

Hemodynamic and serum biochemical alterations associated with intravenous administration of three types of contrast media in anesthetized dogs

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Objective—To determine the incidence and type of alterations in heart rate (HR), peak systolic blood pressure (PSBP), and serum biochemical variables (total bilirubin, BUN, and creatinine concentrations) associated with IV administration of ionic-iodinated contrast (IIC), nonionic-iodinated contrast (NIC), and gadolinium dimeglumine (GD) contrast media in anesthetized dogs.

Animals—280 anesthetized dogs undergoing cross-sectional imaging.

Procedures—HR and PSBP were recorded at 5-minute intervals for 20 minutes for untreated control dogs and dogs that received IIC, NIC, or GD contrast medium. The development of an HR of < 60 beats/min or > 130 beats/min that included a $\geq 20\%$ change from baseline was considered a response. The development of PSBP of < 90 mm Hg or > 160 mm Hg that included a $\geq 20\%$ change from baseline was considered a response. Pre- and postcontrast serum biochemical values were recorded.

Results—Of dogs receiving IIC medium, 3% (3/91) had a response in HR and 4% (4/91) had a response in PSBP at ≥ 1 time points. None of the dogs receiving NIC medium had a response in HR; 1 of 16 had a response in PSBP. Of dogs receiving GD contrast medium, 1% (1/92) had a response in HR and 4% (4/92) had a response in PSBP. Of control dogs, 2% (2/81) had a response in HR and 4% (3/81) had a response in PSBP. No serum biochemical alterations were observed.

Conclusions and Clinical Relevance—IV administration of contrast media in anesthetized dogs caused moderate bradycardia, tachycardia, hypotension, or hypertension. (*Am J Vet Res* 2008;69:1268–1273)

In people, adverse effects associated with the IV administration of contrast media for the purpose of diagnostic imaging are well documented.^{1–3} Contrast medium-induced reactions in people are classified on the basis of acute, delayed, or systemic effects. Acute reactions are the most common and occur within the first hour following contrast medium administration, with 70% of reactions occurring in the first 5 minutes.⁴ Acute reactions can be further subdivided into mild, intermediate, and severe reactions.³ Mild reactions typically do not require intervention, whereas intermediate and severe reactions prompt the administration of medications and hemodynamic support. Delayed reactions are uncommon, typically involve skin rashes, and occur more than 1 hour but within 7 days of contrast medium administration.³ Certain people with preexisting conditions such as food allergies, asthma, and atopy appear predisposed to acute and delayed contrast medium-induced reactions.^{1,3}

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ABBREVIATIONS

GD	Gadolinium dimeglumine
HR	Heart rate
IIC	Ionic-iodinated contrast
NIC	Nonionic-iodinated contrast
PSBP	Peak systolic blood pressure

Systemic effects are a separate category of contrast medium adverse effects related to toxic effects of the contrast medium that encompass complications such as contrast medium-induced nephrotoxicosis.

Iodine-based contrast media that are used IV for excretory urography, selective and nonselective angiography, and contrast-enhanced computed tomography can be subdivided into ionic and nonionic categories. Mild acute reactions, such as arm pain, flushing, nausea, pruritus, headache, vomiting, and urticaria occur in as many as 15% of people given IIC media and 3% of people given NIC media.⁵ Intermediate acute reactions encompass more serious manifestations of the mild reactions and may extend to moderate hypotension, hypertension, and bronchospasm.³ Severe acute reactions occur much less frequently (ie, 0.04% to 0.22% of people receiving IIC media and 0.004% to 0.04% of people receiving NIC media) but can be life threat-

ening and include convulsions, unconsciousness, laryngeal edema, severe bronchospasm, cardiac dysrhythmia, cardiac arrest, and cardiovascular and pulmonary collapse.^{4,6} The most common adverse systemic effect of iodine-based contrast media is contrast medium–induced nephrotoxicosis, which is defined as a 25% increase in serum creatinine concentration within 3 days of contrast medium administration.⁷ Contrast medium–induced nephrotoxicosis occurs in 0% to 10% of people with normal renal function and in 12% to 27% of people with preexisting renal compromise.⁷

Gadolinium-based contrast media that are administered IV for contrast-enhanced magnetic resonance imaging have a lower rate of complications with an overall incidence of acute reactions (mild to severe) reported in 0.48% to 19.9% of people.^{2,8} Systemic reactions also appear to be rare with a slight, transient increase in serum total bilirubin concentration thought to be secondary to mild hemolysis reported in some people.⁸ More recently, a severe late adverse reaction to gadodiamide contrast media has been reported and called nephrogenic systemic fibrosis. This disease develops in people with end-stage renal disease that receive gadodiamide and results in necrotizing dermatitis and renal sclerosis 2 to 75 days following contrast medium administration.⁹

Despite the wealth of studies investigating contrast medium–induced adverse effects in people, there is a paucity of information regarding such events in animals within the veterinary literature. As advanced imaging techniques such as computed tomography and magnetic resonance imaging become more commonly used in the veterinary community, the administration of contrast media is performed more frequently. Thus, an understanding of the frequency and types of reactions following contrast medium administration is increasingly important. Although it is difficult to detect mild reactions such as pruritus, nausea, and injection site pain in animals, adverse effects of IIC media in veterinary patients including vomiting, anxiety, hypotension, and cardiac and respiratory arrest have been anecdotally described, with a mortality rate of 1 in 80 animals.¹⁰ Clinical reports describing contrast-induced renal failure secondary to IIC medium administration in 1 dog¹¹ and 1 cat¹² have also been published.

The purpose of the study reported here was to determine the frequency and types of hemodynamic alterations associated with the IV administration of contrast media in a large number of anesthetized dogs. Substantial changes in HR and PSBP in response to contrast medium administration have been described for people and are felt to be indicators of potentially more serious adverse effects.¹³ Thus, changes in these hemodynamic variables were chosen for evaluation. The assessment of responses was limited to serum biochemical variables that have been previously reported to change in response to contrast medium administration in people. The prevalence of reactions in dogs was compared among those receiving IIC, NIC, and GD contrast media. It was hypothesized that IIC media would result in more frequent and severe alterations in hemodynamic variables in dogs than NIC and GD contrast media.

Materials and Methods

Criteria for selection of cases—The medical records database at the University of California, Davis, School of Veterinary Medicine was searched for anesthetized dogs that had received iodinated contrast media IV for computed tomography or GD-based contrast media for magnetic resonance imaging procedures between April 2005 and April 2006. Dogs were included in the study population if their medical records contained information regarding HR or PSBP prior to (baseline) and at 5-minute intervals following IV administration of contrast media. Dogs were excluded if they received dopamine IV during the study period.

The medical records database was also searched for dogs undergoing magnetic resonance imaging but not receiving IV administration of contrast medium to provide control data. For control dogs, baseline was arbitrarily defined as the measurement recorded 15 minutes after the start of magnetic resonance imaging. Values from these dogs were used to establish the normal variation in HR and PSBP in anesthetized dogs undergoing noncontrast imaging.

Procedure—Medical records were reviewed for information regarding breed, sex, body weight, and history. The HR and PSBP, as determined by Doppler, oscillometric, or direct techniques, were recorded immediately prior to (baseline) and for four 5-minute intervals (20 minutes) following contrast medium administration. An alteration in HR outside of reported reference range values (< 60 beats/min or > 130 beats/min) and representing at least a 20% change from baseline was considered important. An alteration in PSBP outside of reported reference range values (< 90 mm Hg or > 160 mm Hg) and representing at least a 20% change from baseline was considered important. The percentage change from baseline was included so that each dog served as its own control. Comments in the record indicating a perceived response to contrast medium administration on the part of the anesthetist were noted. Conditions such as chronic bronchitis or allergic skin disease were recorded as indicators of potential hypersensitivity, and these dogs were assessed for a possible association between allergic conditions and contrast medium–induced reactions as has been demonstrated for people.

When results of serum biochemical analyses were available, the serum total bilirubin (to assess for GD-induced hemolysis), BUN, and serum creatinine (to assess for renal effects of contrast media) concentrations were recorded for precontrast and postcontrast imaging time points. For inclusion, precontrast biochemical information must have been obtained within 5 days of the imaging procedure. The time between the collection of blood samples was noted.

Statistical analysis—Values are reported as mean \pm SD. An ANOVA was used to compare age and weight of dogs between the different contrast medium groups. Values of $P < 0.05$ were considered significant.

Results

During the inclusion period, 158 dogs received the GD contrast medium^a (gadopentetate dimeglumine,

469.01 mg/mL [285 mOsm/kg of water]) for magnetic resonance imaging, 92 of which met the inclusion criteria. During the same period, 134 dogs received iodinated contrast media IV for computed tomography examinations, 114 of which were given the IIC medium^b (iothalamate sodium, 400 mg of iodine/mL [2,300 mOsm/kg of water]) and 20 of which were given the NIC medium^c (iopamidol 41%, 200 mg of iodine/mL [413 mOsm/kg of water]). Of the 114 dogs that received IIC medium, 91 met the inclusion criteria. Because the number of dogs that received the NIC medium was low, medical records were searched back to June 2002, and an additional 11 dogs were evaluated for inclusion. Of the 31 total dogs that received NIC medium, 16 met the inclusion criteria. Contrast media were administered by hand at an approximate rate of 2 mL/s. Eighty-one dogs undergoing magnetic resonance imaging without contrast medium administration but with at least 20 minutes of HR and PSBP data were included as a control group. All dogs were hemodynamically supported with IV administration of fluid during anesthesia.

A variety of breeds were represented in each of the contrast medium and control groups, with no breeds being appreciably overrepresented in any group. Ages for control (ie, dogs receiving no contrast medium), IIC, NIC, and GD-contrast group dogs were 7.6 ± 3.7 years, 8.6 ± 3.5 years, 8.8 ± 3.4 years, and 7.5 ± 4.0 years, respectively. Body weights for control, IIC, NIC, and GD-contrast group dogs were 27.8 ± 12.2 kg, 26.1 ± 14.1 kg, 21.1 ± 15.7 kg, and 27.5 ± 14.9 kg, respectively. No significant differences were found in age or body weight among any groups.

Of dogs receiving IIC medium, 2 of 91 (2%) became tachycardic (HR of 162 and 144 beats/min at 5 and 10 minutes, respectively, after contrast medium administration), and 1 of 91 (1%) became bradycardic (HR of 59 beats/min at 20 minutes after contrast medium administration). Of dogs receiving NIC medium, none had alterations in HR. Of dogs receiving GD contrast medium, 1 of 92 (1%) became tachycardic (HR of 134 beats/min at 5 minutes after contrast medium administration) and none became bradycardic. Of 81 control dogs, 2 (2%) became tachycardic and none became bradycardic; 1 control dog had an HR of 157, 132, and 142 beats/min at 10, 15, and 20 minutes after baseline, respectively, and 1 control dog had an HR of 138 beats/min at 20 minutes after baseline.

Of dogs receiving IIC medium, 2 of 91 (2%) became hypotensive (PSBP of 84 and 85 mm Hg at 5 minutes after contrast medium administration) and 2 of 91 (2%) became hypertensive; 1 dog had a PSBP of 184 mm Hg at 5 minutes after contrast medium administration, and 1 dog had a PSBP of 190 and 200 mm Hg at 5 and 10 minutes, respectively, after contrast medium administration. Of dogs receiving NIC medium, 1 of 16 became hypertensive (PSBP of 197 mm Hg at 10 minutes after contrast medium administration). Of dogs receiving GD contrast medium, 4 of 92 (4%) became hypertensive; 1 dog had a PSBP of 165 mm Hg at 10 minutes after contrast medium administration, 2 dogs had a PSBP of 165 and 189 mm Hg at 20 minutes after contrast medium administration, and 1 dog had a PSBP of 172 and 175 mm Hg at 15 and 20 minutes, respectively, after contrast medium administration. Of

81 control dogs, 3 (4%) became hypertensive (PSBP of 232 mm Hg, 238 mm Hg, and 161 mm Hg at 5, 10, and 15 minutes, respectively, after baseline).

When dogs with substantial changes in either HR or PSBP were evaluated for the presence of preexisting hypersensitivity conditions, it was found that, of dogs receiving GD contrast medium, 5 of 92 had preexisting conditions that might predispose to contrast-induced hypersensitivity (4 with atopic dermatitis, 1 with food allergies). One of the 5 dogs became hypertensive reaching a PSBP of 172 mm Hg at 15 minutes and 175 mm Hg at 20 minutes following contrast medium administration. Of dogs receiving IIC medium, 9 of 91 had preexisting conditions that might predispose to contrast-induced hypersensitivity (9 with atopic dermatitis). None of the 9 dogs had substantial alterations in HR or PSBP. Of dogs receiving NIC medium, 1 of 16 had a preexisting condition that might predispose to contrast-induced hypersensitivity (1 with atopic dermatitis). This dog did not have substantial HR or PSBP alterations.

The anesthetist documented a perceived response to contrast medium administration in 4 dogs receiving IIC medium. Specific changes included 1 dog with an increased HR (HR increased from 85 to 129 beats/min at 10 minutes after contrast medium administration), 1 dog with an increased HR (HR increased from 90 to 115 beats/min at 5 minutes after contrast medium administration) and respiratory rate (magnitude of change not recorded), 1 dog with a decreased PSBP (decreased from 112 to 98 mm Hg at 5 minutes after contrast medium administration), and 1 dog with a decreased HR (HR decreased from 90 to 62 beats/min after contrast medium administration) with arrhythmia. No dogs given NIC or GD medium had perceived reactions to the contrast medium noted in the anesthesia record.

Of 92 dogs that received GD contrast medium, 16 had preimaging and postimaging values for serum total bilirubin concentration; there was a mean of 33 ± 20 days (range, 5 to 57 days) between the collection of blood samples. All dogs had a serum total bilirubin concentration (reference range, 0 to 0.4 mg/dL) within the reference range before imaging. Only 1 of 16 dogs had a serum total bilirubin concentration above the reference range (0.6 mg/dL) at 10 days after administration of GD contrast medium. Serum biochemical analysis performed on day 11 following administration of GD contrast medium revealed a serum total bilirubin concentration (0.3 mg/dL) within reference range in that dog. The BUN and serum creatinine concentrations were available before and after imaging for 19 of 92 dogs; there was a mean of 43 ± 60 days (range, 5 to 270 days) between the collection of blood samples. Of the 19 dogs, 1 had an elevated BUN concentration (45 mg/dL; reference range, 8 to 31 mg/dL) but a serum creatinine concentration (0.8 mg/dL; reference range, 0.5 to 1.6 mg/dL) within reference range before imaging. The BUN concentration decreased (38 mg/dL) but remained above the reference range, and creatinine remained unchanged 4 days after imaging. Of the 19 dogs, 2 had high serum creatinine concentration (1.7 and 1.8 mg/dL, respectively) but BUN concentrations (24 and 17 mg/dL, respectively) within reference range before

imaging. Serum creatinine concentration remained unchanged in 1 dog (1.7 mg/dL) at 29 days after imaging with multiple subsequent results of serum biochemical analysis revealing creatinine values in the reference range. Serum creatinine concentration decreased in the other dog (0.9 mg/dL) at 5 days after imaging. No dogs had an increase in BUN or serum creatinine concentration following administration of GD contrast medium.

Of 91 dogs that received IIC contrast medium, 23 had preimaging and postimaging values for serum total bilirubin concentration; there was a mean of 60 ± 62 days (range, 7 to 240 days) between the collection of blood samples. Of the 23 dogs, 1 had an elevated serum total bilirubin concentration (0.8 mg/dL) before imaging. This dog had a serum total bilirubin concentration (0.1 mg/dL) within reference range at 1 day after imaging. The BUN and serum creatinine concentrations were available before and after imaging for 25 of the 91 dogs; there was a mean of 60 ± 62 days (range, 7 to 240 days) between the collection of blood samples. Of the 25 dogs, 1 had an elevated BUN concentration (34 mg/dL) before IIC medium administration. The BUN concentration of this dog decreased to 29 mg/dL at 96 days after imaging. This dog had a creatinine concentration within the reference range before imaging (1.5 mg/dL), which was increased to 1.7 mg/dL at 96 days after imaging. One of the 25 dogs had a severe elevation of the BUN concentration (110 mg/dL) at 7 days after IIC medium administration but was diagnosed with a gastrointestinal bleeding disorder. No other dogs had an increase in BUN or serum creatinine concentrations following IIC medium administration.

Of 16 dogs that received NIC medium, 6 had preimaging and postimaging values for serum total bilirubin concentration; there was a mean of 43 ± 24 days (range, 26 to 90 days) between the collection of blood samples. All dogs had serum total bilirubin concentrations within reference range before and after administration of NIC medium. The BUN and serum creatinine concentrations were available before and after imaging for 7 of the 16 dogs; there was a mean of 38 ± 24 days (range, 8 to 90 days) between the collection of blood samples. All dogs had BUN concentrations within the reference range before and after administration of NIC medium. One of the 16 dogs had a high serum creatinine concentration (1.8 mg/dL) before imaging; the concentration returned to within reference range (1.2 mg/dL) at 8 days after administration of the NIC medium.

Discussion

Results of this study indicate that physiologically important changes in HR and PSBP occur subsequent to IV administration of contrast media in anesthetized dogs. The percentage of dogs developing hypertension and hypotension is slightly higher than that described for people.¹³ This observation is likely related to the fact that people are rarely anesthetized for imaging studies and are consequently not monitored as closely as our anesthetized dogs. In a study by Kurabayashi et al,¹³ a small number of dramatic alterations in blood pressure were seen in awake people with no discernible clinical signs and were felt to be the precursors to potentially serious hypertension or hypotension. Thus, changes

in hemodynamic variables may go unnoticed in people unless continuous monitoring is implemented, thereby lowering the number of detectable reactions.

The high frequency of hemodynamic alteration may also be related to the fact that dogs in this study were under anesthesia and changes in HR and PSBP can occur in relation to anesthetic depth. Moreover, the type of premedication and anesthetic maintenance was not standardized because of the retrospective nature of this study. It has been previously shown that the type of anesthesia can substantially affect hemodynamic status.¹⁴ Although the rate was not always available for assessment, IV administration of fluids is a standard protocol at this institution and may also have contributed to alterations in HR and PSBP. The contribution of anesthesia and fluid administration to the hemodynamic changes described in this study is supported by the fact that control dogs receiving no contrast media often had changes in HR and PSBP while under anesthesia. In addition, more dogs (control and contrast groups) had developed substantial change in HR or PSBP at the 15- and 20-minute time points, whereas most contrast medium-induced reactions in people occur within the first 5 minutes.⁴ Thus, it is feasible that the changes in HR and PSBP at the later time points were unrelated to contrast medium administration.

In fact, when considering only the early (5- and 10-minute) time points, it appears that the IIC group dogs developed the most hemodynamic alterations. In addition, dogs receiving IIC medium (4/91 [4%]) were the only dogs to develop cardiovascular reactions prompting comment by the anesthetist. None of the 4 dogs developed responses that fit the criteria of this study and therefore were not included in the overall percentage of dogs calculated as having developed substantial alterations. However, on the basis of the concerns of the anesthetist, the 4 dogs may truly belong in the group of dogs considered to have had a substantial response. Consequently, it was thought that similar to the data described for people, IIC media are more likely to cause true acute (5 to 10 minutes after medium administration) contrast-associated alterations in hemodynamic variables in dogs than other types of contrast media.

The responses of all of the dogs could be classified as moderate in severity on the basis of the criteria established for people. No dogs developed acute adverse contrast medium-induced reactions that could be classified as severe. This finding is not surprising given the low incidence of acute severe contrast-associated reactions in people and the low number of dogs included in each contrast medium group in this study. Similarly, there did not appear to be an association between dogs with conditions predisposing to hypersensitivity reactions and changes in HR or PSBP in this study. Studies including larger numbers of dogs would be necessary to better define the true incidence of severe acute contrast reactions and the associated risk factors.

Dogs developed increases and decreases in HR and PSBP in association with contrast medium administration. The mechanism through which alterations in HR and PSBP occur is unknown. In people, contrast-induced hypersensitivity is only partially understood and is likely related to a combination of factors including

peripheral effects on the vasculature and primary effects on the myocardium.¹⁵ Reactions are generally considered to be nonallergic immune responses related to the osmolality, viscosity, and chemotoxic effects of the medium. The intravascular introduction of hyperosmolar substances, specifically IIC media, results in rapid expansion of the plasma volume through osmosis of extravascular and intracellular fluid.¹⁵ The hyperosmolality of the intravascular medium results in peripheral vasodilation with subsequent hypotension, followed by the release of vasoactive substances such as histamine and the inhibition of acetylcholinesterase.^{1,15} Contrast medium injection is also associated with cardiac electrophysiologic alterations including changes in sinus rate, intracardiac conduction velocity, and duration of the ventricular depolarization-repolarization process, resulting in a subsequent predisposition to tachyarrhythmias.^{15,16} Nonionic media result in a similar but less profound effect on the cardiovascular system.¹⁵

Gadolinium-induced hemolysis resulting in elevation of serum total bilirubin concentration in people is felt to be related to chelation of RBCs resulting in cell fragility and destruction.⁸ Gadolinium and iodine contrast-induced renal adverse effects most commonly occur in people with existing kidney disease.^{9,17} The precise mechanism behind contrast medium-induced nephrotoxicosis is unclear. Iodinated contrast media have been shown to exert direct toxic effects on renal epithelial cells, resulting in cytoplasmic vacuolization and lysosomal alteration in the proximal convoluted tubular cells.¹⁸ Oxygen free-radical production, reduction in antioxidant formation, and lipid peroxidation have all been documented in the kidney through experimental animal studies after exposure to iodinated contrast media.^{19,20} Medullary ischemia is also induced by iodinated contrast media through direct renal vasoconstriction and impaired oxygen delivery caused by RBC aggregation.^{21–23} The causation between GD contrast media and nephrogenic systemic fibrosis is not understood.²⁴

Only a small number of dogs in this study had serum biochemical data available before and after IV contrast medium administration. This fact limits the ability to predict the incidence of hemolytic and renal adverse effects on the basis of the data acquired. Moreover, none of the dogs for which serum biochemical data were available had substantial renal compromise before contrast medium administration, limiting the likelihood that this type of adverse effect might occur. Keeping this in mind, there are several reasons why alterations in serum total bilirubin, BUN, and creatinine concentrations may not have been detected in our study dogs. First, the primary prophylactic strategy for preventing contrast nephrotoxicity in people is adequate hydration.²⁵ Although fluid administration rate was not recorded for the dogs in our study, most dogs anesthetized at our institution receive IV fluid support, thus reducing the probability of dehydration. Alternatively, it is possible that blood samples were not collected or not assessed at the appropriate interval to detect contrast medium-induced nephrotoxicosis or hemolysis. Most contrast medium-associated renal failure occurs within 24 to 48 hours of medium administration with a return to near baseline at 7 to 10 days.²⁶ Likewise, hemolysis associated

with GD administration is transient and acute.⁸ The mean time to follow-up for serum biochemistry assessment in the dogs of this study ranged between 33 and 60 days depending on the group. Thus, some dogs may have had transient and mild serum biochemical changes immediately following contrast medium administration. Still other dogs were lost to follow-up or euthanized on the basis of their clinical condition. Larger studies including more dogs and frequent early blood sample collection after contrast medium administration would be necessary to further define the incidence of contrast medium-induced adverse effects.

In conclusion, changes in HR and PSBP occur in association with IV administration of IIC, NIC, and GD contrast media in anesthetized dogs. Both increases and decreases in HR and PSBP occurred with most media. It appears that IIC media more frequently result in alterations in HR and PSBP with at least 4% of dogs having a moderate reaction to contrast medium administration. Studies involving larger numbers of dogs would be necessary to determine the importance of conditions predisposing to hypersensitivity in regard to contrast medium-induced reactions. Adverse systemic effects associated with contrast medium administration were not detected in our study dogs.

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- a. Magnevist, Berlex Imaging, Berlex Laboratories, Wayne, NJ.
 - b. Conray 400, Mallinckrodt Inc, St Louis, Mo.
 - c. Isovue-200, Bracco Diagnostics Inc, Princeton, NJ.
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