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Comparison of the fed and fasting states on the absorption of melphalan in multiple myeloma

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Summary. *Melphalan absorption was studied over three consecutive days in five patients with multiple myeloma. On 1 day melphalan (approximately 7 mg/m² = 10–12 mg) was administered IV, on 1 day PO fasting, and on 1 day PO after a standard breakfast. The order was different for each patient to minimise trends that might affect absorption. Melphalan concentrations were determined by high-pressure liquid chromatography and fitted to biexponential equations by computer. The parameters of these equations were in broad agreement with previously published data, and melphalan absorption varied between patients. Considerable differences were observed in the melphalan concentration curves between the 'PO fed' and 'PO fasting' days: on the PO fed days the delay before absorption started was longer (1.1 ± 0.5 h as against 0.3 ± 0.1 h); peak plasma levels were one-third the value (65 ± 15 ng/ml; 195 ± 80 ng/ml) and occured at twice the time after administration (2.8 ± 0.8 h; 1.3 ± 0.3 h); and areas under the curve were smaller 10.8 ± 4.7 min × μg/ml; 23.8 ± 13.8 min × μg/ml). There was a significant difference between the fraction of the dose of melphalan absorbed on the PO fed day (0.49 ± 0.20) and on the PO fasting day (0.93 ± 0.22), with $P < 0.005$. This work suggests that melphalan should be taken first thing in the morning to obtain greatest absorption.*

Introduction

For over 20 years melphalan has been used as the cytotoxic drug of choice in myeloma and other neoplasms, but little was known about its pharmacology. More recently methods have been developed to measure melphalan in plasma samples from patients by high-performance liquid chromatography [4, 8] and mass spectrometry [10]. Using these, a number of groups have observed considerable variation in melphalan absorption [2, 3, 16, 17] and peak plasma levels [15].

Earlier results of ours [3] had suggested that melphalan absorption might be increased by prior ingestion of food, and so in this study we have investigated five patients in a controlled study and found the opposite to be true: melphalan absorption is more complete on an empty stomach.

Materials and methods

Experimental design. Five patients with multiple myeloma who had received no more than two prior courses of melphalan treatment (7 mg/m² per day on 5 consecutive days every 4 weeks) were studied. They were given three doses of melphalan (approximately 7 mg/m²) on consecutive days, one PO fed, one PO fasting, and one IV; the order was different for each patient to eliminate the effects of one study on another. On the PO fed day patients received a breakfast consisting of cornflakes, egg and toast, containing 22 g protein, 25 g fat, and 95 g carbohydrate (total = 710 kcal), and the melphalan tablets were administered immediately afterwards. On the PO fasting day no food was allowed from midgnight until 4 h after the melphalan had been given. The tablets were given with approximately 50 ml water and a drink was allowed after 2 h. No dietary limits were placed on the IV day. Patients were seated for drug administration and for 30 min afterwards. Concurrent prednisolone was given and other drugs (mainly analgesics) were allowed as required.

Blood samples were taken into lithium heparin before administration of melphalan and at approximately 5 (IV only), 15, 30, 60, 90 min and 2, 3, 4, 6, and 8 h after. Plasma was prepared by centrifugation at 1,800 *g* at 4° C and frozen until it could be analysed by high-pressure liquid chromatography (HPLC).

Creatinine and paraprotein concentrations were measured by routine procedures in the Area Central Laboratories at the Royal United Hospital. Glomerular filtration rates (GFR) were calculated according to a formula adapted from Cockcroft and Gault [9]:

$$\mathrm{GFR} = \frac{k[140 - \text{age (years)}] \times \text{wt (kg)}}{\text{plasma creatinine } (\mu M)} \quad (1)$$

where $k = 1.23$ for males and 1.04 for females.

Melphalan measurement. Melphalan was determined in plasma samples by our own method, which is described in detail elsewhere [4]. Briefly, an internal standard was added to 1 ml plasma and the melphalan adsorbed onto a 0.6-ml column of XAD-2 (BDH, Poole, UK). Methanol was used to elute the drug, and the eluate injected directly into the HPLC.

The HPLC consisted of a pump and fixed wavelength (254 nm) detector (Laboratory Data Control, Stone, UK) and a 25 × 0.5 cm column packed with Spherisorb ODS (5 μm). The mobile phase was made by mixing methanol and 0.75 g sodium dodecylsulphate/litre 4 : 1 (v/v) and adjusting the pH to about 3.0 with concentrated sulphuric acid. The flow rate of the mobile phase was 1.0 ml/min and the detector sensitivity usually 0.002 AUFS. Melphalan concentrations were calculated from the ratio of the peak heights of melphalan to internal standard.

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Detailed data analysis has been described before [3]. Melphalan concentration-versus-time data were fitted by nonlinear regression computer program NONLIN [11] to biexponential equations of the form

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (2)$$

for IV data, or

$$C = B'(-e^{-k_a(t-t_0)} + e^{-\beta(t-t_0)}) \quad (3)$$

for oral data, where C is the concentration of melphalan in plasma (ng/ml) at time t (min), t_0 is the delay (min) before absorption starts, A, B, and B' are parameters measured in ng/ml, α and β are apparent first-order distribution rate constants (min^{-1}), and k_a is the apparent absorption rate constant (min^{-1}). Plasma half-lives ($t_{1/2}$) were calculated from these parameters, and areas under the curve (AUC) were calculated by trapezoidal approximation. The fraction of oral melphalan absorbed *(F)* was calculated as

$$F = \frac{\text{AUC PO}}{\text{AUC IV}} \quad (4)$$

Results

Details of the two male and three female patients investigated in this study are shown in Table 1. It can be seen that the response to melphalan and prednisolone varied widely. FW is now being treated with cyclophosphamide, vincristine, and prednisolone following return of his paraprotein to pretreatment concentrations, whilst the paraprotein level of VS is now below detection. Interestingly, we had tested this latter patient in our in vitro chemosensitivity assay [5, 6] and found her to be sensitive to melphalan and prednisolone in vitro before her treatment was started. Glomerular filtration rates are variable and, although the two low values (VS and CD) seem to correlate with better prognosis, they may be a cause of poorer absorption.

Figures 1–3 show the concentration-versus-time data for the patients in this study. CF showed a very rapid decline in plasma melphalan concentration after PO dosing, whereas VS and CD showed relatively prolonged terminal half-lives.

In Table 2, the means (± SD) of the parameters of the curves calculated by computer from the data in Figs. 1–3 are given. They show considerable variation from patient to patient. As a good curve fit could not be obtained for the data from the PO fasting day of CF, some of the parameters for that day are calculated from the remaining four patients.

Peak plasma levels of 195 ± 80 ng/ml were observed on the PO fasting day at 1.3 ± 0.3 h, whereas on the PO fed day the peak levels were only 65 ± 15 ng/ml at over twice the time after melphalan administration (2.8 ± 0.8 h). The time before absorption started was 0.3 ± 0.1 h on the PO fasting day, as opposed to 1.1 ± 0.5 h when the patients were fed.

In Table 3, the figures for the areas under the curve show considerable variation. There was, however, consistently greater absorption of melphalan when the patients were fasting, with AUC PO fasting/AUC IV averaging 0.93 ± 0.22 (mean ± SD; range 0.62–1.20) whereas AUC PO fed/AUC IV was only 0.49 ± 0.20 (range 0.19–0.68). Analysis of these values by a paired t-test gave $t = 6.23$, with $P < 0.005$. The value of 0.52 ± 0.18 calculated for AUC PO fed/AUC PO fasting suggests that on average nearly twice as much melphalan was absorbed when the patients were fasting as when they were fed.

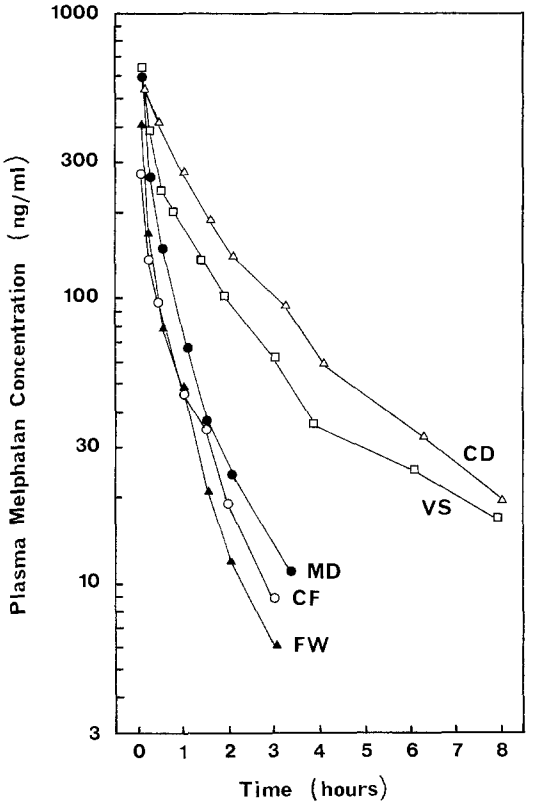

Fig. 1. Concentration-versus-time data after IV administration of melphalan

Table 1. Patient details

Patient	Age (years)	Weight (kg)	Body surface area (m^2)	Response		Glomerular filtration rate (ml/min)	Melphalan dose (mg)
				PPL decrease[a] (%)	Sustained for months		
CF	47	64	1.7	35	> 12	92	12
FW	61	59	1.6	20	8	70	11
MD	75	62	1.6	30	> 13	60	10
VS	69	56	1.5	90	> 5	35	11
CD	74	75	1.8	75	> 6	27	12

[a] Decrease in paraprotein level after 6 months of treatment

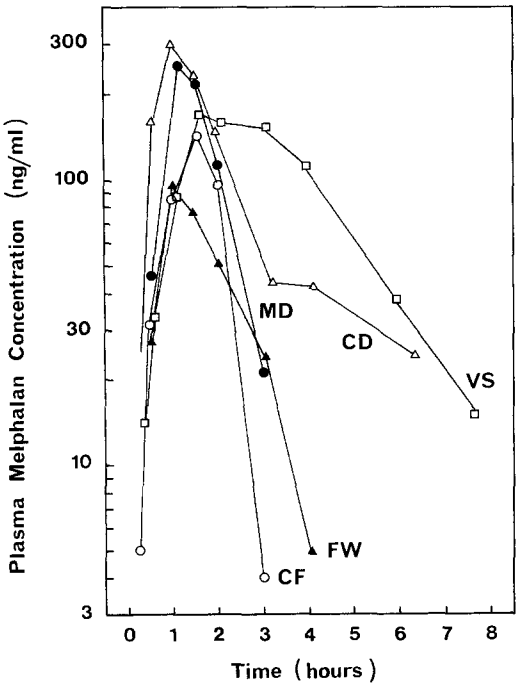

Fig. 2. Concentration-versus-time data after administration of melphalan PO fasting

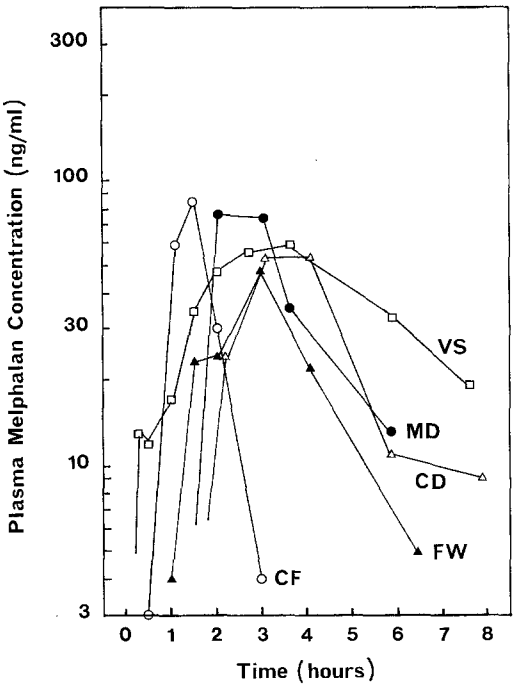

Fig. 3. Concentration-versus-time data after administration of melphalan PO fed

Table 2. Parameters calculated from the computer-fitted curves

Parameter	IV	PO fasting	PO fed
A (ng/ml)	490 ± 150	–	–
Delay (min)	–	24 ± 6	66 ± 30
α (min^{-1})	0.085 ± 0.054	–	–
k_a (min^{-1})	–	0.043[a] ± 0.026	0.018 ± 0.010
B (ng/ml)	150 ± 50	1,970[a] ± 2,270	760 ± 440
β (min^{-1})	0.0115 ± 0.0055	0.0168[a] ± 0.0090	0.0137 ± 0.0075
$t_{1/2}\,\alpha$ (min)	14 ± 14	–	–
$t_{1/2}\,k_a$ (min)	–	27[a] ± 25	49 ± 24
$t_{1/2}\,\beta$ (min)	74 ± 38	50[a] ± 23	62 ± 29

[a] These parameters caculated with data from only four patients

Table 3. Of melphalan: areas under the curve and absorption

Patient	AUC (min × μg/ml)			Absorption	
	IV	PO fasting	PO fed	Fasting	Fed
CF	10.2	12.2	5.8	1.20	0.58
FW	11.3	9.8	7.7	0.87	0.68
MD	19.3	20.6	11.6	1.07	0.60
VS	45.0	39.8	18.1	0.88	0.40
CD	58.4	36.4	10.9	0.62	0.19
Mean	28.8	23.8	10.8	0.93	0.49
SD	21.7	13.8	4.7	0.22	0.20

Discussion

Since methods have been available to measure melphalan concentrations in human plasma [4, 8, 12], we and others have noticed variation of melphalan absorption from patient to patient [2, 3, 17] with, in one patient, no detectable melphalan in any of the samples taken over 24 h [2]. Our earlier data also suggested that the ingestion of food before melphalan may increase the absorption of the drug [3]. However, the first two of these studies of PO absorption of melphalan were uncontrolled experiments in that oral and IV data were collected some weeks apart, with the possibility of changes in unknown parameters that might affect absorption.

In the present work, a study period of three consecutive days was used, with each patient receiving the three different regimens in a different order to rule out any possible trends over the 72 h. Twenty-four hours was considered enough time between administrations, as melphalan levels by this time have been shown to be undetectable [1, 2].

The result of this more carefully controlled study decisively reverses the suggestion we made earlier that melphalan may be absorbed more completely after food. It also clearly shows that melphalan behaves like other drugs that are incompletely absorbed from the gastrointestinal tract (e.g., methotrexate [13]), where the general expectation would be for more drug to

be absorbed in the fasting state. We have, however, found a higher melphalan absorption (0.93 ± 0.22; Table 3) than in a similar group of myeloma patients studied by Woodhouse et al. [15] (0.78 ± 0.16) and the one melanoma and four ovarian cancer patients of Alberts et al. [2] (0.56 ± 0.27). This may simply reflect the very variable absorption of melphalan already noted, but the lower values observed by Alberts et al. [2] may also be due to the possible involvement of the gastrointestinal tract in their ovarian cancer patients (with potential malabsorption of melphalan); in our patients melphalan absorption is less likely to be affected in this way.

The parameters found by computer (Table 2) when calculating a best fit curve to the data (Figs. 1–3) are in broad agreement with previously published work [1–4, 7, 10, 15–17] with rapid half-lives resulting in minimal levels of drug being detectable by 8 h.

Although this has not been noted in previous studies, glomerular filtration rates (Table 1) correlate quite well with AUC IV in this study. More interestingly, the response of the patient seems to correlate with AUC PO fed and *not* with the absorption of the drug. Although it is possible that nausea would be experienced more often by a patient taking melphalan on an empty stomach, the very signficant difference in absorption of the drug between PO fed and PO fasting days suggests that best absorption would be achieved if melphalan was taken with an early morning drink. This also ties in well with the suggestion of Simpson and Stoney [14] (extrapolating from experiments on the circadian variation of melphalan toxicity in mice) that melphalan should be administered at the beginning of the day to achieve least myelosuppression per unit dose. When the drug is given orally it should be remembered that regular blood counts and dosage escalation must be undertaken to ensure greatest effectiveness of the drug, and it could well be argued that due to the problems of drug absorption, IV administration of melphalan should be used more widely.

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