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Ultrasonographic evaluation of the effects of azithromycin on antral motility and gastric emptying in healthy cats

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Abstract

Background: Erythromycin, a macrolide antibiotic with motilin agonist properties, shortens gastric emptying (GE) time in healthy cats. Azithromycin, another macrolide antibiotic, is effective for treatment of gastric paresis in people.

Objectives: To evaluate the effects of azithromycin on GE and gastric motility in healthy cats in comparison with erythromycin (positive control) and placebo.

Animals: Eight healthy purpose-bred cats.

Methods: Prospective, blinded, crossover study. Cats received either azithromycin (3.5 mg/kg PO q24h), erythromycin (1 mg/kg PO q8h), or placebo for 24 hours before and during evaluation of GE. A validated method using ultrasound for sequential measurements of antral area as well as amplitude and frequency of contractions was used to assess GE and evaluate gastric antral motility postprandially over an 8-hour period.

Results: GE was significantly faster ($P < .05$) after administration of azithromycin and erythromycin when compared to placebo in the late phase of fractional emptying from 75% (mean ± SD: 327 ± 51 minutes, 327 ± 22 minutes, and 367 ± 29 minutes, respectively), to 95% fractional emptying (399 ± 52 minutes, 404 ± 11 minutes, and 444 ± 24 minutes, respectively). The drugs had no significant effect on antral motility variables at any time point.

Conclusions and Clinical Importance: Azithromycin and erythromycin shorten GE time in a comparable manner in healthy cats. Evaluation of their efficacy in cats with gastric dysmotility is warranted.

KEYWORDS
azithromycin, erythromycin, gastric dysmotility, gastric emptying time, motilin, prokinetic

Abbreviations: AUC, area under the curve; BCS, body condition score; BW, body weight; CA, contraction amplitude; CF, contraction frequency; GD, gastric dysmotility; GE, gastric emptying; GI, gastrointestinal; MI, motility index; MMC, myenteric motor complex.

1 | INTRODUCTION

Gastric dysmotility (GD) can complicate gastrointestinal (GI) and other illnesses encountered in cats.[1,2] Clinical signs associated with GD are nonspecific and include nausea, inappetence, abdominal discomfort, regurgitation, and vomiting.[1,2] They might be difficult to differentiate from those of concurrent illness, stress, or other confounding factors. In addition, standard methods of assessing gastric motility are often labor intensive, invasive, and thus impractical in the veterinary hospital setting.[2] These factors can complicate recognition and delay treatment of GD which adversely affects cats by prolonging hospitalization and impeding recovery.[1,2]

At present, treatment options for GI motility disorders are limited.[2] This is due to the sparse number of prokinetic drugs available, as well as the logistical challenges associated with the acquisition and administration of some of those drugs. In addition, limitations associated with measuring GI motility have resulted in failure to accurately assess the efficacy of prokinetics. In cats, there is a paucity of information regarding the in vivo effects of prokinetics.[3] Thus, treatment protocols are largely based on studies performed in other species or on anecdotal evidence.

The role of motilin in GI motility in cats is poorly understood due to the unique motility patterns documented in that species.[4] In people and dogs, type III myenteric motor complexes (MMC III) are stimulated by motilin and are primarily responsible for interprandial GI motility.[5] While MMC III do not appear to occur in cats,[4] motilin receptors associated with smooth muscle have been identified in the GI tract of the cat, with the highest concentrations found in the gastric antrum and duodenum.[6] Additionally, multiple studies have demonstrated that motilin or motilin agonists enhance GI motility in cats.[3,4,7] Thus motilin receptors should be considered an important target in the treatment of GD in cats.

Recently, a noninvasive ultrasonographic technique was validated to assess gastric emptying (GE) time and gastric antral motility in healthy cats,[8] and used to successfully evaluate the effects of various drugs on GI motility variables in healthy cats.[3] The latter study found that administration of erythromycin, a macrolide antibiotic that acts as a motilin agonist,[9] resulted in more rapid GE.[3] Azithromycin, another macrolide antibiotic, also has agonistic properties on motilin receptors and is effective for treatment of gastroparesis in humans.[10-12] Unlike erythromycin, azithromycin has excellent oral bioavailability in cats as well as a longer half-life, making it an attractive alternative for treatment of motility disorders in cats.[13,14]

The aim of this prospective, randomized, double-blinded, crossover study was to assess the effects of azithromycin on GE and antral motility in healthy cats in comparison to positive control (erythromycin) and placebo. We hypothesized that administration of azithromycin would result in shorter GE time and increased antral motility resembling the effects observed with erythromycin when compared to placebo.

2 | MATERIALS AND METHODS

2.1 | Animals

Eight healthy purpose-bred domestic shorthair cats were used in this study. Before the study, cats were acclimated to the feeding schedule and restraint required to complete the study for at least 2 weeks. The cats utilized in the study were deemed healthy based on physical examination, CBC, and biochemistry profile. A 9-point system was used to assign body condition score (BCS) to each of the cats (9 = obese, 5 = optimal, and 1 = extremely underweight).[15] Their ages, sex and weights were also recorded. When not being evaluated, the cats were housed in 2 groups of 3 to 5 cats and fed ad libitum. During periods of fasting and measurements, cats were housed individually. The study was approved by the LSU IACUC (Protocol 18-068) and performed in an AAALAC accredited facility.

2.2 | Study design

A prospective, randomized, double-blinded crossover study design was used. A previously validated ultrasound method for assessment of GE and gastric motility variables was utilized in order to compare the effects of azithromycin to those of erythromycin and placebo on antral motility and GE time.[8] Each cat received 1 of 3 interventions given with a syringe: azithromycin 3.5 mg/kg PO q24h, erythromycin 1 mg/kg PO q8h (positive control), or an amount of water similar to the volume of the erythromycin dose PO q24h (placebo) for 24 hours before the start of the measurements and throughout the day of the measurements. Each cat was fasted for 18 hours before evaluation. On the morning of the measurement day, drugs were administered 15 minutes. Before the meal was offered. The dosage and frequency of azithromycin administration used in our study was extrapolated from the dose used in the treatment of gastric paresis in humans as well as the results of a brief pilot study.[10,11,16] In our pilot study, GE of 2 cats was evaluated using the method described below after administration of azithromycin 2 mg/kg q8h, azithromycin 3.5 mg/kg q24h, and no intervention. The results of our pilot study indicated that, taking into consideration the long half-life of the drug in cats,[13] azithromycin 3.5 mg/kg q24h appeared to be effective. After each evaluation, a washout period of at least 2 weeks was observed before the next measurement, which was equal to at least 10 serum half-lives for all drugs used. Cats were randomized to an intervention sequence using a random number generator. The person performing the ultrasound and the staff holding the cats were blinded to the drug each cat received until the whole study was completed.

2.3 | Test meal

The test meal used for the evaluations consisted of a maintenance laboratory diet (LabDiet 5003-Laboratory Feline Diet, LabDiet, St

Louis, MO) and 1 teaspoon of canned cat food (Purina Pro Plan Veterinary Diets EN Gastroenteric Feline Formula, Nestle Purina Pet Care Company, St Louis, MO). The test meal provided approximately 20% of the estimated daily energy requirement of each cat, as determined by the equation: $70 \times BW^{0.75}$, where BW is the body weight (in kilograms) of the cat. Cats had 20 minutes to consume at least 70% of the test meal. The food was weighed before and after meal consumption to determine percent consumed. The time it took each cat to consume the test meal was recorded. If the cat did not consume the entire meal, a time of 20 minutes was recorded for that meal.

2.4 | Ultrasonography

All sonographic evaluations were performed by a single sonographer (SR) trained by a board-certified radiologist (LG) and using a 12 MHz linear array transducer (Hitachi Noblus, Hitachi Aloka Medical America, Inc, Wallingford, CT) as previously described.[8] Briefly, cats were placed in dorsal recumbency with the probe placed just caudal to the xiphoid and pointed dorsocranially to visualize the gastric antrum just caudal to the liver. In all cats, the gastric antrum was identified as a round or ovoid structure during the evaluation. Ultrasound was performed before meal ingestion (baseline), immediately after ingestion (Time 0), then every 30-minutes for the first 240 minutes, then every 60-minutes to a total of 480 minutes. When the antrum was empty, the rugal folds of the stomach had a characteristic wagon-wheel appearance, which has been previously described.[3,8] After meal ingestion, antral distension allowed for visualization of the lumen as a hyperechoic region. Occasionally, the presence of gas within the antral lumen of the antrum created distal acoustic shadowing, preventing visualization of the distant wall.

Ultrasonographic assessment of GE time and gastric motility was performed as previously described.[8] Still images of the antrum in transverse were obtained during maximal relaxation and contraction and the areas were measured using the built-in caliper by tracing the serosal margin of the antrum. Where acoustic shadowing made it impossible to visualize the entire serosal margin, the measurement was made with the assumption that the antrum had a round to oval shape. Measurements of the contracted and relaxed antrum were made in triplicate for each time point. For most time points, the diameter of the relaxed antrum was static. Periodically, the antrum would dilate immediately before a contraction event. In those cases, the largest antral area measurements were obtained. The mean of the 3 measurements was used for statistical analysis. The baseline antral measurement was subtracted from each subsequent measurement and results were divided by the maximal antral area obtained throughout the evaluation. Measurements were expressed as percent maximum antral area and plotted against time. If any antral measurement was less than the baseline antral measurement, a value of zero was recorded for the percent maximum antral area for that measurement. The total area under the curve (AUC) was calculated for the 480 minute period and GE time for each given emptying stage (25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, and 95% based on AUC) was determined with a commercially available software (R version 3.2.2, The R Foundation for Statistical Computing, Vienna, Austria).

Contraction frequency (CF) was determined by counting the number of contractions observed in a 2-minute period at each time point. Contraction amplitude (CA) was determined for 3 separate contractions at each time point and was calculated by subtracting the antral area during contraction from the relaxed antral area and dividing by the relaxed antral area. Motility index (MI) was calculated by multiplying mean CA by CF and plotted against time. The total AUC was calculated for the 480-minute period of the MI, CA, and CF curves for each cat and each intervention (R version 3.2.2, The R Foundation for Statistical Computing, Vienna, Austria).

2.5 | Statistical analysis

The normality of data distribution was tested by the D'Agostino and Pearson omnibus normality test. With the exceptions of the subjects' age and BCS, all data were normally distributed. Unless otherwise stated, all data are reported as means and standard deviations. A mixed model ANOVA with cat as a random effect and intervention as a fixed effect was used to assess the difference in the amount of food consumed and time required for test meal consumption between drugs. A mixed model ANOVA with cat as a random effect and intervention as fixed effect was used to assess the difference in each fractional GE time, MI, CA and CF at each time point and MI AUC, CA AUC and CF AUC among groups. Post hoc pairwise comparisons were examined with the Tukey's test as appropriate. Two statistical software programs were used (JMP Statistical Discovery, SAS, Cary, NC, and GraphPad Prism, GraphPad Software Inc., La Jolla, CA) as appropriate, and a value of $P < .05$ was considered significant.

3 | RESULTS

Four cats were spayed females and 4 were neutered males with a median age of 9 years (range, 8-13 years). The mean weight ± SD of the cats was 6.15 ± 1.69 kg. The median BCS of the cats was 7.5/9 (range, 4-9). All cats ate at least 70% of the test meal within the 20-minute time period. The mean percentages of the test meal consumed were 92 ± 12% for azithromycin, 89 ± 12% for erythromycin, and 89 ± 13 for placebo, and were not different between interventions ($P = .62$). The mean time required to consume the test meal was 10.6 ± 3.7 minutes for azithromycin, 11.6 ± 4.8 minutes, for erythromycin, and 12.3 ± 4 minutes for placebo, and was also not different between interventions ($P = .23$).

There was no difference in the mean time to reach maximal percentage antral area between interventions (azithromycin 292.5 ± 117.6-minutes, erythromycin 277.5 ± 73-minutes, and placebo 307 ± 158.5-minutes, $P = .83$). Figure 1 shows percentage maximal antral area plotted against time. GE was significantly faster after administration of azithromycin and erythromycin when compared to

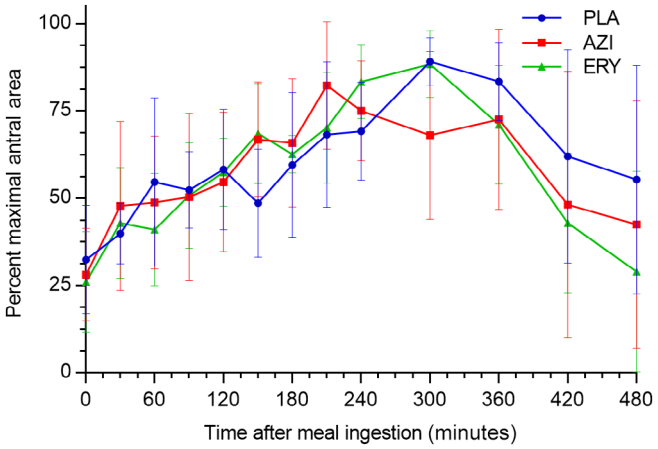

FIGURE 1 Cumulative sonographic measurements after placebo, azithromycin, and erythromycin, expressed as a percentage of the maximal antral area plotted against time after test meal ingestion in 8 healthy domestic shorthair cats. Mean values with SD are shown. Azi, azithromycin; Ery, erythromycin; Pla, placebo

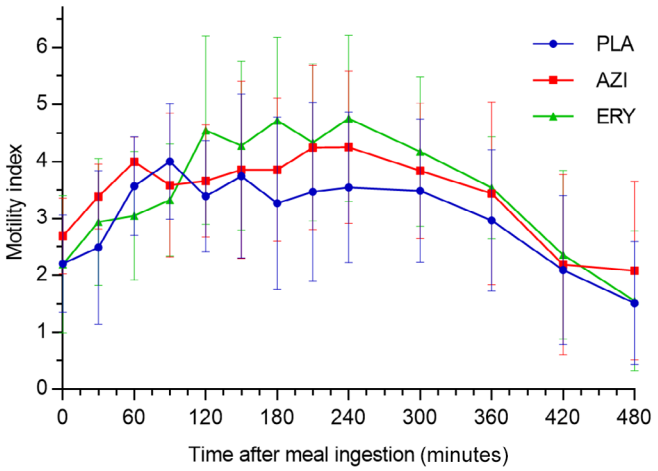

FIGURE 2 Postprandial motility index curves generated by graphing the mean ± SD of the MI (product of antral contraction amplitude and contraction frequency) over time after placebo and azithromycin and erythromycin in 8 healthy domestic shorthair cats. Azi, azithromycin; Ery, erythromycin; Pla, placebo

placebo in the late stages of GE (75%-95% fractional emptying, azithromycin $P = .02$-$.04$, erythromycin $P = .03$-$.05$). There was no difference in GE between azithromycin and erythromycin administration at any stage of GE. Group means and standard deviations of times for each stage of GE are shown in Table 1.

The MI for azithromycin was higher than that of placebo for all time points except 90-minutes, however this difference was not statistically significant at any time point. The MI for azithromycin was also increased compared to erythromycin at time points from 0- to 90-minutes and at the final reading at 480-minutes, though these differences failed to reach statistical significance at any time point. The MI for erythromycin was higher than that of placebo at all but 4 time points (Time 0, 60, 90, and 480-minutes), and at time point 240-minutes this difference was significant ($P = .03$). The MI for each intervention plotted against time is shown in Figure 2. The AUC of the MI curves for each of the interventions were not statistically significant from each other (azithromycin: 1659 ± 428.6, erythromycin: 1738.9 ± 505, and placebo: 1456 ± 501, respectively, $P = .11$).

Upon evaluation of individual indicators of motility, CA and CF, no difference was observed among the groups at any of the time points. The total AUC of CA after administration of azithromycin or erythromycin was not significantly larger than the total AUC of CA after placebo (azithromycin $P = .73$, erythromycin $P = .19$). Likewise, the total AUC of CF was also not statistically different for cats receiving azithromycin ($P = .8$) or erythromycin ($P = .99$) when compared to placebo.

4 | DISCUSSION

Our study showed that azithromycin, like erythromycin, significantly accelerated GE in the late stages of fractional GE compared to placebo in healthy cats. These findings support our hypothesis that azithromycin and erythromycin have similar gastric prokinetic effects in cats and confirm the value of these macrolide antibiotics as gastric prokinetics in cats. However, the interventions appeared to have only marginal effects on antral motility variables. This contrasts with a comparable study that documented a significant increase in MI, CA, and CF at time points corresponding to the timing of maximal antral area after administration of erythromycin as compared to placebo.[3] In addition, the previously observed double peak pattern in the time course of the MI appeared less pronounced in the present study.

When comparing the results of this study with those of previous studies evaluating GE in cats using ultrasound,[3,8] the time to maximal antral area was longer than had been reported in both previous studies (92 ± 36 min[8] and 109 ± 51 min[3]). The times for various stages of GE were also mildly to moderately prolonged. Our cats were 2 to 2.5 year older than those used in the previous studies, however age does not appear to impact GE in cats.[17] In addition, the operator of the present study was different. While interoperator variability has not been investigated for ultrasound assessment of GE in cats or in dogs, it is conceivable that it might account for some differences. Overall, the interanimal variability in GE was reflected by the amplitude of SD relatively to mean GE time and seemed to decrease in the later phases of fractional GE as previously shown.[8] In the present study, it was highest in cats receiving azithromycin, which might have been due to individual variability in the response to the drug. Finally, our inability to detect statistical differences for the antral motility variables could also be attributed to the shorter course of prokinetics in our study (24 hours vs 48 hours).

Remarkably, despite the lack of significant increase in indicators of motility, azithromycin and erythromycin both shortened the GE. Interestingly, gastric motility variables do not always correlate with GE. The administration of bethanechol, a cholinergic drug, increased antral contractility but does not result in shorter GE time in

TABLE 1 Group means and standard deviations for sonographic gastric emptying times for each stage of fractional GE in cats receiving placebo, azithromycin, or erythromycin

GE stage													
	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%	90%	95%
GET PLA (min) Mean	159.7	189.1	211.8	232.1	270.8	251.4	290.6	309.8	328.7	346.0	368.2	384.5	401.6	421.0	444.2
SD	30.3	33.0	33.8	33.3	29.8	32.1	27.7	27.3	28.5	30.7	29.3	28.6	30.6	29.5	23.7
GET AZI (min) Mean	145.7	170.0	189.3	207.6	245.3	226.5	263.3	281.0	298.5	311.8	326.6[a]	342.6[a]	361.1[a]	378.3[a]	398.5[a]
SD	36.9	36.2	37.8	40.8	46.2	43.6	49.5	53.3	56.6	53.2	51.2	51.0	53.1	53.1	51.8
GET ERY (min) Mean	151.7	174.2	195.7	216.4	252.2	234.9	269.4	285.8	302.0	314.9	327.2[a]	342.2[a]	360.1[a]	381.9[a]	403.7[a]
SD	27.5	30.2	31.0	30.6	30.7	30.3	31.0	29.8	29.1	26.1	22.3	20.6	19.0	16.5	11.4

Abbreviations: Azi, azithromycin; Ery, erythromycin; GET, gastric emptying time; Pla, placebo.
[a]GE was significantly faster ($P < .05$) following administration of azithromycin and erythromycin when compared to placebo in the late stages of GE (75%-95% fractional emptying).

people and in cats.[18-20] In addition, in a study comparing GE time and motility variables in healthy dogs using a wireless motility capsule, dogs observed in a hospital environment had significantly longer GE time compared to when they were at home.[21] However, the study found that the median values for 3 of the 4 indicators of motility evaluated were higher in the hospitalized group, suggesting increased motility despite having slower GE, although these differences in motility variables failed to reach statistical significance.[21] These findings and those of our study support that GE reflects the coordination and efficiency of the gastric antral pump, pylorus, and duodenum as opposed to the sum of the activity of each individual component.

Motilin is an important hormone involved in regulation of GI motility. Motilin, motilin analogues, and other motilin agonists, such as erythromycin and azithromycin have all been shown to modulate smooth muscle activity in the GI tract in people and dogs.[7,9-12,16,22,23] Both azithromycin and erythromycin are macrolide antibiotics that have agonistic effects on motilin receptors in the GI tract. Erythromycin is a well-known treatment for GI motility disorders in veterinary species, and its efficacy has been established in canine models of gastroparesis.[9,22] Due to poor oral bioavailability in cats, the use of erythromycin for GD has historically been questionable.[14] However, PO administered erythromycin was recently shown to be an effective prokinetic in healthy cats,[3] and this is further supported by the results of our study. In human medicine, azithromycin offers the advantages of less frequent dosing due to its longer duration of action, decreased risk of cardiac electrical disturbances and fewer drug interactions when compared to erythromycin.[10-12,16] Furthermore, tachyphylaxis might be less common in people taking azithromycin for GD than it is reported with use of erythromycin as a GI prokinetic.[24] While relatively little is known about the use of azithromycin as a promotility agent in companion animals, it is an interesting alternative to erythromycin for several reasons. The bioavailability of PO administered azithromycin ranges from 50% to 60% in cats, whereas serum concentrations of erythromycin are undetectable after oral administration.[13,14] Yet, we did document an effect of erythromycin on GE in our cats as had been previously shown.[3] A potential explanation for this comes from published data suggesting that serum concentrations of erythromycin do not reflect tissue concentrations.[3] That said, in a patient with suspected GI dysfunction a drug with superior bioavailability might be preferable. Furthermore, the reported serum elimination half-life of azithromycin is substantially longer than that of erythromycin after IV injection (mean ± SD of 35 hours and 1.94 ± 0.21 hour, respectively).[13,14] In addition, the half-life of PO administered azithromycin in small intestinal tissue is also 35 hours.[13] This allows for less frequent dosing, which is an important consideration, especially in cats which can be difficult for owners to medicate. Finally, azithromycin is widely available as both an injectable and oral medication, and less expensive than erythromycin, making it a more attractive treatment option for both in-hospital and at-home use.

The use of antibiotics for a purpose other than treatment of a bacterial infection raises several concerns. First, it might contribute to antibiotic resistance, especially when antibiotics are used at subtherapeutic doses and for inappropriate durations,[25,26] as is the case in the use of

azithromycin and erythromycin for the treatment of GD. Second, use of antibiotics might also adversely affect the gut microbiome.[27,28] While studies evaluating the effects of erythromycin or azithromycin on the gut microbiome of the cat are lacking, a report in children demonstrated that administration of azithromycin results in a temporary reduction in microbiota richness and diversity for several months beyond cessation of treatment.[29] Both the implications for antibiotic resistance and the impact on the gut microbiome should be carefully considered before initiation of GD treatment with either azithromycin or erythromycin.

Our study had several limitations. First, there are no published reports of dosing recommendations regarding azithromycin for the treatment of GD in companion animals. Therefore, our dose selection was based on extrapolation of the dose utilized for gastroparesis in human medicine, the available literature on pharmacokinetics of the drug in cats,[13] anecdotal use within our hospital, and a brief pilot study. It is possible that a different dose might have yielded a more dramatic effect on GE. Also, we administered the medications shortly before ingestion of the test meal. A study performed in dogs showed that ingestion of a meal diminished the effects of motilin analog administration.[30] A more dramatic effect on antral motility might have been documented if we had administered the drugs in the interprandial period. Further studies to evaluate optimum dosing strategies for azithromycin in the treatment of GD are warranted. Most cats in our study were overweight to obese. Finally, this study was performed in purpose-bred cats who were presumed healthy based on routine evaluation. Further studies assessing the effects of these drugs on client-owned cats with clinically relevant GD are needed.

5 | CONCLUSION

This study confirms the value of ultrasound to evaluate GE in cats. Moreover, in healthy cats, administration of azithromycin or erythromycin resulted in comparable shortening of GE time in the late stages of GE when compared to placebo. However, the drugs did not appear to significantly impact the antral motility variables measured in this study. Further investigations are needed to evaluate various dosing strategies to achieve maximal effects, and to assess the effects of these gastric prokinetics in cats with spontaneous GD.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Azithromycin and erythromycin are not approved for use in cats in the USA. Azithromycin was used as a GI prokinetic at a dose 1.5-3 times below the recommended antimicrobial dose. Erythromycin was used as a GI prokinetic at a dose 10-20 times below the recommended antimicrobial dose.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by Louisiana State University IACUC (protocol 18-068).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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