Doxorubicin: Finding the Right Dose

Doxorubicin (DOX) is a widely used chemotherapy drug with a narrow therapeutic window. Large interpatient variability exists in the development and degree of myelosuppression following equivalent dosages. Pharmacokinetic (PK) studies, which describe the relationship between drug dose and exposure, have been used to predict clinical effects, but they are laborious and expensive. Pharmacodynamic (PD) studies involve the relationship between exposure and efficacy or toxicity. Traditionally, chemotherapeutic drugs are dosed based on body surface area (BSA) to normalize the maximum tolerated dose. BSA may correlate better than weight with physiologic processes influencing drug activity; however, BSA dosing causes increased toxicity in smaller dogs, may not account for breed differences, and does not account for the effect of disease states on drug disposition.

Size-independent factors such as absorption from the administration site, distribution and storage in tissue, enzymatic and nonenzymatic metabolism, and excretion are likely to have a greater effect than body size.

This study described the development and validation of a limited-sampling strategy in which blood samples were obtained from 27 dogs 3 times within 1 hour following DOX treatment to accurately predict drug exposure. This strategy will be used for further studies to evaluate the relationship of exposure to toxicity, possibly enabling refinement of dosing variables and the use of therapeutic drug monitoring to ensure optimized dosing.

Commentary
This is a good first step toward answering the question of optimal dosing of chemotherapy in dogs. The calculation based on BSA is imperfect, and, clinically, this is translated as huge variations in toxicity of a drug used at the predetermined dosage. Indeed, small dogs tend to be relatively overdosed using the BSA formula; however, we also see large dogs occasionally experiencing high-grade toxicities and small dogs having no adverse effects. Basing a drug calculation on PK parameters may be more accurate, and the method used here appears less cumbersome. Further studies are necessary to determine the accuracy and applicability of this strategy for optimal dosing.—Cecilia Robat, DVM, DACVIM (Oncology)

Disequilibrium Syndrome in a Blocked Cat

A 5-year-old neutered cat developed neurologic signs subsequent to rapid resolution of azotemia after treatment for urinary obstruction, suggesting a process similar to dialysis disequilibrium syndrome (DDS). At hospital admission, the cat was stabilized, a urinary catheter was placed to relieve obstruction, and IV fluid therapy was initiated to help reverse significant hyperkalemia and azotemia. Several hours later, the patient had a grand mal seizure, subsequently developing respiratory arrest requiring endotracheal intubation. After a bolus of hypertonic saline, his neurologic status improved and he began breathing on his own. Following a second neurological episode, a CRI of hypertonic saline was started; eventually, the cat became more responsive and had no further seizures.

DDS has been reported in human and veterinary patients undergoing dialysis for renal disease and was initially associated with rapid decrease in blood urea nitrogen concentrations. This is the first known report of DDS-like signs secondary to treatment for urethral obstruction. Currently, 2 theories exist to explain the pathogenesis of DDS; both assume an initial hyperosmolar state and development of a gradient between the blood and cerebral tissue. When a rapid reduction in peripheral osmolality occurs via dialysis, there is a shift of fluid intracellularly, causing neuronal swelling, increased intracranial pressure, and the resulting clinical signs. Treatment is typically achieved through the administration of an osmotic agent.

Commentary
Dialysis and continuous renal replacement therapy (CRRT) are becoming more readily available, and awareness is increasing. The blocked cat in this report (although he was not dialyzed) will be familiar to many, although his complication—DDS—likely will not. I have seen many blocked cats but never treated one that developed postobstructive seizures or dialysis disequilibrium. This case is useful to bridge the gap between the familiar (blocked cat) and the unfamiliar (dialysis and CRRT). This study is helpful to increase sentence of this rare complication of a common disease and raise awareness about a possible complication of a promising treatment modality.—Tony Johnson, DVM, DACVECC

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