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Interaction of cimetidine with oral melphalan

A pharmacokinetic study*

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Summary. The effects of pretreatment with cimetidine (200 mg three times daily, 400 mg at night) on the pharmacokinetics of oral melphalan (10 mg) have been investigated in patients with multiple myeloma. Cimetidine pretreatment reduced the bioavilability of oral melphalan by approximately 30% ($P < 0.05$). The elimination rate of melphalan from plasma was significantly increased by cimetidine ($P < 0.05$), the half-life being reduced from 1.94 ± 0.55 h to 1.57 ± 0.53 h. Cimetidine appeared to reduce the interindividual variability in melphalan absorption, but at the cost of reduced bioavailability.

Introduction

The alkylating agent melphalan given p.o. as a single agent is extensively used in the treatment of multiple myeloma [6]. It has also been used for the treatment of other forms of malignant disease, usually in combination chemotherapy. In high doses the intravenous form is used as preconditioning prior to marrow transplant procedures in some centres.

The pharmacokinetics of oral melphalan for the conventional doses used in the therapy of myeloma [8] and for higher doses [1, 2] have previously been reported. These studies have shown that melphalan has a relatively short half-life in plasma of between 60 and 90 min. Moreover, the oral bioavailability of melphalan was variable, being between 25% and 100% [2, 8]. This variability in bioavailability may be related to the instability of melphalan in solution [3, 4].

The current study was initiated to investigate the effects of H2 receptor blockade produced by cimetidine on the oral bioavailability of melphalan.

Methods

The study was approved by the Ethics Committee of the University of Newcastle upon Tyne. All patients gave informed consent. Eight patients completed the study protocol, which was double blind (Table 1). They received, in random order, 5 days' pretreatment with a full dose of cimetidine, 200 mg three times daily and 400 mg at night, or matching placebo. On the 6th treatment day with cimetidine they commenced their normal course of melphalan (Alkeran, Wellcome Medical Division) 10 mg p.o. daily in the morning for 5 days, and the cimetidine or placebo was continued concurrently. On the first day of the melphalan course patients attended the clinical laboratory at 9 a.m. having taken their cimetidine on rising, but having refrained from eating breakfast.

After baseline blood samples had been drawn, the patients took their melphalan tablets with 100 ml water. Blood for plasma melphalan estimation was drawn at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4 and 5 h. Samples were kept on ice, centrifuged at 4° C and stored at −50° C prior to assay, usually within 7 days of sampling.

Melphalan was estimated in plasma by HPLC as previously described [7]. Essentially the assay entailed an initial extraction with isopropyl alcohol containing the internal standard (*N*-acetylprocainamide). The supernatant was back-extracted into chloroform, which was evaporated to dryness under nitrogen. Samples were reconstituted in mobile phase, 70% methanol and 30% 0.01 *M*, sodium dihydrogenous phosphate (pH 3), and injected onto a Spherisorb ODS 10 μm 25 cm × 4 mm steel column with spectrofluorimetric detection (excitation 256 nm and emission 360 nm).

Blood samples for full blood count and platelet estimation (Coulter Counter) and urea and electrolyte estimation were obtained before the dose of melphalan (after 5 days of cimetidine) and again 10 days later. Compliance was estimated by tablet counts.

The pharmacokinetic parameters of oral melphalan were calculated by standard techniques. The elimination half-life was calculated by least-squares regression analy-

Table 1. Patient details

Pt. no.	Age	Sex	Diagnosis	Other medication
1	60	M	IgG multiple myeloma	Nil
2	60	F	Monoclonal gammopathy	Bendrofluazide-K
3	51	F	IgG multiple myeloma	Penicillin V
4	70	M	IgG multiple myeloma	Oxytetracycline
5	78	F	IgG multiple myeloma	Bumetanide K
6	75	M	IgG multiple myeloma	Nil
7	75	F	IgA multiple myeloma	Betahistine
8	67	F	IgG multiple myeloma	Nil

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Table 2. Melphalan – kinetic data

Placebo Subject		$t_{1/2}$ (h)	AUC 5 h (μg/l · h)	AUC ∞ (μg/l · h)
1		1.26	261	285
2		0.91	354	368
3		0.82	169	177
4		4.95	385	785
5		1.88	251	349
6		2.52	620	860
7		1.30	385	432
		1.94	346.4	465.1
	SEM	0.55	54.7	97.3
Active				
1		1.22	168	206
2		0.44	100	111
3		0.33	171	175
4		4.47	200	522
5		0.90	194	223
6		2.04	334	447
7		1.59	342	417
8		(0.6)	(54)	(73.8)
		1.57	215.6	300
	SEM	0.53	33.9	59.9
Mean difference		0.38	130.8	165
	$t =$	2.50	3.11	2.88

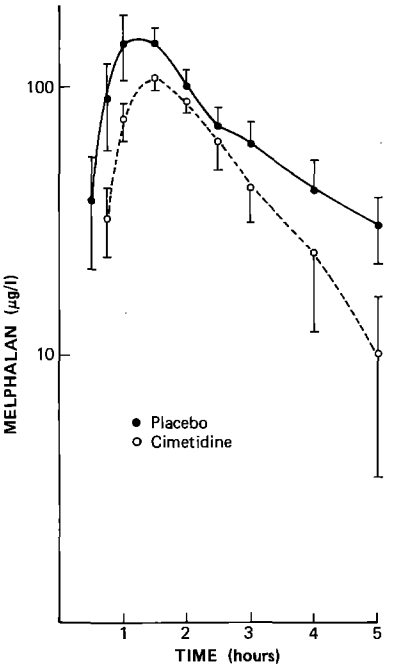

Fig. 1. Plasma concentrations of melphalan following pretreatment with placebo (●) or cimetidine (○) ($n = 7$)

sis, and the area under the curve (AUC) by the trapezoidal rule. Extrapolation of the unknown area beyond the last plasma concentration measured was from C_t/K_{el}, where C_t is the last concentration point and K_{el} the elimination rate constant. Statistical analysis was by the paired *t*-test.

Results

The samples from the placebo phase of one patient were lost during analysis. Statistical analysis was therefore carried out on the data of the seven patients in whom matched samples from cimetidine and placebo treatments were available. Tablet counts suggested full compliance with therapy.

Melphalan kinetics

Pretreatment with cimetidine for 5 days produced a significant ($P < 0.05$) reduction in the bioavailability of melphalan (Table 2) by approximately 30%. This was associated with an elimination rate which was also more rapid, resulting in a significant ($P < 0.05$) change in half-life from 1.94 ± 0.55 h to 1.57 ± 0.53 h.

There was no statistically significant difference in the time to measured peak melphalan concentration (placebo 1.4 ± 0.19 h, cimetidine 1.6 ± 0.13 h), and although the measured peak concentration was lower with cimetidine, at 110 ± 11.6 μg/l this was not statistically significantly different from the placebo value of 182.1 ± 25.7 μg/l. The range in peak melphalan concentration was 3-fold after placebo pretreatment but only 2-fold after cimetidine (Fig. 1).

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There was no significant effect of cimetidine, as compared with placebo, on the white cell count, platelet count or electrolytes and serum creatinine and urea measured on the last day of the melphalan course (Table 3). Similarly, there were no differences at day 10. There were no adverse effects of the addition of cimetidine to the melphalan course in these patients with myeloma.

Table 3. Effect of placebo or cimetidine on total white cell count, platelet count, urea and creatinine before and after 5 days of melphalan therapy (Mean ± SEM)

	WBC × 10/l	Platelets × 10/l	Urea (mmol/l)	Creatinine (μmol/l)
Placebo				
Pre	4.57 ± 0.61	275.4 ± 13.9	7.93 ± 1.90	116.1 ± 23.6
Post	4.08 ± 0.40	248.1 ± 22.5	9.14 ± 1.98	115.0 ± 27.0
Placebo				
Pre	3.51 ± 0.24	297.6 ± 23.8	7.61 ± 0.72	101.0 ± 13.3
Post	3.91 ± 0.35	263.3 ± 23.6	6.82 ± 0.56	113.4 ± 15.9

Discussion

Previous studies on the pharmacokinetics of melphalan have shown that its bioavailability is variable [1, 2, 8]. This is thus a potential source of the variation in clinical response to this agent. Melphalan has a short half-life in plasma, which approximates to that observed in vitro, and probably represents spontaneous breakdown of the molecule [3]. Thus, the elimination of melphalan in humans is not likely to be affected by an alteration in the activity of hepatic microsomal enzymes, which are well recognised to be impaired by cimetidine.

On the other hand, the stability of melphalan in solution is temperature- and pH-dependent [3, 8]. Thus, at an alkaline pH melphalan is more unstable. Therefore it is probable that the reduction in bioavailability of melphalan produced by cimetidine is due in part to the alteration in gastric acidity that H2 blockade produces. Other possible effects might also include a change in hepatic blood flow [5].

One patient (pt 3) showed little change in an already low bioavailability with cimetidine treatment. It seemed possible that she might have achlorhydria, and she was therefore subjected to a pentagastrin test. This showed that her gastric acid secretion was normal. Factors other than gastric pH alone therefore appear to be important in determining melphalan bioavailability.

We have no explanation for the increase in elimination rate of melphalan we have observed with cimetidine, but it is possible that this reflects a dose-dependent interaction between melphalan and plasma.

In conclusion, we suggest that clinicians should be aware of the wide interindividual differences in melphalan bioavailability, which have been demonstrated again by our studies. Furthermore, this variability can be reduced to some extent by cimetidine, but this is at the cost of a further reduction in bioavailability.

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