

Use of hyaluronidase for the treatment of extravasation of chemotherapeutic agents in six dogs

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- ▶ Extravasation of chemotherapeutic agents is a complication of chemotherapy for various malignancies.
- ▶ Leakage of the drug into the perivascular space may result in severe tissue damage and development of deep ulcerations; débridement, excision, and skin grafting may be required for healing if intervention treatments are not promptly instituted.
- ▶ Infiltration of hyaluronidase around the site immediately after extravasation and then at weekly intervals may promote recovery with minimal fibrosis.

A 10-year-old female Boxer dog was referred for treatment of mediastinal lymphoma. The dog had been treated previously with 3 cycles of doxorubicin^a plus cyclophosphamide,^b resulting in complete remission of the tumor for a period of 10 weeks. Physical examination revealed that the dog was in considerable respiratory distress. Radiography confirmed the presence of a large mediastinal mass. Results of a CBC, bone marrow aspiration biopsy, and abdominal ultrasonography did not indicate other organ involvement with lymphoma. Results of serum biochemical analyses were within reference ranges. At this time, the dog was treated with a mechlorethamine^c-vincristine^d-procarbazine-prednisone combination protocol, and complete remission of the tumor was achieved after 1 cycle of chemotherapy. The treatment regimen was scheduled to be repeated for 1 year. During the fifth month of therapy, extravasation of mechlorethamine^c (3 mL, 3 mg) and vincristine^d (0.7 mL, 0.7 mg) occurred despite the use of an IV catheter placed in the right cephalic vein. Because of a sensation of increased resistance at the beginning of the chemotherapy administration, it was estimated that extravasation of the entire volume of chemotherapeutic agents had occurred. The day after treatment, the dog was returned to the clinic because of marked lameness and swelling of the right forelimb. On the craniomedial aspect of the limb, a 10-cm strip of soft tissues extending proximally from the carpus was swollen, with a 4-cm central indurated area; the dog would bear little or no weight on the right forelimb and showed signs of pain upon palpation. The dog was treated, according to recommendations in the human

literature,¹⁻⁶ with 300 units of hyaluronidase^e diluted with 6 mL of saline (0.9% NaCl) solution administered circumferentially by use of 6 SC injections with a 25-gauge needle around the extravasation area. Care was taken to infiltrate the central induration. No other measures were taken to control the consequences of the extravasation. The infiltration was repeated 7 and 14 days later. The amount of swelling decreased by approximately 50% during the day after the first infiltration of hyaluronidase. The lameness improved greatly during the same period. Gradual resolution of the swelling occurred during the following 20 days (a further reduction of approximately 30% after the second infiltration treatment, with resolution of the swelling within a few days after the third and last treatment). The lameness completely resolved after the second dose of hyaluronidase. The resultant fibrosis of the cephalic vein was considered mild and was localized craniomedially to a region 10 cm proximal to the carpus. Intravenous chemotherapy was continued as per protocol at the end of the third week following the extravasation event, and the tumor was known to be in remission after 2 years.

A 10-year-old female Bouvier des Flandres was referred for treatment of non-weight-bearing lameness and swelling of the soft tissues of the right forelimb (extending 12 cm above the carpus), caused by extravasation of vincristine (0.8 mL, 0.8 mg, according to the referring veterinarian) that occurred during the treatment for a transmissible venereal tumor. Signs of mild pain were elicited during palpation of the forelimb; otherwise, the dog was quiet, alert, and responsive. The transmissible venereal tumor appeared to be in complete remission. The dog was treated with hyaluronidase once per week, as described, for 4 weeks. Five days after the first infiltration of hyaluronidase, swelling of the forelimb was reduced by approximately 50%. Four days after the second dose of hyaluronidase, the dog was able to bear weight on the affected limb. After the last treatment, only a mild fibrosis was present at the site of extravasation. Fourteen months after the extravasation event, the dog was doing well, and neither the transmissible venereal tumor nor the leg swelling had recurred.

A 3-year-old male American Pit Bull Terrier was referred for evaluation and treatment of multicentric stage IV lymphoma. Previous treatment with combination chemotherapy had been unsuccessful. The dog was treated with a mechlorethamine-vincristine-procarbazine-prednisone protocol. Extravasation of vincristine (0.7 mL, 0.7 mg) and mechlorethamine (3 mL, 3 mg) occurred during the second cycle of chemotherapy

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because of poor condition of the dog's peripheral vasculature. As a result of the extravasation event, erythema and extensive swelling of the left hind limb developed during the following day. Palpation of the swollen region of the limb induced aggressive behavior and yelping. Six treatments of 300 units of hyaluronidase were administered to the dog, beginning immediately after the occurrence of the drug leakage. One week after the first treatment, the swelling had decreased by approximately 40% and continued to decrease during the following treatments. After the third injection, signs of pain were resolved completely, and erythema had decreased by approximately 60%. The only residual adverse effect was mild erythema of the affected limb that resolved 1 month after the last infiltration of hyaluronidase. Three months after the extravasation event, the dog had continued to receive chemotherapy, with partial remission of the neoplasia and with no episodes of leg swelling or lameness.

A 9-year-old male Beagle was affected by extravasation of doxorubicin during treatment of multicentric stage III lymphoma at our institution. The dog was quiet, alert, and responsive after the event, but physical examination revealed signs of inflammation of the right forelimb, and signs of intense pain were elicited upon palpation. A focal area of swelling on the medial aspect of limb, approximately 3 cm above the elbow, was observed; the size of the swelling, as measured with a caliper, suggested a volume of approximately 30 mL of doxorubicin (15 mg) had been extravasated. Attempts to withdraw some of the extravasated drug from the swollen area were unsuccessful. Because of the limited availability of bis 3,5-dimethyl-5-hydroxymethyl-2-oxomorpholin-3-yl (DMH3), the recommended treatment for doxorubicin extravasation,¹ the dog was treated with 300 units of hyaluronidase administered by use of 6 injections around the extravasation site, according to recommendations in human medicine.⁷⁻⁹ The dog tolerated the treatment well, even though infiltration was associated with signs of pain. The swelling decreased by approximately 50% during the first 4 weeks of treatment, beginning 5 days after the first infiltration of hyaluronidase, but the dog continued to lick and bite the affected limb. Local infiltration with dexamethasone (2 mL, 20 mg) was added to the treatment protocol at the time of the second dose of hyaluronidase. Dexamethasone was injected in a circumferential pattern around the extravasation site, immediately prior to infiltration of hyaluronidase; the combination treatment further decreased the swelling and signs of inflammation, resulting in improved pain control. Treatment of the limb was discontinued after 4 treatments with hyaluronidase and 3 with dexamethasone. Two months after the last infiltration, there was substantial fibrosis (3 × 5 cm) localized at the site of the initial focal swelling, but the function of the limb was not affected. No signs of pain were elicited during physical examination.

An 11-year old male mixed-breed dog was referred for treatment of a large retrobulbar lymphoma. The dog was quiet, alert, and responsive and had received supportive therapy at another institution. The condition of the dog's peripheral veins was very poor; fragility of the

left cephalic vein contributed to the extravasation of vincristine (approx 0.6 mL, 0.6 mg) during induction of chemotherapy. An area approximately 4 cm above the left carpus was affected; the signs of pain shown by the dog suggested that extravasation of the whole bolus had occurred. The extravasation site was promptly injected with hyaluronidase (300 units) in a perilesional pattern. The dog was sent home and treated with prednisone according to the lymphoma protocol (30 mg/m² for 7 days, then 20 mg/m² for 7 days, then 10 mg/m² for 7 days). The dog developed mild lameness of the left forelimb and began licking the extravasation site. These problems resolved without additional therapy within 10 days of the extravasation event. Because the dog's lameness had almost resolved by the time of the second appointment and the extravasation site did not show signs of an adverse reaction, the second dose of hyaluronidase was not administered. During recheck appointments, the extravasation site appeared normal, and the owner reported no signs suggestive of pain or discomfort. However, the patient was euthanatized after 6 weeks because of poor response of the tumor to chemotherapy.

A 10-year-old male Labrador Retriever with stage IV multicentric lymphoma was affected by extravasation of doxorubicin as a result of accidental removal of a catheter from the left cephalic vein during the third chemotherapy cycle. The amount of extravasated drug was approximately 10 mL (6 mg), as estimated from the duration of infusion and the volume of unused drug-saline solution. The extravasation site was treated with weekly infiltration of 300 units of hyaluronidase for approximately 4 weeks. Moderate cutaneous erythema at this site was evident the day after extravasation and was exacerbated by the dog licking at that area. An area of swelling (3 × 5 cm) was present at the extravasation site. The erythema resolved during a period of 2 weeks. The swelling resolved after the fourth infiltration of hyaluronidase, resulting in a residual 1.5-cm² painless fibrotic area at the extravasation site (7 cm above the carpus). At the completion of the sixth cycle of doxorubicin, the tumor was in remission. The owner reported that the dog's quality of life was good, and there has been no evidence of adverse effects from the extravasation.

During the past decade, the demand for chemotherapeutic management of malignancies in companion animals has increased, resulting in prolonged survival times and improved quality of life of pets with neoplasia. The use of antineoplastic drugs is not without risk for patients because of a reported lack of target cell specificity.¹⁰ The toxic effects frequently reported in the literature are systemic; the drugs and their metabolites can induce a wide range of adverse effects.¹¹ Limited information is available regarding the cytotoxic effects of extravasation of chemotherapeutic agents, and treatment options in veterinary medicine are anecdotal and not well defined.¹⁰⁻¹² The prevalence of extravasation of chemotherapeutic drugs in veterinary medicine has not been determined; however, data available from humans indicate the prevalence ranges from 0.1 to 6.5%, although an accurate measure has proven difficult.¹ Perivascular leakage of many anti-

neoplastic agents can cause severe local tissue damage and deep ulcerations that progress during a period of weeks.¹³ These lesions are slow to heal and often require skin grafting, although the graft is not always successful. When left untreated, extravasation injuries rapidly progress from swelling and erythema to partial- or full-thickness soft-tissue necrosis that ultimately results in ulceration. Initial severe damage may involve nerves and tendons, often necessitating aggressive surgical débridement and even limb amputation. Full-thickness skin ulcerations are a substantial source of illness in veterinary cancer patients and are perceived by pet owners to decrease quality of life, often leading to the termination of the chemotherapy or even euthanasia.

The risk of local injury following extravasation is not equivalent for each chemotherapeutic agent, and drugs are classified as vesicant, irritant, or nonvesicant.¹ Vesicant drugs are capable of inducing a blister, with or without tissue destruction. Irritant drugs may cause signs of pain when injected, with or without an inflammatory response. Nonvesicant drugs seldom generate acute reactions or tissue necrosis.¹ Tissue necrosis develops through several mechanisms, many of which are not completely understood. Some drugs (eg, anthracyclines) are absorbed locally by cells and cause cell death after binding to DNA.^{1,6} After cell death, the drug is released by the cells during endocytolysis, causing additional damage in a dose-dependent manner.^{1,7} The persistence of drug molecules in the tissues impairs the healing process through cyclic destruction of healthy cells, resulting in chronic nonhealing lesions. On histologic examination, these lesions are characterized by a bland coagulative necrosis, neutrophilic infiltration, and dermal septation; unlike chronic radiation-induced ulcers, the vessels adjacent to the drug-induced lesions are patent.⁶ Several months after the occurrence of extravasation, high concentrations of DNA-binding drugs have been measured at the extravasation site by use of high performance liquid chromatography.¹⁴ Drugs that do not bind to DNA (eg, vincristine) have a different mechanism of action regarding connective tissue damage, apparently mediated by the lipophilic solvents commonly used in their commercial formulations.¹ Authors investigating skin lesions induced by extravasation of different medical preparations advocated other mechanisms for this damage, such as the physicochemical properties of the drugs (osmolality and alkalinity) or their ability to induce local ischemia.^{13,15}

Hyaluronidase appears effective in reducing skin damage and loss following extravasation of chemotherapeutic agents. This enzyme temporarily decreases the viscosity of the glycosaminoglycan hyaluronic acid. Glycosaminoglycans and proteoglycans are components of ground substance, in which connective tissue fibers and cells are embedded. This material is important in controlling diffusion of materials to and from cells. As hyaluronic acid becomes less viscous, greater diffusion of the chemotherapeutic agents into the surrounding tissues is promoted, and their local concentrations are decreased.^{4,6,15} The 6 dogs in this report were administered hyaluronidase to treat extravasation

injuries from drugs such as doxorubicin and mechlorethamine for which other treatments have been recommended; these include topical administration of dimethylsulfoxide^{1,6} or intralesional administration of DHM3⁹ for doxorubicin, and perivenous administration of sodium thiosulfate for mechlorethamine.¹ The results of hyaluronidase treatment compared favorably with those obtained with other treatments recommended for use in humans. The hyaluronidase treatment also appeared to have been effective against the simultaneous extravasation of 2 chemotherapeutic drugs, vincristine and mechlorethamine, that have different mechanisms of action resulting in complete prevention of cutaneous ulcerations.

In these dogs, hyaluronidase was administered weekly until clinical signs (swelling, erythema, signs of pain) were no longer observed; a focal area of fibrosis developed at the affected site in some dogs. The number of hyaluronidase treatments required to achieve this goal varied among dogs. The optimal hyaluronidase treatment interval is not known, and hyaluronidase infiltrations administered once per week may be unnecessarily frequent. For 1 of the dogs, treatment with hyaluronidase was administered with intralesional injection of dexamethasone for 3 of the 4 treatments because of persistent inflammation and signs of pain at the extravasation site. Treatment with dexamethasone is considered a palliative measure and is not thought to increase the efficacy of hyaluronidase.⁶

Several factors influence the likelihood of extravasation injury in patients undergoing chemotherapy. These factors include age, state of consciousness, behavior, condition of the animal's venous circulation, and type, location, and placement of the IV catheter.^{1,6,13,16} Diseases that have a negative correlation with risk of drug extravasation are lymphedema, cranial vena cava syndrome, and peripheral neuropathy.^{1,2,6} Drug extravasation was attributed to behavior problems in 2 dogs reported here, to poor condition of the peripheral veins of 2 dogs, and to the use of a butterfly needle instead of a polytef catheter for the administration of chemotherapy in another dog.

To avoid extravasation when administering a potentially cytotoxic agent, all possible precautions must be taken, such as ensuring patency of IV catheters, monitoring the injection site carefully, and using patient restraint or sedation when necessary. Although the occurrence of extravasation of antineoplastic agents can be decreased by application of suitable precautions, such events result in serious adverse reactions, the treatment of which can be highly frustrating. Weekly perivascular infiltration of extravasation sites with hyaluronidase was used with success in these 6 dogs. Hyaluronidase appears to be a safe treatment and may play a useful role in the prevention or reduction of local toxicosis induced by extravasation of chemotherapeutic agents.

^aAdriblastina, Pharmacia & Upjohn, Milano, Italy.

^bEndoxan-Asta, Asta Medica SpA, Milano, Italy.

^cCaryolysine, Laboratoires Synthelabo, Le Plessis-Robinson, France.

^dVincristina Teva, Teva Pharma Italia Srl, Milano, Italy.

^eJaluran, Pfizer Italia SpA, Latina/Roma, Italy.

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