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Pharmacokinetics of high-dose intravenous melphalan in children and adults with forced diuresis

Report in 26 cases

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Summary. The pharmacokinetic parameters of the alkylating agent melphalan were determined in 15 children and 11 adults with advanced malignant solid tumors. High IV bolus doses of 140 mg/m^2 were given under standard hyperhydration conditions and followed by autologous bone marrow grafting. In all cases the time-concentration curves could be best fitted to a biexponential pattern. A high scattering of drug concentrations was observed in our patients, the disposition half-lives ranging in the whole group from 17.8 to 71.2 min. The areas under the curves also showed a wide variation, ranging from 175 to 682 mg l^{-1} min^{-1}. In all patients, melphalan levels in plasma were unmeasurable at 8 h or earlier, indicating that bone marrow can be safely reinfused at that time. No difference was apparent between children and adults regarding the drug pharmacokinetics. In each of 11 cerebrospinal fluid samples drawn 45–150 min after melphalan administration, drug levels were unmeasurable.

Introduction

The alkylating agent melphalan has been in use for 30 years in a variety of malignant tumors. It is well known that this nitrogen mustard produces damage mainly to DNA, especially its guanine bases. This biochemical cross-linking action results in the main pharmacological effect, impairment of DNA replication, mitotic division eventually leading to cell death.

Given by mouth, the usual dosage of melphalan is about 1 mg/kg body weight. However, it is known that this route of administration can result in considerable variations in absorption leading to variable bioavailabilities [1, 2, 13]. On the other hand, the IV route resulted in more pronounced side-effects, namely leukopenia and thrombocytopenia, as described by Cornwell et al. in myeloma patients [5], but may be more effective.

A dose-effect of melphalan in the treatment of solid tumors was demonstrated in the original work of McElwain et al. [11]. Furthermore, these authors were able to overcome the myelotoxicity arising from high-dose melphalan (HDM) by combining chemotherapy with autologous bone marrow grafting (ABMG). A massive chemotherapy program has been developed in our institution in connection with autologous bone marrow "rescue".

It was therefore of importance to study melphalan pharmacokinetics in patients receiving HDM given either alone or with other chemotherapeutic agents.

The present study was undertaken in an attempt to reach some conclusions about the following topics:

- The pharmacokinetics of HDM in our patients under hyperhydration conditions.
- Determination of possible differences between HDM pharmacokinetics in adults and children, using a consistent hyperhydration schedule.
- Estimation of the extent of blood-brain barrier crossing by melphalan given by the systemic route.

The timing of the ABMG procedure after administration of HDM might be linked to pharmacokinetic data in the future; in addition, the use of such data could contribute to an optimization of melphalan dosage.

Patients and methods

Patients. Twenty-six patients (15 children, 11 adults) were studied; their main characteristics are presented in Table 1. Twenty-three were entered on the phase II massive therapy program for solid tumors at the Centre Léon Bérard; three patients with malignant lymphomas entered a phase III collaborative study. Six patients received HDM as their only chemotherapy. In all cases, HDM was the last chemotherapeutic drug given 24 h after the preceding drug of the combination therapy. In children, the parents were informed by one of us of the scientific goal of the procedure and gave informed oral consent. In the case of adults, each patient was informed and gave consent to the study.

Patients received 140 mg/m^2 melphalan. The drug (Alkeran, Wellcome Lab.) was given IV as a rapid 5-min infusion after careful dilution in its own solvent immediately before the injection, supervised by one of us in every case.

All patients received hyperhydration regimen consisting of 3 l m^{-2} day^{-1} of a 2:1 infusion of 5% glucose: 1,4% sodium bicarbonate. This regimen was maintained from 24 h after HDM. Frusemide (Lasilix) was administered when necessary to maintain a urine flow rate of about 2 ml m^{-2} min^{-1}.

Bone marrow rescue was always given to the patients at least 24 h after HDM. The ABMG was fresh marrow, harvested within a few hours prior to the HDM in 6 cases, and frozen marrow, collected 7–98 days before, in 20 cases.

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Table 1. Patients characteristics

Pt no., sex	Age years	Weight kg	Dosage mg	Treatment[a]	Diagnosis[b]	Creatinine clearance (ml min^{-1} per 1.73 m^2)
1 F	11	26	140	M	Rhabdomyosarcoma	94
2 F	49	57	225	M	Ovarian carcinoma	85
3 M	2	12	70	M	Neuroblastoma	111
4 M	8	24	130	M	Ewing's sarcoma	77
5 F	30	61	240	M	Mesothelioma	110
6 M	1.3	10.6	70	V-TBI-M	Neuroblastoma	108
7 F	10	15	100	V-TBI-M	Ewing's sarcoma	130
8 M	9	25	140	V-TBI-M	Neuroblastoma	–
9 M	34	71	265	VP 16-M	Embryonal carcinoma + choriocarcinoma	147
10 F	4	13.5	90	V-TBI-M	Neuroblastoma	152
11 F	7	20	115	V-TBI-M	Neuroblastoma	117
12 M	12	14.5	80	V-TBI-M	Neuroblastoma	87
13 M	2.3	12.5	75	V-TBI-M	Ewing's sarcoma	157
14 M	10	25.8	150	V-TBI-M	Ewing's sarcoma	162
15 F	46	67	250	M	Ovarian adenocarcinoma	59
16 F	18.5	47.5	215	V-TBI-M	Ewing's sarcoma	135
17 M	17	55	230	V-TBI-M	Neuroblastoma	113
18 M	12.3	32.5	175	V-TBI-M	Neuroblastoma	167
19 M	3	15	100	V-TBI-M	Rhabdomyosarcoma	155
20 F	16.5	40	190	VP 16-M	Embryonal carcinoma + choriocarcinoma	167
21 M	4	16.5	100	V-TBI-M	Rhabdomyosarcoma	143
22 M	45	75	270	BEAM	NHML	95
23 M	57	75	260	BEAM	NHML	69
24 M	14	46	200	BEAM	NHML	127
25 M	26	60	250	V-TBI-M	Ewing's sarcoma	143
26 M	15	44	230	V-TBI-M	Ewing's sarcoma	177

[a] M, melphalan; V, vincristine; TBI, Total-body irradiation; BEAM, BCNU, VP 16, cytosine arabinoside, melphalan
[b] NHML, non-Hodgkin's malignant lymphoma

Each patient had had a silicone Broviac catheter introduced into the superior vena cava via the subclavian vein: all blood samples were taken through this catheter.

In most patients, creatinine clearance was measured, and also calculated by means of the following equations, derived from the review of Lott and Hayton [10]:

$$\text{Ccr (ml/min)} = \frac{(140 - \text{Age}) \cdot \text{Body weight}}{k \cdot \text{Scr (mg/dl)}}$$

for patients aged 20 and more, where $k = 72$ for males, and $k = 85$ for female patients, and

$$\text{Ccr (ml/min per 1.73 m}^2\text{)} = \frac{0.55 \cdot \text{Body length (cm)}}{\text{Scr (mg/dl)}}$$

for patients under 20.

Since good accordance had been found between measured and calculated values, for all patients but one renal function was assessed from serum creatinine measurement.

Blood sampling. All blood samples (3–5 ml) for the pharmacokinetic study were drawn into cooled heparinized glass tubes (heparinate lithium, Vacutainer). After a reference blood sample had been taken, melphalan was administered and time 0 was the end of drug infusion. Sampling times were 5, 10, 15, 30, 45, 60 min, and 2, 4, 6, 8, 24 h. During the later part of the study, additional samples were drawn at 1.5, 2.5, 3.5, and 12 h to increase the accuracy of determination of the terminal phase of drug decay in plasma. Samples were immediately placed in an ice-bath. Blood was centrifuged at 2000 *g* at 0–4 °C for 5 min, in a refrigerated centrifuge. Plasma was immediately stored at −25 °C pending estimation of melphalan levels.

Melphalan assay. Melphalan was assayed following a procedure described by Chang, using high-pressure liquid chromatography (HPLC) [4]. The apparatus used was a Roche-Kontron HPLC System 600 equipped with two pumps activated by a solvent flow programmer series 200. Optical densities were measured by an UV detector 730 LC, and data were processed by a Shimadzu recorder-integrator CR-1B.

Separations were performed with a reverse-phase C-18 precolumn connected to a Nucleosil C-18 column, 12.5 cm (5 μm particle size). Elution was usually achieved at a flow rate of 1 ml/min with a mobile phase of methanol-water-acetic acid (60%–39%–1%).

Unchanged melphalan was detected at the λ max (260.5 nm), as was the internal standard dansyl-L-proline (DNS-Prol).

Data processing. Plasma concentrations (C) of melphalan were plotted versus time on a semilogarithmic scale. All curves obtained for drug decay could be best fitted to a biexponential equation using a programmable Sirius system (Sirius System Technology) by means of the PHARM program [8]. Hence, the general equation for the pharmacokinetic curves was:

$$C = C_\alpha e^{-\alpha t} + C_\beta e^{-\beta t},$$

where C_α and C_β represent the extrapolated values of drug concentration at time 0, respectively, and α and β are the

apparent first-order distribution rate constants, respectively. Others parameters calculated were:
- Distribution plasma half-life ($t_{½\alpha}$);
- Disposition plasma half-life ($t_{½\beta}$);
- Area under curve (AUC), defined as:

$$AUC = C \cdot T = \int_0^\infty C \cdot dt;$$

- Total plasma clearance (Cl);
- Volume of distribution at the steady state (V_{dss}).

All parameters, especially AUC, were calculated using the fitted model. Raw parameters were considered for comparison with the results of other authors. However, AUC, Cl, and V_{dss} were corrected according to Gibaldi and Perrier [7] for the 5-min infusion time.

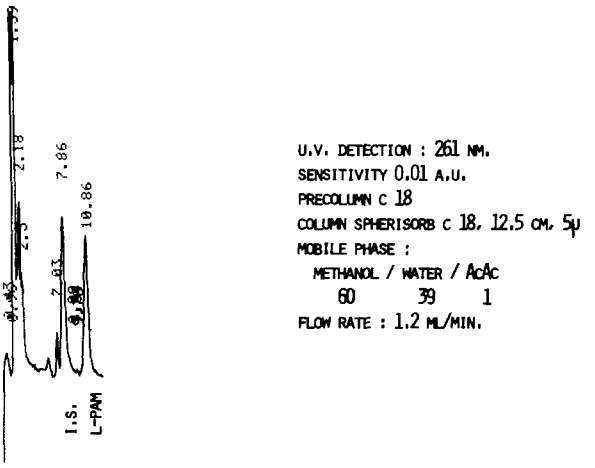

Fig. 1. Typical chromatogram of a plasma extract (plasma taken 30 min after melphalan therapy). *I.S.*, internal standard (dansyl-proline); *L-PAM*, melphalan

Results

Figure 1 shows a typical chromatogram obtained in the usual conditions of melphalan assay. The technique used allows drug measurements as low as 0.035 mg/l, but interfering endogenous compounds in plasma usually increase this about 0.1 mg/l.

Melphalan levels measured with this technique allowed us to plot individual decay curves of the drug in plasma. Plasma concentrations versus time are presented in Fig. 2. In all patients, the fall in early concentrations was extremely rapid, and was followed by a regularly shaped elimination phase. The levels of melphalan in the 5-min samples showed very wide variation between patients, and subsequent plasma levels varied by a factor of about 10. Four hours after the IV push, concentrations less than 0.4 mg/l were always found, and in no instance, could melphalan be detected at 8 h. In all cases, pharmacokinetics could be best adjusted to a two-compartment open model as described above. Individual pharmacokinetic parameters are listed in Tables 2 and 3 (respectively uncorrected and corrected for the 5-min infusion time). In spite of the standardization of the hydration program and of the dosage of melphalan related to body area, these values also show a wide range over the patient sample. All parameters listed by column in Tables 2 and 3 underwent a linear correlation test of each one versus one other. Apart from the usual physiological correlations no other significant correlation could be established.

Table 2. Melphalan pharmacokinetic parameters in the patient group: uncorrected data

Pt no.	$T_{1/2\alpha}$ (min)	$T_{1/2\beta}$ (min)	AUC (mg l^{-1} min)	Cl (l min^{-1} m^{-2})	V_{dss} (l m^{-2})	C_0 (mg l^{-1})	C_α (mg l^{-1})	C_β (mg l^{-1})
1	5.5	39.1	323	0.415	20.0	13.13	8.62	4.52
2	3.9	69.7	347	0.382	34.2	13.12	10.25	2.87
3	17.4	71.2	422	0.320	23.0	9.57	7.23	2.34
4	11.6	58.6	467	0.295	19.0	12.51	8.71	3.80
5	3.2	20.8	208	0.645	14.5	19.78	15.20	4.58
6	4.5	46.2	590	0.228	8.8	49.95	45.50	4.45
7	4.3	19.3	175	0.782	19.5	9.99	4.76	5.24
8	2.6	17.8	235	0.557	11.8	23.53	16.90	6.63
9	4.0	53.5	589	0.230	14.1	31.75	26.06	5.69
10	9.1	27.9	367	0.403	10.8	17.69	12.76	4.93
11	3.5	24.7	343	0.394	13.0	16.99	8.60	8.39
12	5.4	29.2	404	0.335	10.7	23.36	16.93	6.43
13	6.8	26.5	212	0.638	16.6	13.01	10.03	2.98
14	9.8	18.0	190	0.707	14.0	10.90	7.92	2.98
15	4.0	43.2	522	0.258	13.2	27.74	21.31	6.43
16	12.1	64.9	305	0.450	24.6	10.72	9.18	1.54
17	4.0	39.8	410	0.315	13.5	29.40	24.73	4.67
18	6.4	47.2	451	0.303	16.6	17.47	12.03	5.44
19	3.6	21.0	313	0.432	11.1	21.82	13.85	7.97
20	4.9	46.1	511	0.265	14.4	22.99	17.16	5.83
21	9.7	60.2	227	0.605	29.4	9.94	8.74	1.20
22	4.8	37.9	443	0.308	14.3	19.40	12.95	6.45
23	5.5	55.9	682	0.202	14.5	18.87	11.54	7.30
24	4.8	45.0	466	0.288	15.2	21.96	16.54	5.42
25	6.6	53.1	307	0.442	23.1	14.95	12.48	2.47
26	11.7	38.3	231	0.590	21.5	9.09	7.08	2.01

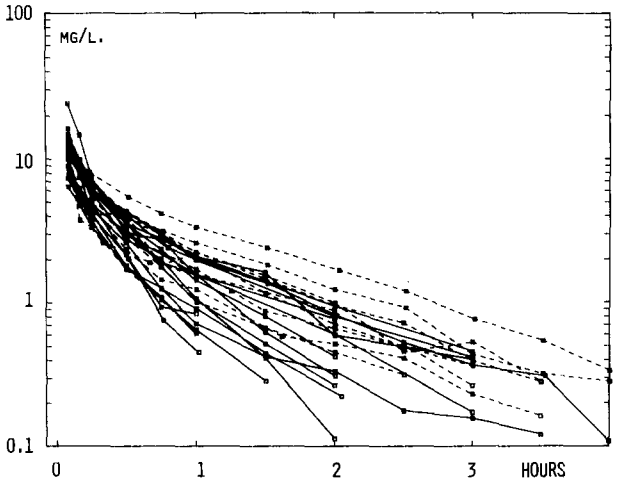

Fig. 2. Plasma kinetics of high-dose melphalan in 26 patients. ——— Children ($n=15$); ------ Adults ($n=11$)

From Fig. 2, it appears that adults and children might have kinetic differences in drug handling, and the parameters of the two groups are therefore considered separately (Table 4). Distribution volumes expressed in liters per square meter are similar in the two groups. However, the areas under the curve appear to be greater in adults, due to the shorter elimination half-lives in children, and total body clearance is greater. However, no statistically significant difference was found between these two sets of data, either by testing differences in mean values, or by means of the Wilcoxon-Mann-Whitney test. Hence, data could be grouped and mean values for the entire population are given in the second part of Table 4.

In order to determine blood-brain barrier crossing by melphalan, lumbar punctures were performed in 11 patients at times ranging from 45 to 150 min after HDM. No extraction procedure was required to assay CSF drug level. In only four samples (drawn at 45, 60, 120, 150 min) was the drug detectable; however, concentrations were found to be very low, close to the limit of detection. Thus, plasma-to-CSF ratios were greater than 100:1 in all cases.

Discussion

Up to the present time, few data have been reported in the literature on the pharmacokinetics of IV melphalan in man, especially after high doses. Studies previously undertaken in humans receiving IV bolus doses of 20–23 mg/m^2 were based on ^{14}C-radiolabeled drug [15]. In one adult patient results showed a distribution volume of 44.3 l, which is within the range found in our study, as was the plasma $t_{1/2\beta}$ of 67 min. However, the long terminal half-life of 160 h reported in the paper cited is probably related to factors other than decay of the parent drug, as underlined later by Pallante et al. on biochemical grounds [12]. These authors were able to estimate melphalan concentrations as low as 2 ng/ml at 24 h using deuterated melphalan and gas chromatography-mass spectrometry. Unfortunately, the disposition phases measured in their five patients were not reported in terms of half-lives.

Notation of IV melphalan dosages variously by amount per square meter or per kilogram of body weight makes comparison difficult between two similar studies independently conducted by Alberts et al. [1] at 0.6 mg/kg

Table 3. Melphalan pharmacokinetic parameters in the patient group: data corrected for the 5-min infusion time

Pt no.	AUC (mg l^{-1} min)	Cl (l min^{-1} m^{-2})	V_{dss} (l m^{-2})
1	359	0.390	22.0
2	383	0.366	36.8
3	447	0.314	32.2
4	500	0.280	23.7
5	264	0.530	15.9
6	732	0.191	12.8
7	202	0.692	19.3
8	302	0.463	11.9
9	679	0.206	15.9
10	413	0.339	13.7
11	389	0.360	12.8
12	466	0.300	12.7
13	247	0.566	21.7
14	218	0.642	16.7
15	601	0.233	14.5
16	332	0.421	39.4
17	493	0.284	16.3
18	528	0.265	18.1
19	374	0.374	11.3
20	572	0.245	16.3
21	253	0.554	48.1
22	495	0.283	15.5
23	731	0.192	15.5
24	527	0.266	17.3
25	348	0.402	30.8
26	254	0.551	30.4

Table 4. Mean values for pharmacokinetic parameters

	$T_{1/2\beta}$ (min)		AUC (mg l^{-1} min)		Cl (l min^{-1} m^{-2})		V_{dss} (l m^{-2})	
	C	A	C	A	C	A	C	A
$\bar{m}$	36.8	47.6	346 (397)	414 (468)	0.447 (0.400)	0.372 (0.336)	16.0 (19.6)	18.4 (22.5)
SD	17.2	13.8	122 (144)	151 (165)	0.170 (0.150)	0.146 (0.126)	5.5 (9.7)	6.7 (9.7)
$\bar{m}$	41.4		375 (427)		0.415 (0.373)		17.0 (20.8)	
SD	16.5		137 (154)		0.162 (0.141)		6.1 (9.6)	

C, children; A, adults
() values corrected for 5-min infusion time

traced with ^{14}C-radiolabeled drug, and Bosanquet and Gilby [2] at 15 mg/m^2 with ^3H-radioactive melphalan as tracer. Nevertheless, these two groups gave identical results for $t_{½\alpha}$, 7.7±3.3 min, and similar values for $t_{½\beta}$ (108 and 83 min, respectively). The total volumes of distribution measured were also very close (0.66 and 0.62 l/kg).

The sensitivity of HPLC assays, avoiding the use of radiolabeled drug in humans, now allows determination of low levels, as by Brox et al. [3], who administered IV melphalan doses of 10, 15 and 20 mg/m^2 to 12 patients with multiple myeloma. Either UV or fluorimetric detection allowed them to determine drug levels up to 2–3 h after administration. They found a disposition phase with $t_{½\beta}$ of 20 min, shorter than in other studies, irrespective of the dose administered.

In a more recent study, Woodhouse et al. [16] compared melphalan pharmacokinetics after oral and IV administration by means of a sensitive HPLC assay in six adult patients with multiple myeloma. Very similar disposition half-lives, respectively 63.6 and 67.3 min, were found in the two situations. They were able to conclude that the disposition of a low dose of melphalan was similar to that of high doses given in solid tumors.

In a pioneering phase I/II study, McElwain et al. administered IV melphalan at 140 mg/m^2 to eight patients with advanced malignant melanoma [11]. They were able to show that the parent drug was measurable in plasma up to 2 h after administration, but not afterwards. Urines carefully collected by catheterization showed highly variable amounts of drug, but elimination was complete at 6 h in all patients. Autologous fresh bone marrow could thus be safely reinfused to each patient 8 h after drug administration. In their patients, the mean profile of plasma melphalan, expressed as a percentage of the 5-min level, was largely similar to ours, bearing in mind their less sensitive assay. They found, as we did, a wide range of levels 5 min after IV administration (5.3–11.5 mg/l).

In a more recent paper, Taha et al. reported on a pharmacokinetic study of high-dose IV melphalan over 12 cycles at 140 or 220 mg/m^2 in children ranging from 2.5 to 16 years [14]. A forced diuresis regimen was used in 6 cycles. Plasma drug levels were assayed by HPLC, and the alkylating activity of plasma samples was also determined. The similar dosages enables a comparison with our own study. Pharmacokinetic data indicate rather different apparent volumes of distribution (26.3±18 l/m^2 in Taha et al.'s patients, compared with 17.0±6.1 l/m^2 in our own). This difference may in part be accounted for by the consideration of $V_{d\beta}$ in Taha et al.'s study, as against V_{dss} in ours. A further different finding is related to elimination half-lives of the parent drug, the cited study yielding a mean $t_{½\beta}$ of 1.3±1 h, as opposed to 0.7±0.3 h in the present work. This difference could arise in part from well-documented renal insufficiencies in Taha's patients; by contrast, our group contained only a few with mild renal insufficiency. However, total drug clearances are more similar, at 18.4±9.4 l h^{-1} m^{-2} in Taha et al.'s study and 24.9±9.7 l h^{-1} m^{-2} in our own.

In a recent study [9] in adults and children, Gouyette and co-workers demonstrated a mean elimination half-life for melphalan of 41 min, identical with that given in the present report. However, in six CSF samples taken from 15 children they found measurable drug levels from 5 min to 6 h following HDM administration, contrasting with our results. This discrepancy could be due to differences in the massive chemo-radiotherapy regimens used, although the mechanism is unclear.

The present study gives clear confirmation in a large group of patients of the biphasic pattern of HDM after IV administration and under standard hyperhydration conditions. A large range of disposition half-lives and AUCs was seen in our patients, in spite of a drug dosage related to body area. These wide variations are not correlated with renal function assessed by GFR; in our opinion, variability in systemic clearance is more important than renal clearance; this notion is further supported by the lack of correlation between drug and creatinine clearances. To date, no kinetic differences have been demonstrated between adults and children, as they have for other anticancer agents, such as VP-16 [6]. In our experience, the blood-brain barrier is crossed only to a minimal extent and in a few patients. In all cases, bone marrow grafting after HDM was successfully performed at 24 h, but consideration of individual pharmacokinetic data could help to reduce the time interval between ABMG and HDM treatment when necessary.

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