ACCIDENTAL METHOTREXATE INGESTION IN A DOG

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INTRODUCTION

Methotrexate[a] (MTX) is an antifolate, antimetabolite that has been used in veterinary medicine for the treatment of lymphoma and osteosarcoma. The medication has a wide range of uses in human medicine, including both neoplastic (lymphoma, leukemia; and head and neck, breast, and bladder cancer) and non-neoplastic diseases (rheumatoid arthritis, graft-versus-host disease after bone marrow transplantation, psoriasis, bacterial and plasmodial infections, and opportunistic infections associated with acquired immunodeficiency syndrome) (1). Antifolate compounds contain a critical substitution of an amino group for the hydroxyl at position 4 on the pteridine ring. This change transforms the molecule from a substrate ion to a tight binding inhibitor of dihydrofolate reductase (DHFR), a key enzyme in intracellular folate synthesis. In proliferating cells, inhibition of DHFR by MTX leads to accumulation of folates in the inactive dihydrofolate form, with variable depletion of reduced folates. The inhibition of DNA synthesis consists of both partial depletion of reduced folate substrates and direct inhibition of folate-dependent enzymes (1). Folate is necessary for the production and maintenance of new cells, as it is essential in the replication of DNA and synthesis of RNA. Leucovorin (5-formyltetrahydrofolate) is converted to intracellular folate and competes with MTX, bypasses the metabolic block induced by MTX, and therefore, prevents further cell destruction by maintaining blood levels of folate. The combination of leucovorin and MTX allows high doses of MTX (up to 100 times the conventional doses) to be used with fewer side effects (2). MTX may be administered orally (2.5 mg tablets) or intravenously (2.5 mg/ml solution). The recommended dose in dogs for the treatment of canine lymphoma is 0.6-0.8 mg/kg IV or PO. Side effects reported in dogs are gastrointestinal (diarrhea, nausea, vomiting and anorexia) and, less commonly, leucopenia (neutropenia), thrombocytopenia, temporary alopecia, pyrexia, skin rashes, and oral lesions (3). In human medicine there are various doses (low, intermediate, and high with leucovorin rescue) and routes of administration (PO, IV, and intrathecal). Plasma pharmacokinetics in people is variable. MTX is thought to generally follow a three phase pattern. The initial distribution phase, which lasts only a few minutes, is followed by a second phase lasting 12 to 24 hours, during which the drug is eliminated within a half life of 2 to 3 hours. The final phase of drug clearance has a half life of 8 to 10 hours (4).

Reported side effects in people include myelosuppression, mucositis, gastrointestinal epithelial denudation, renal tubular obstruction and injury, hepatotoxicity, pneumonitis, hypersensitivity, and neurotoxicity (4). Nephrotoxicity, myelotoxicity, neurotoxicity and mucositis were more common at intermediate to high doses (4). In people, gastrointestinal mucositis has been reported to appear 3 to 7 days after MTX therapy and precedes the decrease in granulocyte and platelet count by several days. Myelosuppression and mucositis are usually completely reversible within 14 days. MTX induced nephrotoxicity is thought to result from the intratubular precipitation of MTX and its metabolites in acidic urine. Antifolates may also exert a direct toxic effect on the renal tubules. Judicious fluid therapy and urinary alkalinization have greatly reduced the incidence of renal failure in high dose regimens (4).

CASE SUMMARY

An eighteen-month old, 13 kg, female intact, mixed breed dog was presented to the Veterinary Teaching Hospital after ingestion of 40, 2.5 mg tablets (100 mg) of the owner's MTX, three to four hours prior to arrival. Since that time no vomiting or diarrhea had been noted; there was no change in behavior. The physical exam revealed no abnormalities. The dog was admitted to the hospital, and apomorphine[b] was administered. As the first dose (0.0.04 mg/kg IM) did not cause vomiting, an additional IV dose (0.03 mg/kg) was then administered. The dog vomited; however, the vomitus did not contain any tablets. The dog was then anesthetized (propofol[c], 4 mg/kg IV; isoflurane[d] 2%, 2 liters O_2/min) for orogastric lavage. There was no further ingesta retrieved from the stomach, and activated charcoal[e] (1 gr/kg) was administered via the orogastric tube. A complete blood count (CBC), complete biochemistry panel, coagulation panel (including PT, PTT, and fibrinogen), arterial blood gases, and urinalysis were all within normal reference ranges. Serum MTX and folic acid levels 12 hours after presentation were 0.09 µmol/l and 4.1 ng/ml (human reference interval 2.4-20 ng/ml), respectively. Treatment was initiated to prevent MTX-associated nephrotoxicity and to treat the potential MTX-induced gastrointestinal mucositis with lactated Ringer's solution (80 ml/hr), amoxicillin with clavulanic acid[f] (13 mg/kg IV q12h), sucralfate[g] (0.5 gram PO q8h), ranitidine[h] (1 mg/kg IV q12h), lactulose[i] (4 ml, 66.7 gr/100 ml q8h), omeprazole[j] (10 mg PO q24h), misoprostol[k] (50 µg PO q8h) and sodium bicarbonate[l] (1/8 teaspoon PO q8h). In addition, since methotrexate ingestion was proven by the positive blood level, leucovorin[m] was administered (20 mg IV q6h). No vomiting, diarrhea, or abnormalities in temperature, pulse, and respiratory rate were noted throughout the first day of hospitalization.

The next day the CBC remained normal. The MTX level was 0.01 µmol/l. There was no clinical evidence of toxicosis; the dog ate had normal urination and normal defecation. Treatment as above was continued for a total of 48 hours. During that time, six doses of leucovorin were administered. The dog was discharged (on day 2) with omeprazole (10 mg PO q24h), famotidine (10 mg PO q24h), sucralfate (0.5 gr PO q8h), misoprostol (50 µg PO q8h),

and amoxicillin with clavulanic acid (13 mg/kg PO q12h). The dog was presented on days 3, 4, 5 and 6 after discharge for recheck examination and CBC. The dog was reportedly normal at home and normal on physical examination. CBCs showed no evidence of leukopenia. Four months later the owners reported that the dog is doing well at home with no apparent abnormalities.

DISCUSSION

Several studies that document the adverse effects of methotrexate in dogs have been published. These studies are useful in the demonstration of side effects due to MTX with several different dose regimens, both IV and oral MTX, and from the recommended dose in dogs to high dose treatment. They showed how these side effects were treated, responded to treatment, and use of leucovorin in high dose MTX therapy. In a study by Fukui et al., twelve beagles were given MTX (2.5 mg/kg IV) to study the drug's emetic effects and the inhibition of emesis with ondansetron (1 mg/kg IV) and/or dexamethasone (2.5 mg/kg IV) (5). The dosage was selected on the basis of a preliminary dose-determination study in which 1 mg/kg IV failed to induce vomiting, whereas dogs receiving 10 mg/kg IV died after showing more than 100 vomiting episodes. No deaths occurred in the dogs that received MTX (2.5 mg/kg IV); however, vomiting was documented in 13/15 dogs treated. In control animals, the first vomiting episode started between 20 and 24 hours after MTX administration, with a second vomiting episode between 28-32 hours post administration that in some cases lasted until 72 hours after treatment. The average number of vomiting episodes from 24-72 hours after MTX was 11.7 (5). This study demonstrates that vomiting was documented in dogs that received lower doses of MTX than the dog presented. The route of administration between this study and our patient was different. In addition, the lethal dose of 10 mg/kg was higher than the dose the dog ingested (7.7 mg/kg).

Another study treated eight dogs with transmissible venereal tumors with oral MTX (2.5 mg/m^2) every other day for six weeks (6). Anorexia, vomiting, hemorrhagic enteritis and weight loss were noted. Withdrawal of the drug resolved the gastrointestinal symptoms. This study shows how a much lower dose of oral MTX induced gastrointestinal side effects.

Bortnowski et al. evaluated L-asparginase and MTX treatment at intermediate doses in eight dogs (7). Since L- asparginase was thought to antagonize the cytocidal effect of MTX, the objective was to reduce the gastrointestinal side effects associated with the MTX. Four dogs were treated with 3 mg/kg, and four dogs were treated with 6 mg/kg. Three dogs that received the higher dose showed signs of depression, anorexia, dehydration, and severe vomiting and diarrhea. One of the dogs had hemorrhagic vomiting and diarrhea and was euthanized. The necropsy revealed severe diffuse ulcerative fibronecrolitic enteritis involving the small intestine. Two of the dogs that received low dose MTX showed signs of anorexia, depression and vomiting that required treatment with chlorpromazine. When the dogs were given MTX at 3 mg/kg without L-asparginase, five of seven dogs developed less severe clinical signs including anorexia, depression, and vomiting. The dose utilized here, 6mg/kg, was similar to the dose ingested in our patient. However, the dogs in this study showed severe anorexia, vomiting, and diarrhea; one dog had to be euthanized.)

High dose MTX treatment with leucovorin rescue in dogs has only been described in one study. Five dogs with appendicular osteosarcomas were treated after amputation with very high doses of MTX (3 to 6 g/m²) with leucovorin rescue (8). Treatment was instituted five to seven days after surgery, and repeated at intervals of three weeks until metastasis were evident. MTX was administered as a 6 hour infusion. In this report, vincristine (1 mg/m^2) was administered thirty minutes prior to the MTX on the theory that it may increase cellular uptake of MTX. Two hours following the MTX infusion, leucovorin was administered at a dose of 15 mg/m² IV every 3 hours for 8 doses, followed by IM injections every 6 hours for 8 doses. Vomiting was not associated with drug administration. Most dogs continued to eat and drink normally, while three dogs experienced vomiting, with or without diarrhea. However, at a dose of 3 g/m² myelosuppression (granulocyte count <2,000 cells/µl) was reported after 12 of 17 treatments, with fever reported at the nadir of six treatments. The serum MTX level at the conclusion of the 6 hour infusion varied among the dogs, due to differences in drug clearance ($2.3 \times 10^{4-}$ to $3.8 \times 10^{4-}$ µmol/l). Fluid therapy and sodium bicarbonate were used to maintain hydration and to avoid nephrotoxicosis, as reported in humans due to precipitation of the drug in the renal tubules (8). No other studies on high dose MTX have been reported in the veterinary literature.

Accidental MTX intoxication has not been reported in dogs or people. The dosage that this dog ingested (7.7 mg/kg) was significantly higher than the reported therapeutic dose for MTX (0.6-0.8 mg/kg) (3). The amount of MTX ingested in this case was eight to ten times higher than doses associated with significant clinical side effects (myelosuppression, anorexia, hematemesis and diarrhea), but lower than a lethal dose (10 mg/kg without leucovorin) (5). The ingested dose was significantly lower than high dose MTX (8), which together with leucovorin rescue was reported to cause myelosuppression, fever, and gastrointestinal signs, but not death. Renal tubular necrosis has been reported in people (1), with high dose MTX, but not in dogs. It is unknown if our therapy prevented renal tubular necrosis in this dog.

The purpose of the treatment initiated in this dog was to prevent the previously reported gastrointestinal signs, myelosuppression and renal toxicity. Since low doses of MTX may cause myelosuppression, white blood cell counts were measured daily for any signs of leukopenia. Due to these reports of myelosuppression, we administered prophylactic antibiotics, until daily CBCs proved to be stable. Leucovorin was administered based on the literature and recommendations from human oncologists. Dosage of leukovorin was based on those recommended for humans with similar MTX levels. Gastrointestinal mucositis, with anorexia, nausea, vomiting and diarrhea has also been commonly reported up to days after ingestion of the MTX. Therefore, the dog was treated gastric protectants. Urinary alkalinization was initiated as it has been shown to reduce the incidence of MTX-induced renal failure in people (4).

This report illustrates that leucovorin therapy and timely supportive treatment may prevent clinical symptoms of toxicosis in dogs with accidental MTX ingestion.

FOOTNOTES

[a] Emthexate®, Pharmachemie (Teva), Netanya, Israel.
[b] Filtalon®, RAFARM, Attiki, Greece.
[c] Diprofol®, Tara Pharmaceutical Industries, Ltd, Haifa, Israel.
[d] Isoflurane®, Rhodia, Bristol, United Kingdom.
[e] Charcodote®, Pharmascience Inc, Montreal, Canada.
[f] Augmentin®, SmithKline Beecham Pharmaceuticals, Brentford, England.

[g] Ulsanic®, Teva Pharmaceutical Industries, Petach Tikva, Israel.
[h] Zantac®, GlaxoSmithKline, Italy.
[i] Avilac®, Agis, Yeruham, Israel.
[j] Omepradex®, Dexcel (Dexxon), Or Akiva, Israel.
[k] Cytotec®, Searle (Pharmateam), Pharmacia Ltd, United Kingdom.
[l] Commercial baking soda.
[m] Leucovorin®, Abic, Netanya, Israel.
[n] Gastro®, Unipharm, Trima, Tel Aviv, Israel.

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