Cancer Chemother Pharmacol (1982) 9:57–60

Cancer Chemotherapy and Pharmacology

Plasma Melphalan and Prednisolone Concentrations During Oral Therapy for Multiple Myeloma

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Summary. *Nine patients with myeloma were studied over 13 oral administrations of 10 mg melphalan and 5–10 mg prednisolone. Plasma melphalan concentrations were estimated by high-pressure liquid chromatography, prednisolone concentrations by quantitative thin-layer chromatography. The mean plasma half-life of unchanged melphalan was 0.9 ± 0.5 (SD) h. The 'lag-time' before melphalan was detected in the plasma varied from 1 to 4 h, the mean peak concentration was 96 ± 21 ng/ml, and the mean area under the plasma concentration by time curve was 160 ± 78 ng h/ml. This variability was consistent with observations made elsewhere following much higher oral doses of melphalan and illustrates the relatively wide inter-individual variability of absorption. Observations made in the same subjects on two separate occasions showed lower variability. The melphalan elimination rate was not significantly affected by moderate impairment of creatinine clearance (to 31 ml/min). Absorption of prednisolone in five of these patients was apparently normal and unaffected by concurrent administration of melphalan.*

Introduction

Melphalan has been used for some 20 years in the treatment of myeloma: more recently various combinations of drugs with melphalan have been investigated, and in particular those with corticosteroids [5] have yielded good clinical responses. Although most usually given orally in low doses, analytical problems have limited the acquisition of pharmacokinetic information regarding this route of administration. A study in which an oral dose of 0.6 mg/kg was given showed extremely variable systemic availability and the time to first appearance of the drug in the plasma ranged from 0.25 to 6 h: in one patient the drug was not found in the plasma at all [2]. In the present paper we report the plasma levels of melphalan estimated by a sensitive high-pressure chromatographic assay following the administration of low oral doses of melphalan to patients with myeloma. The absorption of concurrently administered prednisolone was also determined in some of these patients.

Materials and Methods

Clinical Details. Details of the nine patients studied are shown in Table 1. All were being treated as outpatients for myloma with 5-day cycles of daily oral melphalan 10 mg (approximately 0.2 mg/kg) and prednisolone 5–10 mg 12-h. Four patients were studied on two occasions: three (FW, PE, WA) on the first and third days of a treatment cycle and one (AM) during two separate cycles, on the first occasion whilst taking cimetidine and on the second after its discontinuation. Many of the patients were also receiving concurrent drug therapy for other non-malignant conditions and it was considered ethically necessary to continue this treatment, which remained constant throughout a melphalan course. All patients freely consented

Table 1. Details of patients studied following oral melphalan and prednisolone for myeloma

Patient	DJ	EW	AM	PH	RE	FW	ES	PF	WA
Sex	M	F	M	F	M	M	F	M	M
Age (years)	40	72	54	57	55	76	77	71	64
Weight (kg)	71	68	83	63	77	57	59	67	77
Creatinine Clearance (ml/min)	119	71	31	100	61	54	44	53	67
Serum Ca^{++} (mmol/l)	2.30	2.21	2.48	2.15	2.45	2.68	2.53	2.20	2.28
Concurrent drug therapy[a]	P(5)	P(10)	P(10) A H Pr Ci*	P(10)	P(10)	P(10) L C F	P(10) O I	P(10) In	P(10)

[a] P, prednisolone (dose in mg); A, allopurinol; H, hydrochlorthiazide; Pr, propranolol; L, levodopa; C, carbidopa; F, folic acid; O, oxprenolol; I, ibuprofen; In, indomethacin; Ci*, cimetidine taken during first study but not second

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0344-5704/82/0009/0057/$ 01.00

Table 2. Summary of pharmacokinetic parameters following oral melphalan administration

Patient	Lag time (h)	Maximum plasma concentration (ng/ml)	Time of observed peak plasma concentration (h)	Elimination rate constant (h^{-1})	Half-life (h)	AUC (ng h/ml)
DJ	1.5	81	2.0	0.59	1.2	175
EW	1.0	129	2.0	0.65	1.1	224
AM (1)	2.5	70	3.0	0.59	1.2	158
(2)	1.0	85	1.5	1.46	0.4	102
PH	2.0	106	3.0	0.29	2.4	385
RE	4.0	136	6.0	0.83	0.8	182
FW (1)	1.0	68	1.5	1.39	0.5	96
(2)	1.5	109	2.0	1.03	0.7	84
ES	1.0	90	1.5	0.95	0.7	148
PF (1)	1.0	97	1.5	1.67	0.4	104
(2)	1.5	106	2.0	1.08	0.6	150
WA (1)	3.0	77	3.0	0.79	0.9	139
(2)	1.0	92	1.5	0.99	0.7	133
Mean	1.7	96	2.4	0.94	0.9	160
SD	1.0	21	1.3	0.39	0.5	78

to undertake the study protocol, which was approved by the appropriate Ethics Committee. On the study day the fasting patients received their medication with approximately 100 ml water, and venous blood samples were taken via a heparin lock at 0 (pre-dose), 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h into lithium heparin tubes. The blood was immediately centrifuged in a refrigerated centrifuge and the plasma then frozen and stored at −20° C.

Haematological and clinical chemistry variables were routinely measured 24–48 h before and 14–21 days after each study. In particular, white blood cell and platelet counts were made by Coulter counter, erythrocyte sedimentation rate (ESR) by Westergren's method, and total paraprotein by quantitative electrophoresis. This last was reported as a percentage of the presenting paraprotein concentration. The creatinine clearance was estimated from the serum creatinine by the method of Cockcroft and Gault [9].

Drug Analysis. Plasma melphalan concentrations were estimated by high-pressure liquid chromatography using minor modifications of our method as described elsewhere [13].

The lower limit of detection by this technique was 25 ng/ml. The recovery of melphalan from plasma was 85.3% ± 4.3%, but variations in recovery were compensated by use of an internal standard. No normal plasma constituents produced interfering peaks at the retention volume of melphalan, but interference by endogenous material made the estimation of monohydroxy- or dihydroxymelphalan impossible in some samples and these compounds were not measured.

Plasma prednisolone estimations were made by a quantitative high-performance thin layer chromatographic method modified as detailed by Al-Habet and Rogers [6]. The lower limit of detection by this assay was 10 ng/ml.

Pharmacokinetic Analysis. The pharmacokinetic analysis was perforce rudimentary. The elimination rate constant (k) was found from the regression of ln (plasma concentration) on time and from this half-life, $t_{1/2} = 0.693/k$. The area under the plasma concentration by time curve was estimated by trapezoidal approximation.

Table 3. Pharmacokinetic parameters after 10 mg oral prednisolone

Patient	Maximum plasma concentration (ng/ml)	Elimination rate constant (h^{-1})	Half-life (h)	AUC (ng h/ml)
DJ	272*	0.173	4.0	1512[a]
EW	227	0.279	2.5	1161
AM (1)	210	0.154	4.5	1481
PH	243	0.439	1.6	1018
RE	332	0.204	3.4	1979
Mean	257	0.250	3.8	1430
SD	48	0.116	0.9	371

[a] Corrected for a dose of 10 mg

Results

The plasma melphalan concentrations following these small oral doses were, as might be expected, very low. In most subjects only four or five of the samples contained sufficient melphalan to allow accurate quantitation by our HPLC technique. The estimates of the pharmacokinetic parameters (Table 2) are therefore correspondingly imprecise, although the values for half-life are based upon at least three points or more. There was a wide variation in the time of the observed peak plasma concentration (range 1.5–6 h), and the maximum plasma concentration had a relative standard deviation of 0.22. The total amount of drug absorbed, as reflected by the AUC, was also variable and had a relative standard deviation of 0.49.

The pharmacokinetic parameters determined from the plasma concentration by time profiles of prednisolone in five patients are shown in Table 3.

The effects of treatment on clinical measurements were variable. In all but one patients (EW) there was a fall in platelet count following treatment (median fall 39,000/mm^3; changes ranged from a fall of 141,000 to a rise of 2,000/mm^3). There was also an inconsistent response of the white blood cell count, the change ranging between a fall of 2,000/mm^3 to a rise of 1,300/mm^3. In all but one object (again EW) there was a decrease in the ESR (median decrease 8 mm; range of change

−109 to +8 mm), although the percentage paraprotein decreased in only four patients (median change −5%; range +16% to −28%). This lack of response of the paraprotein to treatment is not unexpected, since some of the patients had received several courses of treatment and had probably reached a plateau of response to this therapy.

Discussion

The plasma melphalan concentrations measured in this group of myeloma patients are comparable with those found by others using gas chromatography and chemical ionisation mass spectrometry for drug estimation [11]. In that study the peak levels were between 50 and 190 ng/ml after oral doses ranging from 0.17 to 0.24 mg/kg to five patients. In a study of 14 administrations of 0.6 mg/kg the mean peak plasma concentration was 280 ng/ml (range 70−630 ng/ml) [2]. Taking these studies into account the peak plasma concentration apparently increases approximately linearly with dose, although there is clearly a wide inter-individual fluctuation. A wide dispersion of lag-times was seen in our patients, as in the study discussed above [2], where the computed model-dependent lag time varied from 0 to 336 min.

Our myeloma patients had an estimated plasma melphalan half-life of 0.9 ± 0.5 h. This is slightly shorter than the value of 1.5 ± 0.95 h found after 0.6 mg/kg [2], but falls within the range 0.6−2.0 h found in five patients after a comparable dose [11]. A study in which C^{14}-labelled melphalan was administered orally as part of a dose of 4.4−6.4 mg/m^2 yielded a mean initial half-life of 1−1.2 h, followed by a prolonged terminal phase in the disappearance of label from the plasma, with an approximate half-time of 160 h [14]. This may represent loss of melphalan from a deep compartment or, more probably, indicate that dihydroxymelphalan (the inactive, major metabolite of melphalan, which has a prolonged elimination) was the major component of this labelled material [1]. In the present study no evidence for a prolonged terminal phase was found (although this could result from the relative insensitivity of the assay).

The intersubject variation in AUC and variable lag time and time to peak are consistent with the erratic oral absorption of melphalan suggested by other studies [2, 14]. There is no significant pre-systemic or first-pass metabolism for melphalan [3], and these observations indicate a variation in drug absorption rather than disposition. This could be the cause of failure of tumour response rather than inherent tumour resistance. By courtesy of Dr R. D. Rubens of the Breast Unit, Guy's Hospital, we have studied the absorption of oral doses of 5−8 mg melphalan in three patients receiving adjuvant chemotherapy following removal of a carcinoma of the breast. In two of these the results were similar to those seen in this group of myeloma patients, but in the third only a single sample at 3 h after 8 mg was found to contain a measurable melphalan concentration. The implication of these results is that oral melphalan dosage requires individual consideration. Nevertheless, the effects of the 5-day course of melphalan (and prednisolone) in our patients were clearly reflected in the decline in platelet counts and other changes. Others have reported that with oral doses of melphalan of 9 mg/m^2 daily for 4 days less than 10% of patients have white cell or platelet suppression [8]. It is a widely held opinion that maximal action of melphalan is associated with leucopenia, but it has not apparently been shown that response in myeloma is correlated with this action.

Presently it is unknown whether the variable oral bioavailability of melphalan is constant within individuals or whether it varies with time, condition of the patient, concomitant food and drug ingestion, etc. In the three subjects studied twice within a single cycle of melphalan treatment the differences in maximum plasma concentration and AUC were of the order of 15%−20%, which may well lie within the limits of experimental error and provides no evidence for wide fluctuations of absorption within individuals. In vitro studies have shown that melphalan tablets dissolve more rapidly at low pH [2] and melphalan hydrolysis is also slower in an acid environment [10]. Patient AM was studied during two separate treatment cycles: first while receiving cimetidine and subsequently without this concurrent therapy. It may be no more than coincidental that the AUC for the first treatment was 50% higher than the second. Certainly the possible interaction between H_2-histamine receptor blockade and melphalan absorption with possible therapeutic benefits deserves closer attention.

The absorption and disposition of prednisolone in these patients was unremarkable and similar to that found in other studies [5], suggesting that there was no intrinsic drug absorption disturbance in these patients with myeloma.

It has been suggested that melphalan dosage be reduced in uraemic myeloma patients, and speculated that the rate of melphalan urinary excretion might be decreased in the presence of renal failure [12]. In dogs with renal insufficiency due to partial nephrectomy a significant increase in the myelotoxic effects of melphalan was noted [4]. Although a significant decrease in systemic and renal clearance of melphalan was demonstrated in these dog studies the overall fraction of melphalan clearance due to urinary elimination was only of the order of 5%−6%, and the main change in melphalan clearance must therefore have been in the non-renal clearance. In man the renal contribution to systemic clearance is similarly minor, and only 13.0% ± 5.4% of an IV dose of 0.6 mg/kg^{-1} appeared in the urine over 24 h [3]. Although the estimates of half-life in the present study are relatively imprecise the coefficient of determination (r^2) for a linear relationship between k and creatinine was only 0.25. This would be anticipated if renal clearance were making only a minor contribution to total systemic clearance. In the absence of accurate elimination data from myeloma patients the effect of renal impairment in modifying melphalan disposition cannot be predicted with confidence.

In adjuvant chemotherapy for breast tumours with cyclophosphamide, methotrexate, and fluorouracil, the best results accrue with the highest doses [7]. If this can be extrapolated to melphalan adjuvant therapy it is clear that oral doses producing low plasma levels (and little toxicity) may be ineffective, perhaps explaining the divergent results in adjuvant chemotherapy trials with melphalan. It has been pointed out that the majority of patients do not develop leucopenia following oral melphalan given according to standard protocols for myeloma, although this often occurs after IV treatment [8]. Similar considerations may therefore apply to the use of melphalan in the chemotherapy of myeloma.

Acknowledgements. R. A.−J. A. was a postgraduate research fellow of Mosul University, Republic of Iraq. We are grateful to S. M. Al-Habet for assistance with plasma prednisolone measurements and to the South East Thames Regional Health Authority for financial assistance. Part of this work was carried out in the Pfizer Clinical Pharmacology Unit at the Kent and Canterbury Hospital.

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Received March 17/Accepted April 27, 1982