Effects of anesthetic drugs on canine splenic volume determined via computed tomography

Caroline F. Baldo, DVM, PhD; Fernando L. Garcia-Pereira, DVM, MS; Nathan C. Nelson, DVM; Joe G. Hauptman, DVM, MS; Andre C. Shih, DVM

Objective—To evaluate effects of commonly used anesthetics administered as single bolus injections on splenic volume.

Animals—10 adult Beagles.

Procedures—A randomized crossover study was conducted. Computed tomography was performed on dogs to determine baseline splenic volume and changes after IV injection of assigned drug treatments. Dogs were allowed to acclimate for 10 minutes in a plastic crate before acquisition of abdominal CT images. Treatments were administered at 7-day intervals and consisted of IV administration of saline (0.9% NaCl) solution (5 mL), acepromazine maleate (0.03 mg/kg), hydromorphone (0.1 mg/kg), and dexmedetomidine (0.005 mg/kg) to all 10 dogs; thiopental (8 mg/kg) to 5 of the dogs; and propofol (5 mg/kg) to the other 5 dogs. Splenic volume was calculated from the CT images with image processing software. A repeated-measures ANOVA was performed, followed by a Bonferroni post hoc test.

Results—No significant difference in splenic volume was detected between the acepromazine, propofol, and thiopental treatments, but splenic volume was greater with these drugs than with saline solution, hydromorphone, and dexmedetomidine. Splenic volume was less with hydromorphone, compared with dexmedetomidine, but splenic volume with hydromorphone and dexmedetomidine did not differ significantly from that with saline solution.

Conclusions and Clinical Relevance—Administration of acepromazine, thiopental, and propofol resulted in splenomegaly. Dexmedetomidine did not alter splenic volume. Hydromorphone slightly decreased splenic volume. Propofol should not be used when splenomegaly is not desirable, whereas hydromorphone and dexmedetomidine may be used when it is best to avoid splenic enlargement. (Am J Vet Res 2012;73:1715–1719)
mining the area of an organ on each CT slice, multiplying the area by the slice thickness, and adding the volume of all slices.\textsuperscript{A} The use of CT volumetry provides an opportunity to noninvasively study the effects of anesthetic drugs on splenic volume. The lack of potentially stressful interaction with patients helps investigators avoid or diminish catecholamine release, which may interfere with baseline measurements and the apparent effect of drugs. An additional benefit of this technique is the ability to acquire volume data without general anesthesia because of the rapid image acquisition afforded by modern multislice helical CT scanners, which further minimizes factors that could influence splenic volume. The purpose of the study reported here was to use CT to measure changes in splenic volume caused by commonly used sedative and anesthetic drugs in dogs.

Material and Methods

Animals—Ten adult Beagles (5 females and 5 males) were included in a randomized crossover study. Dogs were assessed as healthy on the basis of results of physical examination, a CBC, and serum biochemical analyses. Dogs were housed separately in a climate-controlled room with a light cycle of 12 hours of light and 12 hours of darkness. Dogs were provided with ad libitum access to a commercial chow formulated for adult dogs and water. Food was not withheld from dogs prior to treatment and data collection. The study was approved by the Michigan State University Institutional Animal Care and Use Committee.

Procedures—On the day of treatment, dogs were transported from the housing facilities to the CT room. A 20-gauge catheter was inserted in a sterile manner in a cephalic vein, and the catheter was connected to a 76-cm extension line primed with 4 mL of heparinized saline (0.9% NaCl) solution. Dogs were placed in a plastic crate secured to the CT table to minimize handling; dogs were allowed to remain in the crate for 10 minutes to allow environmental acclimation preceding drug administration.

Each dog received 5 of 6 treatments. Four treatments (saline solution, hydromorphone, acepromazine maleate, and dexmedetomidine) were administered to all 10 dogs, but thiopental was administered to only 5 dogs, and propofol was administered to the other 5 dogs. Treatments were administered at intervals of 7 days in a randomized order determined via a software randomization tool.\textsuperscript{A} Treatments consisted of IV administration of 5 mL of saline solution, acepromazine maleate\textsuperscript{b} (0.03 mg/kg), thiopental\textsuperscript{c} (8 mg/kg), propofol,\textsuperscript{d} (5 mg/kg), hydromorphone\textsuperscript{e} (0.1 mg/kg), and dexmedetomidine\textsuperscript{f} (0.005 mg/kg). The 76-cm extension line was long enough to extend outside the crate and allowed injection of drugs without the need for the investigators to interact with the dogs. After administration of each drug, the extension line was flushed with 4 mL of heparinized saline solution.

A multislice CT scanner\textsuperscript{g} was used to acquire images before and 10 minutes after IV injection of each assigned treatment. Images were obtained by use of a low-pass filter at a slice thickness of 2.5 mm, collimator pitch of 1.375, 512 X 512 matrix, 120 kVp, 350 mAs, and a field of view large enough to encompass the abdomen. The CT images were imported into commercially available software.\textsuperscript{h} The splenic area was manually highlighted on each slice by 1 investigator (CFB) and confirmed by a board-certified veterinary radiologist (NCN). Splenic volume was then calculated by the software program. The image processing software displayed total organ volume on the basis of the total number of voxels for all slices combined. The software also displayed 3-D models of the spleen from the manually highlighted data, which allowed verification of overall splenic shape and position.

Blood samples for measurement of Hct were collected at the time of catheter insertion and again after each set of CT images was obtained. Blood samples were placed in heparinized Hct capillary tubes and centrifuged in a microcentrifuge at 13,000 X g for 5 minutes. Measurement of Hct was obtained immediately after centrifugation. The Hct values before and after drug administration were compared within each treatment. Also, Hct values after drug administration were compared with the postadministration Hct for saline solution.

Statistical analysis—A multivariate ANOVA was used to evaluate effect of week of treatment. Errors generated for volume means were evaluated to determine whether they had a normal distribution. A repeated-measures ANOVA was performed to evaluate dog and drug effects (and the interaction of these 2 factors) on spleen volume. A repeated-measures ANOVA was used to analyze Hct data and included effects of drug, time (before and after drug administration), and the drug-by-time interaction. Data with significant (P < 0.05) differences were further analyzed with the post hoc Bonferroni test. Because of multiple comparisons (6 drugs), the probability (P < 0.05) was divided by the number of comparisons (6 X 5/2 = 15), which generated a new value for significant differences. Thus, results for the post hoc Bonferroni test were considered significant at values of P ≤ 0.003. All data were analyzed with commercial statistical software.\textsuperscript{i}

Results

Data were normally distributed. Week of treatment did not have a significant (P = 0.899) effect on splenic volume.

Mean splenic volume differed significantly (P < 0.001) among treatments (Figure 1). Splenic volume differed significantly (P = 0.003) between hydromorphone and dexmedetomidine; however, splenic volume for hydromorphone and dexmedetomidine did not differ significantly (P = 0.005 and P = 0.789, respectively) from the splenic volume for saline solution. Compared with splenic volume after saline solution, splenic volume was significantly greater after acepromazine (P < 0.001), thiopental (P = 0.001), and propofol (P < 0.001). In addition, splenic volume for propofol, acepromazine, and thiopental were each significantly (P < 0.001) greater than the splenic volume after dexmedetomidine or hydromorphone.

Week of treatment did not significantly (P = 0.051) affect baseline Hct in samples obtained at the time of
Propofol, acepromazine, and thiopental induced significant (P < 0.001) decreases in Hct from baseline values before drug administration. Within a drug, value differs significantly (P < 0.001) from the value for thiopental, propofol, dexametomidine, and acepromazine. †Value differs significantly (P < 0.001) from the value for thiopental, propofol, dexametomidine, and acepromazine. *Value differs significantly (P < 0.001) from the value for saline solution.

Figure 1—Mean ± SEM CT splenic volume in Beagles after IV administration of a bolus of thiopental (8 mg/kg [n = 5]), saline (0.9% NaCl) solution (2 mL [10]), propofol (5 mg/kg [5]), hydromorphone (0.1 mg/kg [10]), dexametomidine (0.005 mg/kg [10]), and acepromazine maleate (0.03 mg/kg [10]). *Value differs significantly (P < 0.001) from the value for saline solution. †Value differs significantly (P < 0.001) from the value for thiopental, propofol, dexametomidine, and acepromazine.

There are several reasons that propofol may not have had an effect on splenic size in previous studies, despite administration of doses similar to that used in the present study. Propofol was not the only agent used in clinical cases in 1 study. The interaction of propofol with other drugs, effects of surgery, and baseline status of the spleen in the face of illness could have played a role in the end result of volume in that study. Measurements were obtained approximately 1 hour after anesthetic induction; thus, given the pharmacokinetics of propofol, onset and duration of an effect may have been missed. To our knowledge, tracing of the spleen on paper is a technique that has not been described in the literature, and this may not be the best scientific method.

Investigators in the study involved in the use of ultrasonographic techniques also failed to detect a change in splenic size after propofol administration. Propofol was used as the sole agent, and measurements were obtained 15 minutes after anesthetic induction, which appears to be an adequate interval. The ultrasonographic technique used to measure height at the splenic hilus as a 2-D indicator of overall splenic size may have been the limiting factor of that study. Ultrasonographic procedures are known to have variability, given the dependence on manual operation that possibly limits the sensitivity to detect changes in size.

Recumbency of the dogs and the choice of height for spleen measurement are additional factors that may explain the lack of change in splenic size. In humans, recumbency and the organ dimension measured can affect ultrasonographic size measurements, compared with size measurements obtained via CT. The authors of that study concluded that the best correlation with values obtained by CT was for spleen size assessed by ultrasonographically scanning humans positioned in right lateral recumbency and measuring the width of the organ from the longitudinal aspect. To our knowledge, similar studies have not been performed in dogs, and the position during recumbency has not been specified in previous studies. It is possible that the position during recumbency chosen in previous studies or the dimension (spleen height) prevented detection of changes in splenic volume when measured ultrasonographically.

The mechanism for propofol-induced splenomegaly is unclear. Propofol causes systemic hypotension, which may result in blood redistribution to the spleen. During hypotension (50 mm Hg) induced in dogs by the administration of propofol at a rate of 13 mg/kg/h, splanchnic blood flow remains unchanged. The authors of that study did not propose a mechanism for such a finding, but redistribution of blood from peripheral to central compartments may be implicated. Propofol also has direct effects on vascular and nonvascular smooth muscle, which may result in relaxation of splenic smooth muscle. Therefore, propofol should not be used when splenic enlargement

Discussion

Thiopental, propofol, and acepromazine increased splenic volume, as determined on the basis of results of CT. The effect of barbiturates and acepromazine on splenic size have been described, but to our knowledge, this is the first report of splenomegaly induced by propofol.
is not wanted. The finding that propofol reduces Hct has been described in another study and may be a result of splenic enlargement and sequestration of RBCs.

Hydromorphone failed to cause a significant difference in splenic size, compared with results for saline solution, and hydromorphone had no effect on Hct. Despite the lack of a significant difference, many dogs had a reduction in splenic volume that may have been clinically relevant. Opioid-induced excitation may have caused increased amounts of adrenaline and noradrenaline and thus splenic contraction, but in the present study, no signs of excitation, except for profuse salivation, were observed in dogs administered hydromorphone. Opioids may cause an increase in vagal tone or sympatholytic effects, which may result in slight decreases in splenic size. Vagal tone originates from central vagal centers and is transmitted by muscarinic receptors on the vagal nerve, which causes a reduction in splenic blood flow and splenic size. This appears to be the most likely mechanism for our finding after administration of hydromorphone. This proposed mechanism is indirect because there is no histologic evidence of parasympathetic innervation in the spleen, but reflex constriction in response to arterial hypotension may be vagally mediated.

The present study revealed that dexmedetomidine administration had no effect on splenic volume. This disagrees with results of another study in which investigators reported a reduction in canine spleen size after IV administration of xylazine (another α2-type receptor inhibitor). In dogs, dexmedetomidine can cause decreases in cardiac output and redistribution of blood flow to vital organs such as the brain, heart, liver, and kidneys at the expense of the spleen and skin. A reduced blood flow (comparable to a reduction in cardiac output) could have caused limited exposure of the spleen to a sufficient concentration of drug to trigger an effect. Furthermore, it is possible the spleen may be devoid of α2-type receptors, the location of the receptors may not be postsynaptic, or most of the α receptors present on the spleen are the α2 postsynaptic type (dexmedetomidine is highly selective for α2 receptors). In fact, a study performed in canine spleens revealed that α2 receptors are primarily localized presynaptically and are of the α2a type, which is coupled to inhibitory protein G. Action on the latter receptor may be manifested as a sympatholytic effect, which could explain the absence of capsular and vascular smooth muscle contraction, and thus the decrease in splenic size, in that study.

In accordance with findings in other studies, thiopental caused a significant decrease of Hct and increase in spleen volume in the present study. Administration of thiopental (5 mg/kg, IV) in cats promotes hypotension after an initial brief increase of sympathetic activity. The predominant reduction of sympathetic activity in cats is thought to be mediated by the vasomotor center (caudal ventrolateral) located in the medulla oblongata. Thiopental causes splenic relaxation even in the denervated organ of dogs, which suggests an additional direct effect. Thus, decreased systemic arterial blood pressure, vasodilation, and direct organ effects on vascular and nonvascular smooth muscle may explain splenomegaly and the decrease in Hct caused by thiopental.

In the present study, the effects observed for acepromazine were similar to those for thiopental. As previously stated, most of the postsynaptic adrenoceptors in the spleen are of the α1-type. The antagonistic action of acepromazine on postsynaptic α1-receptors likely results in smooth muscle relaxation and subsequent splenic enlargement.

In the present study, we did not examine correlations between Hct and splenic volume because the means generated by this study design were not independent. Even so, the overall pattern was for a decrease in Hct that followed splenic relaxation. On the other hand, splenic contraction did not result in an increase in Hct.

Similar to other studies involving the use of conscious animals, the present study posed a few challenges. Although dogs were allowed time to acclimate to positioning on the CT table, there likely was some stress. To our benefit, the dogs used were housed in our research facility and used in other studies; thus, acclimation, handling, exposure to various environments, and transport within our facility were part of their routine. Even so, increases in stress hormones (ie, catecholamines, renin, glucocorticoids, and growth hormones) may be associated with even simple procedures such as venipuncture and may occur within seconds and persist for days. Moreover, it may require up to 40 days for the Hct to normalize after a stressful event. Observation of the dogs while in the crates and the lack of change in the baseline Hct obtained during our study, coupled with the total study duration of > 40 days, may indicate that the degree of stress was mild. Ten minutes was allowed for the dogs to adapt to the CT environment and plastic carrier to decrease stress effects on splenic volume. This interval appears to be appropriate because the recovery time of spleen size to baseline values after exogenous administration of adrenaline in unanesthetized dogs is approximately 13 minutes.

The dogs were tolerant to confinement in the plastic crate, but the crate did allow the dogs to have some mobility. Motion was generally not a problem. However, if there was substantial motion evident at the level of the spleen on CT images, the CT images of the abdomen were immediately obtained again.

Thiopental was withdrawn from the United States veterinary market during the study, which required us to use propofol as a substitute. Therefore, 5 dogs received thiopental and the other 5 dogs received propofol.

Computed tomography is accurate for the determination of spleen volume and has been adopted as the criterion-referenced standard in many studies involving assessment of organ volume. Manual delineation of the parenchyma is an operator-dependent task that requires hand-and-eye coordination and subjective decisions concerning the delineation of low-contrast edges. Interobserver variability was not assessed in the present study, but the board-certified veterinary radiologist performed few corrections of the initial splenic outlines, which suggested that interobserver variability would be low. Investigators in a recent study compared the manual delineation of the spleen in human patients and found an interobserver variability of...
We did not evaluate interobserver and intraobserver variability in the present study, but corrections performed by a board-certified veterinary radiologist of the delineated areas did not generate a substantial change in area from the original values obtained. In the authors’ opinion, the greatest difficulty was identifying areas of low contrast, such as the ones typically found between liver-spleen interfaces. The advantage of producing 3-D models of the spleen was that it allowed assessment of the shape of the spleen and exclusion of any extrasplenic area that distorted the model.

In the present study, propofol caused splenic enlargement comparable to that caused by acepromazine and thiopental, whereas dexmedetomidine had no effect on splenic size. The effect of hydromorphone may have been clinically relevant, despite the fact hydromorphone did not cause a significant reduction in spleen size. The Hct was reduced by acepromazine, thiopental, and propofol, which may not be clinically important in otherwise healthy patients but could be deleterious for anemic or ill patients. It is unknown whether these effects will persist in patients anesthetized with different drug dosages or drug combinations or that have other conditions (such as anemia) that could also affect splenic size.

References

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