Acute sterile hemorrhagic cystitis after a single intravenous administration of cyclophosphamide in three dogs

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Three dogs receiving cyclophosphamide IV as part of a combination chemotherapeutic regimen developed macrohematuria, stranguria, and pollakiuria within 24 hours of administration of the first dose of this drug. An 11-year-old spayed mixed-breed dog with an oral squamous cell carcinoma was administered 250 mg of cyclophosphamide/m² of body surface, followed by actinomycin D (0.5 mg/m²), and thymine (0.2 mg, PO, q 24 h). A 4-year-old male castrated Gordon Setter was treated with 100 mg of cyclophosphamide/m², and with 30 mg of doxorubicin/m², for an undifferentiated carcinoma of the zygomatic salivary gland. A 6-year-old male German Shepherd Dog with a cutaneous hemangiosarcoma was administered 140 mg of cyclophosphamide/m², in addition to 30 mg of doxorubicin/m². Both dogs receiving doxorubicin were treated with diphenhydramine (2.2 mg/kg of body weight, IM), an H₁ antihistamine, before chemotherapy to prevent acute toxicosis. Aerobic bacterial culture, antimicrobial susceptibility testing, and urinalysis were performed on urine obtained by cystocentesis from all 3 dogs after hematuria was observed. Sterile hemorrhagic cystitis was diagnosed on the basis of large numbers of RBC in the urine, absence of pathogens on bacterial culture of urine, and clinical signs.

All dogs subsequently received antibiotics to prevent development of bacterial urinary tract infections secondary to breakdown of the urinary bladder mucosal barrier. Two of the dogs were euthanatized because of their primary disease within 2 weeks of the development of hemorrhagic cystitis. In the third dog, clinical signs associated with hemorrhagic cystitis resolved within 2 weeks after discontinuation of cyclophosphamide administration and after treatment with trimethoprim-sulfadiazine (15 mg/kg, PO, q 12 h).

Cyclophosphamide, an alkylating agent derived from nitrogen mustard, is used to treat neoplastic (eg, lymphoma, sarcomas, and carcinomas) and nonneoplastic (eg, rheumatoid arthritis, systemic lupus erythematosus, and immune-mediated hemolytic anemia) diseases. Alkylating agents act through covalent bonding and crosslinking of DNA, and interfere with DNA replication and RNA transcription. They are subsequently activated to alkylating and cytotoxic metabolites by the mixed-function-oxidase hepatic microsomes. The active alkylating agent is phosphoramidate mustard.

Cyclophosphamide may be administered PO or IV, and is metabolized similarly in dogs and human beings. Plasma concentration in human beings peaks 1 hour after IV infusion, and the half-life of cyclophosphamide after IV administration is approximately 5 hours in human beings not receiving drugs that may induce hepatic microsomal enzyme activity. Intravenous administration of this drug results in urinary excretion of 90% of the parent drug and its metabolites. Hepatic and renal functions do not appear to affect the toxicity of cyclophosphamide, although impaired hepatic function may prolong the half-life.

Toxic effects of cyclophosphamide include myelosuppression (nadir of leukopenia at 7 to 14 days), gastrointestinal tract inflammation and degeneration, carcinogenesis, and sterile hemorrhagic cystitis. Transitional cell carcinomas of the urinary bladder have been reported in human beings and in dogs receiving chronic treatment with cyclophosphamide, whereas squamous cell carcinoma, adenocarcinoma, and sarcomas have been reported only in human beings. Long-term use of cyclophosphamide (> 8 weeks) results in pathologic changes of the urinary bladder, including submucosal edema, necrosis, and hemorrhage; extensive fibrosis, and dystrophic mineralization in human beings and in dogs. Hepatic activation of cyclophosphamide also generates the active metabolite acrolein, an aldehyde that causes hemorrhagic cystitis. Approximately 25% of phosphoramidate mustard, the active alkylating metabolite of cyclophosphamide, remains in plasma for at least 24 hours, and acrolein is released in the urine from 4-hydroxycyclophosphamide. Extensive uroepithelial damage with secondary bladder necrosis develops after limited exposure to acrolein. The bladder is probably

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more susceptible than is the rest of the urine-collecting system to pathologic changes caused by prolonged contact of the mucosa with acrolein.  

Although cyclophosphamide-induced cystitis (CIC) in dogs has been documented in the literature numerous times, acute episodes developing within 24 hours of administration of the first dose have not been reported previously in this species with the use of therapeutic doses. A study designed to evaluate toxic effects of IV administration of cyclophosphamide in dogs revealed hematuria in all dogs on the first and third day after treatment; however, the dosages inducing these effects were much higher than those used therapeutically (80 mg/kg vs approx 3 to 10 mg/kg).  

In a comprehensive study of dogs and cats with CIC, Crow et al. found that the median lag period between initiation of cyclophosphamide treatment (at 50 mg/m² or approximately 1.7 mg/kg, PO, every other day) and the onset of clinical signs was 18 weeks. The reported prevalence of CIC in these dogs was 7% (14/203). These investigators also noticed increased frequency of CIC in females and decreased frequency in dogs concurrently receiving prednisone, compared with frequencies in males and in dogs not given prednisone, respectively.  

In a review of 100 human patients with CIC, Stillwell and Benson found that IV administration of cyclophosphamide resulted in hemorrhagic cystitis at lower cumulative doses and earlier than with oral administration. Three patients in that study were reported to have developed hemorrhagic cystitis within 24 hours of IV administration of a single initial dose of cyclophosphamide. Therefore, increased risk of CIC may be associated with IV administration of this drug.  

Although unlikely, it is possible that the drugs concurrently administered to the dogs of this report increased the risk of cystitis, because all 3 dogs received antineoplastic antibiotics (doxorubicin or actinomycin) in conjunction with cyclophosphamide. A synergistic effect of cyclophosphamide and actinomycin or doxorubicin on the bladder mucosa must be considered in these cases, although such effects have not been documented in the literature. Evidence of doxorubicin or actinomycin causing sterile hemorrhagic cystitis has not been reported.  

Various preventive measures can be used to decrease the frequency or severity of cystitis in dogs receiving cyclophosphamide PO. A simple measure consists of administering the medication in the morning when feasible, and allowing increased opportunities to urinate to decrease contact of the toxic agent with the bladder mucosa. Additionally, diuresis can be induced by encouraging increased water intake (eg, providing fresh water and salty foods). Administration of prednisone on the same day as the cyclophosphamide may help decrease the rate of CIC. In a study of 203 dogs, Crow et al. found that dogs concurrently receiving prednisone had a decreased frequency of CIC, compared with that of dogs not receiving prednisone. Concurrent glucocorticoid administration increases diuresis and also inhibits activation of cyclophosphamide by hepatic microsomal enzymes, thereby delaying its metabolism. In dogs receiving high doses of cyclophosphamide IV without concurrent prednisone treatment, careful monitoring and preventive measures such as those listed previously should be considered, because such dogs may be at an increased risk for acute hemorrhagic cystitis. Furthermore, the risk of CIC may be decreased by administration of cyclophosphamide PO instead of IV.  

Other more aggressive preventive measures include administration of acetylcysteine, sodium 2-mercaptoethanesulphonate, prostaglandin F₂α, and diuretics. Intravesical instillation of acetylcysteine inactivates acrolein, thus preventing CIC. This is potentially useful in patients receiving single, high-dose IV administration of cyclophosphamide, although its practicality is questionable in veterinary medicine. Sodium 2-mercaptoethanesulphonate reduces the prevalence of sterile hemorrhagic cystitis by 85% in human beings; it inhibits urotoxicity by increasing excretion of cysteine and increasing concentrations of thiol, which react with cyclophosphamide metabolites. Treatment with prostaglandin F₂α before chemotherapy also results in decreased prevalence of CIC in rats, and furosemide also may be potentially useful in preventing this syndrome. Factors determining frequency of CIC include drug route of administration and dosage, patient hydration status, urine output and voiding frequency, functional capacity of the gastrointestinal tract and liver, and the effect of renal function in drug metabolism.  

Formalin and dimethyl sulfoxide (DMSO) have been used successfully to treat dogs and human beings with CIC, and prostaglandin E also has been used in human beings. Irrigation of the bladder with 1% formalin in anesthetized patients has proven effective in controlling hemorrhage from the telangiectatic capillaries in the mucosal and submucosal layers of the bladder. Formalin acts by hydrolyzing proteins and coagulating superficial tissues without causing complications in dogs and human beings. Intravesical administration of 50% DMSO has been used in human beings and dogs to treat CIC. The mechanism is incompletely understood, although DMSO is known to inhibit prostaglandins by scavenging free radicals and to stabilize lysosomal membranes. It also may inhibit the influx of macrophages to the bladder lining. Other measures that should be instituted after the development of sterile hemorrhagic cystitis include permanent discontinuation of cyclophosphamide, encouraging diuresis, and administering bactericidal antibiotics (trimethoprim-sulfadiazine, 22 mg/kg, q 12 h) because of compromise to the bladder mucosa.
Sterile hemorrhagic cystitis can develop acutely (ie, < 24 hours) after the IV administration of cyclophosphamide in dogs. Appropriate precautionary steps therefore should be taken, even when the drug is being administered only intermittently.