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Short communication

Impact of omeprazole on the plasma clearance of methotrexate

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Abstract. Omeprazole inhibits the gastric hydrogen pump and is an effective treatment for peptic ulcers. Methotrexate is a chemotherapeutic agent that inhibits dihydrofolate reductase and is eliminated by a hydrogen-ion-dependent mechanism in the kidney. We present evidence that omeprazole inhibits methotrexate clearance and may result in potentially toxic methotrexate levels.

Introduction

Omeprazole inhibits the hydrogen-potassium adenosine triphosphatase (H^+, K^+-ATPase) and is used in the treatment of peptic ulcers [3]. Omeprazole is a substituted benzimidazole that selectively reduces gastric acid pH by blocking the gastric H^+, K^+-ATPase [3, 22]. It is more effective than H2-receptor antagonists in treating duodenal ulcers and is the treatment of choice for Zollinger-Ellison syndrome [7, 14, 17]. A patient with osteogenic sarcoma treated concurrently with high-dose methotrexate and omeprazole had delayed renal clearance of methotrexate. The pharmacokinetics of the high-dose methotrexate clearance returned to normal after the omeprazole had been discontinued.

Case report

A 41-year-old man was treated with total lymphoid irradiation in 1971 for Stage IIEB nodular sclerosing Hodgkin's disease. He received, 4,400 cGy to Waldeyer's ring, to the mantle field, and to an inverted Y and 1,640 cGy to the left lung. Approximately 20% of the left kidney volume was included in the inverted Y field. He remained well until March of 1991, when he developed low-back pain. In May 1991, he developed lower extremity weakness and a magnetic resonance imaging (MRI) scan demonstrated a mass at T-12. Osteosarcoma was confirmed by biopsy. His tumor was surgically debulked, radiotherapy was delivered to the T12-L1 region, and he was started on chemotherapy. Approximately 30% of the left kidney volume was treated to a dose of 2,472 cGy, half of which overlapped with the previously irradiated kidney volume. The patient was treated with 600 mg/m^2 cyclophosphamide, 15 mg/m^2 bleomycin, and 0.6 mg/m^2 actinomycin-D according to the protocol of Link et al. [15]. He then received 12 gm/m^2 methotrexate, with leucovorin rescue starting 24 h after methotrexate administration. At the time of treatment, he was on the following medications: senna, 1 tablet p.o. q.h.s.; levothyroxine, 0.1 mg p.o. every morning; omeprazole, 20 mg p.o. g.h.s.; acyclovir, 400 mg p.o. five times daily; baclofen, 10 mg p.o. every morning; $FeSO_4$, 325 mg p.o. every morning; and docusate sodium, 100 mg p.o. b.i.d. Fruit juices, sources of vitamin C, and aspirin were stopped.

During the first cycle of treatment, the patient's serum methotrexate levels as determined by fluorescence polarization immunoassay remained elevated for several days (Fig. 1). Serious toxicity can occur when methotrexate concentrations exceed 10^{-5} *M* at 24 h or 5×10^{-7} *M* at 48 h [1, 2, 19]. The patient was aggressively hydrated and his urine, alkalinized. Leucovorin was given for 8 days. The patient experienced no mucositis, diarrhea, or other manifestation of methotrexate toxicity. He had normal renal function, with serum creatinine values being 0.8 mg/dl at the initiation of treatment and 0.7–1.0 mg/dl during the period of elevated methotrexate levels and during follow-up. There was no evidence of third-space collections of fluid, and none of his medications was known to inhibit methotrexate elimination.

Although there was no report of omeprazole inhibiting methotrexate elimination, the omeprazole was stopped. Methotrexate is secreted in the kidney by a hydrogen-ion-dependent mechanism [2, 6, 19, 27] and there are recent reports in animals indicating that omeprazole can inhibit

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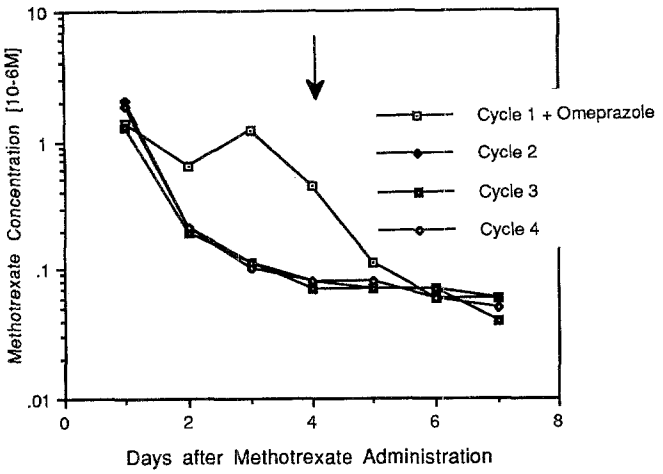

Fig. 1. The patient's serum concentration of methotrexate. The patient was receiving omeprazole concurrently during the initial portion of cycle 1. The *arrow* indicates the point at which omeprazole was stopped during cycle 1

hydrogen-ion transport in the kidney [27]. These reports indicate that omeprazole inhibits the H^+, K^+-ATPase in both the rat and the rabbit kidney as well as the gastrointestinal tract [6, 8, 10, 27]. Moreover, recent reports indicate that the H^+, K^+-ATPase mediates K^+ absorption in the inner stripe of the outer medullary collecting system and promotes acidification of the urine [21]. Therefore, the omeprazole was stopped. No other medication was changed. After the omeprazole had been stopped, the patient's serum methotrexate levels rapidly declined (Fig. 1). Furthermore, serum methotrexate levels rapidly declined with normal kinetics for three consecutive cycles of methotrexate after the omeprazole had been discontinued (Fig. 1).

Discussion

Methotrexate circulates in the serum as a weak organic acid with pKa values of 4.84 and 5.51, and over 95% of the delivered dose is eliminated unmetabolized in the urine [2]. Methotrexate is actively secreted in the distal nephron by a hydrogen-ion-dependent mechanism [1, 2, 9, 19]. Pharmacokinetic analysis indicates that methotrexate is eliminated predominantly by renal tubular excretion and glomerular filtration. The half-life is approximately 2 h. Following the i.v. injection of methotrexate, the highest concentrations accumulate in the kidneys, with lower concentrations occurring in the plasma, erythrocytes, muscle, and spleen [16]. The kinetics of methotrexate elimination can be described by a two-compartment model. In this model, the majority of the methotrexate is rapidly cleared from the blood by the kidney. A smaller fraction is eliminated with a half-life of about 8 h, and this rate is determined by the movement of methotrexate from the peripheral compartment into the blood [11, 16]. Salicylates, probenicid, and vitamin C have been reported to compete with methotrexate elimination [4, 5, 12, 18]. The mechanism of this competition is thought to occur through a common anion pump. Endogenous and exogenous organic ions, including urate, ketoacids, penicillins, salicylates, diuretics, radiocontrast media, and probenecid, use this pathway [23]. Our findings suggest that omeprazole may inhibit the H^+, K^+-ATPase in the human kidney, thereby blocking the active secretion of methotrexate by the kidney and resulting in the retention of potentially toxic levels of methotrexate.

The plasma half-life of omeprazole is 0.5–1.5 h, but the compound is tightly bound to plasma proteins and has a longer effective half-life resulting in hydrogen-ion transport inhibition in the stomach for up to 24 h [3]. There are no data on the duration of the effect of omeprazole on the kidney; however, our data would suggest that this half-life is short. Stopping omeprazole several days prior to methotrexate would seem prudent until further data have been obtained.

The growing use of omeprazole for treatment of peptic ulcers and the widespread use of methotrexate for a variety of medical conditions, including cancer, rheumatoid arthritis [4, 24, 25], cutaneous sarcoidosis [26], cardiac allograft rejection [20], cutaneous polyarteritis nodosa, and Behcet's disease [13], suggest that a number of patients may be at risk for methotrexate toxicity from omeprazole. In addition, omeprazole may block the elimination of other medications that are cleared by a hydrogen-ion-dependent mechanism in the kidney, including the penicillins and related antibiotics, diuretics, and other medications secreted by the anion pump. Further study is required to elucidate fully the pharmacologic interaction between omeprazole and weak anions.

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