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Short communication

The effect of cotrimoxazole on the absorption of orally administered 6-mercaptopurine in the rat

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Summary. The effect of cotrimoxazole (CTX) on plasma levels of 6-mercaptopurine (6-MP) was studied in the rat. Animals receiving CTX in conjunction with 6-MP were found to have a marked but non-significant decrease in the area under the plasma time curve as compared with animals receiving 6-MP alone. It is suggested that the bioavailability and thereby, the antileukaemic effect) during maintenance therapy of ALL of 6-MP may be decreased by the co-administration of CTX.

Introduction

Although 6-mercaptopurine (6-MP) has been a mainstay of maintenance therapy in acute lymphoblastic leukaemia (ALL) for many years, very few studies have been carried out on its interactions with co-administered drugs. Rees et al. have suggested that cotrimoxazole (CTX), an antibiotic used in patients on immunosuppressive therapy, affects the disposition of 6-MP [4]. They reported that in children receiving CTX during maintenance therapy, correlations between red blood cell (RBC) 6-thioguanine nucleotide (6TGN) concentrations and 6-MP dose and between RBC 6TGN and absolute neutrophil count (ANC) broke down. In a previous paper from the same laboratory it was suggested that intracellular 6TGN, being an active metabolite of 6-MP, would give an excellent indication of 6-MP utilisation [3]. Thus the failure of the above correlations with 6TGN concentration is indicative of some perturbation in the pharmacokinetics or utilisation of 6-MP.

In the present study we have investigated the effect of CTX on the pharmacokinetics of oral 6-MP after both acute and chronic oral dosing of CTX in the rat as an animal model.

Materials and methods

6-MP was obtained from Sigma Chemical Co Ltd (Poole, Dorset, UK). CTX was used as Septrin I.M. (160 mg trimethoprim, 800 mg sulphmethoxazole per 3 ml) obtained from Wellcome Medical Division (Crewe, Cheshire, UK).

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Eighteen male Wistar-Albino rats were used for the experiment (weight range 249–336 g). The animals were randomly split into three groups of six and each group was treated as follows:

Group 1. The rats were denied food overnight and a dose of 6-MP (8.5 mg/kg dissolved in 0.02 *M* NaOH) was administered by oral gavage. Blood samples were taken from the tail vein into heparinised tubes at 10, 20, 30, 40, 50, 60, 75, 90 and 120 min.

Group 2. The rats were denied food overnight and a combined dose of 8.5 mg/kg 6-MP and 1.8 mg/kg CTX (as measured by trimethoprim), dissolved in 0.02 *M* NaOH, was administered by oral gavage. Blood samples were taken as described for Group 1.

Group 3. These animals were predosed for 4 days with 1.8 mg/kg CTX dissolved in distilled water administered by oral gavage. On day 5 the animals were denied food overnight, 6-MP was administered together with CTX (dissolved in 0.02 *M* NaOH), and pharmacokinetic data were measured in blood samples taken as described above.

In all groups the blood was centrifuged as soon as possible (9950 g for 5 min), and the plasma was immediately removed and stored at −20 °C until analysed. All dosing was carried out between 09.00 and 09.30 h.

Concentrations of 6-MP were measured according to the method of Burton et al. [1], with the extraction procedure scaled down to accommodate 200 µl plasma.

Results

The concentration-time curves for 6-MP alone and 6-MP in combination with CTX are shown in Fig. 1. It can be seen from these curves that the mean 6-MP levels were lower when CTX was co-administered, either as a single dose or after pretreatment for 4 days, than when 6-MP alone was given. However, the interindividual variations in plasma 6-MP concentrations were large and no statistical significance could be found by either the unpaired *t*-test or a Mann-Whitney U-test. A marked but nonsignificant decrease in the mean area under the curve (AUC) (Table 1), calculated using the STRIPE pharmacokinetic program [2], was also observed when the animals were dosed with 6-MP in conjunction with CTX.

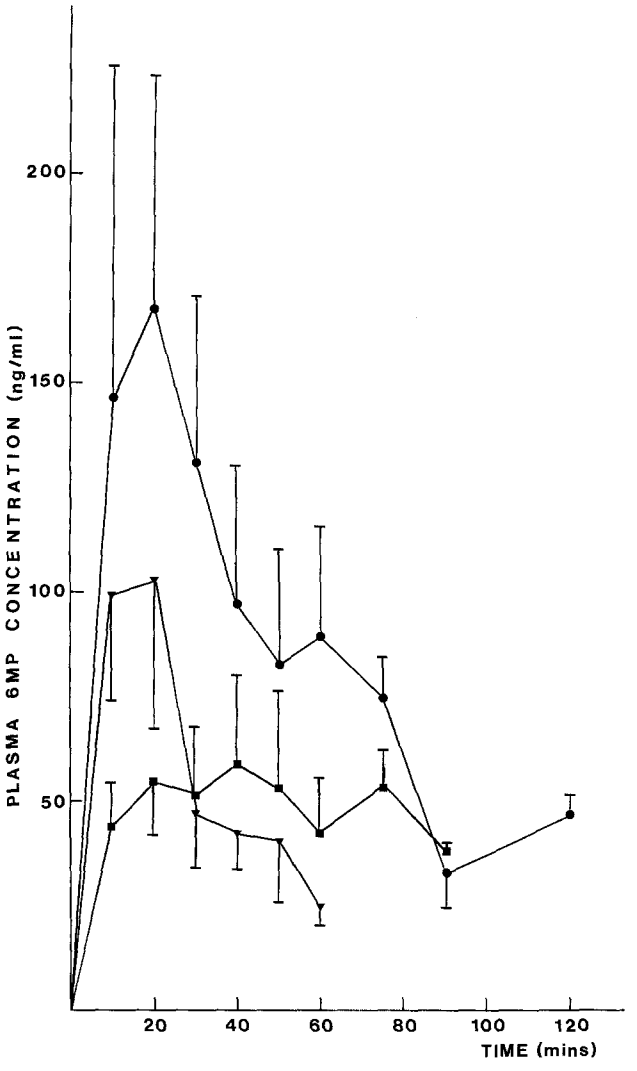

Fig. 1. Plasma 6-MP concentrations (±SD) following oral administration of ● 8.5 mg/kg 6-MP; ▼ 8.5 mg/kg 6-MP+1.8 mg/kg CTX; ■ 8.5 mg/kg 6-MP+1.8 mg/kg CTX after pretreatment with 1.8 mg/kg/day CTX for 4 days

Discussion

A major problem with the investigation of the pharmacokinetics of orally administered 6-MP is the large interindividual variation in plasma levels of the drug. Zimm et al. have pointed out the possible importance of this variability in the effectiveness of therapy [5]. In the 14 patients in their study the peak plasma concentration had a percentage co-efficient of variation (%CV) of 57.3% and the %CV of the AUC was 48.2%. These compare with the variations observed in rats (81.0% for peak height, 59.8% for AUC with 6-MP alone). We suggest, therefore, that experiments on 6-MP pharmacokinetics should be carried out using each individual as their own control.

This pilot study has suggested that in the rat there may be a decrease in 6-MP bioavailability when it is administered with CTX. The perturbations of the correlations observed by Rees et al. [4] between 6TGN and 6-MP dose and ANC were thought to be due to changes in absortion or metabolism of 6-MP. From our results it is likely that the changes are due to 6-MP absorption rather than metabolism, since both acute and chronic dosing of CTX produced a similar effect.

Further studies on the interactions of 6-MP with CTX and other drugs are currently being undertaken and could give important information on the optimal prescribing of 6-MP during maintenance therapy.

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Table 1. Areas under the curve for 6-MP- and (6-MP + CTX)-treated groups

	6-MP alone	6-MP + CTX	6-MP + CTX after pretreatment with CTX
AUC (min × ng/ml)	7180 ± 5247	2547 ± 859	3064 ± 3790
P	–	NS	NS