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Pharmacokinetics of Oral Melphalan in Relation to Renal Function in Multiple Myeloma Patients

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Abstract—*The impact of renal function on oral melphalan pharmacokinetics was studied in 15 patients with multiple myeloma. A two-fold interindividual variation in the plasma concentration–time curve (AUC) was found. An increase in AUC and melphalan mean residence time (MRT) was noted in patients with renal dysfunction. No correlation was found between GFR and the terminal plasma half-life time. We conclude from these results that renal dysfunction is associated with an increase in AUC and MRT of oral melphalan. A careful follow-up of hematological toxicity and possibly a dose reduction of melphalan are proposed for myeloma patients with renal impairment.*

INTRODUCTION

MELPHALAN is an alkylating agent used in the treatment of multiple myeloma for 30 years. The possible benefit of intensive combination chemotherapy has not been universally confirmed [1]. Hence, intermittent oral courses of melphalan and prednisone (MP) are still considered primary standard therapy for patients with multiple myeloma by most clinicians. Despite widespread clinical use, the pharmacokinetics of oral melphalan still is not fully understood. The absorption of melphalan is incomplete and prone to large interindividual variation [2, 3]. The two major mechanisms of melphalan elimination are suggested to be hydrolysis [2] and renal excretion [2, 4]. Renal dysfunction during the course of the disease occurs in the majority of multiple myeloma patients [5]. Therefore, it is of great clinical interest to determine if this factor has an impact on melphalan pharmacokinetics and accordingly should be taken into account in the dosage of melphalan. The present study was undertaken in order to further clarify this question.

MATERIALS AND METHODS

Patients

Fifteen patients with multiple myeloma were tested. The clinical characteristics of the patients are shown in Table 1. The clinical staging system by Durie and Salmon [6] was used. The median age was 64 years (range 48–83). The patients had received different numbers of intermittent oral melphalan/prednisone (MP) courses with a 6 week interval before testing. All were in good physical condition, but some with renal dysfunction. The pharmacokinetics of melphalan were studied on the first day of the test course which was started 6 weeks after the previous course. The oral melphalan dose was 0.25 mg/kg, and was given together with 100 ml water. No food was allowed 8 h before and 4 h after melphalan administration. Prednisone was given after the test. The same batch of tablets (Wellcome, U.K.) was used throughout the study.

Blood sampling

Blood samples (5 ml) were collected in glass tubes (Vacutainer®) containing 250 IU, freeze-dried heparin and immediately placed on ice. Samples were taken just before melphalan administration and 15 min, 30 min, 45 min and 1, 2, 3, 4, 5 and 6 h after medication. After centrifugation at 10°C, the plasma fraction was removed and stored at −20°C until analysis.

Melphalan assay

Melphalan was determined in plasma (1.00 ml) by liquid chromatography with fluorometric detection after derivatization with *N*-acetylcysteine. The exact procedure and instrumentation have been described earlier [7].

Pharmacokinetic analysis

Pharmacokinetic parameters were determined by a non-linear estimation program using a

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Table 1. Characteristics of multiple myeloma patients

Patient No.	Age (years)	Clinical stage	Amino acid levels (μmol/l)		GFR (ml/min)	S-creatinine (μmol/l)
			Leucine	Glutamine		
1	50	II	103	716	111	80
2	81	I	114	624	60	90
3	77	III	91	596	57	99
4	79	III	81	526	11	300
5	69	III	123	523	63	133
6	83	III	77	497	35	134
7	75	III	96	521	33	180
8	65	III	106	608	84	97
9	66	II	120	631	70	84
10	48	III	99	641	101	80
11	54	II	120	517	89	90
12	67	I	106	562	62	130
13	63	II	64	551	88	78
14	59	I	102	595	78	80
15	61	III	129	800	69	90

Gauss–Newton–Hartley algorithm with initial estimates from a stripping procedure. The reciprocal of plasma concentrations were used as weights in the iterative procedure. The choice of exponential terms in the equations describing the plasma pharmacokinetics was based on the *F*-ratio test. The area under the plasma concentration–time curves and the area under the first moments curves were calculated by the linear trapezoidal rule with extrapolation to infinite time. The maximum plasma concentration and the time for the maximum plasma concentration were evaluated from the fitted equation describing the plasma concentration time course.

Plasma amino acid analysis

Plasma levels of glutamine and leucine were analyzed with a routine ion binding chromatography method using an amino acid analysator (Liquimat III, Contron, Switzerland).

Glomerular filtration rate (GFR)

GFR was determined by standard methods using [^{51}Cr]EDTA clearance. The patients were tested 2 weeks before melphalan administration. Plasma clearance (ml/min) was corrected for body surface area.

Statistical analysis

Associations were evaluated by Kendall's independent test. Median values and confidence intervals were calculated by the Wilcoxon signed-ranks test as outlined by Tukey.

RESULTS

All plasma concentration–time data could adequately be described by an open one-compartment model with first-order absorption. The pharmacokinetic parameters determined are given in Table 2. The plasma concentration–time curve for three patients representing normal (GFR = 111 ml/min) (A), moderately (GFR = 33 ml/min) (B) and severely impaired (GFR = 11 ml/min) (C) renal function respectively is shown in Fig. 1. The absorption of melphalan was fast with an absorption lag time of less than 0.5 h. Median time to achieve peak concentration was 1.00 h (range 0.49–1.84 h). A two-fold interindividual variation in the plasma concentration–time curve (AUC) (corrected for dose and body weight) was observed. The area under the plasma concentration–time curve decreased with increasing GFR ($P = 0.001$) (Fig. 2). Also the mean residence time (MRT) of melphalan demonstrated a significant correlation with GFR ($P = 0.03$) (Fig. 3). There was a tendency ($P = 0.11$) that patients with low GFR absorbed the drug more slowly. No correlation ($P = 0.3$) was found between GFR and the elimination plasma half life time ($t_{1/2}$) of melphalan (Fig. 4). The median plasma concentration of leucine and glutamine was 102 μmol/l (range 64–129) and 594 μmol/l (range 497–800) respectively (Table 1). No correlation was found between the plasma levels of these amino acids and melphalan absorption time, AUC or elimination $t_{1/2}$. There was a trend that patients with low GFR values had lower plasma levels of glutamine ($P = 0.06$) and leucine ($P = 0.13$).

DISCUSSION

In the present study the impact of renal function on oral melphalan pharmacokinetics was investigated. The area under the plasma concentration–time curve (AUC) was found to cor-

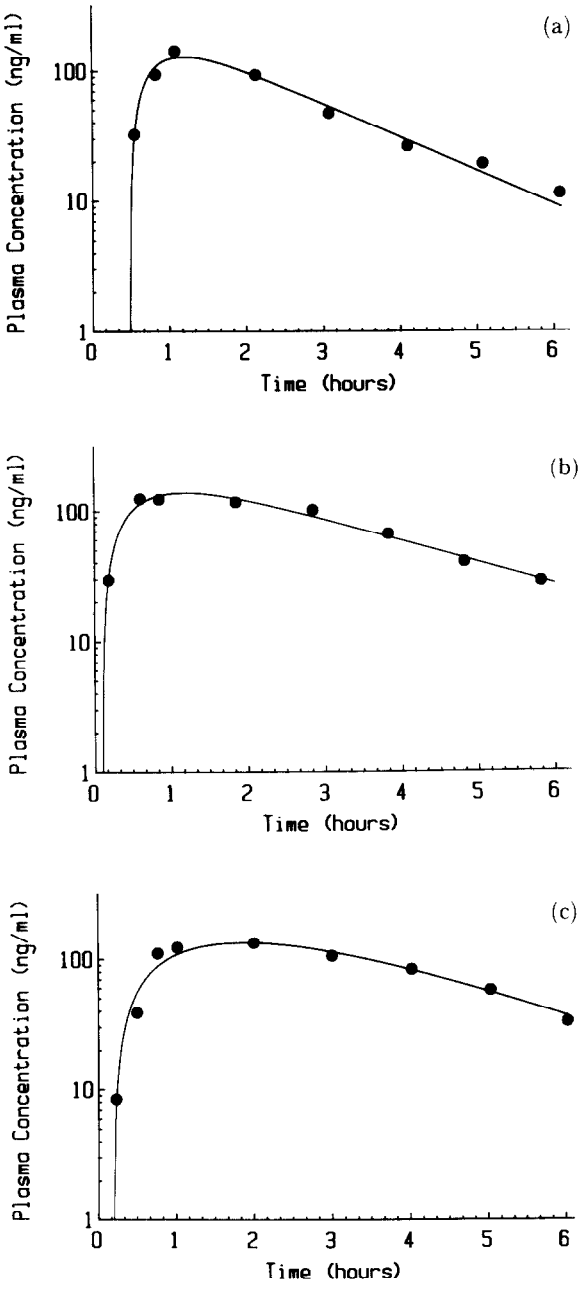

Fig. 1. Plasma concentration–time curve of melphalan for patient No. 1 with normal (GFR = 111 ml/min) (A), patient No. 7 with moderately (GFR = 33 ml/min) (B) and patient No. 4 with severely impaired (GFR = 11 ml/min) (C) renal function.

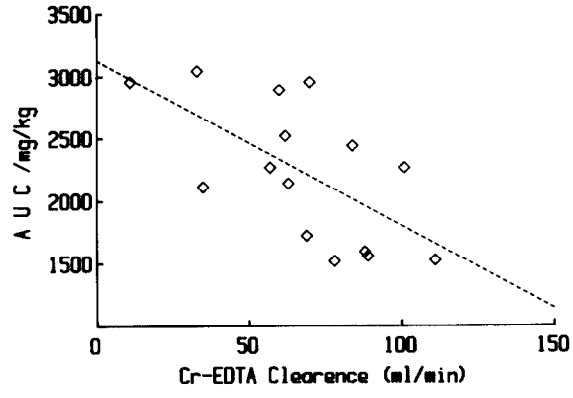

Fig. 2. AUC (corrected for dose and body weight) of melphalan in relation to GFR.

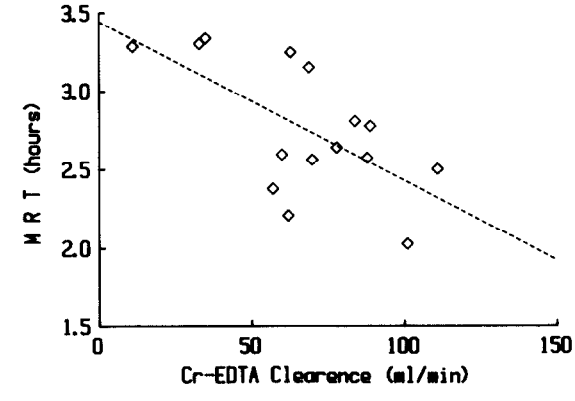

Fig. 3. Mean residence time (MRT) of melphalan in relation to GFR.

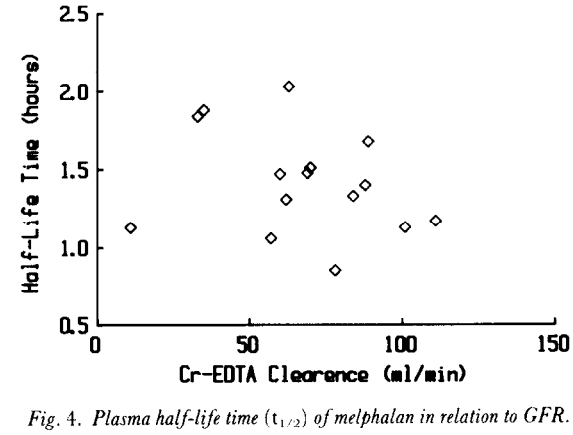

Fig. 4. Plasma half-life time ($t_{1/2}$) of melphalan in relation to GFR.

relate inversely with glomerular filtration rate (GFR) and with mean residence time. However, there was no correlation between melphalan plasma half-life time and GFR.

An initial reduction of melphalan dosage has been proposed for patients with renal dysfunction [8], but the results of previous pharmacokinetic studies testing this hypothesis are not uniform. Adair *et al.* [9] found a correlation between the elimination rate of melphalan and GFR. However, the method of calculating GFR from serum creatinine used in this study is less reliable than the values obtained by Cr-EDTA clearance [10], which might explain the different results of this and our study. Also in the study by Alberts *et al.* [11] melphalan plasma half-life time was found to correlate with renal dysfunction. However, since this study was performed on dogs and i.v. melphalan was used, some caution should be taken with regard to the extrapolation of these results to humans. In the study by Zucchetti *et al.* [12], renal dysfunction was associated with prolonged melphalan plasma half-life time. It cannot be excluded that treatment with cisplatin before testing has influenced these results. In several other studies no correlation between GFR and plasma half-life time was found [13–16]. The inverse corre-

Table 2. Melphalan pharmacokinetics after oral administration

Patient No.	Dose (mg)	t_{max} (h)	C_{max} (ng/ml)	$t_{1/2}$ (h)	MRT (h)	AUC* (mg/kg)
1	15	1.19	128	1.17	2.50	1.53
2	15	0.78	237	1.47	2.59	2.89
3	15	1.23	175	1.06	2.38	2.27
4	15	1.84	132	1.13	3.28	2.96
5	20	0.61	130	2.03	3.24	2.14
6	15	0.94	149	1.88	3.33	2.11
7	10	1.15	137	1.84	3.30	3.04
8	20	1.34	177	1.33	2.81	2.44
9	12.5	0.63	137	1.51	2.56	2.95
10	17	0.70	240	1.13	2.03	2.27
11	15	0.51	119	1.68	2.77	1.56
12	10	0.49	201	1.31	2.21	2.52
13	10	0.79	117	1.40	2.57	1.60
14	15	1.66	108	0.85	2.64	1.52
15	10	1.51	72	1.48	3.15	1.72

*AUC expressed in $\mu g \times ml^{-1} \times h$.

lation between AUC and GRF found in this study indicates that renal function has an impact on melphalan pharmacokinetics, but most probably by some other mechanism than affecting the rate of elimination. Different results have previously been observed with regard to the influence of GFR on AUC. Adair *et al.* [9] found an inverse correlation between GFR and AUC but no correlation was found by Ardiet *et al.* [13]. Moreover, in the study by Bosanquet and Gilby [17] a correlation probably exists although no statistical data were given. The exact mechanism for this relation remains unclear. The increased MRT in patients with renal insufficiency suggests that these patients are exposed for a longer period of time to the drug, which might have an impact on its pharmacological activity.

In a previous report on i.v. melphalan therapy, myelotoxicity was reported to be more severe in patients with renal dysfunction [18]. However, no data were presented on the degree of myeloma bone marrow infiltration. Since renal dysfunction is more common at an advanced clinical stage, it cannot be excluded that extensive myeloma bone marrow infiltration would be the main reason for the suppression of peripheral blood counts found in this patient group.

The low levels of leucine and glutamine found in patients with low GFR values might promote the myelotoxic effect of melphalan, since both amino acids are competitive inhibitors of cellular melphalan uptake [19].

Based on the pharmacokinetic results from this and other studies, it cannot be generally recommended that the melphalan dosage should be reduced in patients with renal dysfunction. The large interindividual variation in absorption of melphalan is probably the most important reason for the wide variation in the clinical response and hematological toxicity between different myeloma patients. Due to the increased AUC and MRT found in renal insufficient patients, we propose a careful follow-up and possibly a dose reduction of melphalan for this patient group.

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