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Rapid Plasma Clearance and Reduced Rate and Extent of Urinary Elimination of Parenterally Administered Methotrexate as a Result of Severe Vomiting and Diarrhoea

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Summary. *A patient received 200 mg methotrexate IM as part of a treatment schedule for malignant melanoma. Severe vomiting and diarrhoea began shortly after treatment and persisted for 4 h. During this period the methotrexate renal clearance rate was 37 ml · min^{-1}, increasing to 97 ml · min^{-1} when vomiting and diarrhoea ceased. Only 26% of the administered dose was recovered in the urine up to 48 h after treatment, whilst the plasma clearance of methotrexate assessed over the same period was 208 ml · min^{-1}. We conclude that a considerable proportion of the dose was lost from the gastrointestinal tract during the period of vomiting and diarrhoea, and that consequently enterohepatic circulation of methotrexate plays an important role in the pharmacokinetics of the drug.*

Introduction

The folate antagonist methotrexate (MTX) is excreted primarily unchanged by the kidneys when low to moderate doses are administered parenterally [1, 3, 8]. However, recent data suggests that enterohepatic circulation of MTX may occur [2, 7] and that metabolism, primarily in the liver or by the gastrointestinal (GI) flora, can play a significant role in the elimination of MTX from the body [2, 4, 6]. We wish to report that aspects of the pharmacokinetics of MTX in a patient who suffered severe vomiting and diarrhoea shortly after treatment provide supporting evidence for the view that enterohepatic circulation is a significant feature of the pharmacokinetics of this drug.

Patient and Methods

A 47-year-old female patient received 200 mg (2.6 mg · kg^{-1}) MTX IM together with 2 mg vincristine and 500 mg DTIC IV as part of a treatment schedule for malignant melanoma. Serial blood and urine samples were collected during the first 48 h of treatment, and aliquots of plasma and urine were stored at −20° C before analysis. The concentration of MTX in the samples was determined by means of a radioimmunoassay similar to that described by Raso and Schreiber [5]. Details of the assay procedure will be published elsewhere [van den Berg et al., submitted for publication]. The area under the plasma concentration-time (CT) curve was calculated with the aid of the trapezoidal rule, and the plasma clearance of MTX was determined from the following equation:

$$\text{Plasma clearance} = \text{Dose}/\text{CT}.$$

Renal clearance was determined from the slope of a plot of the cumulative amount of MTX excreted in the urine against CT up to the point of urine collection.

Results

The patient suffered severe vomiting and diarrhoea, which began 30 min after treatment and persisted for 4 h. The concentration of MTX in the plasma following IM injection of 200 mg is shown in Fig. 1. Absorption of the drug was rapid, and subsequent elimination was characterized by two distinct phases. Between approximately 2 and 8 h after treatment the plasma concentration declined monoexponentially with a half-life of 3 h, with the slower phase of elimination ($t_{1/2}$ = 8.4 h) becoming apparent some 20 h after treatment.

A plot of the cumulative amount of MTX excreted in the urine against CT up to the point of urine collection normally results in a straight line with a slope equal to the MTX renal clearance rate. However, as shown in Fig. 2, for this patient such a plot yielded a biphasic curve, with the renal clearance rate considerably reduced during the period of vomiting and diarrhoea. The rate was calculated to be 37 ml · min^{-1}, increasing to 97 ml · min^{-1} shortly after vomiting and diarrhoea ceased. Urinary flow was 40–50 ml · h^{-1} during the first 24-h period after treatment, and the creatinine clearance rate was 77 ml · min^{-1}. Only 26% of the administered dose of MTX was recov-

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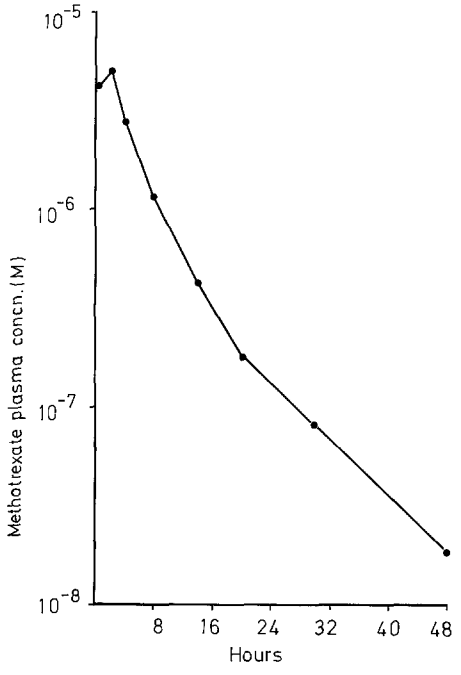

Fig. 1. Semilogarithmic plot of MTX plasma CT following administration of 200 mg IM

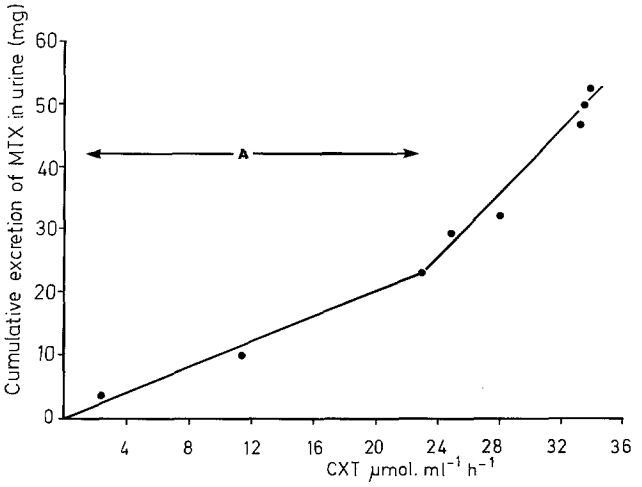

Fig. 2. Cumulative urinary excretion of MTX plotted against area under the plasma CT curve up to the point of urine collection. During the period designated 'A' the patient suffered severe vomiting and diarrhoea

ered in the urine within 48 h. Reduced urinary clearance of a drug excreted primarily by the kidneys would be expected to increase the CT value and consequently decrease the calculated plasma clearance value. However, the plasma clearance of MTX calculated from the data shown in Fig. 1 was 207.8 ml · min^{-1}. The CT value for this patient of 33.7 μmol · ml^{-1} · h^{-1} following a MTX dose of 2.6 mg · kg^{-1} is similar to values we have obtained in patients receiving approximately half this dose by the same route of administration [van den Berg et al., submitted for publication].

Discussion

The data presented lead us to conclude that a considerable fraction of the total dose of MTX administered to this patient was either metabolized or excreted nonrenally. The renal clearance rate was considerably reduced during the period of vomiting and diarrhoea (Fig. 2), whilst the plasma concentration of MTX fell rapidly (Fig. 1). Metabolism of MTX could account for the difference between renal and total-body clearance of the drug. We have not yet been able to assess the ability of the major metabolites of MTX [2] to cross-react with the antibodies used in our assay, and so the 26% of total immunoreactivity recovered in the urine may represent both MTX and metabolites. The data strongly suggest that much of the drug was lost from the GI tract as parent drug or metabolites during the period of vomiting and diarrhoea, which in turn supports the view that enterohepatic circulation plays an important role in the pharmacokinetics of MTX [2, 7].

It is possible, therefore, that severe vomiting and diarrhoea shortly after treatment will reduce the bioavailability of MTX even when it is administered parenterally, which may result in the affected patients not receiving adequate therapy.

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