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Research Paper

Modification of gastric pH in the fasted dog

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Abstract

Objectives The aim was to compare the ability of pretreatments to consistently adjust gastric conditions to low or high pH in the fasted state in dogs.

Methods Four male Labrador/Labrador-cross dogs weighing 25–35 kg were surgically equipped with a ventricle fistula cannula in the stomach and a jejunal nipple valve stoma. Dogs were fasted overnight before the experiments, with free access to water. The pH in the dogs' stomach was modified either orally with buffers (0.1 mol/l HCl-KCl, 0.05 mol/l glycine-HCl, 0.1 mol/l citrate or 0.1 mol/l BIS-TRIS) or intravenously with pharmacological agents (pentagastrin 4–6 μg/kg, ranitidine 50 mg or omeprazole 1 mg/kg). Intragastric pH was recorded continuously for 2 h with an electrode connected to an ambulatory pH meter. Chyme was collected simultaneously from the jejunal stoma as an approximate measure of gastric emptying.

Key findings 0.1 mol/l HCl-KCl buffer p.o. and 1 mg/kg omeprazole i.v. attained low and high gastric pH more reproducibly (11/11 and 6/7 experiments met target values of pH < 3 and > 4, respectively) and for a longer duration (average time exceeding target value 90 and 103 min, respectively) than the other buffers and pharmacological pretreatments. The starting pH did not alter the modifiers' capacity to increase or decrease the pH. However, the lag time before chyme appeared at the jejunal stoma appeared to be longer when the pH was low and shorter when the pH was high.

Conclusions To achieve a consistently low gastric pH in fasting dogs, 0.1 mol/l HCl-KCl buffer should be administered orally, 15 min before the dosage form. To elevate the gastric pH reproducibly, omeprazole 1 mg/kg should be administered intravenously at least 90 min before oral administration of the dosage form.

Keywords dogs; gastric pH; omeprazole; pentagastrin; ranitidine

Introduction

The dog is the most extensively used animal model in drug bioavailability studies. Not only can dogs be easily assimilated into a research environment, they also have many similarities with humans in terms of gastrointestinal (GI) anatomy and physiology. Important similarities include the monogastric digestive tract, a migrating motor complex of approximately 2 h in the fasted state, and the ability to increase gastric acid output in response to meal intake.[1] Dogs with a body mass of 25–30 kg have upper GI dimensions that are similar to those in a 70 kg human.

However, the pH in the stomach of healthy fasted dogs is more variable (pH 1–8)[2] than in fasted healthy humans (pH 1.5–2.5).[3] This difference can be explained by the much lower basal secretion of gastric acid in dogs (0.1 mEq/h) than in man (2–5 mEq/h), resulting in a higher and broader range of pH values in dogs.[4] This underlying physiological difference between the two species may explain some of the discrepancies in oral bioavailability data observed between dogs and humans with substances/formulations that are pH dependent,[5–7] since the oral bioavailability of a drug that exhibits pH-dependent dissolution may be altered if the gastric pH changes.[5]

Modification of the gastric pH may be necessary to ensure that levels in dogs used in pharmacokinetic studies are representative of human pH values. The pH can be modified with an orally administered buffer or by pharmacological intervention. With the latter, the

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effect of the modifier on distribution, metabolism and excretion of the experimental drug also has to be considered.[5]

The aims of this study were: (i) to compare the ability of various pretreatments (buffer solutions and drugs) to modify gastric pH in fasted dogs in terms of the extent and duration of change; (ii) to evaluate the correlation between gastric emptying (GE) and pH; (iii) to determine the most suitable time at which to administer the test formulation after the pretreatment.

To monitor the intragastric pH continuously, we fitted dogs with a gastric cannula and measured the gastric pH using an electrode connected to an ambulatory pH meter, based on the work of Kromer *et al*.[8] Simultaneous recovery of chyme through a jejunal stoma was used as an approximate measure of GE.

Materials and Methods

Buffer solutions

The following buffers were used as pH-modifying agents: HCl-KCl, glycine-HCl, citrate and BIS-TRIS. HCl, KCl and glycine were purchased from Merck (Darmstadt, Germany). Citrate and BIS-TRIS were purchased from Sigma (Steinheim, Germany). Concentrations used in the study are listed in Table 1.

Drugs

The following drugs were used as pH-modifying agents: pentagastrin injection BP (Cambridge Laboratories Ltd, Wallsend, UK), Zantac injection (ranitidine, GlaxoSmith Kline, Solna, Sweden) and Losec injection (omeprazole, AstraZeneca AB, Sodertalje, Sweden).

Administration of pH-modifying agents

Buffers were administered orally (p.o.) via an orogastric tube. Pharmacological agents (omeprazole, ranitidine, pentagastrin) were administered intravenously (i.v.) into a foreleg vein. After i.v. administration, water was administered p.o. to match total fluid intake in all pretreatments.

Animals

Four male dogs (Labradors and Labrador crosses) age 2–7 years and weighing 25–35 kg were used. The dogs were surgically equipped with a chronic ventricle fistula (VF) cannula in the stomach and a chronic jejunal nipple valve stoma.[9] The VF cannula was made out of titanium and was inserted approximately 5 cm into the corpus of the stomach. The jejunal nipple valve stoma was made surgically at the mid-jejunum, approximately 75 cm below the pylorus.

After surgery, the animals were allowed to recover for at least 4 weeks before participating in the study.

The study was approved by the Animal Ethics Committee of Gothenburg (Ethics approval numbers 2172000 and 492004).

Study design

The dogs were fasted overnight before the study, with free access to water. Just before the start of the experiment, the VF cannula was opened and the stomach emptied. A plastic tube was inserted into the jejunal stoma and tied to the dog's back with a gauze bandage. The distance for insertion of the plastic tube was determined individually for each dog using an auriscope.

In the case of pH modification using buffers, 75 ml of the buffer solution was administered p.o. using an orogastric tube, followed by 10 ml water and 10 ml air to rinse the tube. Measurement of pH was started before buffer administration to obtain a baseline value and continued for 2 h after buffer administration (Figure 1).

Pharmacological agents were administered i.v. into a foreleg vein over a period of 2 min; 75 ml water was then

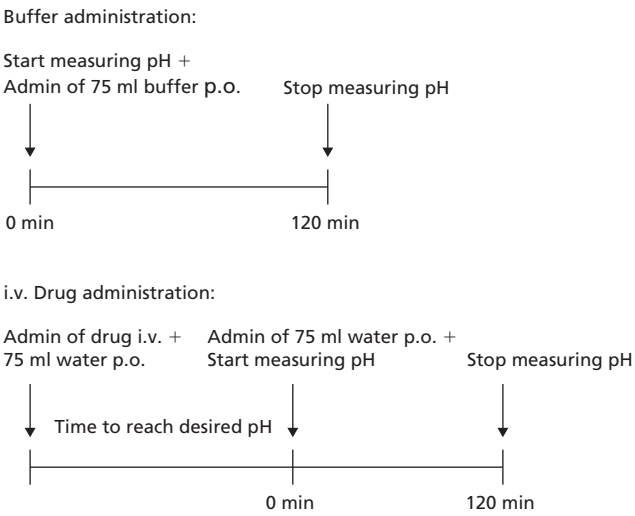

Figure 1 Summary of the administration and pH measuring procedure

Table 1 Doses and volumes of the different pH modifiers

Buffer solution/drug	Route	Concn/dose	Volume (ml)	Water (ml)	Anticipated pH
HCl-KCl buffer	Oral	0.1 mol/l[a]	75	–	1.2
Glycine-HCl buffer	Oral	0.05 mol/l[b]	75	–	2.2
Citrate buffer	Oral	0.1 mol/l	75	–	6.2
BIS-TRIS buffer	Oral	0.1 mol/l	75	–	6
Pentagastrin	i.v.	4–6 μg/kg	–	75	1
Ranitidine	i.v.	50 mg	–	75	6
Omeprazole	i.v.	1 mg/kg	–	75	6

[a]With respect to HCl; [b]with respect to glycine.

administered p.o. using an orogastric tube, to match the fluid intake to that in the buffer experiments and to facilitate chyme recovery. When the desired pH was reached, another 75 ml water was administered, the experiment started and the pH was measured for a further 2 h (Figure 1).

Chyme was collected from the jejunal stoma as an approximate measure of GE, recognising that the time to reach the mid-jejunum will tend to overestimate the true GE time. The chyme was collected into graduated glassware and the time of collection and volume of chyme noted. The chyme collection ended when a total volume of 75 ml had been recovered or after 2 h, whichever came first.

pH measurement

A pH electrode was inserted through the VF cannula with approximately 5 cm of the electrode reaching into the stomach. The electrode was held in place with a specially manufactured screw cap and rubber tubes to prevent leakage through the hole drilled in the stopper. The pH electrode was connected to a pH meter (Digitrapper pH, SynMed medicinteknik, Stockholm, Sweden) which continuously measured the gastric pH.

Presentation and statistical evaluation of results

Results are presented for each individual experiment as a pH–time profile. The arithmetic mean profile is also given for each treatment; it should be noted, however, that pH is not normally distributed and average values serve as only an approximate representation of the 'usual' response.

The following parameters are reported for each buffer and drug: % of experiments in which the target pH was achieved, the average (arithmetic mean) time to reach the target pH, and the duration of pH modification (expressed as % experiments in which the duration exceeded 30, 60, 80 or 120 min, as appropriate). The qualitative relationship between GE and pH at the time of emptying is also shown, although there are too few data to draw any statistical conclusions.

When evaluating the results, it is important to bear in mind that when buffers were given to modify gastric pH, the pH measurements started immediately before administration of buffer and continued for 120 min. By contrast, when drug pretreatments were administered, pH measurements were started *after* the desired pH level was reached (i.e. after the second water administration; see Figure 1). Therefore, the durations between buffers and drugs cannot be compared directly.

Results

Agents to reduce gastric pH

Figure 2 shows the pH profiles following the various pretreatments intended to maintain a gastric pH below 3.

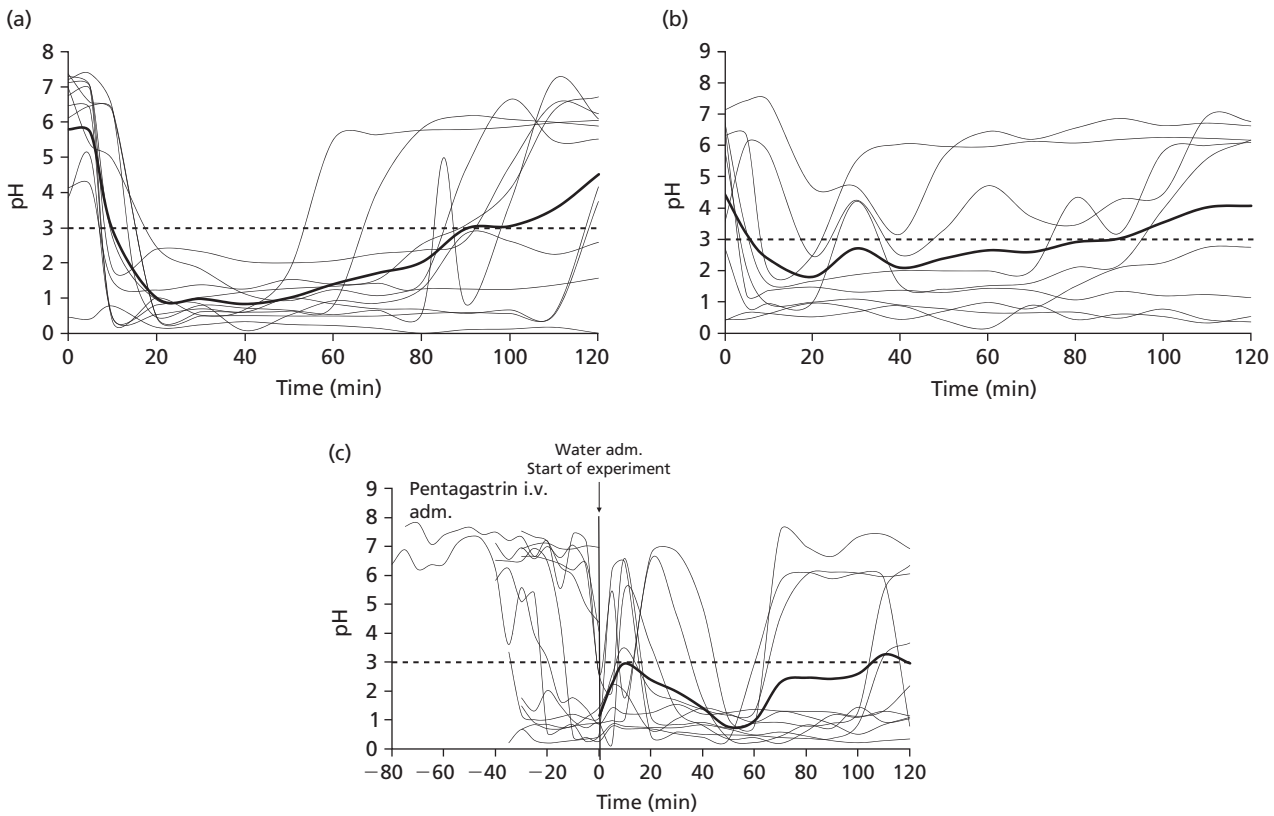

Figure 2 Individual pH–time profiles in four dogs: (a) 11 experiments after oral administration of 75 ml 0.1 mol/l HCl-KCl; (b) 9 experiments after oral administration of 75 ml 0.05 mol/l glycine-HCl; (c) 13 experiments after i.v. administration of pentagastrin (4, 4 + 2 or 6 μg/kg) followed by 75 ml water p.o. In three pentagastrin experiments the pH remained too high and these experiments were discontinued. Average profiles for each pretreatment are shown as a thick line. Adm., administration; i.v., intravenous

HCl-KCl buffer (Figure 2a)

The starting pH was initially above 3 in 10 of 11 experiments. Following the pretreatment, the gastric pH was successfully reduced to or maintained below pH 3. The average time to reach the target value was 10 min. In all cases, the target pH value was reached within 20 min of administering the HCl-KCl buffer. The pH remained under the target value of pH 3 for 100 min or more in 55% of the experiments, for more than 80 min in 73% and for more than 60 min in 82%. The average duration of pH modification was 90 min.

Glycine-HCl buffer (Figure 2b)

The starting pH was initially above 3 in six of the nine experiments. The glycine-HCl buffer lowered the pH to below pH 3 in four of these six experiments. The average time to reach the desired pH was 7 min (this average excludes experiments in which the target pH value was not achieved). The desired pH (pH < 3) was maintained for 100 min or more in 38% of experiments, for more than 80 min in 50% and for more than 60 min in 63%. However, the duration of pH modification was less than 30 min in 37% of the experiments. The average duration of pH modification was 70 min.

Intravenous pentagastrin (Figure 2c)

The effect of i.v. pentagastrin on gastric pH was variable, even when the stomach was flushed out with 75 ml water. In approximately half of the 13 experiments, the pH profiles were very unstable over time and in the other half of the experiments the profiles stabilised at a low pH. Results are shown in Figure 2c.

Doses of 4 μg/kg (n = 5) and 4 μg/kg followed by another 2 μg/kg (n = 2) proved unable to consistently achieve the target pH. Subsequently, six experiments were performed at 6 μg/kg pentagastrin given as a single bolus.

Out of 13 experiments, the starting pH was above 3 in nine. Pentagastrin decreased the pH to the desired level in only six of these nine experiments. In the experiments when the target pH was reached, the average time taken was 21 min and the desired pH was maintained for more than 60 min in only 40% of experiments. In the rest of the experiments the reduction in pH lasted less than 15 min. The average duration of pH modification was 46 min. The duration of pH within the target range showed no relationship to the dose of pentagastrin.

Elevation of gastric pH

Figure 3 shows the pH profiles after administration of pretreatments designed to elevate gastric pH.

Citrate buffer (Figure 3a)

The starting pH was already above 4, the target value, in five of the eight experiments. In the three experiments with lower starting pH, citrate buffer increased the pH to the desired level, although in one case the effect was transitory (< 5 min). In the

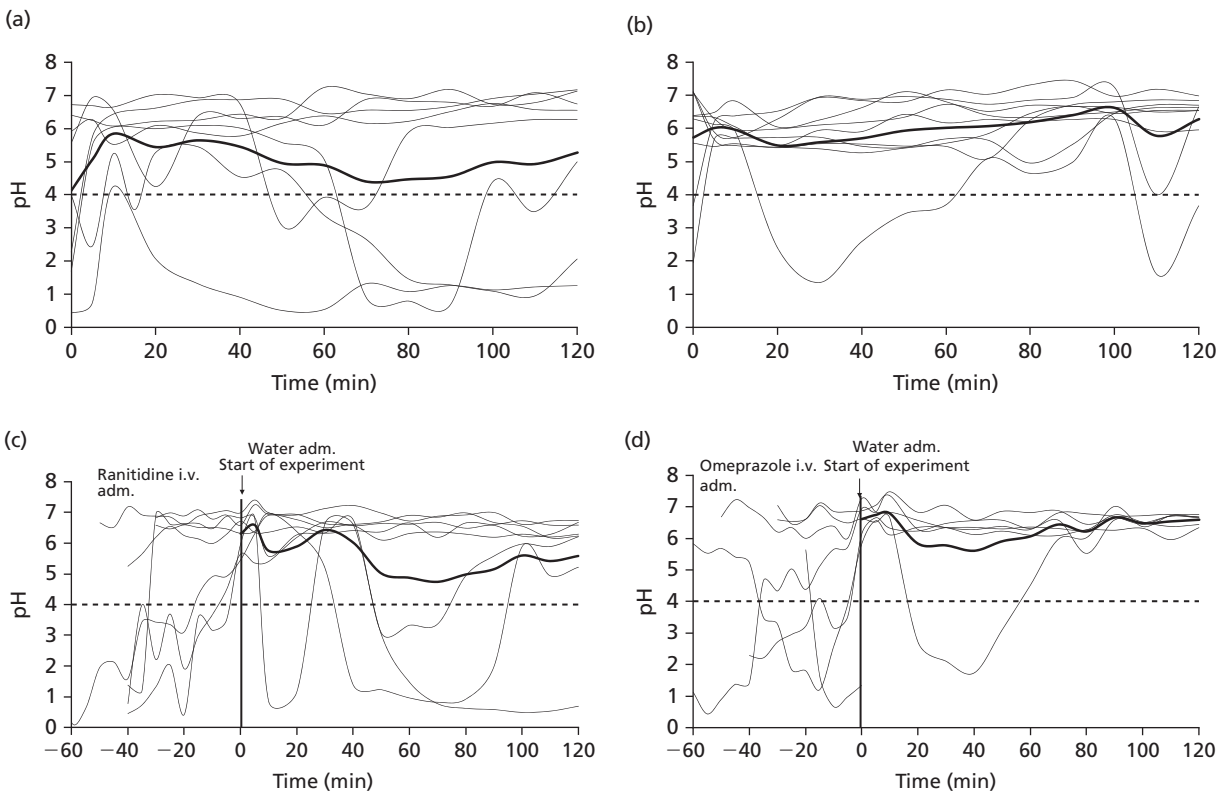

Figure 3 Individual pH–time profiles in four dogs: (a) eight experiments after oral administration of 75 ml 0.1 mol/l citrate buffer; (b) nine experiments after oral administration of 75 ml 0.1 mol/l BIS-TRIS buffer; (c) eight experiments after i.v. administration of 50 mg ranitidine followed by 75 ml water p.o.; (d) seven experiments after i.v. administration of 1 mg/kg omeprazole followed by 75 ml water p.o. In one omeprazole experiment the pH remained low and this experiment was discontinued. Average profiles for each pretreatment are shown as a thick line. Adm., administration; i.v., intravenous

other five experiments, the target pH was maintained after administration of the citrate buffer. The target pH was maintained for more than 100 min in 50% of experiments, and for longer than 30 min in 75%. However, the duration of pH modification was less than 10 min in 25% of experiments. The average duration of pH modification was 90 min.

BIS-TRIS buffer (Figure 3b)

The BIS-TRIS buffer was able to achieve/sustain pH above the target value in all nine experiments. The starting pH was below 4 in two experiments, and in both cases the target pH was reached within 2 min. The target pH was achieved for more than 100 min in 89% of the experiments and only 11% of the experiments had a duration time of < 15 min. The average duration of pH modification was 107 min.

Ranitidine (Figure 3c)

Ranitidine achieved/sustained pH above 4 in all eight experiments. The starting pH was below 4 in four of the eight experiments and the average time to reach the target pH was 46 min. Target pH level was maintained for more than 120 min in 63% of experiments, for longer than 60 min in 63%, and for longer than 30 min in 88%. The average duration of pH modification was 86 min.

Omeprazole (Figure 3d)

The starting pH was below 4 in three of seven experiments. Omeprazole increased the pH to the desired level in two of these three and the average time to reach the desired pH was 50 min. Of the experiments in which target pH was achieved, it was maintained for longer than 120 min in 83%. In the other experiment the pH level fell below the target level after less than 20 min. The average duration of pH modification was 103 min.

Effect of gastric pH on gastric emptying

In earlier in-house studies, it had been observed that GE seemed to be slower when the gastric pH was low (when low pH was achieved with HCl-KCl administration) and this also appeared to be the case in the present study. Figure 4 shows that the time to recover the chyme at the jejunal fistula (used as a proxy of GE in this study) tends to be longer when gastric pH is below 3 than when it is above the target value. By contrast, when pentagastrin was used as the pretreatment, GE time ranged from just a few min to almost 100 min (results not shown).

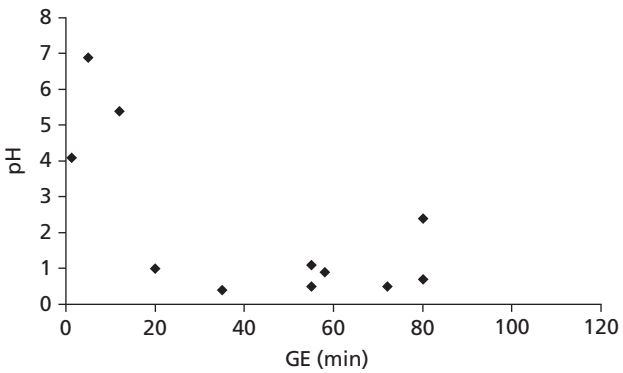

Figure 4 The effect of gastric pH on gastric emptying. The onset of gastric emptying (GE) as estimated by arrival of chyme at the mid-jejunal fistula, correlated to pH in 11 experiments in which 75 ml 0.1 mol/l HCl-KCl was administered p.o. to four fasted dogs

Intrasubject variability

Four experiments were conducted with HCl-KCl in Dog 1. In all four trials, the starting pH was high but decreased to below the target value. GE times were variable and gastric pH did not appear to influence GE in any consistent manner (Figure 5a). In Dog 2, the starting pH was high in one trial but low in the other. Nevertheless, target pH values were reached with the HCl-KCl pretreatment in both cases (Figure 5b).

Two experiments were conducted with omeprazole in Dog 2. The pH was initially high in one and low in the other. Pretreatment with omeprazole increased the pH in the latter experiment to above the target value. The GE appeared to be unaffected by pH in both experiments (Figure 6a). Two experiments were conducted in Dog 3, and the pH was initially high in both. However, in one experiment the pH inexplicably decreased immediately after i.v. administration of omeprazole, while in the other experiment the early GE caused a rapid decrease in pH to below the target value (Figure 6b).

Discussion

Previous experience with buffer modification of gastric pH in dogs

There are few reports in which buffers have been used without the addition of a pharmacological modifier. Some examples of pH modification with buffer include use of 0.05 mmol/l citric acid at a dose of 5 ml/kg, which markedly increased the absorption of a weak base and poorly soluble substance,[11] use of HCl solution to lower the gastric pH of Beagles,[10] and use of Sörensens phosphate buffer (1/15 mol/l), pH 8.3 (162 mOsm/l) to neutralise intragastric pH.[12] To our knowledge, this is the first report of the use of glycine and BIS-TRIS buffer to modify gastric pH in dogs.

Previous experience with pharmacological modification of gastric pH in dogs

Other groups have also used omeprazole to increase the pH in the canine stomach (e.g. Yamada *et al.*).[5] They attained pH above 6 after i.v. administration of omeprazole 1 mg/kg. Akimoto *et al.* showed that Beagle dogs pretreated with ranitidine are a useful animal model to evaluate the absorption behaviour of drugs under conditions of low acidity.[7] Ranitidine was chosen over other H2-receptor antagonists because it is less likely to cause drug–drug interaction via inhibitory effects on the cytochrome P450 systems. Little variation in the gastric pH was found, and the mean gastric pH induced by ranitidine 1 h after the i.v. administration was 7.5. In addition, this level of pH was maintained consistently for 4 h. However, in that study the starting gastric pH was already high in most of the dogs. In a further study by Vashi *et al.*,[13] ranitidine-HCl was administered as a 150 mg tablet (Zantac) every 3 h for four

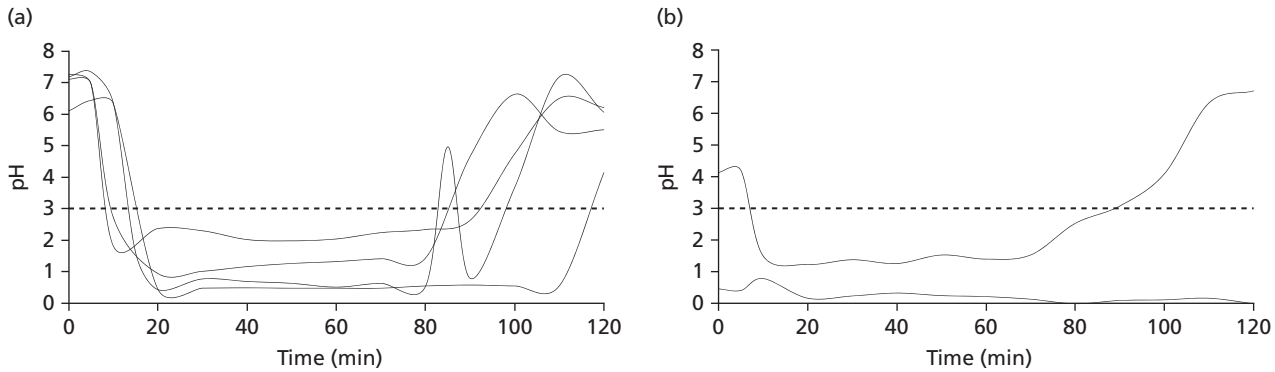

Figure 5 pH–time profiles from (a) four experiments with Dog 1 and (b) two experiments in Dog 2, in which 75 ml 0.1 mol/l HCl-KCl was administered p.o.

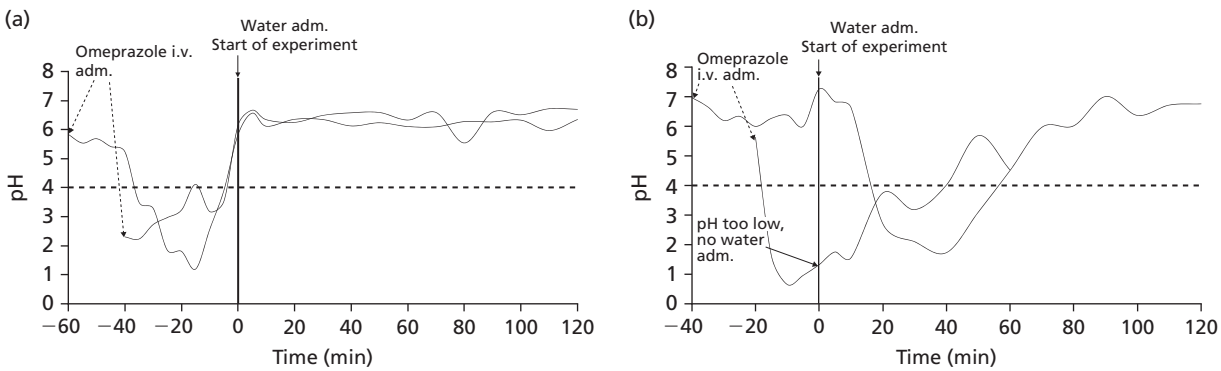

Figure 6 pH–time profiles after administration of 1 mg/kg omeprazole i.v. followed by 75 ml water p.o. in (a) Dog 2 ($n = 2$) and (b) Dog 3 ($n = 2$). Adm., administration; i.v., intravenous

doses. The pH readings ranged from 1 to 2.5 in the absence of ranitidine. During the ranitidine treatment, the pH ranged from 4.5 to 7 and gastric pH was elevated for at least 6 h. Mori and Kondo[14] showed that two intramuscular injections of famotidine 1 mg/kg, given 1 hour apart, raised the gastric pH in Beagles and achieved pH values of 5.9–8.6. Similar to the Akimoto study,[7] the starting pH was below 4 in only two of the six experiments.

Pentagastrin appears to be the most widely used pharmacological modifier to reduce gastric pH in dogs used to screen drugs and formulations. It is reasonable to expect that a weak base with poor aqueous solubility would have enhanced solubility in a more acidic environment[15] and thus be absorbed better than when the gastric pH is high. Pentagastrin is an analogue of gastrin that has been shown to reproducibly stimulate gastric acid secretion.[16] However, two research groups have reported that pentagastrin seems to delay GE.[15,17] Gastric pH values below 2 are usually achieved in dogs pretreated with pentagastrin. Some research groups report reaching the target pH value as early as 20 min after administration.[18] However, Kanerva *et al.*[4] did not attain the expected results after 20 min and therefore proposed that the experimental drug should be administered at least 20 min after pentagastrin administration. Sagara *et al.* reported a low, stable pH 45 min after pentagastrin administration[17] and Yamada *et al.* 0.5–1.5 h after treatment.[5] This low pH was maintained for 2.5 h, after which it increased. Akimoto *et al.*[7] administered 6 μg/kg pentagastrin intramuscularly to eight Beagle dogs and recorded an average minimum pH of 1.95 ± 0.07. In this study, the minimum pH was reached in about 1 h and was maintained for 1–2 h. Considerable intersubject variability in the pH profile was evident. Mori and Kondo[14] administered pentagastrin 15 μg/kg intramuscularly at 3 h intervals and attained a low pH within the first 30 min, which was then maintained for the next 2 h, during which the pH ranged between 1.2 and 2.4, even though starting pH was above 5 in five of the six dogs.

Effect of starting pH

Starting pH was low in about 30% of the experiments and high in about 70%. The success rate of the pH modifiers in terms of increasing or decreasing the pH above/below the acceptance limit was 73% and 76%, respectively. From these results it can be concluded that the initial pH does not affect the capacity of modifiers to increase or decrease the pH.

Lowering of gastric pH

We compared the ability of HCl-KCl buffer, glycine-HCl buffer and i.v. pentagastrin to lower gastric pH in dogs to below pH 3. Results with the HCl-KCl buffer were in good

accordance with previous in-house work and demonstrated that this buffer is consistently able to lower the pH to less than 3: pH was decreased to below 3 with this buffer in all of the experiments with an initial pH above 3. The average time to reach the desired pH was 10 min. These results are all the more convincing since in 10 of the 11 experiments the pH was initially above the target value. By contrast, the target value was achieved in only two-thirds of the experiments with glycine-HCl buffer.

Although pentagastrin appears to be widely used to reduce gastric pH in dogs when screening drugs and formulations, we found that it had a variable and unreliable effect on modifying gastric pH. At a dose of 4 μg/kg, results were highly variable, and adding another 2 μg/kg did not elicit the expected response. As a result, 6 μg/kg given as a single bolus dose was used for further experiments. Although the pH was successfully increased in some of these experiments when water was administered, in total pentagastrin was able to reduce the pH to the desired level in only two-thirds of the studies. Furthermore, the time taken to achieve the desired pH decrease was rather long, 30–45 min.

In summary, glycine-HCl was not an efficient means of lowering pH, and pentagastrin elicited a slow response and highly variable results. As a result, we concluded that HCl-KCl is preferred as it quickly and consistently lowers gastric pH in Labrador dogs.

Elevation of gastric pH

Citrate buffer, BIS-TRIS buffer and i.v. ranitidine and omeprazole were used in this study to modify the pH to above 4. Citrate buffer successfully elevated the pH to the desired range in two-thirds of the experiments in which initial pH was low. The average time to reach this pH was 7 min. The success rate was 100% with BIS-TRIS buffer, but in this case starting pH was low in only two of the experiments. As a result, the average time to reach the desired pH with BIS-TRIS was only 1.5 min. Ranitidine elevated to or maintained the pH at the desired level in all experiments (although the pH was not always sustained over the observation period) and for omeprazole the success rate was 67% when the starting pH was low. The lag time before the desired pH was reached was in the order of 30–60 min for both ranitidine and omeprazole. We noticed that ranitidine caused mild symptoms of runny nose in one dog, although this did not result in respiratory problems and the dog showed no signs of discomfort.

In summary, citrate buffer did not give satisfying results and with the BIS-TRIS buffer there were not enough data to draw any firm conclusions. Ranitidine was efficient in increasing the pH, however the duration time was not as long as for omeprazole. As a result, we concluded that omeprazole is the preferred drug to increase and maintain a high pH.

Duration of pH modification

Of the pH-lowering agents, HCl-KCl buffer had the longest duration of action; omeprazole and BIS-TRIS buffer had the longest duration of action among the pH-elevating agents. However, it should be remembered that in most of the BIS-TRIS buffer experiments, the gastric pH was already high before buffer administration. Pentagastrin had the shortest duration of pH modification of the acidifiers (only 46 min) and in approximately half of the experiments the pH curves were very unstable over time. The duration of pH alteration could not be extended by increasing the dose of pentagastrin. The results with pentagastrin in this study are not in accordance with studies by other research groups, in which a low pH was maintained for 2.5 h[18] or 2 h [14] but similar variability was reported by Akimoto *et al.*[7]

Relationship between gastric pH and gastric emptying

When viewing the overall results for the buffers and pharmacological modifiers, there is a tendency for the GE (as measured by the time for the chyme to reach the jejunal fistula) to be longer when gastric pH is low. These results concur with the data of Mummaneni *et al.*,[10] who demonstrated that lag times to onset of cimetidine plasma levels in Beagles were much shorter when cimetidine was administered to dogs with elevated gastric pH compared with low gastric pH. In previous in-house experiments there were indications of a delay in GE at low pH after HCl-KCl administration, also supporting results from the present study. Two research groups have also reported that pentagastrin seems to delay GE.[15,17] A prolongation of GE after administration of acidifiers is likely to be due to the 'acid brake', a feedback mechanism that delays GE in response to low pH in the duodenum. On the other hand, Mori and Kondo found that gastric pH did not affect the half-life of GE or the orocaecal transit time.[14]

Conclusions

From the results using the low-pH modifiers, it can be concluded that 0.1 mol/l HCl-KCl buffer was the most consistent and should thus be the acidic pH modifier of choice. Based on the profiles, we recommend that test formulation are administered 15 min after the HCl-KCl buffer.

Evidence from this study suggests that omeprazole is the most useful agent for elevating gastric pH in dogs. Although the BIS-TRIS buffer also maintained an elevated pH well, too few data were generated with an initially low gastric pH to draw a firm conclusion about its reliability. In these studies, results with ranitidine were unsatisfactory, even though other researchers have obtained good results with this agent. We recommend waiting 90 min after i.v. administration of 1 mg/kg omeprazole to achieve the desired pH before administering test formulations.

With these pretreatments, the gastric pH in dogs can be adjusted to closely resemble conditions in healthy humans (low pH, with HCl as the main acidifier) and in humans with elevated pH due to therapy with gastric acid blockers or alterations in gastric pH with ageing or ethnic background.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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