Which is More Effective in Altering the Intra-Gastric pH in Dogs, Omeprazole or Ranitidine?

A Knowledge Summary by

Adam Swallow BVSc MRCVS [1*]

[1] University of Bristol, Senate House, Tyndall Ave, Bristol, BS8 1TH
[*] Corresponding Author (adam.swallow@bristol.ac.uk)

ISSN: **2396-9776**
Published: **05 May 2016**
in: **Vol 1, Issue 2**
DOI: http://dx.doi.org/10.18849/ve.v1i2.14
Reviewed by: **Nieky van Veggel (MSc)**

Next Review Date: **05 May 2018**

OPEN ACCESS PEER REVIEWED

Clinical bottom line

Based on the current available evidence, omeprazole is the superior choice for raising intra-gastric pH.

Question

In canine patients requiring suppression of gastric acid production, is ranitidine as effective as omeprazole in raising the intra-gastric pH?

Clinical scenario

You are presented with a 7 year old male neutered Labrador who has acute onset vomiting. The dog has previously been diagnosed with severe hip dysplasia with secondary osteoarthritis and is on long term oral meloxicam therapy. However, two weeks ago he began vomiting intermittently which has now progressed to haematemesis. You have provisionally diagnosed gastric ulceration whilst histopathology on your mucosal biopsies is pending. You wish to start the dog on a gastro-protectant. Your practice has both ranitidine and omeprazole available but you are wondering which one would be best to use.

The evidence

The available evidence studied was generally well planned and consists of well-controlled studies. It is disappointing that no trials in a clinical setting were available, although it is appreciated that the phrasing of the PICO could have affected this outcome. A repeat literature search looking for evidence of efficacy in terms of managing gastric lesions would be beneficial in this regard. Whilst there is more evidence available evaluating the efficacy of omeprazole compared to ranitidine, in the majority of studies omeprazole emerged as the superior choice compared to ranitidine; the effect was more reliable and persisted for longer. Whilst specific criteria for treating acid-related diseases are not published for the dog, unlike in human medicine, it would seem that omeprazole is the most likely candidate to achieve these requirements.

Summary of the evidence

Bersenas et al (2005)	
Population:	Healthy intact Beagles, bred for the purpose of the study.
Sample size:	12
Intervention details:	Intra-gastric pH was measured continuously in 24hr periods, in both a fed and fasted state. They were then treated for 7 days with a gastric-acid suppressant (1 of 4 for a week, ultimately received all of the treatments) or saline control and gastric pH recorded on days 0, 2, 6. Then the effect of omeprazole and famotidine combined was assessed.
Study design:	Randomised controlled trial
Outcome studied:	Aimed to determine the normal gastric secretion pattern of dogs and

	the degree of gastric acid suppression that could be achieved with 4 different agents.
Main findings: (relevant to PICO question):	• Feeding resulted in a decreased gastric pH. • Omeprazole (1mg/kg) was given once a day orally, and ranitidine every 12 hours intravenously (2mg/kg). • Omeprazole did significantly suppress gastric acid secretion compared to saline, whereas ranitidine did not (mean gastric pH on day 2 2.53 for ranitidine, vs 3.86 for omeprazole and day 6 2.05 versus 4.09). • Omeprazole managed to maintain a gastric pH of >3 for 70.2% of the time on day 6, (66.9% on day 2) versus 37.2% of the time for ranitidine (44.6% for day2). • Drug carry-over effects were noted; these were reportedly adjusted for in the statistical analysis. • Omeprazole sodium bicarbonate suspension did cause vomiting and diarrhoea in 4/6 dogs (done separately to omeprazole tablet dosing). • Twice daily omeprazole was the only product that met criteria for permitting acid-relating injuries to heal as assessed using human criteria (pH >3-4 for >75% of the day).
Limitations:	• Injectable drugs were blinded whereas omeprazole was not. • Omeprazole given orally, other agents were given IV. • Large age range in dogs existed. • Dose of omeprazole varied between dogs from 0.8-1.3mg/Kg. Other medicines were dosed accurately per Kg bodyweight. • No referenced compatibility studies used to adding saline to injectable solutions to make them 3ml in volume. • Only Beagles used in the study; unknown if breed variations exist? • Discussed but did not test the theory of using ranitidine at a dosing frequency of q8hrs; in humans it has been shown to have a linear relationship between dosing and gastric acid suppression. • Multiple confounding factors limit the usability of the obtained data.

Katz et al (1987)	
Population:	Female Mongrel dogs with either a chronic gastric fistula or a Heidenhain pouch of the greater curvature of the stomach.
Sample size:	N= 5- 7
Intervention details:	• Dogs had a single piece, plastic cannula inserted into a chronic gastric fistula along the greater curvature of the stomach. • The fistula or the Heidenhain pouch was created at least 4 weeks prior to any of the experiments. • Dogs were fasted overnight prior to any experiments but allowed free access to water. Water was withheld on the

	day of the experiment. • For the gastric fistula dogs: On the day of the experiment, the gastric content was drained and then basal secretions were collected for around 30 minutes. • Oral medications were given via the gastric cannula at a volume of 0.2ml/kg. Intra-venous medications (compound dissolved in 0.1N hydrochloric acid) were given via a foreleg vein. • After "oral" dosing, 30 minutes was allowed before gastric stimulation. However, following intra-venous injection gastric stimulation occurred straight away. • Gastric stimulation involved either: betazole hydrochloride (8mg/kg), tetragastrin (0.5mg/kg) or 2-Deoxy-glucose (100mg/kg) were provided sub-cutaneously. These doses were designed to cause maximal gastric secretory activity. • Gastric secretions were collected via passive drainage every 30 minutes for 3 hours. Volume of secretion, acid concentration and total acid output were calculated. • Prior to the experiment, control values for total acid output was determined for each dog. • Dogs were used no more than once a week for experiments. • For the Heidenhain pouch dogs: Dogs were again fasted overnight before being placed in a sling on a Pavlov stand and an intra-venous catheter was placed in the cephalic vein. • Maximal gastric secretion was stimulated with bethanecol (120ug/kg/hr) or histamine (50ug/kg/hr) in a volume of 30ml/hr. • ORF 17583 or its vehicle (0.5% carboxymethylcellulose for all compounds) was provided orally via gavage 30 minutes before the bethanecol or 75 minutes after the histamine infusion started. • Gastric content was collected via passive drainage every 15 or 30 minutes and secretion volume, acid concentration and total acid output was calculated. • Dogs with Heidenhain pouch were also stimulated by means of a meal following an 18 hour fast, but only ORF 17583 was assessed here. • A total acid output of 450µEq was used to denote a 50% of maximal response in this study, based on previously published work. • Students t-test was used to compare the results with significance set at $P < 0.05$. • Dose-response curves were created following gastric stimulation.
Study design:	Non-randomised controlled trial.
Outcome studied:	• To examine the gastric anti-secretory effect of ORF 17583 in dogs and rats. In dogs, this effect was characterized against histaminergic and non-histaminergic stimulation. • To compare the potency of ORF 17583 to ranitidine,

	cimetidine, famotidine and omeprazole. • To investigate the duration of the anti-secretory effect of ORF 17583 in comparison to ranitidine.
Main findings: (relevant to PICO question):	• ORF 17583 yielded marked gastric acid suppression against all secretagogues, nearing 100%. • Each of the other compounds markedly suppressed acid production in a dose-related manner. Each compound was able to achieve marked acid suppression. • The overall potency was famotidine= ORF 17583= omeprazole > ranitidine > cimetidine. • Ranitidine was found to have a relatively good oral bioavailability of 2.4 (or 42%); determined by comparing the oral to the intra-venous potency ratio. A value of 1 indicated excellent bio-availability. • After a supra-maximal dose of ranitidine (4mg/kg orally), marked acid suppression (>80% of supramaximal secretion) was noted 4 hours later. However, no effect was seen at 24 or 48 hours. • Ranitidine showed evidence of around 25% suppression of gastric acid output after 16 hours following betazole stimulation, down from >80% at 0.5 hours.
Limitations:	• This paper primarily looked at the effect of ORF 17583 and not necessarily the effect of ranitidine compared to omeprazole. Not all details of the results are presented here as they were not relevant to the PICO. • Not all results were presented in written form, only in graphical form so understanding the exact effects is difficult. • The exact number of dogs used in each experiment was not stated, merely a range of 5- 7dogs. This is still a small number though. • It would have been useful had the authors looked at the effect of a meal on all of the different compounds, not just ORF 17583 as this method of stimulation is physiological and therefore more applicable to practice. • Again, this is not a clinical study and so the clinical relevance of these results is unclear. • P-values are not presented in this paper for the dog results and so it is not known if the difference between the gastro-protectants used was significant or not. • It is interesting that omeprazole was dissolved in a low concentration of acid as omeprazole is known to be unstable at low pH. However a marked effect on acid output would imply that this did not affect the omeprazole in this study.

Kromer et al (2000)	
Population:	Male Beagle dogs aged 2-8yrs
Sample size:	Unknown.
Intervention details:	Gastric pH was monitored after being stimulated using either

	histamine or carbachol. The dogs received either pumaprazole IV, ranitidine IV or omeprazole per os (PO).
Study design:	Controlled trial
Outcome studied:	Whether or not the medications had any effect on the intra-gastric pH.
Main findings: (relevant to PICO question):	• Study found that whilst pumaprazole was the most effective, ranitidine resulted in mild elevations in gastric pH although there was marked variation in the effect seen. • Omeprazole was not really discussed, more it mentioned that the effects seen would likely be additive over a periods of 2-3days.
Limitations:	• Numbers used were unknown. • No blinding or randomisation was performed. • No advanced statistical analysis was performed. • Only graphical results were shown, it was difficult to observe what the mean pH values were. • Discussion was not easy to follow. • Method of delivery of the drugs was not consistent.

Okabe et al (2001)	
Population:	Male and female Beagles with denervated gastric pouches (Heidenhain pouch)
Sample size:	N=10.
Intervention details:	Intra-gastric pH was measured in response to stimulation of acid production using either histamine, pentagastrin or carbachol. Then various preparations of ant-acids were given and the intra-gastric pH was measured by serial cannula samples.
Study design:	Controlled laboratory trial.
Outcome studied:	Whether or not the intra-gastric pH could be affected, and therefore basal gastric acid secretion, by various pharmaceutical interventions.
Main findings: (relevant to PICO question):	• Omeprazole was effective in reducing gastric acid secretion when applied locally to the Heidenhain pouch, and also when given intra-venously. • This effect seemed slightly improved with application prior to histamine infusion. • Ranitidine appeared to have no effect on histamine-stimulated gastric acid secretion when applied into the Heidenhain pouches. • Higher doses appeared to be needed to be effective when using locally applied omeprazole vs. systemic therapy using omeprazole, The role of a topical effect of omeprazole on the apical cell border was proposed.
Limitations:	• Small numbers used, no study calculations performed. • Measurements made were not continuous, but intermittent

	sampling performed. • Did not take into account the time potentially needed for the agents to be effective. The time for which the effect persisted for however was measured. • High doses of omeprazole were infused into the gastric pouch, beyond normal clinical doses. • Did not describe an effect of ranitidine given systemically. • The published reports does not go into detail about the effect of ranitidine on intra-gastric pH when given systemically, it merely notes that it was effective in elevating the gastric pH.

Polentarutti et al (2010)	
Population:	Male Labrador/ Labrador crosses 25-35Kg in weight.
Sample size:	N=4.
Intervention details:	Intra-gastric pH was monitored and chyme collected to monitor gastric emptying after either oral buffers or intra-venous pharmaceutical agents.
Study design:	Prospective experimental trial
Outcome studied:	Whether or not the agents of interest where able to consistently alter the gastric pH in fasted dogs.
Main findings: (relevant to PICO question):	• Ranitidine was successful in raising the gastric pH to target level (>4) in all 8 experiments performed. Average time to onset was 46 minutes (although each dog was quite variable) and lasted, on average, 86minutes. • In the ranitidine experiments, the pH was >4 in 4/8 experiments at the start. • For omeprazole, the target pH was <4 in 3/7 experiments. In 2/3 experiments a target of >4 was achieved, whilst in 1 the pH fell. The average duration of pH modification was 103mins, with an average time to onset of 50mins. • Starting pH did not affect efficacy. • Authors concluded that omeprazole was more reliable and produced a better effect over ranitidine.
Limitations:	• Very few dogs used in the study, authors did acknowledge this. • No control agents were used, • No advanced statistics were used to analyse the data. • pH was not measured before administration of intra-venous agents, measurements began just after it was given. • A set dose or ranitidine was used, whereas omeprazole was dosed according to body weight (50mg versus 1mg/Kg).

Stachura et al (1983)	
Population:	Mongrel dogs weighing 14- 18Kg with a gastric fistula and a denervated fundic pouch (Heidenhain pouch).

Sample size:	N= 4
Intervention details:	• The gastric fistula was placed 6 months prior to the experiments. • Animals were fasted but had ad libitum water for at least 18 hours prior to each experiment (four experiment in total per dog). • Gastric fluid and mucosal samples were all collected via the gastric fistula. • Gastric acid stimulation was achieved using histamine, infused at 40ug/kg/hr to achieve 50% of maximal stimulation. • Omeprazole was given intra-venously at 1mg/kg either 30 minutes before or 60 minutes after starting the histamine stimulation. The omeprazole was dissolved in 5ml of 10mmol sodium bicarbonate, and then in saline. • Ranitidine was dissolved in 50ml of saline and provided intra-venously at 0.5mg/kg either 30 minutes before or 60 minutes after the start of the histamine infusion. • Multiple mucosal samples were obtained using biopsy forceps via the gastric fistula 30 and 60 minutes after the administration of either omeprazole or ranitidine. These were obtained from the fundic gland area. • During histamine infusion, mucosal samples were collected 60minutes after the start of the infusion of histamine alone or histamine combined with either omeprazole or ranitidine. • Samples were then washed of all mucous in saline before being fixed for histological and ultra-structural examination with electron microscopy. • For the ultra-structural assessment, a semi-quantitative assessment using the previously published scale by Fallenius et al (1981, 1982). Data was represented as mean ±SD of 15-25 measurements. This scale was: 0= resting, 1= half-stimulated, 2= fully stimulated cells. • Gastric secretions were collected continuously via the gastric fistula and Heidenhain pouch. These were vided into aliquots every 15 minutes. • Gastric secretory volume and acid output were calculated and presented as 30 minute outputs as a mean± SEM. • A t-test was used to compare the mean responses to histamine alone and to pre-treatment or to combination of histamine with omeprazole/ ranitidine. Significance was regarded as $P < 0.05$.
Study design:	Non-randomised, controlled trial.
Outcome studied:	To compare the anti-secretory effects on the stomach of omeprazole and ranitidine. Also, to compare the effect on the morphological appearance of the parietal cells of the stomach following histamine stimulation before and during treatment with either omeprazole or ranitidine.

Main findings: (relevant to PICO question):	• Basal acid output from the gastric fistula and Heidenhain pouch were negligible and were not presented. • Both omeprazole and histamine almost completely prevented gastric acid secretion in response to histamine stimulation. • In control experiments, acid output elevated to 11.3 ±1.8 mmol H+/ 30min after histamine infusion in the gastric fistula; in the Heidenhain pouch this was 2.7 ±1 mmol H+/ 30min. • With prior histamine stimulation, omeprazole reduced the acid output 62% and ranitidine by 82%. This was reduced by 80% in the Heidenhain pouch. • Histology of the oxyntic mucosa was unremarkable in all specimens. Parietal cells of the resting mucosa were rich in tubulovesicles and canaliculi poorly presented and collapsed. Microvilli on the apical surface were short and stubby. • Following histamine stimulation, the tubulovesicles decreased in number and the canaliculi expanded. Pre-treatment with ranitidine or omeprazole prevented this change. Microvilli in these canaliculi became longer and more slender. The use of ranitidine or omeprazole following stimulation promoted a return to the resting state. • Histamine stimulation following pre-treatment with ranitidine failed to result in change from the resting state. • However, changes in the form of reduced tubulovesicles and an increase in canaliculi was seen with omeprazole pre-treatment. Mostly however the canaliculi were condensed, with tightly packed microvilli and little free space. Normally, much more free space would be seen in active parietal cells. • The use of ranitidine or omeprazole resulted in an increase in bacterial entrapment in the canaliculi. Additionally, the parietal cells were more irregular in shape and contained condensed mitochondria (signaling a low energy state). • Morphological index on parietal cells was 0.2±0.4 as a control. Histamine stimulation alone gave a morphological assessment of 1.7±0.4. Both ranitidine and omeprazole yielded a morphological score of 0.2 ±0.4 or 0.5. respectively as a baseline. • Ranitidine restored the histamine-stimulated morphology to 0.4±0.6 and omeprazole to 0.3±0.5 after pre-treatment with histamine. • Histamine infusion following omeprazole pre-treatment yielded a morphology score of 1.8 ±0.4. Ranitidine pre-treatment yielded a morphology score of 0.
Limitations:	• This is not a physiological study and used only 1 type of secretagogue. Therefore the clinical applicability should be interpreted with caution. • Statistical analysis was not performed and so it is difficult to know whether or not the d ifference between omeprazole and ranitidine was significant.

	• Only a small number of dogs were used in this study and the breed used was not stated. • Baseline data was not presented, even though it is stated to be negligible the actual values would be useful. • Whether any of the dogs required sedation was not clarified; this might have affected the results. • The authors state they aimed for 50% of maximal secretion, but how this value was arrived at was not discussed.

Appraisal, application and reflection

The trials were all very specific in their objectives and the measurement of gastric pH often used similar methods. However, not many of the studies evaluated the response to stimulation with food material, so whilst the effects on acid secretion following chemical stimulation are clear, it has not completely proven that these effects are the same when stimulated with a food material.

For clarity, the full reference for the scale (Fallenius et al, 1981, 1982) referred to by Stachura et al (1983) is included in the reference list despite the actual paper not being reviewed for the Knowledge Summary should any readers wish to investigate this further.

Finally, in this summary only papers in which the effects of both ranitidine and omeprazole were compared were investigated. There are several other papers which investigated the efficacy of these compounds in various settings, either in isolation or in combination with alternative gastro-protectants. However, to investigate these further is deemed to be outside the scope of the current PICO although there is definitely the potential for either a systematic review or a meta-analysis which would likely enhance our current understanding of gastro-protectants in the dog.

Methodology Section

Search Strategy	
Databases searched and dates covered:	The search string was applied to the CAB abstracts and Pub Med databases searching from January 1973 to January 2016.
Search terms:	(Dog OR dogs OR canine OR bitch OR bitches OR puppy OR puppies) AND (omeprazole OR gastroguard OR losec OR zantac OR ranitidine) AND (pH OR acid).
Dates searches performed:	Monday 18th January 2016

Exclusion / Inclusion Criteria	
Exclusion:	Single-case reports, or articles in which the effect of both omeprazole and ranitidine in the intra-gastric pH (either directly or indirectly) in dogs was not evaluated, or articles where the full text could not be located, or were not available in English.
Inclusion:	Journal articles published between 1973 and the present, which specifically investigated and compared the effect of both omeprazole and ranitidine on the intra-gastric pH in dogs (either directly or indirectly). Both clinical and laboratory studies were considered.

Search Outcome					
Database	Total number of results	Excluded- not available in the English language	Excluded- single case report/ book chapter/ conference proceedings/ review articles etc.	Excluded- not relevant to the PICO	Total relevant papers
CAB Abstracts	33	0	3	30	0
Pub Med	266	0	8	252	6
Total relevant papers when duplicates removed					6

CONFLICT OF INTEREST

The author declares to conflict of interest.

REFERENCES

1. Bersenas, A.M.E. et al. (2005) Effects of ranitidine, famotidine, pantoprazole, and omeprazole on intragastric pH in dogs. *American Journal of Veterinary Research*, 66 (3), pp. 425-431 http://dx.doi.org/10.2460/ajvr.2005.66.425
2. Fallenius, E. et al. (1981) Substituted benzimidazoles inhibit gastric secretion by blocking H+/ K+-ATPase. *Nature* 29:159- 161 http://dx.doi.org/10.1038/290159a0
3. Fallenius, E. et al. (1982) Inhibition of acid secretion in isolated gastric glands by substituted benzimidazoles. *American Journal of Physiology* 243: G505- G510.
4. Katz, L.B.Tobia, A.J. and Shriver, D.A. (1987) Effects of ORF 17583, other histamine H2-receptor antagonists and omeprazole on gastric acid secretory states in rats and dogs. *Journal of Pharmacology and Experimental Therapeutics,* 242 (2), pp. 437-42.
5. Kromer, W. Postius, S. and Riedel, R. (2000) Animal Pharmacology of Reversible Antagonism of the Gastric Acid Pump, Compared to Standard Antisecretory Principles. *Pharmacology,* 60 (4), pp. 170-187 http://dx.doi.org/10.1159/000028367
6. Okabe, S. Shimosako, K. and Amagase, K. (2001) Pharmacological regulation of gastric acid secretion in the apical membrane of parietal cells; a new target for antisecretory drugs. *Journal of Physiology and Pharmacology,* 52 (4 Pt 1) pp. 639-56.
7. Polentarutti, B. et al. (2010) Modification of gastric pH in the fasted dog. *Journal of Pharmacy and Pharmacology*, 62 (4), 462-469 http://dx.doi.org/10.1211/jpp.62.04.0008
8. Stachura, J. et al. (1983) Comparison of the effect of omeprazole--a substituted benzimidazole--and ranitidine--a potent H2-receptor antagonist--on histamine-induced gastric acid secretion and the ultrastructure of canine parietal cells. *Hepatogastroenterology,* 30 (5), pp. 205-10.

Intellectual Property Rights

Authors of Knowledge Summaries submitted to RCVS Knowledge for publication will retain copyright in their work, but will be required to grant to RCVS Knowledge an exclusive license of the rights of copyright in the materials including but not limited to the right to publish, re-publish, transmit, sell, distribute and otherwise use the materials in all languages and all media throughout the world, and to license or permit others to do so.

Authors will be required to complete a license for publication form, and will in return retain certain rights as detailed on the form.

Veterinary Evidence and EBVM Network are RCVS Knowledge initiatives. For more information please contact us at editor@veterinaryevidence.org.

RCVS Knowledge is the independent charity associated with the Royal College of Veterinary Surgeons (RCVS). Our ambition is to become a global intermediary for evidence based veterinary knowledge by providing access to information that is of immediate value to practicing veterinary professionals and directly contributes to evidence based clinical decision-making.

www.veterinaryevidence.org

RCVS Knowledge is a registered Charity No. 230886.
Registered as a Company limited by guarantee in England and Wales No. 598443.

Registered Office:
Belgravia House
62-64 Horseferry Road
London SW1P 2AF