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Short communication

The effect of food on the oral administration of 6-mercaptopurine*

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Summary. The effect of food on the bioavailability of 6-mercaptopurine (6-MP) has been investigated. Seven patients were studied on two separate occasions. On the first occasion 6-MP was administered p. o. after an overnight fast and on the second, 15 min after a standard breakfast. 6-MP concentrations were determined by high-performance liquid chromatography. Variable plasma drug levels were observed between individual subjects in the fasting state. The peak levels of 6-MP were lower and took longer to be achieved following administration after a standard breakfast than after an overnight fast. In two subjects levels were undetectable (< 20 ng/ml). In view of these observations it is suggested that 6-MP should be administered before food if maximum blood levels are to be achieved.

Introduction

The empirical determination of the 6-mercaptopurine (6-MP) dosage used in the maintenance chemotherapy of acute lymphoblastic leukaemia (ALL) has recently been questioned. Zimm et al. [7] have expressed concern at the variable, and in some cases very low, plasma concentration of 6-MP in patients receiving the drug by mouth and have suggested that dosage should be modified according to pharmacokinetic principles. Schouten et al. [6] have also suggested that 6-MP is not optimally prescribed. The reasons were based on their findings that plasma 6-MP concentrations in patients are frequently considerably lower than required for in vitro cytolytic effects.

Variable plasma concentrations following oral dosage of many drugs have been reported. The major factor involved in this variability is absorption from the gastrointestinal tract. For example, Bosanquet and Gilby [1] have reported a decrease in the bioavailability of melphalan when administered immediately after a standard meal. In view of these observations it was decided to evaluate the effect of food on the bioavailability of 6-MP in leukaemic patients.

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Methods

The seven subjects, aged between 10 and 70 years, were patients in first remission of ALL, receiving daily 6-MP as part of maintenance therapy. All had normal renal and hepatic functions (Table 1).

They were studied on two separate occasions. The first daily dose of 6-MP (31.2–81.1 mg/m^2) was administered after an overnight fast. On the second day the same dose was administered 15 min after breakfast, which consisted of a glass of orange juice, a bowl of cereal, two pieces of toast with butter and marmalade and a cup of tea or coffee. Drinks were allowed following the 60-min blood sample. Blood samples (5 ml) were taken by venepuncture, immediately before the dose was administered and subsequently at 15, 30, 45, 60, 75, 90, 120, 150 and 180 min after

Table 1. Peak 6-MP levels and time to peak level after an overnight fast and a standard breakfast, in seven patients

Subject	Age (years)	Dose (mg/m^2)	Peak 6-MP Level (ng/ml)		Time to peak level (min)	
			Fast	Break	Fast	Break
JR	10	60.0	225.2	83.0	15	90
MB	63	73.5	302.6	47.6	90	150
RP	23	39.0	37.5	ND[a]	75	ND[a]
DS	20	31.2	36.4	23.8	45	120
RS	68	81.1	94.8	111.5	150	120
ME	70	66.7	83.2	80.3	120	150
LH	50	47.6	73.7	ND[a]	45	ND[a]

[a] All points on the concentration time curve were below the limit of detection (20 ng/ml)

administration. The blood was collected into heparinised tubes and separated immediately; the plasma was stored at −20 °C until analysed. 6-MP was assayed by the high-performance liquid chromatography method of Burton et al [2]. Statistical analysis was carried out using Spearman's rank correlation coefficient and Student's *t*-test.

Results

Although there was a wide variation in drug dose (31.2–81.1 mg/m^2) and age of patients (10–70 years), no statistical correlation was found between these variables and either peak 6-MP levels or area under the curve (Table 1). All zero-time samples were below the limit of detection (20 ng/ml) and are not shown in Fig. 1. Several samples from some subjects were also below the limit of detection, and all samples from two subjects (RP and LH) were below 20 ng/ml following the standard breakfast.

Although there was a trend towards lower peak levels and longer times to peak level when the dose was administered after a breakfast, the differences were not statistically significant. Out of the seven subjects only one (RS) had a higher peak level and a shorter time to peak level after a breakfast. Comparison of areas under the curve could not be carried out as some patients had not been sampled for long enough.

Discussion

Even though the number of patients used in this pilot study is small, there is a definite trend in the results suggesting an impairment of absorption following food in the majority of subjects. A delay in absorption would be expected as, in addition to any general effect, such as changes in gut transit time [5], 6-MP can form mixed disulphides with other thiols in the food, e.g. in proteins.

We share the concern of Zimm et al. [7] at the variable drug levels of 6-MP acheived in patients. It is probable that a long-term steady-state level of 6-MP is more important than peak levels after administration. It has been suggested that intracellular levels of 6-MP metabolites are important determinants of effect [4], as the metabolites build up in a cell during the course of treatment. No attempt was made to correlate results with outcome of treatment, but the relationship between intracellular metabolites with either peak plasma levels or steady-state levels remains to be determined. In our study all zero-time samples were below 20 ng/ml, so it was impossible to determine a steady state if one existed.

The management of patients receiving maintenance chemotherapy involves the adjustment of drug dosage according to the degree of neutropenia induced. Prior to adjusting the dose of 6-MP it may be expedient, in the first instance, to improve the absorption of the drug by administration when patients are in the fasting state.

The effect of food on the bioavailability of various drugs has recently been discussed [3]. It was concluded that "for the practising clinician the practical implications of all this research are straightforward. Most drugs may be given at mealtimes." This may be true for many drugs, but in view of the decreased bioavailability due to the presence of food, patients should be advised to take 6-MP some time before meals in order to achieve maximum plasma levels.

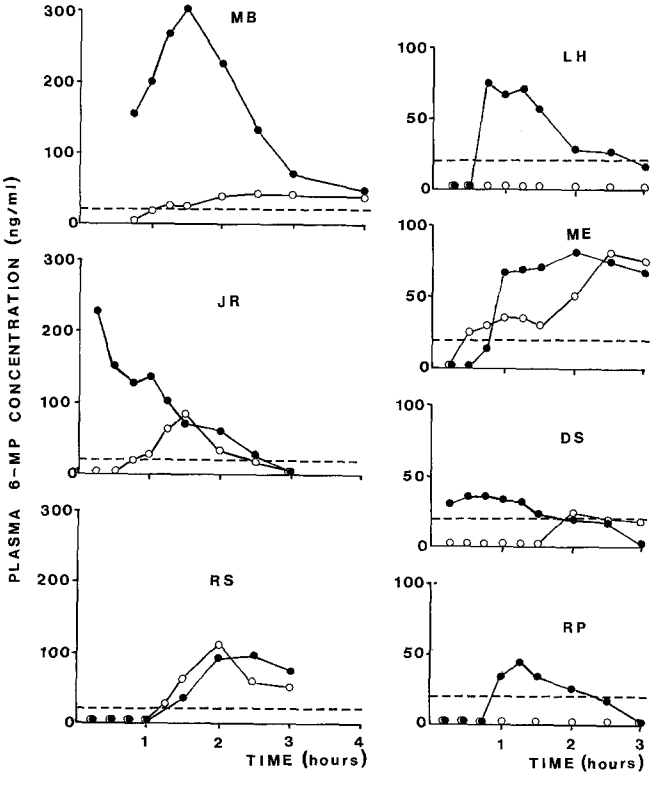

Fig. 1. Concentration-time curves for individual patients after administration of 6-MP immediately after an overnight fast (●) and after a standard breakfast (○). - - -, Limit of detection (20 ng/ml)

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