Does ranitidine administration improve gastrointestinal hypomotility in dogs?

A Knowledge Summary by

Lara Brunori DVM CertAVP(ECC) MRCVS [1*]

[1] VetsNow 24/7 Pet Emergency Hospital, 123–145 North Street, Glasgow, G3 7DA

[*] Corresponding Author (lara.brunori@gmail.com)

ISSN: **2396-9776**
Published: **11 Feb 2021**
in: **The *Veterinary Evidence* journal Vol 6, Issue 1**
DOI: **10.18849/VE.V6I1.357**
Reviewed by: **Gonçalo Serrano (DVM MSc) and James Swann (MA VetMB DACVIM DECVIM MRCV)**
Next Review Date: **14 May 2022**

OPEN ACCESS PEER REVIEWED

KNOWLEDGE SUMMARY

PICO question

In dogs presenting with gastrointestinal (GI) hypomotility is ranitidine administration (any route) beneficial in improving GI motility?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

One prospective controlled clinical trial and five experimental crossover studies

Strength of evidence

Weak

Outcomes reported

The vast majority of the evidence investigating ranitidine as a prokinetic has been carried out in experimental settings both *in vivo* with healthy conscious and anaesthetised dogs and *in vitro*. Under these circumstances ranitidine has shown some prokinetic properties. However, it is difficult to translate these results into reliable clinical recommendations, as the doses mentioned in these studies are often higher than the ones clinically recommended and healthy canine patients might respond differently to clinically affected ones

Conclusion

Although in experimental settings ranitidine has shown some prokinetic activities, no reliable clinical recommendations can be drawn from the appraised studies. There is a need of prospective clinical trials evaluating the administration of ranitidine to dogs presenting with GI hypomotility. Until further relevant studies become available, the efficacy of ranitidine administration as a prokinetic agent in dogs with GI hypomotility remains uncertain

How to apply this evidence in practice

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care.

Clinical Scenario

You are presented with a 3-year-old mixed breed female neutered dog diagnosed with postsurgical GI hypomotility on ultrasound. You wonder if the administration of ranitidine will be helpful in improving your patient's GI motility.

The evidence

The evidence currently available on the use of ranitidine as a prokinetic agent pertains, for the vast majority, to experimental settings. Five single centred experimental non-randomised non-blinded crossover studies (Fioramonti et al., 1984; Bertaccini et al., 1985; Mizumoto et al., 1990; Kishibayashi et al., 1994; and Lidbury et al., 2012) investigated potential prokinetic properties of ranitidine both *in vitro* (Bertaccini et al., 1985; and Mizumoto et al., 1990) and/or *in vivo* on healthy conscious or anaesthetised dogs (Fioramonti et al., 1984; Bertaccini et al., 1985; Mizumoto et al., 1990; Kishibayashi et al., 1994; and Lidbury et al., 2012). Although four out of five studies (Fioramonti et al., 1984; Bertaccini et al., 1985; Mizumoto et al., 1990; and Kishibayashi et al., 1994) found some degree of gastrointestinal motility stimulation post-ranitidine administration, these results are difficult to compare and generalise due to the limited number of animals included in each study, different patient populations evaluated (conscious vs anaesthetised, starved vs non-starved), a variety of techniques employed to estimate GI motility and discordant dosing regimes or route of administration.

One single centred randomised non-blinded prospective controlled clinical trial (Favarato et al., 2012) investigated the effect of ranitidine on the incidence of post-anaesthetic regurgitation in dogs undergoing elective surgical procedures, however the results of this paper are hindered by a type II error due to a too small sample size and a low incidence of regurgitation episodes in this population.

Summary of the evidence

Lidbury et al. (2012)	
Population:	Privately owned healthy adult dogs
Sample size:	Eight dogs (one excluded due to self-limiting diarrhoea prior to any intervention)
Intervention details:	Measurement of gastric emptying time, small and large bowel transit time, and total transit time via wireless motility capsules (WMC) before and after administration of ranitidine at 2 mg/kg adminsistered orally (PO) twice daily (BID) in dogs hosted in their home environment
Study design:	Single centred experimental non-blinded crossover study
Outcome studied:	Assess the effect of oral ranitidine (2 mg/kg BID) on GI transit times using the WMC system
Main findings: (relevant to PICO question):	No statistically significant effects of oral ranitidine on GI transit times were found in this group of dogs • Gastric emptying median time before ranitidine 719 (622–1320) min vs after ranitidine 757 (628–1128) min ($p=0.6149$) • Small intestinal median transit time before ranitidine 183 (92–290) min vs after ranitidine 162 (86–215) min ($p=0.5007$) • Large intestinal median transit time before ranitidine 1398 (644–2588) min vs after ranitidine 1227 (490–2634) min ($p=0.6215$) • Small and large intestinal median transit time before ranitidine 1636 (746–2588) min vs after ranitidine 1227 (490–2634) min ($p=0.6215$)

	• Total median gastrointestinal transit time before ranitidine 2735 (1898–3296) min vs after ranitidine 2083 (1248–3262) min (p=0.2759)
Limitations:	• Only healthy dogs enrolled • Small sample size (potential type II error) • Authors cannot rule out that a higher dose of ranitidine could have caused a detectable decrease in GI transit times

Favarato et al. (2012)	
Population:	Healthy female dogs admitted for elective ovariosalpingohysterectomy at the Veterinary Hospital of the Universidade Federal de Viçosa (Minas Gerais, Brazil) from 2007 to 2009
Sample size:	90 dogs
Intervention details:	Population randomised into three groups: • Control group (n=30): no drugs received before and during surgical procedure, other than the ones included in the standard anaesthetic protocol* • Metoclopramide group (n=30): metoclopramide 1 mg/kg intravenous (IV) 5 minutes before anaesthetic induction, followed by 1 mg/kg/h continuous rate infusion (CRI) immediately after anaesthetic induction and the infusion maintained throughout the general anaesthetic • Ranitidine group (n=30): ranitidine 2 mg/kg IV 6 hours before anaesthetic induction * anaesthetic protocol consisting of: acepromazine, propofol and isofluorane
Study design:	Single centred prospective randomised non-blinded controlled clinical trial
Outcome studied:	• Determine whether administration of metoclopramide during the pre- and transanaesthetic periods could prevent episodes of gastroesophageal reflux • Determine whether administration of ranitidine during the pre- anaesthetic period could prevent episodes of gastroesophageal reflux
Main findings: (relevant to PICO question):	Overall, only 7.8% of dogs (7/90) presented with gastroesophageal reflux episodes: 13.3% (4/30) in the control group, 6.66% (2/30) in the ranitidine group and 3.33% (1/30) in the metoclopramide group. No statistically significant difference ($p<0.05$) was found between different treatment group. Therefore, no beneficial effects could be demonstrated for the administration of 2 mg/kg IV ranitidine 6 hours preanaesthetic on the rate of gastroesophageal reflux during general anaesthesia
Limitations:	• Low incidence of gastroesophageal reflux in the population leading to potential type II error • Only healthy dogs enrolled

Kishibayashi et al. (1994)	
Population:	Healthy mongrel mixed sex dogs and healthy male Beagle dogs
Sample size:	• 17 anaesthetised mongrel dogs • 19 conscious Beagle dogs

Intervention details:	Anaesthetised dogs (n=17):
	• Rubber balloons inserted into the gastric antrum and colon
	• Respiration rate and pattern measured with glass tube inserted in trachea
	• Blood pressure measured via femoral artery catheter
	• Slow (10s) IV injections of:
	  ○ KW-5092 0.03 mg/kg; 0.1 mg/kg; 0.3 mg/kg; 1 mg/kg
	  ○ Neostigmine 0.03 mg/kg; 0.1 mg/kg
	  ○ Ranitidine 1 mg/kg; 3 mg/kg;10 mg/kg
	Conscious dogs (n=19)
	• 2 weeks prior to the beginning of the study 'strain gauge force transducers' were surgically implanted onto the seromuscular layer of the GI tract in the gastric antrum, duodenum, ileum and colon to measure circular muscle contractions
	• Slow (10s) IV injections of:
	  ○ KW-5092 0.03 mg/kg; 0.1 mg/kg; 0.3 mg/kg; 1 mg/kg
	  ○ Neostigmine 0.01 mg/kg; 0.03 mg/kg; 0.1 mg/kg
	  ○ Ranitidine 1 mg/kg; 3 mg/kg
	• Oral administration of:
	  ○ KW-5092 1 mg/kg; 3 mg/kg; 10 mg/kg
	  ○ Neostigmine 1 mg/kg; 3 mg/kg
	  ○ Ranitidine 10 mg/kg; 30 mg/kg

Study design:	Single centred experimental non-blinded non-randomised crossover study
Outcome studied:	Effects of KW-5092 (synthetic ranitidine derivative with negligible H2-receptor blocking activity) on GI motor activity in anaesthetised dogs and in conscious dogs in the digestive state, compared with those of neostigmine and ranitidine
Main findings: (relevant to PICO question):	Anaesthetised dogs (average results): • Ranitidine at 1 mg/kg IV significantly enhanced the gastric antral motor activity (gastric antral motor index increased by 200% within 10 minutes post injection) • Ranitidine at 3 mg/kg significantly enhanced gastric antral and colonic motor activity (gastric antral and colonic motor index both increased by 250% within 10 minutes post injection) • Ranitidine at 10 mg/kg IV significantly enhanced gastric antral and colonic motor activity (gastric antral motor index increased by 400% and colonic motor index increased by 1000% within 10 minutes post injection) • Ranitidine at doses higher than 3 mg/kg IV decreased blood pressure, frequency and amplitude of respiration

	Conscious dogs (average results): • Ranitidine at 1 mg/kg IV significantly enhanced the gastric antral motor activity (gastric antral motor index increased by 120% at 30 minutes post injection) • Ranitidine at 3 mg/kg IV significantly enhanced gastric antral (motor activity increased by 200% at 30 minutes post injection) and colonic motor activity (increased by 280% at 10 min post-injection). However at this dose, ranitidine also induced severe side effects like temporal suppression of gastric antral motor activity (66%), collapse (66%) and akinesia (33%) • Ranitidine PO at 10 mg/kg and 30 mg/kg significantly enhanced the gastric antral (motor index increased by 150% and 250% respectively at 1 hour post administration) and ileal motor activities (motor index increased by 150% and 200% respectively at 1 hour post administration) without inducing behavioural side effects
Limitations:	• Statistics were not discussed at all within the paper (i.e. number of animals excluded) • Material and methods lack details especially in terms of route of administration, dosages and respective timings • High doses of ranitidine administered • Only healthy dogs enrolled

Mizumoto et al. (1990)	
Population:	*In vivo* part of the study conducted on healthy mixed breed adult dogs
Sample size:	• Four conscious dogs • Five anaesthetised dogs
Intervention details:	*In vivo*: • Extraluminal force transducers implanted in the serosal surface from the gastric body to the duodenum • Measurements of gastric motility index in conscious dogs receiving two 5 minutes infusions of acetylcholine (ACh) at 0.05 mg/kg/min intercalated with 0.3, 1.0 and 3.0 mg/kg/h IV infusions of ranitidine • Measurements of gastric motility index in conscious dogs receiving slow IV boluses of ranitidine at 0.3, 1.0 and 3.0 mg/kg • Measurement of blood pressure in anaesthetised dogs receiving IV boluses of 0.3, 1.0 and 3.0 mg/kg ranitidine IV • All measurements were repeated during saline infusion as a control *In vitro*: • Measurement of ACh esterase activity at increasing concentration of ranitidine
Study design:	Single centred experimental *in vivo* and *in vitro* non-blinded non-randomised crossover study

Outcome studied:	*In vivo:* • Effect of ranitidine infusions (0.3, 1.0 and 3.0 mg/kg/h) on ACh-induced contractions in conscious dogs • Effect of ranitidine boluses (0.3, 1.0 and 3.0 mg/kg) on gastric motor activity in conscious dogs • Effect of ranitidine boluses (0.3, 1.0 and 3.0 mg/kg) on blood pressure in anaesthetised dogs *In vitro:* • Median concentration of ranitidine to achieve acetylcholinesterase inhibition
Main findings: (relevant to PICO question):	*In vivo:* • IV infusion of ranitidine at a dose of 1.0 and 3.0 mg/kg/h markedly enhanced ACh-induced contractions (motor index ratio of 2.04 ± 0.46 and 2.89 ± 0.57 respectively vs 0.77 ± 0.06 of saline control) in conscious dogs • A bolus of 3mg/kg of ranitidine IV significantly increased gastric motor activity (motor index ratio of 1.87 ± 0.27 vs 1.02 ± 0.04 of saline control) in conscious dogs • A bolus of 3 mg/kg of ranitidine IV significantly decreased blood pressure (decrease of 106 ± 10/74 ± 11 vs 19 ± 10/27 ± 5 of saline control) in anesthetised dogs *In vitro*: • Inhibition of acetylcholinesterase activity was noted at a median ranitidine molar concentration of 3.5 x 10^{-6}M
Limitations:	• Only healthy dogs enrolled • Small sample size (potential type II error) • Materials and method section is lacking details especially regarding the saline control for the *in vivo* part

Bertaccini et al. (1985)	
Population:	*In vivo* part of the study conducted on healthy mixed breed adult dogs
Sample size:	30 anaesthetised dogs
Intervention details:	*In vivo* (n=30 dogs): • Gut motility was measured by means of a surgically inserted small rubber balloon filled with water and connected with an external manometer • IV boluses of ranitidine at 0.25, 0.5, 1.0 and 2.0 mg/kg followed by injections of stimulatory substances: ceruletide, acetylcholine, angiotensin and physalaemin *In vitro*: • Small strips of ileum were surgically removed and suspended in an organ bath • Changes in isometric tension were measured by a transducer connected with a microdynamometer • Stimulatory compounds and ranitidine were sequentially added to the bath

Study design:	Single centred experimental *in vivo* and *in vitro* non-blinded non-randomised crossover study
Outcome studied:	*In vivo:* • Observe ileal motility after ranitidine injections at 0.25, 0.5. 1.0 and 2.0 mg/kg • Observe the effect of ranitidine on ceruletide-, acetylcholine-, angiotensin- and physelaemin- induced motility *In vitro:* • Observe the effects on ileal tissue preserved in an organ bath with increasing concentration of 1) ranitidine; 2) ranitidine + ceruletide; 3) acetylcholine; 4) angiotensin; and 5) physelaemin
Main findings: (relevant to PICO question):	*In vivo* (average results): • Ranitidine boluses at all doses (0.5–2.0 mg/kg) had a slight and erratic stimulatory effect on basal motility, causing an increase of both tone and amplitude of phasic contractions • Ranitidine (doses not specified) consistently potentiated contractions induced by acetylcholine and angiotensin • Ranitidine boluses at 2.0 mg/kg also caused a constant potentiation of contraction (more than 200%) induced by ceruletide (5 ng/kg). This effect was prevented by administration of small doses of atropine (5–10 µg/kg) *In vitro* (average results): • Ranitidine by itself starting at 10^{-4}M was able to increase basal ileal tissue motility as well as potentiating acetylcholine induced contractions
Limitations:	• No details regarding statistical analysis within the paper • Only healthy dogs enrolled • Materials and method section is lacking details especially regarding the saline control for the *in vivo* part and the number of tissue strips for the *in vitro* part

Fioramonti et al. (1984)	
Population:	Female mongrel dogs (12–16 kg) chronically fitted with intraparietal electrodes in the gastric antrum, duodenum and jejunum
Sample size:	Four dogs

Intervention details:	• Record of physiological GI motility via chronically fitted intraparietal electrodes in the antrum, duodenum and jejunum
	• IV injections of:
	  ○ Ranitidine 1 mg/kg and 3 mg/kg
	  ○ Oxmetidine 1 mg/kg and 3 mg/kg

Study design:	Single centred experimental non-blinded non-randomised crossover study
Outcome studied:	• Comparison between the effects on GI motility of oxmetidine and ranitidine in dogs

	• Record of GI motility post ranitidine and oxmetidine injections via the above mentioned intraparietal electrodes
Main findings: (relevant to PICO question):	In all four dogs ranitidine at both doses induced a stimulatory effect on GI motility, while oxmetidine did not
Limitations:	• Small sized sample • Administered doses and respective timings are not clearly stated • Only healthy dogs enrolled

Appraisal, application and reflection

This summary stems from the need to look for further guidance in the treatment of a frequently encountered disorder in clinical practice. Dysmotility of the gastrointestinal (GI) tract, characterised by the inhibition of forward movement of ingesta, is a common cause of upper GI signs in dogs (Hall, 2008).

The physiological regulation of coordinated GI movements requires a complex interaction between multiple neurohumoral factors and the enteric nervous system (Whitehead et al., 2016). Any disruption to this finely tuned mechanism can result in oesophageal motility disturbances, delayed gastric emptying and functional ileus (Whitehead et al., 2016). A number of pathologies have been associated with GI hypomotility: infectious diseases (i.e. parvovirosis and ascarid infestation), inflammation of the GI tract (i.e. gastritis, enteritis, ulcers, and post-surgical gastroparesis), neoplasia with severe infiltrative processes (i.e. alimentary lymphoma), metabolic disturbances (i.e. hypokalaemia, hypoadrenocorticism, diabetes mellitus, uraemia), drug administration (i.e. opioids, adrenergic agonists and cholinergic antagonists) and acute stress with significant sympathetic stimulation (Hall, 2008).

Motor neurones located within the GI wall are usually excited by substances like acetylcholine, serotonin and substance P, while other signalling compounds like somatostatin, nitric oxide, catecholamines and gamma-ammino butyric acid tend to inhibit neuromuscular transmission (Whitehead et al., 2016).

The cornerstone of GI hypomotility treatment consists in the administration of agents promoting an excitatory response within the GI nervous system, these drugs are usually referred to as ‘prokinetics’.

The veterinary literature offers few reviews suggesting the use of a number of prokinetic drugs based on their mechanism of action (Hall & Washabau, 1999; and Whitehead et al., 2016).

Ranitidine is frequently mentioned in these reviews and it is often considered in practice for the treatment of dogs with GI hypomotility due to its acetylcholinesterase inhibitor effect (Hall & Washabau, 1999).

A thorough search has been performed using both CAB Abstract and Pubmed databases and applying multiple search word combinations.

The current available literature concerning ranitidine in dogs with upper GI disturbances is mainly focused on its H2-antagonist properties and gastroprotectant activity (Marks et al., 2018).

The few studies centred on its role as an acetylcholinesterase inhibitor and prokinetic have mainly been carried out in experimental settings and on healthy canine patients (Fioramonti et al., 1984; Bertaccini et al., 1985; Mizumoto et al., 1990; Kishibayashi et al., 1994; and Lidbury et al., 2012). Two studies included *in vitro* experiments (Bertaccini et al., 1995; and Mizumoto et al., 1990) and they both proved ranitidine to have consistent anticholinesterase properties. The same papers also showed a pro-kinetic effect *in vivo* at clinically relevant doses.

Two *in vivo* only studies found ranitidine administered both orally and intravenously to have stimulatory effect on GI motility (Fioramonti et al., 1984; and Kishibayashi et al., 1994) however the doses administered in these papers were generally higher than the one currently indicated in clinical practice. Two more recent studies (Favarato et al., 2012; and Lidbury et al., 2012) investigating ranitidine administered at 2 mg/kg either orally or intravenously to healthy dogs who failed to show GI motility enhancement.

Overall, interpretation of the available evidence to draw clinical practice recommendations is significantly hindered by the fact that only healthy patients have so far been included. Furthermore, the populations considered are difficult to compare as some studies evaluated conscious patients and others anaesthetised patients as well as starved animals vs non-starved animals. These are all variables that in humans have been proven to modify GI motility (Luckey et al., 2003) as well as the GI tract response to prokinetic administration (Smout et al., 1985). On top of this there is also a significant variability, amongst the available literature, in the techniques employed to estimate GI motility, as well as discordant dosing regimes and route of administration.

In light of all the above, it is fair to conclude that ranitidine has shown effective prokinetic activity *in vitro* and *in vivo* when healthy experimental dogs have been evaluated, although often at dosages higher than the ones commonly recommended in clinical practice. Its efficacy in clinical scenarios with dogs presenting for hypomotility disorders, has yet to be evaluated. Further studies will be needed to try and support its rational use in canine patients with GI hypomotility.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts on the OVID interface – 1973 to 2020 Week 18 PubMed on NCBI interface – 1920 to May 2020
Search terms:	CAB Abstracts: 1. (dog or dogs or canine or canines or canis).mp. or exp dogs/ or exp canis/ 2. (vomit* or emesis or anorexi* or inappetence or hyporexia or gastri* or gastroent* or gastrointestinal disorders or enteropat*).mp. or exp vomiting/ or exp anorexia/ or exp gastroenteritis/ or exp gastritis/ 3. (ranitidine or H2-antagonist* or H2 antagonist* or H2 blocker or histaminergic antagonist* or acetylcholinesterase inhibitor or parasympathetic agent*).mp. 4. 1 and 2 and 3 PubMed: 1. (dog or dogs or canine or canines) 2. (vomit or emesis or anorexia or inappetence or hyporexia or gastritis or gastroenteritis or gastrointestinal disorders or enteropathy) 3. (ranitidine or H2-antagonist or H2 antagonist or H2 blocker or histaminergic antagonist or acetylcholinesterase inhibitor or parasympathetic agent) 4. 1 and 2 and 3
Dates searches performed:	14 May 2020

Exclusion / Inclusion Criteria	
Exclusion:	Book chapters, clinical review articles, single case reports, articles not relevant to PICO, articles not available in English
Inclusion:	Articles available in English which were relevant to PICO

Search Outcome

Database	Number of results	Excluded – book chapters	Excluded – review articles	Excluded – single case reports	Excluded – not relevant to PICO	Excluded – full article not available	Excluded – not available in English	Total relevant papers
CAB Abstracts	57	3	2	1	48	1	1	1
PubMed	202	0	1	0	199	0	0	2
Additional papers*								3
Total relevant papers when duplicates removed								**6**

*Referenced by relevant papers or suggested by reviewers

CONFLICT OF INTEREST

The author declares no conflicts of interest.

Acknowledgement: Clare Boulton, Head of Library and Knowledge Services

REFERENCES

1. Bertaccini, G., Coruzzi, G. & Poli, E. (1985). 'Histamine H2 receptor antagonists may modify intestinal motility independently of their primary action on the H2 receptors'. *Pharmacological Research Communications*. 17(3), 241–254. DOI: https://doi.org/10.1016/0031-6989(85)90099-2
2. Favarato, E.S., Souza, M.V., Costa, P.R.S., Favarato, L.S.C., Nehme, R.C., Monteiro, B.S. & Bonfá, L.P. (2012). 'Evaluation of metoclopramide and ranitidine on the prevention of gastroesophageal reflux episodes in anesthetized dogs'. *Research in Veterinary Science*. 93(1), 466–467. DOI: https://doi.org/10.1016/j.rvsc.2011.07.027
3. Fioramonti, J., Soldani, G., Honde, C. & Bueno, L. (1984). 'Effects of ranitidine and oxmetidine on gastrointestinal motility in conscious dog'. *Agents and Actions*. 15(3–4):260–263. DOI: https://doi.org/10.1007/BF01972359

4. Hall, J.A. (2008). 'Gastric motility disorders & prokinetic therapies in small animals'. Proceedings ACVIM Forum, San Antonio, Texas, USA, 4–7 June, 2008. Veterinary Proceedings. 670–672.
5. Hall, J.A. & Washabau, R.J. (1999). 'Diagnosis and treatment of gastric motility disorders.' *Veterinary Clinics of North America: Small Animal Practice*. 29(2), 377–395. DOI: https://doi.org/10.1016/S0195-5616(99)50027-2
6. Kishibayashi, N., Tomaru, A., Ichikawa, S., Kitazawa, T. & Shuto, K. (1994). 'Enhancement by KW-5092, a novel gastroprokinetic agent, of the gastrointestinal motor activity in dogs.' *Japanese Journal of Pharmacology*. 65(2), 131–142. DOI: https://doi.org/10.1016/S0021-5198(19)35772-5
7. Lidbury, J.A., Suchodolski, J.S., Ivanek, R. & Steiner, J.M. (2012). 'Assessment of the variation associated with repeated measurement of gastrointestinal transit times and assessment of the effect of oral ranitidine on gastrointestinal transit times using a wireless motility capsule system in dogs'. *Veterinary Medicine International*. 2012:Article ID 938417. DOI: https://doi.org/10.1155/2012/938417
8. Luckey, A., Livingston, E. & Taché, Y. (2003). 'Mechanisms and Treatment of Postoperative Ileus'. Arch Surg. 138(2):206–14. DOI: https://doi.org/10.1001/archsurg.138.2.206
9. Marks, S.L., Kook, P.H., Papich, M.G., Tolbert, M.K. & Willard, M.D. (2018). 'ACVIM consensus statement: Support for rational administration of gastrointestinal protectants to dogs and cats.' *Journal of Veterinary Internal Medicine*. 32(6), 1823–1840. DOI: https://doi.org/10.1111/jvim.15337
10. Mizumoto, A., Fujimura, M., Iwanaga, Y., Miyashita, N., Yoshida, N., Kondo, Y. & Itoh, Z. (1990). 'Anticholinesterase activity of histamine H2-receptor antagonists in the dog; their possible role in gastric motor activity'. *Neurogastroenterology and Motility*. 2(4), 273–280. DOI: https://doi.org/10.1111/j.1365-2982.1990.tb00035.x
11. Smout, A.J., Bogaard, J.W., Grade, A.C., ten Thije, O.J., Akkermans, L.M. & Wittebol, P. (1985). 'Effects of cisapride, a new gastrointestinal prokinetic substance, on interdigestive and postprandial motor activity of the distal oesophagus in man'. *Gut*. 26(3), 246–51. DOI: https://doi.org/10.1136/gut.26.3.246
12. Whitehead, K., Cortes, Y. & Eirmann, L. (2016). 'Gastrointestinal dysmotility disorders in critically ill dogs and cats'. *Journal of Veterinary Emergency and Critical Care*. 26(2), 234–253. DOI: https://doi.org/10.1111/vec.12449