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The effect of food on oral melphalan absorption

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Summary. Fifteen patients receiving oral melphalan (4.2–5.3 mg/m^2) for a variety of neoplastic disorders were studied. Ten patients received the drug on separate occasions, with and without a standardized breakfast. Eight of these patients also received an IV bolus dose (5 mg/m^2) to determine bioavailability. Serial melphalan plasma samples were taken over 5 h after administration and assayed by high-performance liquid chromatography. The median area under the curve (AUC) when taken fasting was 179 (range 95–336) ng · h · ml^{-1}, and when taken with food, 122 (47–227) ng · h · ml^{-1}, the median reduction being 39% ($P<0.01$). In one patient, who died before completing the study, the drug was not detectable at all after being taken with food. In the eight patients who were also given IV melphalan, the median terminal melphalan half-life (57 min, range 38–71) was no different from its oral half-life [55 (27–104) min fasting; 55 (30–72) min with food] ($P>0.1$). In these patients bioavailability was 85% (26–96)% when the drug was taken fasting and 58% (7–99)% when taken with food ($P<0.025$). Median clearance following IV administration was 362 ml/min/m^2 (range 104–694). It was found that the melphalan level in a single plasma sample drawn 1.5 h after administration was highly predictive of oral melphalan AUC ($r_s=0.915$, $P<0.1$). This study suggests that to ensure optimum absorption of the drug, melphalan should not be taken with food.

Introduction

The alkylating agent melphalan is used in the therapy of a number of malignancies, particularly multiple myeloma. As in the case of mercaptopurine [12], oral bioavailability of the drug is known to be highly variable [1, 3, 4, 8, 9, 11], probably due to variable absorption from the gut [9], since first-pass metabolism has not been demonstrated. Concurrent food intake may contribute to this variability, and initial studies by Bosanquet and Gilby [3] indicated that food enhanced melphalan absorption. However, a subsequent controlled study in five patients by the same workers [4] suggested the opposite. The question is an important one, since melphalan is normally taken as a single daily dose, often with breakfast.

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We have investigated the effect of a standardized breakfast on melphalan absorption in 10 patients, using a simple and sensitive high-performance liquid chromatographic-fluorescence assay. Bioavailability was determined in eight of these patients. The relationship between the drug level in a single plasma sample drawn 1.5 h after oral dosage and area under the plasma level-time curve of the drug was also investigated in a total of 15 patients.

Methods

Patients. Fifteen patients receiving oral melphalan (4.2–5.3 mg/m^2) for a variety of neoplastic disorders were studied (Table 1). The drug was given in monthly courses consisting of single doses each day for 7 days. Twelve patients had received up to 30 doses of maintenance therapy prior to the study. Three patients (nos. 2, 4 and 6) volunteered for the melphalan study although they were not receiving maintenance melphalan therapy. All patients gave informed consent before proceeding with the study. Patients 1–10 were given morning oral doses of melphalan on two separate occasions, greater than 1 day but less than 1 month apart. On one of these occasions the drug was

Table 1. Patient characteristics

Patient/ sex	Age (years)	Surface area (m^2)	Melphalan dose (mg)	(mg/m^2)	Disease
1/M	72	1.5	8	5.3	IgA λ myeloma
2/F	63	1.5	8	5.3	Accelerated phase C.G.L.
3/M	51	1.9	8	4.2	IgG K myeloma
4/M	76	1.9	8	4.2	Blast crisis of C.G.L.
5/F	68	1.6	8	5.0	IgG K myeloma
6/M	58	2.1	10	4.8	Diffuse poorly differentiated L.L
7/F	75	1.5	8	5.3	IgG/IgA myeloma
8/F	79	1.8	8	4.4	IgG K myeloma
9/M	58	1.8	8	4.4	IgG K myeloma
10/M	72	1.8	8	4.4	IgA K myeloma
11/M	73	2.0	8	4.0	IgG K myeloma
12/M	71	1.8	7	3.9	IgA K myeloma
13/M	69	1.8	8	5.3	IgG λ myeloma
14/F	72	1.9	8	4.2	Light chain disease (λ)
15/F	66	1.4	8	5.7	IgG λ plasmacytoma
Mean	68	1.7	8	4.7	
sd	7.7	0.2	0.6	0.6	

taken after an overnight fast and on another, with a standardized breakfast consisting of: 150 ml low-fat milk, 10 ml orange juice, 1 egg, 2 pieces of toast, 5 g margarine, 20 g marmalade, 20 g cheese, and 100 ml unsweetened black coffee or tea (21 g protein, 20 g fat, 59 g carbohydrate: in all, 610 Kcal). Eight of these patients also received an IV bolus dose of melphalan (5 mg/m^2), and the order of the three studies was randomized. Five further patients were given oral melphalan on one occasion only, four while fasting and one with the standardized breakfast. Concurrent medication was the same on each study day for each particular patient. Blood samples were taken from a heparin lock immediately before administration and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 5 h after for both routes of administration. Renal function was normal in all but patients 1 and 4, whose serum creatinine levels were 2.0 and 2.5 mg/dl (180 and 220 μmol/l), respectively, at the time of the studies. No patient vomited after administration of the drug.

Melphalan assay. Blood samples were placed on ice immediately after collection and centrifuged within 1 h at 4 °C. Plasma was stored at below −20 °C until assayed. Melphalan was quantititated in plasma using a solid-phase extraction technique. Three-millilitre cartridges (Bond Elute 607203 from Analytichem International Inc., Harbor City, CA 90710, USA) supported by a Vac-elut™ vacuum manifold (Analytichem) were preconditioned with 2 × 3 ml methanol followed by 2 × 3 ml water. Then 200 μl 0.1 *M* phosphate buffer at pH 2.1 was added to the column, followed by 1 ml plasma (standard or patient) and 5 μl dansyl proline (50 μg/ml in methanol). The extraction was carried out by drawing the plasma-buffer mixture through the column at reduced pressure. The column was then washed with 2 ml water, and the drug and internal standard were eluted with 2 × 400 μl methanol. The methanol eluates were evaporated and the residue reconstituted in 40–80 μl methanol and 35 μl was injected into the chromatograph. Chromatography was carried out on a Brownlee HPLC cartridge column system consisting of a 22 cm × 4.6 mm analytical cartridge and a 3 cm × 4.6 mm precolumn, both packed with 5 μ C18. The flow rate was 1.6 ml/min and column temperature, 50 °C; the mobile phase consisted of 55% 10 m*M* sodium phosphate buffer (pH 3.0) and 45% methanol. A Schoeffel fluorimeter was used to detect the compounds at an excitation wavelength of 265 nm and 340 nm emission cut-off. Quantitation was performed by comparing peak height ratios in patient samples with a set of plasma standards in each run. The limit of detection of the assay was approximately 2 ng/ml, reproducibility 3.0% and 4.6% with a recovery of 88.4% and 83.3% at 100 and 500 ng/ml, respectively. Injection of the samples in methanol did not interfere with the peak shape of melphalan or the internal standard. The approximate retention times of melphalan and the internal standard were 6 and 16 min, respectively. The internal standard could be excluded to reduce analysis time if all pipetting and sampling steps were performed with high precision.

Pharmacokinetic analyses. Data was analysed by both model-independent and conventional compartmental methods, and the results were compared. The former provided estimates of half-life, area under curve (AUC), clearance, bioavailability, and absorption half-time using methods described by Gibaldi and Perrier [5]. The conventional approach was based on a one-compartment model with first-order absorption, incorporating a lag-time for orally administered drug, and a two-compartment model for drug administered by IV bolus. Melphalan concentration-time data were fitted by means of the nonlinear regression analysis program, BMDPAR [2] and the equation coefficients were used to derive AUC, clearance, terminal half-life, and absorption half-time. Differences between AUC, clearance, and terminal half-life were less than 10% with the two methods. However, estimates of absorption half-time were obviously in error with the model-independent approach, since there was no allowance for a lag-time prior to the onset of absorption. In this case values of absorption half-time obtained with the compartmental approach were used, and otherwise, documented parameters were obtained with the model-independent approach. Allowance was made for differences in oral doses between patients when calculating bioavailability.

Statistical analysis. Nonparametric tests were used to compare pharmacokinetic data, since the distribution of parameters obtained in these studies was unknown. The Wilcoxon signed rank test was therefore used to test for differences between paired observations. Krustal Wallis' one-way analysis of variance was used to test for differences in melphalan half-life following administration IV, PO with food, and PO fasting administration. Spearman's rank correlation coefficient (r_s) was used to test for a relationship between melphalan plasma levels and AUC.

Results

Fifteen patients (Table 1) received at least one dose of oral melphalan. In patients 1–10, who received oral melphalan with and without food, melphalan AUC was smaller with

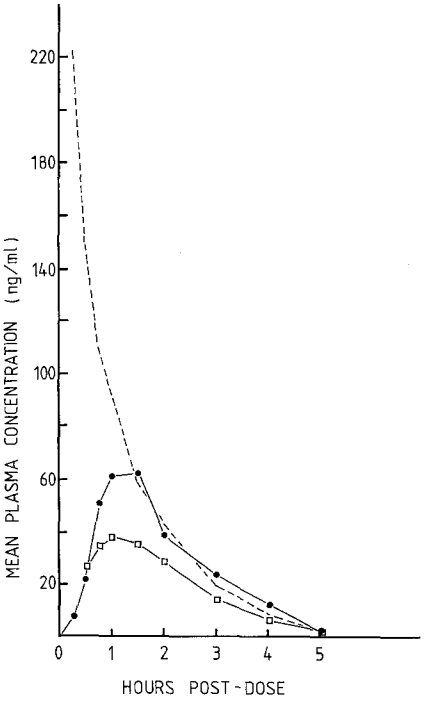

Fig. 1. Mean plasma levels of melphalan in patients 1–10 following oral administration (4.2–5.3 mg/m^2) with (□) and without (●) food, and in patients 1–8 following IV bolus administration (5 mg/m^2) (-------)

Table 2. Area under plasma level-time curve and bioavailability of melphalan in patients

Patient	$AUC_0 \rightarrow \infty$ (ng · h · ml^{-1})			Bioavailability (%)	
	Oral fasting	Oral with breakfast	IV	Oral fasting	Oral with breakfast
1	186	46.9	639	29.1	7.3
2	197	154	301	65.5	51.2
3	95.5	100	101	95.5	99.0
4	301	227	351	85.8	64.5
5	171	125	194	87.9	64.4
6	146	65.8	206	70.9	31.9
7	132	119	157	83.9	76.0
8	336	167	505	66.3	33.1
9	124	10.9 (0)[a]	–	–	–
10	105	0	–	–	0
11	153	–	–	–	–
12	104	–	–	–	–
13	–	22.0	–	–	–
14	113	–	–	–	–
15	223 (249)*	–	–	–	–

[a] Results in parentheses are repeat of studies undertaken 1 week later in patient 9 and 9 months later in patient 15

food in all but patient 3 (Table 2). Only traces of melphalan were detected in the plasma of patient 9, and none at all in patient 10, when the drug was given with food. Reproducibility of absorption within a patient was checked in patient 9 by repeating the oral study with food 1 week later and in patient 15 by repeating the oral study fasting 9 months later. AUC was 10.9 and 0 ng · h · ml^{-1}, respectively in patient 9, and 223 and 249 ng · h · ml^{-1} in patient 15. Median melphalan AUC in patients 1–10 was 159 ng · h · ml^{-1} when taken fasting and 103 ng ml^{-1} h^{-1} ($P<0.01$) when taken with food, the median reduction being 39%. In patients 1–8, who also received IV melphalan, the median clearance was 362 ml/min/m^2 (range 104–694), AUC 340 ng · h · ml^{-1} (range 101–639) and terminal half-life 57.0 min (range 38.0–70.6). The latter was not significantly different from that obtained after oral melphalan, either with (median 55.0 min, range 20.8–71.7) or without (median 55.3 min range 26.8–104) food. Individual estimates of AUC in patients receiving IV melphalan are shown in Table 2. The median time to peak in patients 1–8 was 75 min (range 45–90) when melphalan was taken fasting and 60 min (range 30–120) when it was taken with food ($P>0.1$). Absorption half-time was also no different fasting (median 16.8 min range 9.1–36.5) than with food (median 12.7 min range 8.3–41.6) ($P>0.1$). Patients 9 and 10 both died before receiving the IV melphalan dose. Mean plasma levels of melphalan in patients 1–10 following oral melphalan with and without food and in patients 1–8 following IV melphalan are shown in Fig. 1.

Bioavailability in patients 1–8 ranged from 29.1% to 95.5% (median 84.9) when melphalan was taken fasting and from 7.3% to 99.0% (median 57.9) when it was taken with food ($P<0.025$) (Table 2). The fall in bioavailability with food in patients 1–8 (27%) was not as great as the fall in AUC in patients 1–10 (39%), owing to the major contribution made to the latter by patients 9 and 10. No attempt was made to relate AUC or bioavailability with response or toxicity in this study, because of the heterogeneity of the patient group studied.

In the 27 pharmacokinetic studies carried out in 15 patients after oral melphalan, with or without food, a close correlation between AUC and the plasma melphalan concentration 1.5 h after administration was observed ($r_s=0.915$; $P<0.01$) (Fig. 2). The 1.5-h plasma levels ranged from 95.5 to 336 ng/ml when melphalan was taken fasting and from 0 to 227 ng/ml when it was taken with food.

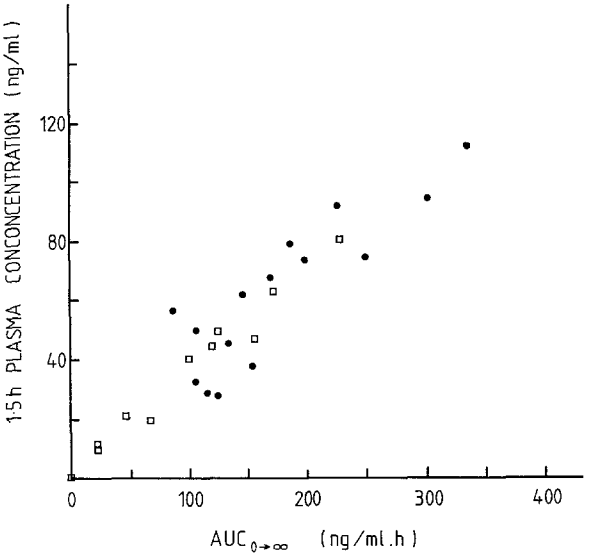

Fig. 2. Correlation between 1.5 h plasma level and AUC in 27 pharmacokinetic studies undertaken in 15 patients following oral administration of melphalan (5 mg/m^2) with (□) and without (●) food

Discussion

The large interpatient variability in AUC reported for both oral and IV melphalan [1, 3, 4, 8, 9, 11] has been confirmed in these studies. The variability was approximately six-fold for IV melphalan and four-fold for oral melpha-

lan taken fasting in both this and a recently published study in five patients [4]. The total clearance of IV melphalan was equally variable. The half-life, however, was less variable, suggesting that changes in volume of distribution had partly off-set alterations in clearance. Food introduced another element of variability, by generally reducing oral melphalan AUC and bioavailability when the drug was taken concurrently. These changes occurred without an alteration in absorption half-time, time to peak or terminal half-life of melphalan.

Our results were generally consistent with the findings of Bosanquet and Gilby's second study [4] on the effect of food on melphalan absorption; that is, that food reduced melphalan absorption, the reduction in AUC being 54% in their study of five patients and 39% in the present study of ten patients. A possible mechanism for the effect of food on melphalan absorption may lie in aminoacid transport. Both L-leucine and L-glutamine have been shown to be competitive inhibitors of melphalan transport across cell membranes [10]. Following ingestion of food, elevated levels of these aminoacids in small bowel lumen contents may competitively inhibit melphalan transport across the gutwall. In fasting patients variability in AUC may be attributable to inherent differences in the active transport of melphalan across the gutwall, as well as variable plasma clearance. The within-patient reproducibility of AUC observed in two patients who were studied twice was consistent with these mechanisms. Other mechanisms, such as direct chemical reaction with gastrointestinal contents or hydrolysis of the drug, are also possible, but would presumably give less predictabel results. Food is known to reduce the bioavailability of several drugs [6], including methotrexate [7], and many mechanisms have been proposed to explain these effects [6].

The excellent correlation between AUC and melphalan plasma level in a single sample drawn 1.5 h after administration of melphalan taken PO either with or without food is an important observation, since response to melphalan appears to correlate with AUC [4]. However, accurate estimation of melphalan AUC required the measurement of serial drug concentrations over a period of at least 4 h after administration. The present study has shown that a single plasma sample drawn 1.5 h after administration reflects AUC and may therefore allow individual tailoring of doses to overcome the problem of variable levels between patients, which could in turn improve clinical response to melphalan.

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