Evaluation of atipamezole as a treatment for dexmedetomidine-induced cardiovascular depression in anesthetized cats

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OBJECTIVE
To evaluate the cardiovascular effects of atipamezole administered at half the volume or the same volume as dexmedetomidine to isoflurane-anesthetized cats.

ANIMALS
6 adult (1 to 2 years old) domestic shorthair cats (body weight, 3 to 6 kg).

PROCEDURES
Each cat was anesthetized with isoflurane and rocuronium 3 times; there was a 1-week washout period between successive anesthetic procedures. For each anesthetic procedure, dexmedetomidine (5 μg/kg) was administered IV. Five minutes after dexmedetomidine was administered, atipamezole (25 or 50 μg/kg) or saline (0.9% NaCl) solution was administered IM. Pulse rate, mean arterial blood pressure (MAP), cardiac output (CO), and systemic vascular resistance (SVR) were measured during anesthesia before dexmedetomidine administration (baseline), after dexmedetomidine administration, and 15, 30, 60, and 120 minutes after administration of atipamezole or saline solution. Pulse rate and MAP were also recorded when MAP was at its lowest value. Hemodynamic variables were compared among treatments at baseline, after dexmedetomidine administration, and after administration of atipamezole or saline solution. Effects of treatment and time on all variables were assessed with mixed-effects models.

RESULTS
Both doses of atipamezole resulted in a significantly lower MAP than did saline solution. Pulse rate, CO, and SVR were not significantly different among treatments after atipamezole or saline solution were administered.

CONCLUSIONS AND CLINICAL RELEVANCE
Atipamezole administered IM at half the volume or the same volume as dexmedetomidine was ineffective at increasing pulse rate or CO in anesthetized cats that received dexmedetomidine. However, atipamezole caused short-lasting but severe arterial hypotension. (*Am J Vet Res* 2019;80:455–460)

Dexmedetomidine is commonly administered to cats before anesthesia, primarily because of its reliable sedative, analgesic, and anesthetic-sparing effects.[1-3] However, dexmedetomidine can cause substantial cardiovascular effects and often results in decreases in PR and CO and increases in SVR and arterial blood pressure.[4,5] Such hemodynamic changes can persist during the perianesthetic period and may warrant treatment.

Atipamezole is an α_2-adrenoceptor antagonist that can reverse the sedative and cardiovascular effects of dexmedetomidine. Atipamezole is not licensed by the US FDA for use in cats, but administration of atipamezole to sedated cats restores the heart rate to presedation values.[1] However, owing to its effects as an α-adrenoceptor antagonist, atipamezole may also cause vasodilation and contribute to arterial hypotension[6]; these effects may be augmented in the presence of inhalation anesthetic agents.[7] Moreover, because inhalation anesthetics mute baroreflexes,[8] it is possible that an expected reflex increase in PR might also be blunted.

The purpose of the study reported here was to evaluate the effects of 2 doses of atipamezole and saline (0.9% NaCl) solution administered IM to isoflurane-anesthetized cats that had also received dexmedetomidine. We hypothesized that treatment with atipamezole at 25 or 50 μg/kg would restore the PR to values similar to those before dexmedetomidine administration and would decrease the MAP, compared with the MAP after treatment with saline solution.

ABBREVIATIONS

CO	Cardiac output
MAP	Mean arterial blood pressure
PR	Pulse rate
SVR	Systemic vascular resistance
TEDV	Total end-diastolic volume
TEF	Total ejection fraction

Materials and Methods

Animals

Six adult (1 to 2 years old) domestic shorthair cats (3 females and 3 males; body weight, 3 to 6 kg) were included in the study. Cats were classified as American Society of Anesthesiologists status I on the basis of results of physical examinations and measurement of Hct and concentrations of total plasma proteins, BUN, and glucose performed before each anesthetic procedure. The study was reviewed and approved by the Institutional Animal Care and Use Committee of Cornell University.

Experimental procedures

A randomized crossover design was used. Cats were anesthetized 3 times; there was a washout period of at least 1 week between successive anesthetic procedures. Effects of IM administration of 2 doses of atipamezole and saline solution were determined. Order of treatments was randomly assigned by removing labels from an opaque envelope. Investigators were unaware of treatment allocation.

For each anesthetic episode, anesthesia was induced by use of an anesthetic machine[a] with isoflurane[b] (5%) in oxygen (5 L/min) in an induction chamber. After each cat lost the righting reflex, it was removed from the induction chamber and the laryngeal mucosa was desensitized with aerosolized 2% lidocaine hydrochloride[c] (0.1 mL). The trachea was intubated with an appropriately sized cuffed endotracheal tube. A 22-gauge catheter was placed in a cephalic vein, and anesthesia was maintained on a pediatric rebreathing circuit with isoflurane (end-tidal concentration, 1.3% to 1.5%) in oxygen (1.5 L/min). Rocuronium boluses (0.3 to 0.5 mg/kg, IV) were administered to prevent spontaneous breathing or movement that would interfere with data collection. Cats were mechanically ventilated by use of pressure-controlled ventilation (peak inspiratory pressure, 8 to 10 cm H_2O). The respiratory rate was adjusted to maintain the end-tidal partial pressure of CO_2 between 35 and 45 mm Hg.

All cats were positioned in dorsal recumbency, and percutaneous catheters for CO measurement were placed in a jugular or femoral vein and a dorsopedal or femoral artery. The catheters were connected to a transducer, which was zeroed to atmospheric pressure at the level of the heart and connected to an amplifier[d] and data acquisition system.[e] The raw output signal was calibrated with a 2-point method (0 and 100 mm Hg) by use of an electronic sphygmomanometer. Results of pulse oximetry, ECG, end-tidal concentrations of airway gases, concentrations of anesthetic agents, and esophageal temperature were monitored throughout the procedure. The PR and arterial blood pressures were recorded continuously from the arterial signal. At each sample collection time, the mean of PR and MAP was calculated for

Table 1—Least squares mean ± SD values for cardiovascular variables measured in 6 healthy isoflurane-anesthetized cats during anesthesia (baseline) and after cats received dexmedetomidine (5 µg/kg, IV) and then received IM injections of a low dose of atipamezole (25 µg/kg; A-LD treatment), a high dose of atipamezole (50 µg/kg; A-HD treatment), or saline (0.9% NaCl) solution.

Variable	Treatment	Baseline	After treatment
MAP (mm Hg)	Saline solution	76 ± 23	149 ± 22
	A-LD	74 ± 12	153 ± 22
	A-HD	75 ± 13	151 ± 22
PR (pulses/min)	Saline solution	148 ± 16	110 ± 12
	A-LD	139 ± 20	100 ± 6
	A-HD	143 ± 21	104 ± 10
CO (mL/min)	Saline solution	532 ± 212	287 ± 66
	A-LD	555 ± 129	290 ± 79
	A-HD	490 ± 145	292 ± 89
Stroke volume (mL)	Saline solution	3.6 ± 1.1	2.7 ± 0.6
	A-LD	4.0 ± 0.9	2.9 ± 0.7
	A- HD	3.6 ± 1.3	2.8 ± 0.9
SVR (dynes/s/cm^5)	Saline solution	11,783 ± 2,854	38,987 ± 7,795
	A-LD	10,887 ± 1,794	44,053 ± 11,492
	A-HD	12,700 ± 3,119	43,785 ± 12,921
TEDV (mL/kg)	Saline solution	37.5 ± 14.0	30.3 ± 8.0
	A-LD	38.1 ± 7.0	33.0 ± 5.0
	A-HD	35.0 ± 10.0	32.8 ± 9.0
TEF (%)	Saline solution	39 ± 7	35 ± 7
	A-LD	42 ± 5	35 ± 6
	A-HD	40 ± 6	34 ± 4

Within a time point, values did not differ significantly ($P < 0.05$) among treatments.

10 consecutive heartbeats. The CO was determined with an ultrasonographic dilution technique,[f] as described elsewhere.[7,9] Briefly, 1 mL/kg of warm (37°C) saline solution was manually injected into the central circulation as rapidly as possible, and the transient reduction in ultrasonographic velocity was measured in the peripheral arterial circulation through a transient extracorporeal loop. Hemodynamic variables derived from the ultrasonographic dilution curve (CO, stroke volume, SVR, TEDV, and TEF) were determined in duplicate.

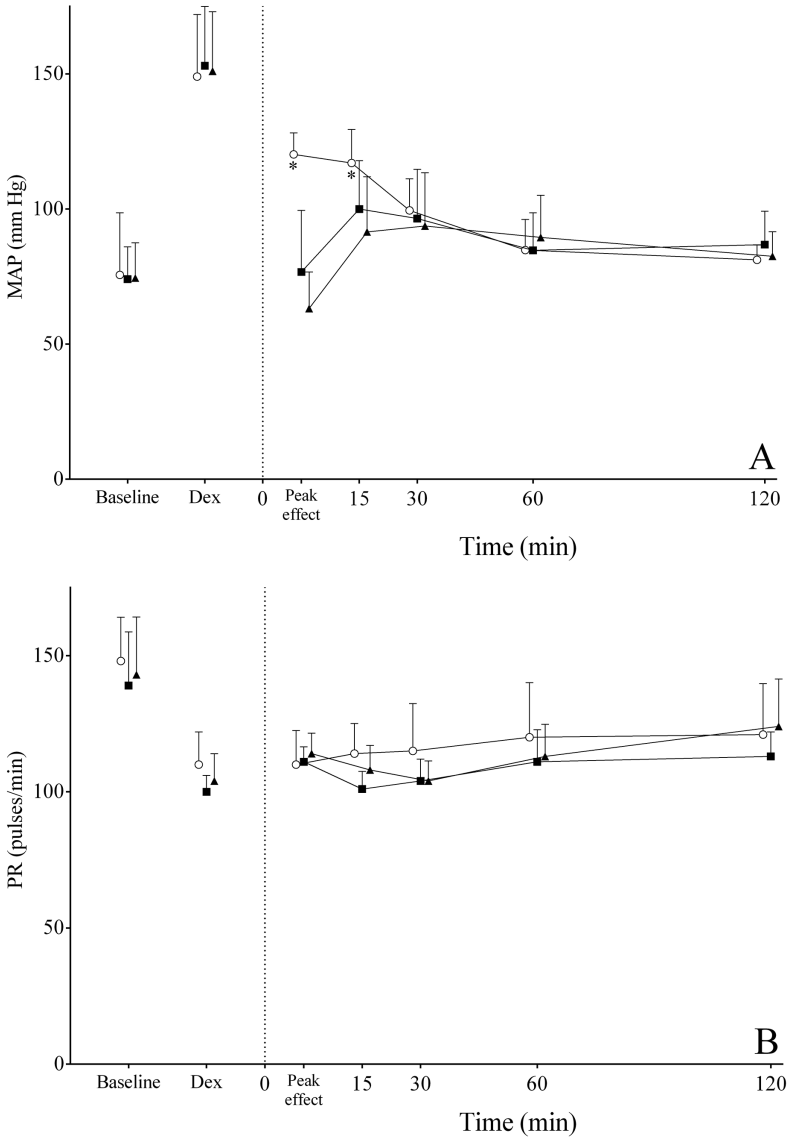

Figure 1—Least squares mean ± SD values for MAP (A) and PR (B) of 6 healthy cats during anesthesia before administration of dexmedetomidine (baseline), 5 minutes after administration of dexmedetomidine (5 µg/kg, IV; DEX) was completed at peak effect of treatment and 15, 30, 60, and 120 minutes after IM administration of atipamezole (25 µg/kg [squares] or 50 µg/kg [triangles]) or saline (0.9% NaCl) solution (circles; time 0). Peak effect was the lowest MAP after treatment administration. For all treatments, mean MAP increased significantly ($P < 0.001$) and PR decreased significantly ($P < 0.001$) over time from peak effect until 120 minutes after treatment administration. *Within a time point, value differs significantly ($P < 0.05$) from the values for both of the atipamezole treatments.

Data collection

After instrumentation was complete, cats were allowed a 20-minute interval before data were collected. Then, PR, MAP, CO, stroke volume, SVR, TEDV, and TEF were measured in the isoflurane-anesthetized cats (baseline). After baseline measurements were obtained, dexmedetomidine[g] (5 µg/kg) was administered via the catheter in the cephalic vein over a 5-minute period by use of a syringe driver. All variables were measured again 5 minutes after dexmedetomidine administration was completed. After that set of measurements was obtained, a low dose of atipamezole[h] (25 µg/kg; A-LD treatment), a high dose of atipamezole (50 µg/kg; A-HD treatment), or saline solution was administered IM into the quadriceps muscles. All injections were standardized to a volume of 1 mL by the addition of saline solution. Values of PR and MAP were recorded at peak effect, which was defined as the point when MAP reached its lowest value after treatment. All variables were also measured at 15, 30, 60, and 120 minutes after treatment.

After data collection was finished, isoflurane was discontinued. Each cat received atropine[i] (0.02 mg/kg, IV) and edrophonium[j] (0.5 mg/kg, IV) and was allowed to recover from anesthesia.

Statistical analysis

On the basis of preliminary experiments and data collected in another study[7] by use of similar methods (mean ± SD MAP, 150 ± 25 mm Hg), it was estimated that a sample size of 5 cats would be necessary to detect a decrease of at least 30% in MAP after treatment with atipamezole (power, 0.97).[k] Six cats were used to account for repeated measures.

Statistical analyses were performed with commercial statistics software.[l] Distribution of the residuals was evaluated for each model. All variables were compared among treatments at baseline and after dexmedetomidine administration by use of linear mixed-effect models, with cat and the cat-by-treatment interaction as random effects. Effects of treatment (A-LD, A-HD, and saline solution), time, and the treatment-by-time interaction were evaluated with linear effect models and Tukey post hoc tests for time points after treatment administration, with cat and the cat-by-treatment interaction as random effects. Bonferroni corrections were used for multiple between-treatment comparisons at selected times. Significance was set at

Table 2—Least squares mean ± SD values of cardiovascular variables in 6 healthy adult isoflurane-anesthetized cats at various times after cats received dexmedetomidine IV and then received a dose of atipamezole or saline solution.

		Time (min after treatment)			
Variable	**Treatment**	**15**	**30**	**60**	**120**
CO (mL/min)	Saline solution	398 ± 87	386 ± 84	407 ± 94	390 ± 68
	A-LD	417 ± 74	393 ± 83	398 ± 81	410 ± 92
	A-HD	398 ± 103	403 ± 122	398 ± 69	410 ± 107
Stroke volume (mL)	Saline solution	3.6 ± 0.5	3.4 ± 0.5	3.5 ± 0.6	3.3 ± 0.5
	A-LD	4.2 ± 0.7	3.8 ± 0.6	3.6 ± 0.6	3.7 ± 0.7
	A-HD	3.8 ± 1.0	3.9 ± 0.9	3.6 ± 0.7	3.4 ± 0.9
SVR (dyne/s/cm^5)*	Saline solution	22,127 ± 4,953	19,625 ± 4,529	15,977 ± 3,640	16,008 ± 2,906
	A-LD	19,255 ± 3,242	19,715 ± 3,489	17,455 ± 3,259	17,360 ± 2,989
	A-HD	19,137 ± 6,310	19,945 ± 7,580	18,397 ± 4,689	16,950 ± 4,255
TEDV (mL/kg)	Saline solution	36 ± 8.3	35 ± 9.5	36 ± 8.7	35 ± 8.2
	A-LD	37 ± 6.0	36 ± 6.3	36 ± 5.6	36 ± 5.2
	A-HD	35 ± 8.3	37 ± 9.3	35 ± 4.8	35 ± 9.3
TEF (%)†	Saline solution	40 ± 8.2	40 ± 6.9	39 ± 7.3	38 ± 6.3
	A-LD	45 ± 4.8	42 ± 6.3	41 ± 7.0	40 ± 7.3
	A-HD	43 ± 6.1	43 ± 7.5	41 ± 6.2	39 ± 0.9

Within a time point, values did not differ significantly ($P \geq 0.05$) among treatments.

*Values decreased significantly ($P < 0.001$) over time within each treatment. †Values decreased significantly ($P = 0.03$) over time within each treatment.

See Table 1 for remainder of key.

$P < 0.05$. Results were reported as least squares mean ± SD.

Results

All cats completed all procedures without complications. Complete data sets were recorded for all cats.

All hemodynamic variables were similar among treatments at baseline and after dexmedetomidine administration **(Table 1)**. After treatment administration, MAP was affected by time ($P < 0.001$), treatment ($P = 0.03$), and the treatment-by-time interaction ($P < 0.001$), whereby the A-HD treatment caused an overall lower MAP than did the saline solution treatment. There was not a significant difference in MAP between the A-HD and A-LD treatments **(Figure 1)**. The A-HD and A-LD treatments resulted in a lower MAP than did saline solution at the time of peak effect of treatment and 15 minutes after treatment. The PR increased significantly ($P < 0.001$) over time, but there were no differences among treatments. Stroke volume, CO, SVR, TEDV, and TEF did not differ significantly among treatments **(Table 2)**. Stroke volume, CO, and TEDV did not change significantly over time, whereas there was a significant decrease in SVR ($P < 0.001$) and TEF ($P = 0.03$) over time.

Discussion

Results of the study reported here indicated that IM administration of atipamezole to isoflurane-anesthetized cats that had previously received dexmedetomidine resulted in a significant decrease in MAP with no increase in PR, compared with results when dexmedetomidine-treated cats received saline solution.

Cardiovascular effects of dexmedetomidine in cats have been reported.[4,5,7] Historically, antimuscarinic drugs (eg, atropine or glycopyrrolate) were evaluated for treatment of dexmedetomidine-induced hemodynamic depression. That approach was discouraged after it was determined that such treatments were ineffective and also detrimental when administered to dogs and cats.[10–12] Use of the specific reversal agent, atipamezole, appeared to be an attractive alternative for treating hemodynamic depression caused by dexmedetomidine. Moreover, atipamezole is effective in treating dexmedetomidine-induced bradycardia when administered to nonanesthetized cats.[1] However, inhalation agents cause vasodilation and blunt the baroreceptor reflexes[8]; as a result, the anticipated increase in PR after atipamezole treatment in anesthetized cats may not be as expected. Results of the present study supported this contention because treatment with 2 doses of atipamezole failed to increase PR in the anesthetized cats.

Treatment with atipamezole was ineffective and also potentially detrimental. Atipamezole resulted in severe hypotension (MAP < 60 mm Hg) in 2 of 6 cats for the A-LD treatment and 4 of 6 cats for the A-HD treatment. However, it should be mentioned that this amount of hypotension was a short-lived event. By 15 minutes after treatment administration, MAP was > 60 mm Hg in all cats, and MAP did not decrease below 60 mm Hg thereafter. Irrespective of the short duration of arterial hypotension, no benefit was observed in terms of PR, which suggested that treatment with atipamezole, at least at these doses, resulted in risks with no apparent benefit. Although it was not evaluated in the present study, it should

also be mentioned that treatment with atipamezole is expected to reverse, at least partially, the desired effects of dexmedetomidine (eg, analgesia and a reduction in anesthetic requirements). If that were to be confirmed, it is possible that intra-anesthetic treatment with atipamezole may increase the requirement for anesthetic agents.

Stroke volume, CO, and TEDV were not affected after treatment was administered or over time. It might appear that this observation is at odds with results of a study[7] of cats in which it was found that values of CO and SVR after administration of atipamezole were restored to values similar to those before dexmedetomidine administration. However, it is possible that the sampling interval in the present study did not allow us to detect such changes. In that aforementioned study[7] of cats, it was suggested that the decrease in CO caused by dexmedetomidine was largely secondary to changes in SVR and not to changes in PR. In the present study, there was a short-lived decrease in MAP; however, CO and SVR were not measured until the next sampling point (15 minutes after treatment). By that time, the MAP had already increased. It is likely that a decrease in SVR paralleled the observed decrease in MAP and that any changes in SVR and CO had largely concluded by the time measurements were obtained. The same could be true about the stroke volume. In the study reported here, the SVR decreased progressively over time for all treatments. These changes may have been in response to the redistribution, metabolism, and elimination of the atipamezole.

The TEDV is a measure of preload and was not affected by treatment or time. It appears that, despite changes in MAP and PR among or within treatments, preload was not substantially affected. Because ventricular filling is one of the main determinants of preload, analysis of these data suggested that ventricular filling was not substantially affected by treatment with atipamezole. The TEF also was not different among treatments. Investigators of another study[7] found that IV administration of atipamezole increased TEF in dexmedetomidine-treated cats. As mentioned previously, the study design did not allow us to evaluate whether a transient change in TEF occurred simultaneously with the decrease in MAP that was detected soon after atipamezole administration.

In the study reported here, we evaluated 2 doses of atipamezole (25 and 50 µg/kg, IM). The dose for atipamezole in dogs results in a volume that is equal or almost equal to that of previously administered dexmedetomidine. Currently, atipamezole is not licensed by the US FDA for use in cats. However, given the widespread use of dexmedetomidine in this species, atipamezole often may be administered to cats. The doses selected for the present study resulted in a ratio (vol:vol [dexmedetomidine:atipamezole]) of 0.5 and 1 for A-LD and A-HD, respectively; those doses have been used commonly at our institution to accelerate recovery from sedation in cats that have received dexmedetomidine. Higher doses of atipamezole have been used in cats in the past. For example, investigators have evaluated the effects after IM administration of dexmedetomidine at 40 µg/kg and atipamezole at 200 µg/kg in cats.[1] Although the volume-to-volume ratio in that study[1] was equal to the ratio for A-LD in the study reported here, we cannot comment as to whether the results of the present study would be replicated with larger doses of atipamezole or an altered volume-to-volume ratio between agonist and antagonist.

The present study had limitations. Although the study design was intended to represent a clinical scenario, dexmedetomidine was injected IV in isoflurane-anesthetized cats instead of IM before anesthetic induction (the latter being the more likely clinical scenario). However, this design allowed us to eliminate interindividual variation that may have occurred from unequal absorption of dexmedetomidine. It also allowed us to standardize time intervals between administration of dexmedetomidine and the treatment agents. Cats in the present study were paralyzed by the administration of rocuronium. Nondepolarizing neuromuscular blocking agents are not a part of most anesthetic protocols for cats; rocuronium was included in the present study to prevent spontaneous breathing that may have affected ventilation or spontaneous movements that may have resulted in accidental dislodging of the catheter inserted in a femoral artery. The CO and other related hemodynamic variables were measured by use of an ultrasonographic dilution technique. To our knowledge, this technique has not been compared with other techniques for use in cats; however, it has been validated extensively for use in several species.[9,13–16] Moreover, this technique is based on the Stewart-Hamilton principle, which relies on conservation of the indicator, complete mixing of the indicator in the bloodstream, and a rapid injection; to our knowledge, these are not species-specific factors.

The present study was conducted to evaluate effects of the IM administration of 2 doses of atipamezole to isoflurane-anesthetized cats. The IM administration of atipamezole at a volume half of or equal to that of dexmedetomidine was ineffective for increasing PR or CO in anesthetized cats that had received dexmedetomidine. However, atipamezole caused short-lasting but severe arterial hypotension.

Acknowledgments

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Footnotes

a. Modulus SE anesthesia machine, Datex-Ohmeda, GE Healthcare, Chicago, Ill.
b. Isotec 5 vaporizer, Datex-Ohmeda, GE Healthcare, Chicago, Ill.
c. Hospira Inc, Lake Forest, Ill.
d. Bridge Amp, ADInstruments, Colorado Springs, Colo.
e. LabChart Pro, ADInstruments, Colorado Springs, Colo.

f. COstatus, Transonic Systems Inc, Ithaca, NY.
g. Dexdomitor, Zoetis, Parsippany, NJ.
h. Antisedan, Zoetis, Parsippany, NJ.
i. AtroJect SA, Henry Schein Animal Health, Dublin, Ohio.
j. Enlon, Mylan Institutional, Rockford, Ill.
k. G*Power, version 3.1.7, Universitat Kiel, Kiel, Germany.
l. JMP Pro, version 12.0.1, SAS Institute Inc, Cary, NC.

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