Evaluation and comparison of xylazine hydrochloride and dexmedetomidine hydrochloride for the induction of emesis in cats: 47 cases (2007–2013)

Jennifer L.Willey DVM Tracy M. Julius DVM

Sean-Paul A. Claypool

Monica C. Clare VMD

From the Veterinary Specialty Hospital of San Diego, 10435 Sorrento Valley Rd, San Diego, CA 92121.

Address correspondence to Dr.Willey (jennifer.willey@vshsd.com).

OBJECTIVE

To evaluate and compare IM administration of xylazine hydrochloride and dexmedetomidine hydrochloride for the induction of emesis in cats.

DESIGN

Retrospective case series.

ANIMALS

47 cats with a history of suspected ingestion of a toxic substance or foreign material between June 2007 and June 2013.

PROCEDURES

Data collected for analysis from the medical records included signalment, drug dose and route of administration, whether a repeated dose of the emetic agent was administered, and outcome (emesis, yes or no).

RESULTS

Cats in the 2 treatment groups did not differ with regard to age, sex, or breed distribution. The range of doses of xylazine administered IM was 0.36 to 0.64 mg/kg (0.16 to 0.29 mg/lb). The range of doses of dexmedetomidine administered IM was 6 to 18 μ g/kg (2.7 to 8.2 μ g/lb). A repeated dose of xylazine or dexmedetomidine was given to 3 and 1 cats, respectively. Emesis was successfully induced in 24 of the 47 (51.1%) cats. Nine of the 21 (43%) cats that received xylazine vomited and 15 of the 26 (58%) cats that received dexmedetomidine vomited. Percentage of cats that vomited after either drug administration did not differ significantly.

CONCLUSIONS AND CLINICAL RELEVANCE

Following IM administration in cats, xylazine and dexmedetomidine were similarly effective for induction of emesis, indicating that dexmedetomidine is a comparable alternative to xylazine for this purpose. Prospective studies are needed to determine the optimal IM dose of dexmedetomidine for induction of emesis in cats. (J Am Vet Med Assoc 2016;248:923–928)

nduction of emesis in veterinary patients is often recommended for initial decontamination following ingestion of noncaustic toxic substances or foreign material. Although dogs are examined and treated for dietary indiscretion more commonly than cats, cats have been reported to ingest various toxicants and foreign material, which may necessitate the induction of emesis.¹⁻⁵

Administration of xylazine hydrochloride has been recommended for the induction of emesis in cats.^{6,7} Xylazine-induced emesis occurs through the drug's action on the chemoreceptor trigger zone of the area postrema in cats.⁸ Furthermore, the emetic dine also acts on central α_2 -adrenoceptors and has a higher selectivity for α_2 -adrenoceptors, compared with xylazine.¹³ Dexmedetomidine, an enantiomer of medetomidine, has been reported to cause vomiting in cats that received the medication at various doses for anesthesia and sedation.¹⁴⁻¹⁹ Additionally, dexmedetomidine has been found to be approximately twice as potent as medetomidine.¹⁴ The use of dexmedetomidine hydrochloride as an emetic agent in cats in clinical and research settings has been infrequently reported.^{1,17}

action of xylazine has been shown to be mediated by

 α_2 -adrenoceptors.⁹⁻¹² In the same respect, medetomi-

With the advent of many new and safer anesthetic agents, xylazine may no longer be stocked in many small animal practices and therefore may not be readily available to practitioners. Given the limited efficacy and potential adverse effects associated with the use

ABBREVIATIONS

CI Confidence interval

of apomorphine in cats²⁰ and risk for aspiration as well as development of hemorrhagic gastritis associated with the use of 3% hydrogen peroxide,²¹ alternative emetics for administration to cats should be explored. Anecdotal reports exist regarding the use of dexmedetomidine in cats, and this agent has also been used with success in the authors' facility. However, to the authors' knowledge, there are no studies comparing the emetic efficacy of xylazine and dexmedetomidine in cats in the clinical setting.

The purpose of the study reported here was to retrospectively evaluate and compare IM administration of xylazine and dexmedetomidine for the induction of emesis in cats. A second objective was to evaluate the dose of dexmedetomidine used for emesis in this study and determine whether an adequate dose for induction of emesis could be extrapolated. We hypothesized that dexmedetomidine would be a comparable alternative to xylazine for the induction of emesis in cats and that doses of dexmedetomidine between 10 and 20 μ g/kg (4.5 and 9.1 μ g/lb) would be associated with a greater emetic success rate than doses < 10 μ g/kg.

Materials and Methods

Case selection

The medical record databases at each of 2 hospital locations (the Veterinary Specialty Hospital Sorrento Valley, San Diego, Calif, and the Veterinary Specialty Hospital North County, San Marcos, Calif) were searched for cats that were given either xylazine hydrochloride or dexmedetomidine hydrochloride for the induction of emesis following ingestion of a toxic substance or foreign material from June 2007 to June 2013. Inclusion criteria included treatment with xylazine^a or dexmedetomidine^b IM for the induction of emesis and a recorded outcome of emesis or no emesis. Emesis was considered an all-or-nothing response. Cases were excluded if the cat had vomited prior to evaluation, the dose of drug was not recorded, the drug was administered via a route other than IM, vomiting occurred after administration of a reversal agent, or both xylazine and dexmedetomidine were administered in an attempt to induce emesis.

Medical records review

Data recorded from the medical records, when available, included signalment (age, sex, and breed), body weight, foreign material or toxic agent ingested, interval between ingestion of foreign material or toxic agent and evaluation, drug dose and route of administration, whether a repeated dose of the emetic agent was administered, outcome (emesis or no emesis), sedative effect after drug administration, whether a reversal agent was administered, time elapsed between drug administration and onset of vomiting, and results of foreign body removal if pursued.

Statistical analysis

Descriptive statistics were calculated for breed, sex, and weight. Continuous data were assessed for

normality with the Shapiro-Wilk test. Normally distributed data are reported as mean, SD, and range. Nonnormally distributed data are reported as median, 95% CI, and range. Independent t tests were used to test the hypotheses that age and weight were independent of treatment group (xylazine or dexmedetomidine); a cross-tabulation was constructed to test whether sex was independent of treatment group.

Cats were grouped by treatment (xylazine or dexmedetomidine); subgroups were established for cats that received a xylazine dose that was > 0.44 mg/kg (0.2 mg/lb) or ≤ 0.44 mg/kg and cats that received a dexmedetomidine dose that was > 10 μ g/kg or \leq 10 µg/kg. Cross-tabulations were constructed for the following combinations: treatment group (xylazine or dexmedetomidine) by emesis (yes or no); xylazine dose (> 0.44 mg/kg or \leq 0.44 mg/kg) by emesis (yes or no); dexmedetomidine dose (> 10 μ g/kg or \leq 10 μ g/kg) by emesis (yes or no); and xylazine dose > 0.44 mg/kg or dexmedetomidine dose > 10 μ g/kg by emesis (yes or no). Pearson χ^2 statistics and *P* values were calculated for each cross-tabulation. Significance was determined at a value of P < 0.05. For cats that received a repeated dose (n = 4 [3 cats treated with xylazine and 1 cat treated with dexmedetomidine]), the rate of emesis between treatment groups was not significantly (P = 0.61) different; only the initial dose was included in data analysis and the cats were grouped as previously described. Cats for which emesis occurred after leaving the clinic were categorized as no emesis. All analyses were carried out with standard software programs.^c

Results

Fifty-five cats were initially considered for the study. Eight cats were excluded from the study for various reasons: vomiting prior to evaluation (n = 1), vomiting after administration of a reversal agent and oral administration of activated charcoal (1), treatment with xylazine followed by dexmedetomidine for the induction of emesis (2), IV drug administration (3), and an incomplete medical record (1). The final sample size for statistical analysis was 47 cats.

Among the 47 cats, breeds included domestic shorthair (n = 34), domestic medium hair (2), domestic longhair (4), Siamese (4), Maine Coon (1), Ragdoll (1), and Persian (1). Of the 47 cats, 29 (62%) were male and 18 (38%) were female. Sex distribution was not significantly (P = 0.53) different between treatment groups (Table 1). The median age of the cats was 3.5 years (range, 0.5 to 13.3 years). Age distribution was not significantly (P = 0.99) different between treatment groups. The mean \pm SD weight of the cats was 4.9 \pm 1.3 kg (10.8 \pm 2.9 lb; range, 2.4 to 8.8 kg [5.3 to 19.4 lb]). Weight was not significantly (P = 0.65) different between treatment groups.

Twenty-six (55%) cats had ingested foreign material and 21 (44%) cats had ingested a toxicant. None of the toxicants had α_2 -adrenoceptor antagonistic or anti-emetic properties.

	Treatment group		
Variable	Xylazine	Dexmedetomidine	P value
No. of cats	21	26	
Age range (y)	0.5–12	0.5–13.3	0.99
Mean weight (kg)	5.03	4.76	0.65
Sex (No. of cats)	Neutered male (14); spayed female (7)	Neutered male (15); spayed female (9); sexually intact female (2)	0.53
Breed (No. of cats)	Domestic shorthair (12); domestic longhair (3); domestic medium hair (2); Siamese (2); Ragdoll (1); Maine Coon (1)	Domestic shorthair (22); Siamese (2); domestic longhair (1); Persian (1)	
No. of cats that vomited after treatment	9	15	0.31

 Table I—Summary data for cats receiving an IM dose of either xylazine hydrochloride or dexmedetomidine hydrochloride for the induction of emesis.

The range of doses of xylazine administered IM was 0.36 to 0.64 mg/kg (0.16 to 0.29 mg/lb). The range of doses of dexmedetomidine administered IM was 6 to 18 µg/kg (2.7 to 8.2 µg/lb). A repeated dose of xylazine or dexmedetomidine was given to 3 and 1 cats, respectively. — = Not applicable.

Twenty-one (45%) cats received xylazine and 26 (55%) cats received dexmedetomidine for the induction of emesis. Doses of xylazine were not normally distributed (Shapiro-Wilk test; P < 0.001); the median dose of xylazine administered was 0.43 mg/kg (0.19 mg/lb; 95% CI, 0.43 to 0.44 mg/kg; range, 0.36 to 0.64 [0.16 to 0.29 mg/lb]). Doses of dexmedetomidine were normally distributed (Shapiro-Wilk test; P = 0.23); the mean \pm SD dose of dexmedetomidine administered was 11 \pm 3 µg/kg (5 \pm 1.4 µg/lb; range, 5.7 to 18.4 µg/kg [2.6 to 8.4 µg/lb]).

Emesis was observed in 24 of 47 (51.1%) cats. Nine of 21 (43%) cats that received xylazine and 15 of 26 (58%) cats that received dexmedetomidine vomited. Although a higher proportion of dexmedetomidine-treated cats vomited, the difference between treatment groups was not significant (P = 0.31).

Cats that received xylazine were categorized into subgroups by use of a cutoff dose of 0.44 mg/ kg, which was chosen on the basis of published doses for induction of emesis.7 Of the 21 cats that received xylazine, 10 (48%) received a dose that was > 0.44 mg/ kg. Of these 10 cats, 2 received a dose of 0.64 mg/ kg. Eleven (52%) cats received a dose that was ≤ 0.44 mg/kg. Emesis was observed in 5 cats that received > 0.44 mg of xylazine/kg and 4 cats that received ≤ 0.44 mg of xylazine/kg. On comparison of the findings for these 2 xylazine dose subgroups, the difference in the proportion of cats that vomited was not significant (P = 0.53). Two cats that received xylazine at a dose of 0.43 mg/kg vomited after leaving the clinic; therefore, the outcome for those cats was reported as no emesis for the purposes of this study.

Cats that received dexmedetomidine were categorized into subgroups by use of a cutoff dose of 10 μ g/kg. Of the 26 cats that received dexmedetomidine, 13 (50%) received a dose that was > 10 μ g/kg and 13 (50%) received a dose that was \leq 10 μ g/kg. Emesis was observed in 8 cats that received a dose that was > 10 μ g of dexmedetomidine/kg and 7 cats that received a dose that was $\leq 10 \ \mu g$ of dexmedetomidine/kg. On comparison of the findings for these 2 dexmedetomidine dose subgroups, the difference in the proportion of cats that vomited was not significant (P = 0.69). Between the subgroups of cats receiving a xylazine dose that was > 0.44 mg/kg and those receiving a dexmedetomidine dose that was > 10 μ g/kg, the proportion of cats that vomited did not differ significantly (P = 0.58).

The interval between drug administration and the onset of vomiting was recorded for only 2 of 9 cats that received xylazine and 3 of 16 cats that received dexmedetomidine. The interval between drug administration and vomiting ranged from 2 to 20 minutes. The interval between suspected ingestion of the foreign material or toxic substance and evaluation at the clinic was reported in 34 of 47 cases and ranged from 10 to 240 minutes.

A reversal agent, either yohimbine^d or atipamezole,^c was administered to 7 of 21 (33%) cats that received xylazine and 24 of 26 (92%) cats that received dexmedetomidine. The level of sedation was recorded for only 2 of the 7 xylazine-treated cats that were administered yohimbine; for those cats, the level of sedation was noted as moderate to extreme. One of the 2 cats received a dose of 0.64 mg of xylazine/kg (0.29 mg/lb), IM, and the level of sedation was noted to be extreme. The level of sedation was recorded for only 3 of the 24 dexmedetomidine-treated cats that were administered atipamezole; for those 3 cats, 2 were reported to be very sedated and 1 was noted to be excessively sedated. The cat that was noted to be excessively sedate had received a dose of 10.68 μ g/kg (4.85 μ g/lb) IM.

Data regarding outcome after emesis induction were available for 29 of the 47 cats. Endoscopy was performed in 7 cats. One of those cats had vomited, but no foreign material was present in the vomitus. This cat had a string foreign body removed endoscopically.The other 6 cats did not vomit, and thus endoscopy was pursued. For 1 cat that underwent endoscopy, no foreign body was identified; the remainder of the cats had various foreign objects removed. No complications were reported during follow-up for the 22 cats that did not undergo endoscopy. Of these 22 cats, 9 did not vomit. Of those 9 cats, 4 had ingested foreign material; 2 cats vomited the foreign material at home and 2 cats were noted to have passed material in their feces multiple days later. Two of the 9 cats ingested parts of a lily; 1 cat was hospitalized overnight and the other was monitored at home, but neither developed clinical signs. Another cat was hospitalized for suspected diltiazem ingestion and was discharged from the hospital the following day. Another cat received supportive care in the hospital following acetaminophen ingestion, but no clinical signs were noted in the medical record. The remaining cat had been evaluated for possible ingestion of brodifacoum and treated as an outpatient; no clinical signs were reported during follow-up.

Discussion

The results of the present study indicated that xylazine and dexmedetomidine, administered IM, were equally effective in inducing emesis in cats that were evaluated at an emergency clinic following ingestion of foreign material or a toxic substance. Emesis was successfully induced in 9 of 21 (43%) cats that received xylazine and in 15 of 26 (58%) cats that received dexmedetomidine.

The emetic effect of xylazine has been reported to be dose dependent^{9,12} with 91% efficacy after IM administration of a 0.5 mg/kg dose and 100% efficacy after IM administration of a 1 mg/kg dose.⁹ Colby et al⁸ reported that an IM dose of 0.66 mg of xylazine/kg is 96% effective for induction of emesis in cats. These success rates differ considerably from that of the present study.Among the cats of the present study that received xylazine, the median dose and efficacy rate were similar to the findings of Bennett et al¹ in a study evaluating lily ingestion in cats. In that study,¹ the dose range of xylazine was 0.4 to 0.5 mg/kg, and 7 of 16 cats vomited (ie, emetic response rate of 44%).Also in that same study,¹ 1 cat received a dose of dexmedetomidine for induction of emesis, which was successful.

The comparatively poorer success rates with regard to emesis in cats in the present study and the study by Bennett et al¹ could be attributed to the lower doses of xylazine administered. The cats in the study reported here received a median dose of 0.43 mg of xylazine/kg, likely because 0.44 mg/kg is a commonly published dose.7 Two cats in the present study received doses of 0.64 mg/kg; one cat vomited, and the other did not. The difference in success rates between other published reports^{9,12} and the present study and the study by Bennett et al¹ may also be attributed to differences in sensitivity to xylazine among individual cats. In a study performed by Lucot et al,¹² the authors reported variable susceptibility to emesis in cats determined on the basis of motion sickness testing. When classified as having low or high susceptibility to motion sickness, the cats had significant differences with regard to sensitivity to xylazine-induced emesis.12 The median effective dose of xylazine (administered SC) for the group with low susceptibility to motion sickness was 0.504 mg/kg (0.229 mg/lb) and the value for the group with high susceptibility to motion sickness was 0.187 mg/kg (0.085 mg/lb).¹² In the present study, there were no significant differences with regard to dose of xylazine received and successful emesis; however, this finding may be attributed to the narrow dose range of xylazine used and small number of cats. Additionally, variable sensitivity to xylazine among individual cats could not be evaluated. Although administration of higher doses of xylazine (≥ 0.66 mg/kg) for emesis, such as those used in the study by Colby et al,⁸ may be more effective in cats, further research in a clinical setting is needed.

In studies^{14,15,19} evaluating the use of dexmedetomidine in cats, emesis was an adverse effect in 7% to 100% of cats receiving IM doses ranging from 15 to 40 μ g/kg (6.8 to 18.2 μ g/lb). In the study¹⁴ that found emesis to occur in 7% of dexmedetomidine-treated cats, a dose of 40 µg/kg, IM, was administered. The low incidence of emesis was attributed to the fact that food had been withheld from the cats prior to administration of the drug. However, in another study,¹⁵ emesis was reported for 6 of 6 cats from which food had been withheld prior to IM administration of either 15 or 30 μ g of dexmedetomidine/kg (6.8 to 13.6 μ g/lb). It is possible that the sensitivity of cats to dexmedetomidine also varies, as does their sensitivity to xylazine.¹² Thus, a dose of dexmedetomidine as low as 15 µg/ kg, IM, may be adequate for the induction of emesis in some cats, but inadequate in others. Because there is no published dexmedetomidine dose for emesis in cats, the dose of dexmedetomidine evaluated in the present study was clinician dependent and therefore not standardized. As a result, the cats in this study received an IM dose of dexmedetomidine in the range of 5.7 to 18.4 μ g/kg. Contrary to a previous report²² of no vomiting by 6 cats after IM administration of 10 µg of dexmedetomidine/kg, emesis was successfully achieved in 15 of the 26 (58%) dexmedetomidinetreated cats in the present study with no significant difference in the proportion of cats that vomited after receiving an IM dose >10 μ g/kg or \leq 10 μ g/kg. On the basis of these findings, it would appear that a dose of 10 µg of dexmedetomidine/kg administered IM is an effective treatment for the induction of emesis in cats; however, a prospective study with a larger number of cats in which dose administration can be controlled is necessary for further evaluation of this treatment.

An additional consideration in choosing the emetic dose of xylazine or dexmedetomidine is the sedative effect of these drugs, which is also mediated via stimulation of the central α_2 -adrenoceptors.²³ In previous studies^{9,12} evaluating the emetic efficacy of xylazine in cats, apparent drowsiness was reported after administration of doses of 0.5 mg/kg (0.23 mg/lb), IM, and 0.66 mg/kg (0.3 mg/lb), SC; cats became laterally recumbent after administration of a dose of 1.0 mg/kg (0.45 mg/lb), IM. Of the 2 cats that received a dose of 0.64 mg

of xylazine/kg IM in the present study, 1 had a note of the level of sedation in its medical record. This cat was reported to have extreme sedation and was given a reversal agent. Among the dexmedetomidine-treated cats, level of sedation was reported for 3 cats; 2 were very sedate and 1 was excessively sedate. The range of dexmedetomidine doses for these cats was 9.43 μ g/kg to 15.63 μ g/kg (4.3 to 7.1 μ g/lb), IM. The cat that was noted to be excessively sedate had received a dose of 10.68 μ g/kg (4.85 μ g/lb), IM. Thus, due to variable sensitivity to dexmedetomidine among the study cats and lack of data regarding level of sedation obtained in the present study, limited conclusions can be drawn in regard to determining an optimal dose for the use of dexmedetomidine as an emetic agent in cats.

Treatment with a reversal agent was given to a higher percentage of cats that received dexmedetomidine (92%), compared with cats that received xylazine (33%). Yohimbine and atipamezole are both α_2 -adrenoceptor antagonists and were used for reversal of xylazine and dexmedetomidine in the present study. A level of sedation was reported for only 2 cats in the xylazine treatment group and 3 cats in the dexmedetomidine treatment group. All of these cats were administered a reversal agent. Because a level of sedation was infrequently reported in the medical records examined, the reason for the discrepancy between groups regarding the frequency of administration of a reversal agent is not clear. It is possible that vohimbine is not as readily available and that it was not widely known that atipamezole could be used to reverse the sedative effects of xylazine.24

In the medical records that contained pertinent data, no overt complications were reported. Thus, findings of the present study have suggested that both xylazine and dexmedetomidine are safe to use for the induction of emesis in cats at the doses evaluated. Adverse effects, aside from sedation, were few. Other possible adverse effects of α_2 -adrenoceptor agonists may include cardiovascular derangements such as bradycardia, atrioventricular block, and vasoconstriction.²³ Although these adverse effects were not reported for cats in the present study, heart rate and blood pressure were not routinely monitored. Regardless, all patients should be monitored closely when treated with these medications and the treatment risks should be discussed with the pet owner prior to drug administration.

Owing to the retrospective design of this study, there were several limitations. First, the dose of each drug given for the induction of emesis was not standardized. Although the dose range was narrower for xylazine than it was for dexmedetomidine, there were no significant differences within each group with regard to emetic efficacy of the various doses. Despite this, the inconsistency in drug doses used may have confounded results. Second, information regarding degree of apparent nausea (ie, ptyalism or retching) could not be extrapolated from the medical records; therefore, emesis was recorded as an all-or-nothing event. This may have resulted in an underestimation of the number of cats that were actually affected by the emetic properties of either drug but unable to elicit an emetic response. Third, medical records lacked data on the time elapsed between drug administration and the onset of emesis or administration of a reversal agent. In some cases, it is possible that the reversal agent was given too soon, which may have impacted the frequency of successful emesis. Finally, the small number of cats included in the study may have led to underestimation of significant differences between treatment groups. Given the frequency of emesis in the present study, a sample size of 174 cats in each treatment group would be necessary to achieve 80% power.

Results of the present study have indicated that dexmedetomidine is a comparable and safe alternative to xylazine for the induction of emesis in cats. A dose of 10 μ g of dexmedetomidine/kg administered IM was used for evaluation in this study. Although this dose appears adequate for use as an emetic agent in cats, future prospective studies that assess patient susceptibility to the emetic effects of dexmedetomidine, allow for control of the dose administered, and include scoring of the level of treatment-associated sedation are needed for further evaluation.

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The authors declare that there were no conflicts of interest.

Footnotes

- a. Anased, Akorn Inc, Decatur, Ill.
- b. Dexdomitor, Pfizer Animal Health, Espoo, Finland
- c. IBM SPSS Statistics for Windows, Version 22.0, IBM Corp, Armonk, NY.
- d. Yonine, Akorn Inc, Decatur, Ill.
- e. Antisedan, Pfizer Animal Health, Espoo, Finland.

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From this month's AJVR

Clinical disease and lung lesions in calves experimentally inoculated with *Histophilus somni* five days after metaphylactic administration of tildipirosin or tulathromycin

Anthony W. Confer et al

OBJECTIVE

To compare clinical disease and lung lesions in calves experimentally inoculated with *Histophilus somni* 5 days after metaphylactic administration of tildipirosin or tulathromycin.

ANIMALS

Twenty-four 3-month-old Holstein and Holstein-crossbreed steers.

PROCEDURES

Calves were randomly allocated to 3 groups of 8 calves. On day 0, calves in group 1 received tildipirosin (4 mg/kg, SC), calves in group 2 received tulathromycin (2.5 mg/kg, SC), and calves in group 3 received isotonic saline (0.9% NaCl) solution (1 mL/45 kg, SC; control). On day 5, calves were inoculated with 10 mL of a solution containing *H somni* strain 7735 (1.6 X 10° CFUs/mL, intrabronchially; challenge). Calves were clinically evaluated on days 5 through 8 and euthanized on day 8. The lungs were grossly evaluated for evidence of pneumonia, and bronchial secretion samples underwent bacteriologic culture.

RESULTS

The mean clinical score for each group was significantly increased 12 hours after challenge, compared with that immediately before challenge, and was significantly lower for tildipirosin-treated calves on days 6, 7, and 8, compared with those for tulathromycin-treated and control calves. The mean percentage of lung consolidation for tildipirosin-treated calves was significantly lower than those for tulathromycin-treated and control calves. *Histophilus somni* was isolated from the bronchial secretions of some tulathromycin-treated and control calves but was not isolated from tildipirosin-treated calves.

CONCLUSIONS AND CLINICAL RELEVANCE

Results indicated that metaphylactic administration of tildipirosin to calves 5 days prior to *H* somni challenge prevented subsequent culture of the pathogen from bronchial secretions and was more effective in minimizing clinical disease and lung lesions than was metaphylactic administration of tulathromycin. (*Am JVet Res* 2016;77:358–366)



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