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Modification of oral methotrexate absorption in children with leukemia

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Summary. *The effect of administering oral methotrexate in different formulations to children with acute lymphoblastic leukemia was evaluated. Methotrexate tablets alone achieved higher mean plasma levels and larger area under the absorption curve than either methotrexate liquid alone or methotrexate tablets taken concurrently with metoclopramide.*

Introduction

Although the prognosis for acute lymphoblastic leukemia (ALL) in children has improved considerably in the last two decades, a substantial proportion of children still develop recurrent disease. A number of factors have been identified in various large series which help to predict which children will have a bad prognosis. A few of these prognostic factors seem to be relevant in all the groups studied. However, the reason why some patients relapse while others remain free of recurrent disease is still largely unexplained.

Methotrexate (MTX) was the first of many agents shown to be effective in ALL, and it is still one of the most important drugs in its treatment. In recent years the pharmacokinetics of MTX have been studied intensively in attempts to understand its therapeutic variability and to improve its potential as an anticancer agent. The absorption pattern has been shown to differ widely among children treated for leukemia [3], and preliminary evidence has suggested that the absorption pattern may possibly be related to prognosis [2]. We therefore decided to investigate the potential for simple methods of altering MTX absorption in a clinical context.

Materials and methods

The study was carried out in patients attending the Oncology Unit, Our Lady's Hospital for Sick Children, Dublin. Eight children who were well established in the continuation phase of their treatment for ALL were enrolled into the study after informed consent had been obtained from their parents. Their ages ranged from 2 to 7 years. All were receiving daily oral 6-mercaptopurine and weekly oral MTX at a dose ranging from 9 to 23.5 mg/m^2, adjusted for individual tolerance. All had been stable at their respective drug dosages for some time and had no evidence of renal or hepatic toxicity at the time of the study.

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Each patient was asked to attend hospital for 3 consecutive weeks on the day that they were due to take their oral MTX and to arrive after an overnight fast. On arrival a 23-gauge butterfly needle was inserted into a peripheral vein; after samples for baseline studies had been obtained the cannula was kept patent with heparinized saline and was carefully washed out before each of the subsequent serial samples was taken.

At attempt was made to keep the circumstances as near to those at home as possible. The patients were given their regular MTX dose followed by a drink of water, and at the same time took their regular daily dose of mercaptopurine. They were allowed to take a light breakfast a minimum of 30 min after their MTX, but this was often later, which may in fact be different from what normally occurs at home. Blood samples were taken hourly for 6 h after MTX had been administered.

In the 1st week standard MTX tablets (2.5 mg) were administered. During the 2nd week the same dose of MTX was given in a liquid form (parenteral MTX, Lederle Laboratories). In the 3rd week MTX tablets were given as in week 1, but at the same time the patients were given metoclopramide (Maxolon) syrup at a dose of 0.3 mg/kg. All patients therefore acted as their own controls, in an attempt to nullify as far as possible the many other factors that can influence absorption and that make many of the published series of patient absorption profiles difficult to interpret.

All samples were separated within 9 h and stored at 4° C. Plasma MTX levels were assayed in a batch each week using an enzyme-linked immunoassay method (EMIT MTX assay, Syva Corporation). Plasma MTX levels are expressed as micromols per liter. Absorption was estimated from the area under the curve calculated by the trapezoidal method. Analysis of variance was used to investigate the significance of differences in plasma levels at each time point and the areas under the curve for each preparation.

Results

No MTX was detected in any of the 24 baseline specimens assayed.

Plasma MTX levels were higher after MTX tablets given alone than after either liquid MTX alone or MTX tablets given with metoclopramide (Fig. 1). The significance of the differences found for each time interval sampled are shown in Table 1. Plasma MTX levels after tablets alone remained superior to those after MTX liquid alone through the first 5 h,

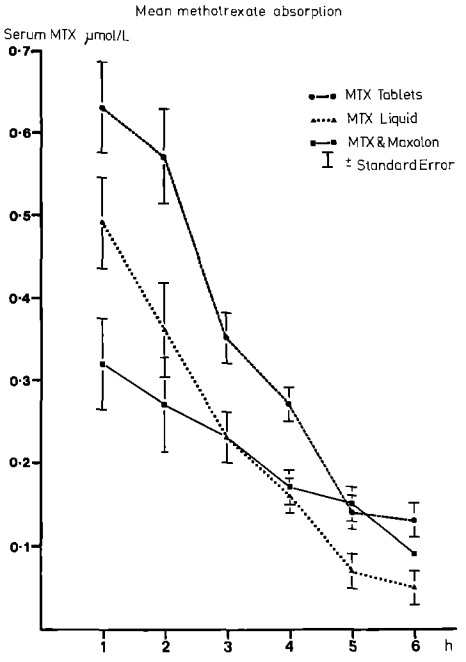

Fig. 1. Mean plasma methotrexate levels

Table 1. Significance of differences in methotrexate absorption profiles (after analysis of variance)

	Time in hours					
	1	2	3	4	5	6
T vs M	$P < 0.01$	$P < 0.01$	$P < 0.02$	$P < 0.01$	NSD	NSD
T vs L	NSD	$P < 0.05$	$P < 0.02$	$P < 0.01$	$P < 0.05$	NSD
L vs M	$P < 0.05$	NSD	NSD	NSD	$P < 0.05$	NSD

T, tablets alone; M, tablets + Maxolon; L, liquid

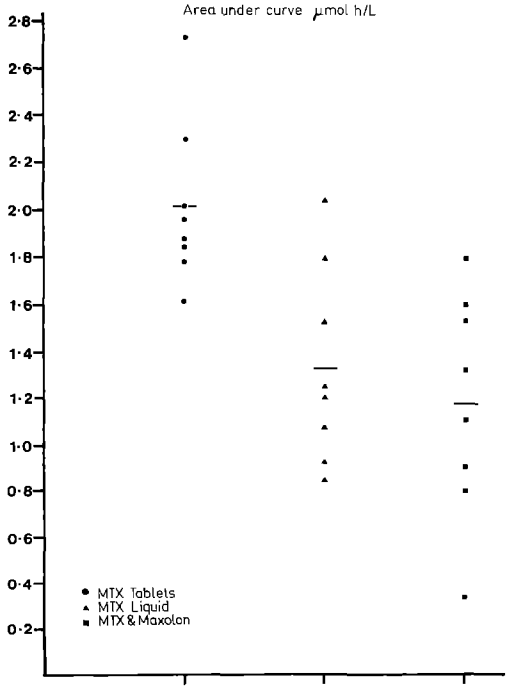

Fig. 2. Area under absorption curve

and superior to MTX tablets plus metoclopramide through the first 4 h, but the differences were no longer significant 6 h after MTX administration. The shape of the absorption curve following MTX plus metoclopramide suggests that the alteration in gut mobility results in a lower peak level and perhaps in a sustained duration of absorption [4].

Results for the area under the absorption curve are shown in Fig. 2. Analysis of variance shows that MTX tablets have a greater average absorption than either MTX liquid alone or MTX plus metoclopramide ($P < 0.01$). There is no significant difference between the latter two preparations.

Discussion

It is not clear which parameters of MTX absorption are most relevant with respect to either antitumor effect or toxicity. The two parameters most widely studied are the peak serum or plasma level achieved and the area under the absorption curve. A number of factors which can modify MTX absorption have been identified. Thus the effects of food have been well studied and described by Pinkerton et al. [5], who showed a significant reduction in peak serum MTX levels and a delay in drug absorption after meals.

Pearson et al. [4] have shown a significant correlation between small bowel transit time and peak time of MTX absorption, and have shown that very fast or very slow transit times produce much lower peak levels. Pharmacological alterations in transit time should be possible with such drugs as metoclopramide and loperamide.

It is possible that absorption may change on successive courses of methotrexate. Craft et al. [1], using a 1-h D-xylose absorption test, have shown that there is a progressive increase in malabsorption related to the cumulative dose of MTX.

The results of our present study indicate that it is possible to alter the absorption profile of MTX either by changing the formulation from tablets to liquid or by changing the rate of gastric emptying with metoclopramide. In both instances, the changes lowered bioavailability and peak concentration but the results clearly suggest that relatively simple manipulations could have a considerable effect on the bioavailability of oral MTX. Given the wide variability of MTX absorption profiles already established, it seems likely that these are suboptimal for some patients. Once it is clear which aspects of the MTX absorption profile are in fact related to prognosis, the goal will be to manipulate the milieu of each patient so as to achieve a profile which approximates as nearly as possible to the ideal.

The relative merits of PO administration of MTX as against IV or IM administration has been evaluated in children with ALL by Pinkerton et al. [6]. There may be a place for IM administration when oral absorption is demonstrated to be poor and cannot be improved by simple manipulations as detailed in this study.

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