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Renal function in the elimination of oral melphalan in patients with multiple myeloma*

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Summary. Pharmacokinetic studies in 11 patients with multiple myeloma were undertaken on the first and last days of one course of chemotherapy. The drug was administered PO in single doses of 6–14 mg daily. Melphalan concentrations were determined by high-performance liquid chromatography. The interpatient variability of pharmacokinetic parameters noted by other authors was observed. Regression analysis showed a significant positive correlation between the elimination rate constant for melphalan and renal function ($P=0.003$). The form of the line which describes the overall elimination rate constant for melphalan is given by the equation: $K_{el}=5.67\times 10^{-3}+[4.90\times 10^{-5}\times \mathrm{GFR}]$. There was also a significant negative correlation between renal function and the area under the plasma melphalan concentration/time curve ($P=0.006$). In vitro stability studies of melphalan in plasma at 37 °C and pharmacokinetic data suggest that hydrolysis and renal clearance are the major mechanisms of melphalan elimination. This work shows quantitatively the relationship between renal function and drug elimination and how the data may be used in predicting melphalan half-life from creatinine clearance.

Introduction

Melphalan (Alkeran) is currently used in the treatment of several malignant disorders, including multiple myeloma and carcinoma of the breast and ovary [10], and although the effectiveness of the drug in the therapeutic management of these conditions is unquestionable, several potentially serious side effects primarily related to bone marrow toxicity may occur [10, 11]. Melphalan (IV)-induced myelosuppression has been shown to occur more frequently in the patients with multiple myeloma who have renal dysfunction than in those with normal renal function [8]. This difference failed to reach statistical significance with oral administration and has been attributed to the lower peak plasma levels of drug associated with this route of administration. These considerations are important in melphalan chemotherapy, because significant renal dysfunction occurs in over 50% of patients with multiple myeloma, 29% suffering renal failure at diagnosis [12]. Infection is a frequent occurrence in myeloma, and nearly 70% of patients die as a result of infection [12]. Thus, melphalan-induced myelosuppression in the myeloma patient may lead to life-threatening infection.

Alberts et al. [4] noted in animal studies that the result of poor renal function was to prolong the elimination half-life of melphalan. Bosanquet and Gilby [5, 6] observed a trend in the relationship between the elimination rate constant and renal function in patients receiving IV melphalan, although no mathematical details were given. However, they were unable to establish a mathematical correlation for drug administered PO. Quantification of the relationship between renal function (glomerular filtration rate, GFR) and melphalan elimination may make the identification of those patients at risk of serious myelosuppression less empirical.

Materials and methods

Melphalan was assayed in plasma by means of isocratic ion-pair-high-performance liquid chromatography (HPLC) [1]. This technique permits detection of drug in plasma to 5 ng/ml using UV absorption at 260 nm. Melphalan was separated on a Spherisorb ODS 5-μm column (250 × 4.6 mm ID). The mobile phase was a mixture of 80% methanol, 20% water, and 0.0135% (wt/vol) sodium dodecyl sulphate. This was adjusted to pH 3.11 with sulphuric acid. Chromatography was performed at 40 °C, using a column oven. Drug extraction necessitated the precipitation of the macromolecular components in 3 ml plasma with 132 μl concentrated perchloric acid. The supernatant was passed through a C_{18} Sep Pak, and polar components were subsequently removed by washing the cartridge with 10 ml 15% methanol in water (vol/vol). Melphalan was eluted from the Sep Pak with 2 ml methanol, 200 μl of which was injected onto the column. Drug retention time was in the order of 9.5 min. No interference from plasma components was observed at the retention time of melphalan in any of the patients.

Details of the 11 patients studied are given in Table 1. Studies were carried out on the first and last days (day 4 or 5) of one course of chemotherapy, after patients had fasted overnight in each case. Patients remained seated throughout the study and were not permitted food or drink until

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Table 1. Details of patients studied

Patient	Sex	Age (years)	Body wt (kg)	Body surface area (m^2)	GFR (ml/min)	Dose (mg)
SM	F	58	53	1.49	58	10
BK	M	42	75	1.82	116	14
VF	F	64	78	1.87	93	10
JW	M	70	70	1.73	44	10
AG	M	54	71	1.75	95	10
WN	M	65	57	1.67	25	6
MB	F	52	60	1.69	91	12
JM	M	61	75	1.82	88	12
PC	M	49	83	1.96	103	10
JC	M	57	63	1.60	71	10
GD	M	64	84	1.97	96	14

3 h after drug administration. Peripheral blood samples (6 ml) were taken before drug administration and 30, 40, 50, 60, 70, 90, 120, 180, 240 and 300 min after the dose. The dose given ranged from 6 to 14 mg daily (WN whose GFR was 25 ml/min, was given a reduced dose in accordance with the guidelines of the MRC Myeloma Trial). Samples taken via a cannula in a forearm vein were stored in heparinized tubes. Plasma samples were kept on ice (6 h) prior to analysis by HPLC upon completion of the study. Stability studies for melphalan indicate that it did not undergo hydrolysis during the conditions reported here for sample collection and extraction.

The rate of the spontaneous degradation of melphalan at 37 °C was determined in normal donor and myeloma plasma. Plasma was incubated at 37 °C and aliquots (1 ml) removed at intervals up to 6 h. Samples were then assayed for the parent compound.

Serum creatinine levels were measured by routine procedure at the biochemistry laboratory of the Royal Victoria Hospital on both days of study. Glomerular filtration rates (GFR) were calculated according to a formula adapted from that of Cockcroft and Gault [6, 7] (Eq. 1).

$$\text{GFR (ml/min)} = \frac{k\,[140 - \text{Age (years)}] \times \text{wt (kg)}}{\text{Serum creatinine } (\mu M)} \quad \text{Eq. 1}$$

$$= k = 1.23 \text{ for men and } 1.04 \text{ for women.}$$

Elimination rate constants were calculated by linear regression of log plasma melphalan/time profiles. The area under the plasma melphalan/time curve (AUC) was calculated using the trapezoidal rule and extrapolated to infinity. Statistical correlation of data was performed by regression analysis.

Results

The pharmacokinetic parameters are given in Table 2, where each value is the mean of those recorded on the 2 days of the study. Results (mean ± SD) were very variable, with peak plasma levels of 105 ± 35 ng/ml. The AUC, GFR, and elimination rate constants also showed considerable variability, with mean values (± SD) of 14.66 ± 5.29 μg.min ml^{-1} 80 ± 27 ml/min, and 9.60 ± 1.68×10^{-3} min^{-1}, respectively. The hydrolysis rate constant for melphalan in myeloma and normal donor plasma was 5.82×10^{-3} min^{-1}, which is in close agreement with the value obtained by Alberts et al. (5.5×10^{-3} min^{-1}) [3]. No significant difference in hydrolysis was noted between patient and normal donor plasma. Stability studies of melphalan in plasma stored on ice for 6 h indicate that it did not undergo hydrolysis in the conditions reported for sample collection. Regression analysis of melphalan concentration against time showed that the slope of the line did

Table 2. Summary of pharmacokinetic parameters following oral melphalan administration

Patient	Time to peak plasma conc. (min)	Peak plasma conc. (ng/ml)	Area under curve (μg · min/ml)	Elimination rate constant ($min^{-1} \times 10^{-3}$)	$t_{1/2}$ (min)
SM	60	171	24.33	8.45	82
BK	68.5	54	6.81	9.40	74
VK	50	118	14.21[a]	11.38	61
JW	56.5	95	13.38[a]	7.24	98
AG	150	77	11.76[a]	11.14	62
WN	90	127	23.71[a]	6.90	100
MB	90	127	12.90	11.54	60
JM	79	85	10.85	10.13	68
PC	50	129	14.55[a]	11.40	61
JC	44.5	109	17.03[a]	8.63	80
GD	56	59	11.56	9.34	74
Mean + SD	72 ± 30	105 ± 35	14.66 ± 5.29	9.60 ± 1.68	75 ± 14

[a] AUC and peak plasma concentration adjusted for a dose of 7 mg/m^2

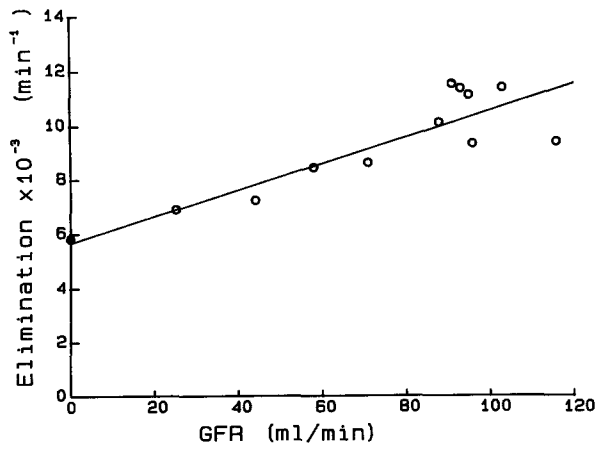

Fig. 1. The relationship of GFR to the overall elimination rate (K_{el}). The equation of the line is given by: $K_{el} = 5.67 \times 10^{-3} + (4.90 \times 10^{-5} \times GFR)$. ○, calculated from patient data; ● Calculated from in vitro hydrolysis of melphalan in plasma at 37 °C. The statistical analysis reported in the text was calculated from patient data only. $N = 11$; $r = 0.81$; $P = 0.003$

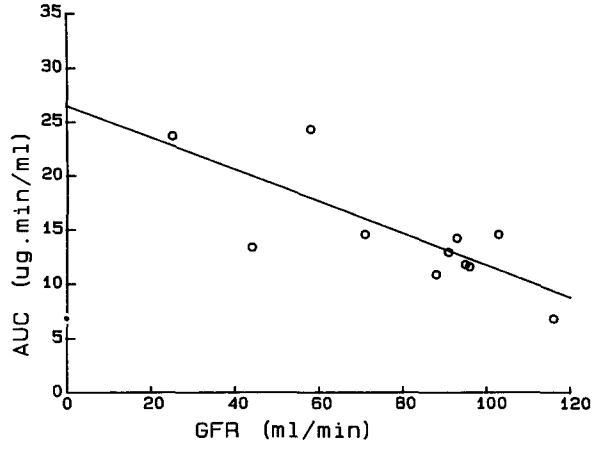

Fig. 2. Relationship of GFR to the AUC. $N = 11$; $r = -0.77$; $P = 0.006$

not differ significantly from zero ($r = -0.14$; $P = 0.75$). The coefficient of variation in concentrations was 4% over this time period.

The elimination rate constant for melphalan in plasma significantly correlated with GFR (Fig. 1 $P = 0.003$). When the in vitro hydrolysis rate constant was included in the regression analysis, significance increased ($P < 0.001$). A negative correlation was found upon regression of GFR with AUC (Fig. 2, $P = 0.006$). Patients with reduced renal function (SH, JW, JC and WN) had significantly higher values for AUC (19.61 ± 5.31 μg min^{-1} ml^{-1} than those with renal function within the normal range (11.81 ± 2.60 μg min^{-1} ml^{-1}) ($P = 0.002$).

There was no statistically significant difference in pharmacokinetic parameters between the 2 days of study, although intrapatient variation was observed. Intrapatient variation was 15% ± 9% (mean ± SD) for elimination rate constants and 26% ± 13% (mean ± SD) for AUC.

Discussion

The intercept on the ordinate of Fig. 1 (5.67×10^{-3} min^{-1}) in close agreement with the in vitro rate constant of hydrolysis for melphalan in plasma at 37 °C (5.82×10^{-3} min^{-1}). This suggests that spontaneous hydrolysis is the major mechanism of extrarenal metabolism of melphalan in man [2]. This conclusion is supported by the work of Evans et al. [9], who showed that melphalan was not subject to hepatic metabolism. The importance of renal elimination is supported by earlier pharmacokinetic studies. In particular, Alberts et al. [2] have shown that 90%–100% of ^{14}C radioactivity can be accounted for in plasma and urine up to 24 h after drug administration. In addition, up to 54% of the total dose administered was excreted in the urine over this period. Bosanquet and Gilby [5] noted a trend in the elimination rate constant/GFR relationship in patients given IV melphalan. However, no data showing the mathematical relationship were provided, and no AUC/GFR correlation was observed.

The line representing the relationship between overall elimination (K_{el}) of melphalan and renal function (GFR) is given by Eq. 2.

$$K_{el} = K_{nr} + \alpha \cdot GFR. \qquad \text{Eq. 2}$$

K_{nr}, the non-renal elimination rate constant obtained from the intercept of the ordinate of Fig. 1, has a value of 5.67×10^{-3} min^{-1}. The slope of Fig. 1 (α) is 4.9×10^{-5} ml^{-1} and, when multiplied by GFR, it gives the renal elimination rate constant. Thus, the overall elimination rate constant becomes: $5.67 \times 10^{-3} + [4.90 \times 10^{-5} \times GFR]$.

Equation 3 describes the elimination rate constant for melphalan in the patient as a fraction (Q) of the 'normal' elimination rate constant, K_n (assuming GFR = 100 ml/min):

$$Q = \frac{K_{el}}{K_n} = \frac{K_{nr}}{K_n} + \frac{\alpha}{K_n} GFR. \qquad \text{Eq. 3}$$

From Eq. 3, a patient with a GFR of 20 ml/min will have an elimination rate 63% of that for a patient with a GFR of 100 ml/min. Using the data presented, it is then possible to calculate the half-life of elimination from Eq. 4 and identify those patients in whom reduced drug clearance may promote myelotoxicity.

$$t_{1/2} = \frac{0.693}{K_{el}}. \qquad \text{Eq. 4}$$

The interpatient variability of AUC observed in this study is in agreement with that observed by other authors [2, 4, 5, 6, 13]. This has generally been attributed to bioavailability alone. However, our work suggests that renal function, in affecting drug elimination, is an important determinant of AUC. While the regression line for Fig. 2 (AUC/GFR relationship) is statistically significant, the rate of increase in AUC with decreasing GFR is marginally greater than can be accounted for by Fig. 1 (K_{el}/GFR). This difference is in the order of 18% greater than would be expected from the equation of the line given by Fig. 1 and may be due to the unusually large AUC observed for patient SM. Nevertheless, the data indicate a clear inverse dependence of AUC on GFR, giving a kinetic basis for the

suggestion made in previous work [8] that the dose should be reduced in patients with renal insufficiency.

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