and were close to the maximal levels of fotemustine; no significant difference was evidenced between these two sets of C_{max} values (Wilcoxon-Mann-Whitney test). Furthermore, the other pharmacokinetic parameters, the half-lives and AUC_{mod} values for 2-chloroethanol and fotemustine (Table 5), did not significantly differ (Wilcoxon-Mann-Whitney test).

Discussion

The aim of this study was to evaluate the pharmacokinetic parameters of high-dose fotemustine and of its main metabolite, 2-chloroethanol. A total of 24 glioma patients treated with surgery, chemotherapy (followed by autologous bone-marrow transplantation) and radiotherapy were included in the pharmacokinetics study. In all, 40 kinetics could be analysed, with dose levels increasing from 2×300 to 2×500 mg/m^2.

The plasma-decay curves of fotemustine could be fitted to a bi-exponential equation, considered as valid owing to the close identity between model-dependent versus model-independent parameters (AUC_{mod} as AUC_{trap} and $C_{max\ mod}$ as $C_{max\ obs}$). However, we found a slight, significant bias between the C_{max} value estimated from the pharmacokinetic model and the observed one (mean ± SD: 3.9% ± 12.09%; confidence interval: [0.15%; 7.65%]). Observed C_{max} values occurred at various times from 15 min to the end of treatment, whereas by definition of the model, the C_{maxmod} value is always found at the end of the infusion. Analytical errors could in part give rise to such a result. The hypothesis of a misspecification of the model could not be retained, given the analysis of standardised residuals for each point of the kinetics. On the whole, this variation seems of very little relevance to the clinical usefulness of these results. The model was characterised by a short distribution half-life (mean, 4.1 ± 2.6 min, range, 0.1–10.2 min) and elimination half-life (mean, 28.7 ± 12.1 min; range, 13.2–63.8 min). There are few reports on clinical studies using fotemustine in cerebral tumours. The results obtained by Lokiec et al. [9] in six cases of brain tumours treated with a "conventional" regimen (100 mg/m^2) showed similar distribution and elimination half-lives of 6 and 30 min, respectively. Since no significant difference was observed in our patients between day 1 and day 2, no modification of elimination for the second dose would appear to be induced by the first administration. The volume of distribution to the steady state (V_{dss}) was considered, since steady-state plasma levels of fotemustine were achieved during the 1-h infusion. The V_{dss} values ranged from 8 to 85 l, with the mean value being 31 ± 20 l. No relationship between V_{dss} and dose level was evident. The V_{dss} values found in our patients are in agreement with those reported by Lokiec et al. (27.9 ± 5.5 l) but are more variable in the 40 kinetics evaluated herein.

Total clearance of the parent drug ranged from 34 to 320 l/h, with the mean value being 109 ± 65 l/h. These values are much higher than those previously observed by Lokiec et al. in the same type of tumours (mean, 49.8 ± 12.1 l/h; range, 8.9–89.4 l/h). This discrepancy could be attributable to differences between the therapeutic protocols used, since our patients received 250 ml 20% mannitol as a 20-min infusion just before fotemustine administration. Osmotic diuresis induced by this procedure may have led to an increase in fotemustine clearance in our patients.

Values for C_{max} did not differ from day 1 to day 2 in the same patient, and they increased with dose levels from 5.35 ± 1.91 mg/l at 300 mg/m^2 daily to 18.08 ± 5.32 mg/l at 500 mg/m^2 daily. For the first dose level (300 mg/m^2 daily), the mean value for C_{max} obtained in our study was only slightly higher than that found by Lokiec et al. after the administration of 100 mg/m^2 fotemustine. This dis-

crepancy was probably due to our administration of mannitol, leading to an increase in drug clearance and thereby decreasing accordingly plasma levels of fotemustine.

Since AUC and C_{max} were strongly correlated, with the regression line lying very close to the identity line ($AUC_{mod} = 0.905\ C_{maxmod} + 1.101$; $r = 0.960$, $n = 40$), the above-mentioned considerations about C_{max} apply to AUC as well. Moreover, the relationship between AUC_{mod} and C_{45} seems very important from an ethical point of view, since only a single plasma sample taken just before the end of the drug infusion could allow the estimation of the corresponding AUC, at least in glioma patients.

Finally, the plasma decay of fotemustine and its main metabolite was similar; the apparent elimination half-life of 2-chloroethanol (30.1 ± 7.2 min) did not significantly differ from the elimination half-life of its parent drug, fotemustine (28.7 ± 12.1 min; Wilcoxon-Mann-Whitney test). This observation is in accordance with the known rapid decomposition of nitrosoureas both in vitro and in vivo [8]. In our patients, the appearance and elimination of 2-chloroethanol was also found to be limited by the kinetics of the parent drug, the true elimination half-life of 2-chloroethanol being less than (or equal to) the fotemustine half-life. Due to the short half-life of the parent drug and to the very low drug levels found in plasma at 4 h after the start of the infusion, the bone marrow can be safely reinfused, probably as soon as 24 h after the second fotemustine administration and anyway at 48 h after the end of treatment.

The alkylating and carbamoylating activities of fotemustine make it a good candidate for dose adjustment by means of the AUC. Since the present study shows similar pharmacokinetic parameters, at least from day 1 up to day 5, one could take advantage of C_{45} measurements at day 1 to make individual dose adjustments of fractionated chemotherapy with fotemustine.

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