Severe reaction to intravenous administration of an ionic iodinated contrast agent in two anesthetized dogs

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Case Description—Acute severe systemic reactions developed during IV administration of an ionic iodinated contrast agent (iothalamate meglumine) in 2 dogs undergoing contrast-enhanced computed tomography.

Clinical Findings—Both dogs developed marked changes in heart rate and systolic arterial blood pressure during or immediately after IV administration of the contrast agent. The first dog became profoundly hypertensive and bradycardic with poor oxygenation, apparent bronchospasm, and prolonged diarrhea. The second dog became hypotensive and tachycardic with erythema on the ventral aspect of the abdomen and pelvic limbs, perioral edema, and diarrhea.

Treatment and Outcome—Both dogs were treated for shock by means of IV fluid administration, and anesthesia was discontinued. The first dog was placed on a ventilator to improve oxygenation but was hypertensive and unresponsive for 6.5 hours following contrast agent administration. Bloody diarrhea persisted once consciousness was regained. The dog was discharged 3 days after contrast agent administration, and diarrhea resolved 15 days later. The second dog responded to phenylephrine administration, but urine output appeared low immediately following recovery from anesthesia. Urine output was normal the following day, and the dog was released 36 hours after contrast administration with no residual adverse effects.

Clinical Relevance—Findings highlighted the potential risk for severe reactions associated with IV administration of ionic iodinated contrast agents in dogs. Both hypertensive and hypotensive responses were seen. Supportive care for systemic manifestations was effective in these 2 dogs, and extended hospitalization was not necessary. (J Am Vet Med Assoc 2008;233:274–278)

A 6-year-old 36.4-kg (80-lb) spayed female American Pit Bull Terrier (dog 1) was referred to the University of California, Davis, School of Veterinary Medicine for surgical resection of a left-sided thyroid mass. The owners had noticed the mass approximately 1 month earlier and reported that it had grown substantially since then. The dog also had a 4-month history of a slowly enlarging right ventral abdominal wall mass. An additional mass on the left lateral aspect of the thoracic wall had been diagnosed as cutaneous squamous cell carcinoma, but had not been treated. On physical examination, the dog had multiple areas of alopecia, a 2-cm pedunculated mass on the right caudoventral aspect of the abdomen, and a 6 × 12-cm, freely movable mass in the mid and left ventral cervical region. Results of the physical examination were otherwise unremarkable.

Results of a CBC, serum biochemical profile (including measurement of serum thyroxine concentration), and urinalysis were within reference limits, and results of thoracic radiography (3 views) and abdominal ultrasonography were unremarkable. Ultrasonography of the ventral cervical region revealed a 5.5-cm complex mass replacing the left thyroid lobe. The right thyroid lobe was identified and appeared normal. Results of cytologic examination of an ultrasound-guided aspirate of the ventral cervical mass were consistent with thyroid carcinoma.

Computed tomography was scheduled for surgical planning purposes. The dog was premedicated with acepromazine (0.02 mg/kg [0.009 mg/lb], SC), hydromorphone (0.05 mg/kg [0.023 mg/lb], SC), and atropine (0.02 mg/kg, SC). Anesthesia was induced with propofol (1.4 mg/kg [0.64 mg/lb], IV) and thiopental (3.4 mg/kg [1.55 mg/lb], IV) and maintained with isoflurane in oxygen. Respiratory rate was determined by observation of the chest and rebreathing bag; pulse rate and arterial blood pressure were measured indirectly by means of Doppler ultrasonic flow detection with the probe placed on the palmar surface of the right paw. The dog was positioned in the gantry of the computed tomography unit, and a hypoattenuating mass in the region of the left thyroid lobe was identified on images of the cervical region. Prior to contrast agent administration, heart rate was 100 beats/min, systolic arterial blood pressure was 110 mm Hg, and respiratory rate was 40 breaths/min. Iothalamate meglumine (430 mg/
an ionic iodinated contrast agent, was administered IV (1,300 mg of iodine/kg [590 mg of iodine/lb]) through a cephalic vein catheter. Immediately following contrast agent administration, the dog became bradycardic (63 beats/min) and severely hypertensive (195 mm Hg). The dog was attached to a ventilator because of hypoventilation and poor oxygenation (Paco₂, 93.7 mm Hg; Paco₂, 48.2 mm Hg). Computed tomography of the thorax was performed and revealed increased opacity of the accessory lung lobe (atelectasis) and apparent widespread bronchoconstriction (Figure 1). Pulses could not be palpated. The rate of IV fluid administration (lactated Ringer's solution) was increased from 400 mL/h to 650 mL/h, and administration of isoflurane was terminated. Heart rate and blood pressure fluctuated substantially over the ensuing 4 hours, with maximal blood pressure of 240 mm Hg measured 2 hours after contrast agent administration. The dog developed bloody diarrhea and remained unresponsive until 6.5 hours after contrast agent administration. Consciousness and attitude were considered normal the following day; however, severe bloody diarrhea persisted. Abdominal ultrasonography revealed severe colonic wall thickening and decreased small bowel motility. Thoracic radiography revealed trace infiltrates in the right middle lung lobe; no abnormalities of the accessory lung lobe were seen. Bloody diarrhea continued but was decreasing in severity at the time of discharge 3 days after computed tomography. Follow-up discussions with the owner indicated resolution of soft feces 15 days after contrast agent administration.

A 3-year-old 48.2-kg (106-lb) castrated male Standard Poodle mix (dog 2) was referred to the University of California, Davis, School of Veterinary Medicine for evaluation and treatment of a rapidly growing oral mass.

Results of histologic examination of biopsy specimens obtained at a referring veterinary hospital had been inconclusive, and the dog had been treated for presumptive oral melanoma with an experimental melanoma vaccine protocol. The owners reported that the dog had not been eating well, but was otherwise normal. On physical examination, the dog had mild generalized dental calculus and gingivitis and moderate to severe mandibular prognathia with reference to the maxilla. There was a 6 x 3-cm ulcerated mass in the caudal right palatal region. The remainder of the physical examination was unremarkable.

Results of a serum biochemistry profile and urinalysis were within reference limits; a CBC revealed leukocytosis (28,910 WBCs/µL; reference range, 6,000 to 13,000 WBCs/µL) attributable to neutrophilia (22,995 neutrophils/µL; reference range, 3,000 to 10,500 neutrophils/µL) and mild monocytosis (1,446 monocytes/µL; reference range, 150 to 1,200 monocytes/µL). Hematologic abnormalities were thought to be secondary to inflammation associated with the oral mass. Results of thoracic radiography (3 views) and abdominal ultrasonography were unremarkable.

Computed tomography was scheduled for surgical planning purposes. The dog was premedicated with glycopyrrolate (0.01 mg/kg [0.0045 mg/lb], SC) and butorphanol (0.2 mg/kg [0.09 mg/lb], SC). Anesthesia was induced with thiopental (7.3 mg/kg [3.3 mg/lb], IV) and midazolam (0.25 mg/kg [0.11 mg/lb], IV) and maintained with isoflurane in oxygen. Vital signs were monitored as described for dog 1. The dog was positioned in the gantry of the computed tomography unit, and a partially mineralized mass involving the alveolar bone of the first and second molars of the right maxilla was seen on images of the skull. Prior to contrast agent administration, the dog became bradycardic (65 beats/min) and severely hypertensive (195 mm Hg); PaO₂, 77 mm Hg). Computed tomography (2, 100 mA, 150 mAs, 512 X 512 matrix, chest algorithm). Notice that bronchi (arrows) in the dog with the contrast agent reaction were constricted (A), compared with bronchi in the healthy dog (B; arrows). L = Left; R = Right.
administration, heart rate was 90 beats/min, peak systolic blood pressure was 110 mm Hg, and respiratory rate was 10 breaths/min. Isothalamate meglumine was administered IV (1,100 mg of iodine/kg [500 mg of iodine/lb]) through a lateral saphenous vein catheter. After 60 mL of the contrast agent had been administered, the dog became tachycardiac (140 beats/min) and severely hypotensive (50 mm Hg) and developed erythema of the pelvic limbs and ventral aspect of the abdomen as well as diarrhea and periorcular edema. Contrast agent administration was discontinued. Pulses could not be palpated; therefore, the rate of IV fluid administration (lactated Ringer's solution) was increased from 250 mL/h to 500 mL/h, administration of isoflurane was terminated, and phenylephrine (4.2 µg/kg [1.9 µg/lb], IV) was administered. Heart rate and peak systolic blood pressure returned to reference ranges (90 beats/min and 100 mm Hg, respectively) 1.5 hours after contrast agent administration. The oral mass was biopsied, and the dog was allowed to recover from anesthesia. After recovery, it was determined that the dog had gained 2.8 kg (6.2 lb) of body weight and had not urinated despite administration of 4 L of fluids over 3.5 hours. A urinary catheter was placed, and urine output was monitored for the ensuing 24 hours while fluids were administered IV at twice the maintenance rate. Urine output 11 hours after contrast agent administration was 6 mL/kg/h (2.7 mL/lb/h). The dog had normal urine production and feaces at the time of discharge 36 hours after undergoing computed tomography. Histologic examination of the biopsy specimen from the oral mass revealed fibrosarcoma, and the dog was euthanatized 9 days later because of the poor prognosis. No residual adverse effects associated with contrast agent administration were evident at the time of euthanasia. A necropsy was not performed.

Discussion

Adverse effects associated with IV administration of iodine-based contrast agents for purposes of diagnostic imaging in people are well documented. In human patients, iodine-based contrast agents are used for excretory urography, selective and nonselective angiography, and contrast-enhanced computed tomography. Various schemes for grading reactions to contrast agents have been reported, with the severity scale described by Ring and Messmer being the most widely used. According to this grading scheme, grade I reactions include mild fever and skin manifestations such as arm pain, flushing, pruritis, and urticaria. Grade II reactions consist of measurable but non–life-threatening cardiovascular reactions (eg, tachycardia and hypotension) and gastrointestinal tract disturbances (eg, nausea, vomiting, and diarrhea). Grade III reactions include more severe manifestations of grade II reactions and include shock and life-threatening spasm of smooth muscle (bronchospasm). Grade IV reactions include cardiac and respiratory arrest.

The pathophysiology of contrast agent reactions is only partly understood and likely involves multiple mechanisms. Most reactions in people are considered to be idiosyncratic or pseudoallergic. Idiosyncratic reactions are those that appear to be genetically pre-determined and related to metabolic or enzymatic imbalances. Pseudoallergic reactions are immunologically mediated events involving complement and histamine activation that lack immunologic specificity. In general, contrast agent reactions in people tend to be unpredictable, are not dose dependent, and involve the release of various biologically active mediators, including histamine, serotonin, prostaglandin, bradykinin, leukotriene, adenosine, and endothelin, with 70% of reactions occurring in the first 5 minutes following contrast agent administration. Certain features appear to predispose people to contrast agent reactions, including advanced age; infirmity; dehydration; and a history of asthma, food allergy, atopy, or a previous contrast agent reaction. Although the incidence of mild reactions following IV administration of ionic, iodinated contrast agents approaches 15% in the general population, severe reactions are uncommon (0.04% to 0.22%).

Nonionic iodinated contrast agents are available and were developed in an attempt to reduce the frequency and severity of contrast agent reactions. The osmolality of these agents more closely resembles that of serum, such that fluid flux is less dramatic with nonionic than with ionic agents and the occurrence of peripheral vasodilation is reduced. Minor acute reactions occur in only 3% of people given nonionic iodinated contrast agents, and the prevalence of severe reactions is low (0.04% to 0.004%).

A recent retrospective study has suggested that hemodynamic alterations are relatively common following IV administration of contrast agent in anesthetized dogs. In that study, 3% of dogs that received an ionic iodinated contrast agent developed a heart rate < 60 beats/min or > 130 beats/min, with a ≥ 20% change from baseline heart rate, and 4% developed a systolic blood pressure < 90 mm Hg or > 160 mm Hg, with a ≥ 20% change from baseline pressure, within 20 minutes after agent administration. Also, changes in heart rate and peak systolic blood pressure were less common in dogs that received a nonionic iodinated contrast agent. On the basis of the severity scale described by Ring and Messmer, all of the dogs in that study that had a reaction would have been classified as having a grade II reaction, and none of the dogs would have been classified as having a grade III or IV reaction. To our knowledge, there are only anecdotal reports of severe reactions (grade III or IV) following IV administration of ionic iodinated contrast agents in the veterinary literature.

Both of the dogs described in the present report had grade III reactions following IV administration of the ionic iodinated contrast agent. Dog 2 developed typical manifestations of a contrast agent reaction, including hypotension, tachycardia, erythema, periorcular edema, and gastrointestinal tract disturbance (diarrhea). Hypotension develops in response to administration of contrast agents because of peripheral vasodilation. The hypertonicity of the agent in combination with the release of vasoactive substances is often blamed for this effect. Tachycardia ensues as a response to systemic hypotension. Although dog 2 did not have any of the typical factors known to in-
crease the risk of contrast agent reactions in people, the dog had recently undergone immunostimulation as a result of the experimental melanoma vaccine administered by the referring veterinarian. Whether the vaccine protocol in dog 2 contributed to the contrast agent reaction is unknown.

Diminished urine output was of concern in dog 2 because contrast medium nephrotoxicosis has been described in people and dogs.\(^4,15\) Contrast medium nephrotoxicosis is defined as an increase in serum creatinine concentration of > 23%, compared with the baseline value, within 3 days after contrast administration,\(^16\) and is most common in people with preexisting renal compromise. In people, contrast medium nephrotoxicosis is self-limiting and resolves within 1 to 2 weeks.\(^16\) However, it can predispose to nonreparative complications and often increases hospitalization time.\(^17\) Renal hypotension and direct cytotoxicity of the contrast agent are considered the main contributing factors in the development of contrast medium nephrotoxicosis.\(^15\) Dog 2 regained normal urine output within 24 hours after contrast agent administration and did not have any evidence of residual renal or other systemic compromise at the time of discharge.

The contrast agent reaction in dog 1 in the present report was indicative of diffuse smooth muscle spasm. Bronchospasm is often seen with grade III reactions\(^4\) and is the likely explanation for the dog's poor oxygenation given the computed tomographic appearance of the lungs. Pulmonary hypertension is also seen with severe contrast agent reactions and may be an additional contributing factor.\(^3\) However, prolonged systemic hypertension is not typical of contrast agent reactions. Although vascular volume expansion occurs with IV administration of ionic contrast agents, this is short-lived and countered by peripheral vasodilation.\(^13\) Perhaps in this dog, smooth muscle spasm induced by the release of biologically active mediators such as histamine and prostaglandin resulted in vascular smooth muscle spasm and secondary systemic hypertension. Presumably, the bradycardia in dog 1 was a response to systemic hypertension.

Alternatively, it is known that the administration of iothalamate meglumine and other ionic iodinated contrast agents in people with hyperthyroidism or an autonomously functioning thyroid mass can precipitate a condition known as thyroid storm.\(^18\) Thyroid storm is a state of decompensated thyrotoxicosis associated with exaggerated clinical features of hyperthyroidism, including hypertension.\(^19\) Although dog 1 did not have biochemical indicators of hyperthyroidism, some contribution from the thyroid mass cannot be discounted. Severe hypertension has also been reported with administration of ionic iodinated contrast agents in people with pheochromocytomas.\(^20\) Dog 1 had no clinical evidence of a pheochromocytoma, and adrenal lesions were not seen during abdominal ultrasonography. However, a previous report\(^21\) indicated that clinical manifestations of pheochromocytomas may be intermittent and difficult to define, with only 50% of histologically identified lesions evident during abdominal ultrasonography.

Treatment for acute contrast agent reactions is largely nonspecific. Hypotension is likely to be a result of vasodilation; therefore, fluid therapy and administration of a vasoconstrictor such as phenylephrine are logical choices. The pathophysiology of hypertension is less well understood, making this complication more difficult to treat. If persistent, a vasoconstrictor with a short duration of action (eg, nitroprusside) should be chosen so that if hypotension ensues, the vasoconstrictor can be eliminated rapidly. Bronchoconstriction is managed by providing a high concentration of oxygen, intermittent positive-pressure ventilation with or without positive end-expiratory pressure, and a systemic bronchodilator such as epinephrine or inhaled bronchodilator such as albuterol.

Findings for the 2 dogs described in the present report highlight the potential risk for severe reactions to IV administration of iodinated contrast agents. Both hypertensive and hypotensive responses may be seen. Supportive care for systemic manifestations was effective in these 2 dogs, such that extended hospitalization was not necessary. A pattern of predisposing features was not identified in these 2 dogs, although the potential roles of the thyroid carcinoma in dog 1 and immunostimulation by vaccination in dog 2 are unclear. Regardless, the use of nonionic iodinated contrast agents should be considered when performing studies requiring IV contrast administration.

References


**Selected abstract for JAVMA readers from the American Journal of Veterinary Research**

Comparison of prothrombin time, activated partial thromboplastin time, and fibrinogen concentration in blood samples collected via an intravenous catheter versus direct venipuncture in dogs

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**Objective**—To compare prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen concentration in canine blood samples collected via an indwelling IV catheter and direct venipuncture.

**Animals**—35 dogs admitted to an intensive care unit that required placement of an IV catheter for treatment.

**Procedures**—Blood samples were collected via IV catheter and direct venipuncture at the time of catheter placement and 24 hours after catheter placement. Prothrombin time, APTT, and fibrinogen concentration were measured.

**Results**—5 dogs were excluded from the study; results were obtained for the remaining 30 dogs. Agreement (bias) for PT was −0.327 (limits of agreement, −1.350 to 0.696) and 0.003 (limits of agreement, −1.120 to 1.127) for the 0- and 24-hour time points, respectively. Agreement for APTT was −0.423 (limits of agreement, −3.123 to 2.276) and 0.677 (limits of agreement, −3.854 to 5.207) for the 0- and 24-hour time points, respectively. Agreement for fibrinogen concentration was −2.333 (limits of agreement, −80.639 to 75.973) and −1.767 (limits of agreement, −50.056 to 46.523) for the 0- and 24-hour time points, respectively.

**Conclusions and Clinical Relevance**—Agreement between the 2 techniques for sample collection was clinically acceptable for PT, APTT, and fibrinogen concentration at time 0 and 24 hours. It is often difficult or undesirable to perform multiple direct venipunctures in critically ill patients. Use of samples collected via an IV catheter to monitor PT and APTT can eliminate additional venous trauma and patient discomfort and reduce the volume of blood collected from these compromised patients. *(Am J Vet Res 2008;69:868–873)*