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Methotrexate-Induced Oral Mucositis and Salivary Methotrexate Concentrations

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Summary. *We examined the plasma and saliva levels of methotrexate (MTX) achieved during the treatment and rescue periods of ten patients receiving 42-h MTX infusions followed by citrovorum rescue. Saliva MTX levels were generally 1%–2% of the simultaneous plasma levels. Four patients developed severe oral mucositis; three patients developed mild to moderate oral toxicity, and three others had no evidence of mucositis. MTX levels in the patients with severe mucositis were not higher and did not persist longer than the levels achieved in patients with mild or absent toxicity. Attempts at reducing the severity of oral mucositis with topical citrovorum mouthwashes or with atropine to suppress salivation were unsuccessful. MTX-induced oral mucositis is not related to salivary MTX concentrations, and the use of topical citrovorum therapy or the supression of salivation does not appear to ameliorate this toxicity.*

Introduction

Oral mucositis is a major form of toxicity associated with high-dose methotrexate (MTX) therapy. A recent report indicated that MTX is excreted in saliva [4]. In response to this observation we examined the relationship of oral mucositis to the concentration of MTX achieved in unstimulated mixed saliva from patients undergoing high-dose IV MTX therapy. In addition we attempted to prevent oral mucositis with either systemic atropine administration or with topical citrovorum therapy. The results of these studies are summarized in this report.

Materials and Methods

All patients were cared for on the Pediatric Oncology Branch of the National Cancer Institute, Bethesda or the Division of Hematology/Oncology, Childrens Orthopedic Hospital and Medical Center, Seattle. Patients' diagnoses included acute lymphocytic leukemia, Burkitt's lymphoma, osteogenic sarcoma, and hypernephroma. Each patient received periodic 42-h MTX infusions with a total dose of either 2760 mg/m^2 (300 mg/m^2 × 1 h followed by 60 mg/m^2/h × 41 h) or 5520 mg/m^2 (600 mg/m^2 × 1 h followed by 120 mg/m^2/h × 41 h). In all cases, an IV dose of citrovorum factor was administered at the end of the 42-h MTX infusion and repeated every 6 h until the plasma MTX concentration fell below 8×10^{-8} *M*. The initial doses of citrovorum were 30 mg/m^2 and 60 mg/m^2, respectively, for the lower-dose MTX and higher-dose MTX groups. All other citrovorum doses were 12 mg/m^2. In nine patients simultaneous samples of plasma and nonstimulated mixed saliva were collected at varying times during the infusion and rescue periods. Saliva was obtained by having the patients drool into sterile specimen cups. MTX concentration was determined by the dihydrofolate reductase inhibition assay [1].

In another group of six patients, 0.8 mg atropine sulfate was administered PO every 6 h beginning 6 h before the start of the MTX infusion and continuing until 6 h after the infusions. The severity of oral toxicity was compared to the patient's degree of mucositis during prior infusions at the same dose of MTX.

In a separate group of 14 patients, topical citrovorum factor therapy was administered as a mouthwash. A cross-over study design was used, in which each patient was randomized to receive or not receive citrovorum mouthwashes during their first course of MTX treatment. During subsequent courses of treatment at the same MTX dose mouthwashes were alternated with no mouthwashes. Each mouthwash treatment consisted of 50 ml water containing 3 mg citrovorum factor (Lederle Laboratory, Pearl River, New York) and 1000 units hyaluronidase. The hyaluronidase was included in an attempt to increase the penetration of citrovorum through the mucous layer and into the mucosal cells [5]. The citrovorum-hyaluronidase solution was swished and gargled for 5 min every 3–6 h during the MTX infusion and for 3 days afterwards. After each 5-min treatment the mouthwash was expectorated and the mouth rinsed with water.

The severity of mucositis was assessed by at least two independent observers. Toxicity was graded as severe, mild to moderate, or absent.

Results

Figure 1 shows the saliva and plasma MTX levels from ten patients. Plasma levels during infusion ranged from 4×10^{-6} *M* to 9.0×10^{-5} *M*, while saliva levels during

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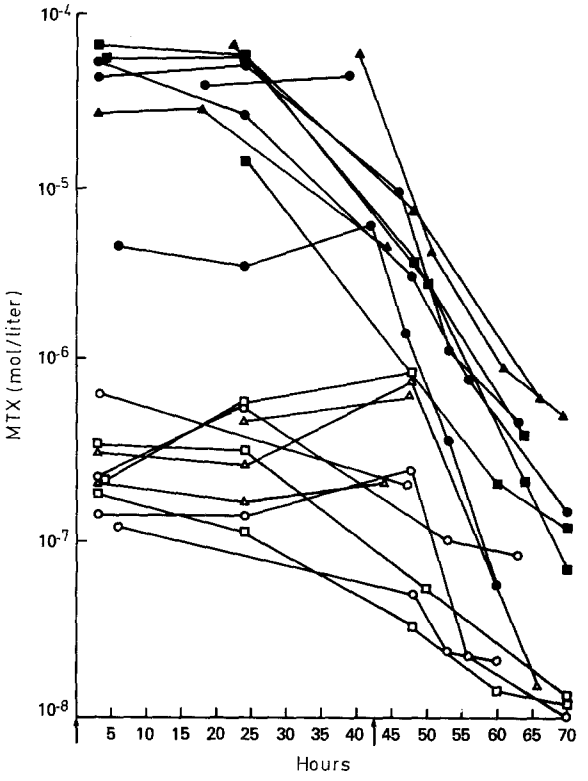

Fig. 1. MTX concentration against time. ●—●, plasma level with severe mucositis; ■—■, plasma level with moderate mucositis; ▲—▲, plasma level with no mucositis; ○—○, saliva level with severe mucositis; □—□, saliva level with moderate mucositis; △—△, saliva level with no mucositis. *Arrows* show start of MTX infusion (left) and end of MTX administration and start of citrovorum factor administration (right)

infusion ranged from 1.2×10^{-7} *M* – 6.0×10^{-7} *M*. In general saliva MTX levels were 50–100 times lower than the simultaneous plasma levels during infusions.

Four patients suffered severe mucositis necessitating parenteral hydration and prolonged hospitalization. Three patients experienced no mucositis, and three others had mild to moderate toxicity. MTX levels in the saliva of the severely affected patients were not higher and did not persist longer than those of any other patient group.

All six patients who received atropine were judged to have received adequate doses. Each patient complained of dry mouth throughout the infusion, and two patients developed resting tachycardias of greater than 100 beats/min. However, subsequent mucositis was unaffected. One patient reported less oral discomfort than during prior infusions, two patients appeared worse, and three others were unchanged.

The use of topical citrovorum-hyaluronidase mouthwashes also failed to ameliorate the MTX-induced oral toxicity. Of 37 high-dose MTX treatment cycles, 22 were conducted with and 15 without topical therapy. Severe mucositis was observed in one (5%) treatment cycle with and in two (13%) cycles without mouthwashes. Moderate mucositis occurred in fourteen (63% cycles with and eight (53%) cycles without mouthwashes, and no toxicity occurred in seven (32%) cycles with and five (33%) cycles without topical therapy. These differences are not statistically significant.

Discussion

The severity of MTX-induced oral mucositis does not appear to correlate with salivary MTX concentrations. Neither does treatment with atropine or topical citrovorum-hyaluronidase appear to modify the subsequent mucositis. These observations are discouraging in that oral mucositis is the most frequent drug-limiting toxicity of prolonged high-dose MTX infusions [2]. The pharmacologic basis of oral ulceration is poorly understood, and until our knowledge of this process is more complete attempts at prevention of mucositis will remain largely empiric.

An interesting pharmacologic observation that emerged from this study was the very low levels of MTX in saliva relative to plasma drug concentrations. In all, 50%–70% of plasma MTX is bound to protein [3]. If saliva drug levels were to parallel free plasma drug levels, as is the case with several other drugs (e.g., theophylline or antipyrine), then saliva MTX concentrations would be approximately 30%–50% of the simultaneous plasma concentrations. In this study the saliva levels were only 1%–2% of the plasma values, suggesting the presence of either a physiologic barrier to MTX influx into saliva or a mechanism for its rapid removal from saliva. The latter explanation seems more likely, in view of the aqueous solubility, molecular weight, and relative degree of ionization of MTX in plasma and saliva.

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