ABOMASAL PH AND EMPTYING RATE IN THE CALF AND DAIRY COW AND THE EFFECT OF COMMONLY ADMINISTERED THERAPEUTIC AGENTS

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1. ABOMASAL PH

A low abomasal luminal pH has also been implicated in the pathogenesis of abomasal ulceration in cattle. Increasing abomasal luminal pH may therefore be of value in treating cattle with abomasal ulceration, and for preventing abomasal ulceration in animals at high risk for ulcer development. A low abomasal pH provides an acidic barrier that offers protection to the rest of the gastrointestinal tract; this barrier function can be described as the “abomasal sterilizer”. As luminal pH increases and becomes more alkaline, the survival rate of ingested pathogenic gram-negative bacteria (such as Salmonella and enterotoxigenic Escherichia coli) increases, thereby increasing the potential risk of small intestinal colonization and diarrhea. A low abomasal pH may therefore be of value in controlling the incidence and severity of diarrhea in neonatal calves (Sen et al. 2006).

Milk-fed calves have low luminal pH values in the pre-prandial period (pH < 2.0), with some pH values being < 1.0 (Figure 1). Suckling milk or milk replacer rapidly increases luminal pH to that of the ingested solution (approximately 6.0). After suckling 2 L of milk or milk replacer, abomasal luminal pH remains constant for up to 2 hours (h), and then gradually decreases to pre-prandial values within 7-9 hours (Ahmed et al. 2001, 2002a, 2002b; 2005b; Constable et al. 2005; Marshall et al. 2005).

In the adult ruminant there is a constant flow of ingesta through the abomasum, such that the abomasal luminal pH remains constant in healthy animals at a pH value of approximately 2.1-2.2 (Sarashina et al. 1990; Geishauser et al. 1996; van Winden et al. 2002; Figure 1). Fasting causes a sustained decrease in abomasal pH in adult cows, in that luminal pH decreases to 1.4 after a 24 h fast. Luminal pH is sustained at 1.4 for the duration of the fast, but increases to 3.0 within 6 hours of feeding (Breukink et al. 1973). Cattle with left displaced abomasum have a low luminal pH (1.6) due to the combined effects of inappetance and abomasal distention (Geishauser et al. 1996); the
latter promotes abomasal secretion. Interestingly, feeding a high-concentrate diet to adult dairy cattle does not change abomasal luminal pH (Svendsen, 1969; Breukink et al. 1977) despite widely held dogma that grain feeding promotes the formation of abomasal ulcers in cattle.

Figure 1. Abomasal luminal pH over 24 hours in a Holstein-Friesian calf at 2 weeks of age (top panel) while being fed 2 L of milk replacer at time = 0 and 12 hours, and at 8 weeks of age (bottom panel) after being weaned

Note the rapid increase in luminal pH after the start of suckling at 2 weeks of age, and the relative constancy of luminal pH after weaning.

2. MEASUREMENT OF ABOMASAL PH

Abomasal luminal pH in calves and adult cattle has been measured by collecting the secretion from surgically created abomasal pouches, diverting abomasal contents through duodenal re-entrant cannulas, obtaining samples through an abomasal cannula at discrete intervals for in vitro analysis, abomasocentesis performed blindly or using ultrasonographic guidance, or introduction of a flexible miniature glass pH electrode through an abomasal cannula (Ahmed et al. 2005a). The first 4 methods do not provide an accurate continuous record of luminal pH, whereas that last technique permits continuous pH recording. Specific methodology for abomasal pH measurement has been reviewed in detail (Ahmed, 2001), with the gold standard method being placement of a glass pH electrode (such as an M3 internal reference glass pH electrode, Medical instruments Corp, Solothurn, Switzerland) into the abomasal lumen through a cannula in the abomasal body or pyloric antrum. Because there is no difference in luminal pH between the two sites in suckling calves (Ahmed et al. 2001, 2002a), measurement of luminal pH through a cannula in either site is appropriate in milk fed calves. Whether pH compartmentalization in the abomasum of adult cattle occurs has not been investigated; it therefore recommended that measurement of luminal pH in adult cattle is performed via abomasocentesis or a cannula placed in the abomasal body. Glass pH electrodes are preferred to antimony pH electrodes for continuous recording of abomasal pH because they drift at a slower rate and abomasal pH should be recorded continuously for periods longer than 12 h.
We have developed a technique for the continuous measurement of abomasal luminal pH in cattle (Ahmed et al. 2001), and a brief description of the measurement technique is as follows. The pH electrodes should be calibrated immediately before insertion and after removal against reference buffer solutions of pH 2.0 and 7.0. The glass-pH electrode is linear over the pH range of 0 to 12; the 2 point calibration process serves to calculate the slope of the analog output from the pH meter and to quantify the drift in pH over the recording period. The glass-pH electrode is connected to a pH meter which, in turn, is connected to an analog-to-digital board. Data should be digitized at 1 Hz and stored on a personal computer. During off line data analysis, abomasal luminal pH should be smoothed using a 60-point moving average, and the lowest smoothed pH value for each minute used as the pH value for that minute. This smoothing procedure minimizes recording artifacts that occur whenever the pH probe transiently contacts the abomasal mucosa as the result of changes in the calf’s position or contraction of the abomasum.

3. EFFECT OF THERAPEUTIC AGENTS ON ABOMASAL PH

An important goal when treating abomasal ulceration in milk-fed calves is to increase luminal pH and thereby inhibit the proteolytic activity of pepsin and chymosin (rennin). Chymosin is the major proteinase present at birth in calves, but pepsinogen secretion occurs at or soon after birth and is quantitatively more important than rennin for proteolysis after day 17 of life. Bovine pepsinogen is activated when pH < 5.0; the optimal pH for activation is 2.0-2.5 (Berghen et al. 1987). Bovine chymosin has an optimal pH for activation of 3.0-3.8 with a rapid increase in activation rate as pH decreases below 4.0 (Barkholt et al. 1979). These results indicate that an abomasal luminal pH > 3.0 and > 4.0 will be accompanied by a slower activation rate of pepsinogen and prochymosin, respectively, thereby markedly decreasing the proteolytic activity of abomasal secretions and facilitating. Because abomasal ulcers are most frequently observed in older calves where pepsinogen is the most important proteolytic agent, a general goal of treatment should be to increase abomasal pH to > 3.0 for as long as possible.

Abomasal luminal pH in cattle can be increased by dietary changes, oral administration of antacids such as Al(OH)₃/Mg(OH)₂ that neutralize secreted acid, and oral or parenteral administration of histamine type-2 receptor antagonists (H₂-blockers) and proton pump inhibitors that inhibit acid secretion. Anticholinergic agents (such as atropine) increase luminal pH, but do not provide a practical treatment because of deleterious side effects. Although efficacy data are presently unavailable for cattle with abomasal ulcers, results of studies in humans with duodenal ulcers indicate that ulcer healing is highly correlated with a drug-induced acid suppression that maintains luminal pH > 3.0 for > 75% of the day (Mela et al. 1992). This should be the therapeutic goal when treating cattle suspected to have abomasal ulceration.

Acid production in the abomasum is stimulated by intake; as food intake increases, the acid output is increased, but because ingested food has a pH > 2.2 and food is a great buffer, the net result of eating is an increase in abomasal luminal pH (Figure 1). Conversely, the net result of fasting is a decrease in pH because of the decline in buffer intake. As a result, the most effective treatment in cattle suspected to have abomasal ulceration is to get the animal to eat. A return to a normal appetite is of much greater clinical benefit than any currently available therapeutic agents, and should be the main focus of treatment.

We have investigated the effect of feeding frequency and route of administration on abomasal luminal pH in dairy calves (Ahmed et al. 2002b). Six male dairy calves with cannulae in the abomasal body were administered the following 6 treatments in a randomized crossover design: 24 h fasting, suckling of an all milk protein milk replacer (12% of body weight/day) at 12 h (2x), 8 h (3x), 6 h (4x), and 3 h (8x) intervals, and ruminal intubation of milk replacer (12% of body weight/day) at a 12 h (2x) interval. Least squares mean 24 h fasting abomasal luminal pH was 1.73,
whereas mean 24 h pH after suckling and intubation of milk replacer every 12 h were higher at 3.44 and 3.17, respectively. Increasing the frequency of milk replacer suckling to 3x, 4x, and 8x increased mean 24 h abomasal luminal pH; however, there was no difference in mean 24 h pH between 3x (3.69), 4x (3.64), and 8x (3.67) suckling. The percentage of the 24 h recording period that abomasal luminal pH was > 3.0 was 0%, 49%, 53%, 61%, 61%, and 71% for fasting, 2x intubation of milk replacer, and 2x, 3x, 4x, and 8x suckling of milk replacer, respectively. These results suggested that increasing the frequency of milk replacer suckling may be efficacious in the treatment and prevention of abomasal ulceration in milk-fed calves.

Orally administered antacids act locally or systemically. Systemic antacids, of which sodium bicarbonate is the best example, induce systemic alkalemia as a result of systemic absorption of sodium and an increase in the plasma strong ion difference. Sodium bicarbonate also acts as a local antacid by interacting with secreted hydrochloric acid in the abomasum: \[ \text{NaHCO}_3 + \text{HCl} \rightleftharpoons \text{NaCl} + \text{H}_2\text{O} + \text{CO}_2 \]. Orally administered sodium bicarbonate acts rapidly and is able to neutralize enough acid to raise luminal pH, induce the release of gastrin, and promote acid secretion. Therefore, sodium bicarbonate markedly increases gastric secretion shortly after its administration, and acid hypersecretion may outlast the presence of bicarbonate in the gastric contents. The production of CO2 is problematic in cattle and calves at risk of developing abomasal displacement or tympany. Sodium bicarbonate is therefore not recommended as an antacid for cattle.

Other local antacids contain a non-absorbable cation or form insoluble products in the alkaline environment of the small intestine. In the acidic environment of the stomach, local antacids remove hydrogen ions from the luminal fluid. Magnesium hydroxide (milk of magnesia) is the most potent orally administered antacid agent in common use; it rapidly and irreversibly reacts with HCl as follows: \[ \text{Mg(OH)}_2 + 2\text{HCl} \rightarrow \text{Mg(Cl)}_2 + 2\text{H}_2\text{O} \]. Magnesium hydroxide also has a weak systemic alkalining effect because magnesium (a strong cation) is partially absorbed in milk-fed calves, thereby increasing the plasma strong ion difference. Aluminum hydroxide is a commonly administered locally acting antacid agent that slowly and reversibly reacts with HCl as follows: \[ \text{Al(OH)}_3 + 3\text{HCl} \rightleftharpoons \text{Al(Cl)}_3 + 3\text{H}_2\text{O} \]. Mixtures of Mg(OH)2 and Al(OH)3 are widely used as orally administered antacid agents in humans, with combined treatment improving palatability, decreasing the incidence of osmotically induced diarrhea, and providing better buffering characteristics. Calcium carbonate is a local antacid that reacts in the stomach similar to sodium bicarbonate: \[ \text{CaCO}_3 + 2\text{HCl} \rightleftharpoons \text{CaCl}_2 + \text{H}_2\text{O} + \text{CO}_2 \]. However, calcium carbonate is a weaker systemic alkalining agent than sodium bicarbonate because calcium is absorbed from the small intestine much less efficiently than sodium. Aluminum hydroxide and calcium carbonate are constipating in humans, whereas magnesium salts may cause frequent liquid movements. As a result, commercially available antacid formulations are usually a mixture of antacids, with a combination of aluminum hydroxide and magnesium hydroxide being widely used in humans.

We have investigated the efficacy of an Al(OH)3/Mg(OH)2 solution in increasing abomasal pH in calves fed milk replacer (Ahmed et al. 2002a). Five male dairy calves were given a commercially available orally administered antacid agent (Extra-strength Maalox®) containing aluminum hydroxide (0.10 g/ml) and magnesium hydroxide (0.09 g/ml). Calves were fed milk replacer at 7:30 AM and 7:30 PM and experimental treatments consisted of oral administration of a high (50 ml) or low (25 ml) dose of the antacid agent at 7:30 AM, 3:30 PM, and 11:30 PM. Administration of the first dose of antacid at the time of the morning feeding increased mean abomasal luminal pH by < 1 pH unit, whereas administration of the second and third doses of the antacid caused a transient (< 3 hours) increase in mean luminal pH of approximately 1.5 (low dose) and 2.5 (high dose) pH units. The most interesting findings of this study were that oral administration of a commercially available oral antacid agent (Extra-strength Maalox®) transiently increased abomasal pH in a dose-dependent manner, and that the extent of acid neutralization was increased when oral antacid agents were administered postprandially (Ahmed et al. 2002a). These results suggested that orally
administered antacid agents may have a role in the treatment of abomasal ulceration in calves; however, the long-term effects of orally administered antacid agents in milk-fed calves and their clinical efficacy in treating abomasal ulceration remain to be determined. Administration of 50 ml of this antacid, every 8 h, should be considered the maximal dosage for milk-fed calves, as this dosage resulted in diarrhea and could potentially induce hypomagnesaemia and strong ion (metabolic) alkalosis (Ahmed et al. 2002a). It is likely that the efficacy of oral antacid treatment in milk-fed calves could be improved with more frequent oral administration of 25 ml of solution. Oral antacids are inexpensive to administer, with a daily cost of treatment for a 40 kg calf of $1.00 (US dollars) for 25 ml of Al(OH)3/Mg(OH)2 every 8 h.

The efficacy of oral antacids in adult cattle is unknown but likely to be negligible because of extensive dilution in the forestomach. Induction of esophageal groove closure by drenching the animal with 10% sodium bicarbonate solution, followed immediately by an Al(OH)3/Mg(OH)2 solution, could theoretically result in reasonable antacid concentrations in the abomasal fluid (Constable et al. 1990), but this supposition has not been verified.

Histamine type-2 receptor antagonists increase luminal pH through selective and competitive antagonism of histamine at the H2-receptor on the basolateral membrane of parietal cells, thereby reducing acid secretion. Cimetidine and ranitidine are synthetic H2-antagonists that have been used extensively to treat gastric ulcers in many species. Parenteral administration of ranitidine (6.6 mg/kg, IM) increased abomasal pH in cattle for 1 h (Wallace et al. 1994), and oral administration of ranitidine and cimetidine increased abomasal pH in suckling calves (Ahmed et al. 2001). Five to 15-day-old calves were surgically instrumented with abomasal cannulae and received the following treatments in a randomized crossover design: milk replacer (60 ml/kg of body weight, every 12 h; untreated control) or milk replacer and oral administration of cimetidine (50 or 100 mg/kg, every 8 h) or ranitidine (10 or 50 mg/kg, every 8 h). Abomasal luminal pH was measured continuously for 24 h using a miniature glass pH electrode. Administration of cimetidine and ranitidine caused a significant dose dependent increase in mean 24 h abomasal luminal pH (Ahmed et al. 2001). The results of this study demonstrated that abomasal acid secretion in milk-fed calves is mediated in part by histamine type-2 receptors, and that cimetidine and ranitidine may be efficacious in the treatment of abomasal ulcers in milk-fed calves. However, compared with foals and adult horses, very high oral doses of cimetidine and ranitidine are needed to cause a clinically relevant increase in abomasal luminal pH in calves. The daily cost of treatment for a 40 kg calf is $24 and $12 (US dollars) for 100 and 50 mg of cimetidine/kg, PO, every 8 hours, respectively, and $6.30 and $1.30 for 50 and 10 mg of ranitidine/kg, PO, every 8 hours, respectively. Based on efficacy and cost, ranitidine (50 mg/kg every 8 hours) is the recommended H2-blocker in calves. It is likely that parenteral administration of lower doses of ranitidine and cimetidine would be efficacious but cost prohibitive in cattle. The efficacy of oral cimetidine or ranitidine in adult cattle is unknown but likely to be much lower than in suckling calves because of massive dilution in the forestomach.

Omeprazole is a potentially useful treatment for abomasal ulceration in cattle, particularly because its prolonged duration of action permits daily treatment, compared with the more frequent treatments required for Al(OH)3/Mg(OH)2, cimetidine, and ranitidine. Omeprazole is a substituted benzimidazole that is a lipid permeable weak base that is a potent, specific, and long acting proton pump inhibitor. After protonation at acidic pH, omeprazole covalently and irreversibly binds to the proton pump H+K+-ATPase that exchanges hydrogen ions for potassium ions at the secretory surface of the parietal cell, thereby decreasing gastric secretion of hydrochloric acid.

Only a small number of studies examining the effects of omeprazole have been completed in ruminants. In two in vivo studies in weaned calves, daily intravenous administration of omeprazole (1.92 to 2.0 mg/kg body weight) increased plasma gastrin concentration and decreased appetite.
(Fox et al. 1989 & 2002), whereas oral administration of omeprazole (2 mg/kg body weight) had no effect on blood gastrin concentration or appetite (Fox et al. 1989). Because the in vivo effect of parenteral or oral omeprazole administration on abomasal luminal pH in cattle was unknown, we were interested in determining whether orally administered omeprazole increased abomasal luminal pH in calves fed milk replacer. Four male dairy calves with cannulae in the abomasal body suckled milk replacer (60 ml/kg body weight every 12 h) and were administered a non-enteric-coated omeprazole (4 mg/kg body weight every 24 h) in a paste formulation for five successive days. Abomasal luminal pH was continuously measured using miniature glass pH electrodes. On the first day of omeprazole administration, mean 24-h pH increased from 2.89 to 4.17. The mean 24-h pH on days 2, 3, 4 and 5 of omeprazole administration were 3.85, 4.02, 3.97 and 3.39 respectively (Ahmed et al. 2005b). The results of this study suggested that oral administration of non enteric-coated omeprazole increased abomasal pH in dairy calves to a similar extent as that seen following 3 times a day oral administration of Mg(OH)\textsubscript{2}/Al(OH)\textsubscript{3} solution, cimetidine, or ranitidine. Omeprazole may therefore be efficacious in the treatment and prevention of abomasal ulceration in suckling calves; however, our results suggested that the antacid effect of omeprazole may decrease over time. If true, the decreased effect of omeprazole-induced acid suppression over time may have been due to synthesis of new proton pumps (H\textsuperscript{+}K\textsuperscript{-}-ATPase) in parietal cells of the rapidly growing calf abomasum, as proton pump synthesis is the major cause for the return of acid secretion after omeprazole administration.

4. ABOMASAL EMPTYING RATE

Abomasal hypomotility and a decreased rate of abomasal emptying are believed to play important roles in the etiopathogenesis of abomasal disorders in adult cattle and calves. An economical, practical, and accurate method for measuring abomasal emptying rate in suckling calves and adult cattle is therefore needed to investigate the etiopathogenesis of abomasal disorders.

The volume and caloric content of an ingested fluid meal are the most important determinants of abomasal emptying rate. Calorically inert isotonic fluids, such as isotonic NaHCO\textsubscript{3}, are evacuated from the stomach in a rapid and exponential manner (Sen et al. 2006). In contrast, caloric fluids such as an isotonic glucose solution and milk replacer, are emptied in a more linear manner (Figure 2); this is a normal physiologic response that ensures nutrients are presented to the small intestine at a relatively constant rate. Other important determinants of emptying rate are the type of protein or fat, osmolarity, and duodenal pH, with luminal pH < 2.0 or > 10.0 decreasing the abomasal emptying rate in suckling calves. Hypertonic (> 300 mOsm/l) solutions decrease emptying rate in calves relative to isotonic electrolyte solutions, with profound inhibition of emptying occurring when osmolarity ≥ 600 mOsm/l (Sen et al. 2006).

![Figure 2. Change in abomasal volume after suckling 2 L of isotonic solution of sodium bicarbonate (open circles) or glucose solution (filled circles) at time = 0 minutes](#)
Volume was determined ultrasonographically. Note the rapid and exponential pattern of emptying after suckling the noncaloric solution (sodium bicarbonate), and the more linear pattern of emptying after suckling the caloric solution (glucose).

5. MEASUREMENT OF ABOMASAL EMPTYING RATE

Abomasal emptying has been studied in calves and adult cattle using the following methods:

- abomasal cannulation techniques including aspiration and dye dilution using phenol red, D-xylose, polyethylene glycol, or Cobalt-EDTA as nonabsorbed markers,
- duodenal re-entrant cannulation and collection of abomasal effluent,
- radiography using a liquid radio opaque material such as barium sulfate suspension,
- radio isotopic techniques using external scanning (nuclear scintigraphy),
- ultrasonographic measurement of abomasal dimensions and calculation of abomasal volume (Figure 2),
- electromyography,
- change in luminal or abomasal effluent pH (Figure 1), and
- oral absorption pharmacokinetics of acetaminophen (Figure 3) and D-xylose (Figure 4), and to a lesser extent, glucose. The advantages and disadvantages of these 8 techniques have been reviewed in detail (Marshall, 2004).

The gold standard method for measuring abomasal emptying is nuclear scintigraphy using technetium-99m (99mTc) and our laboratory has developed a scintigraphic technique for use in the standing milk-fed calf (Marshall et al. 2005). The simplest and most accurate noninvasive method for measuring emptying rate is acetaminophen absorption, and this is the preferred method for assessing abomasal-emptying rate in field studies. Acetaminophen and D-xylose are water-soluble and assess the emptying rate of the liquid phase (such as milk or milk replacer), but not the solid or semi-solid phase. However, acetaminophen and D-xylose absorption tests provide an accurate indication of abomasal emptying rate in adult ruminants because the abomasal contents are at least 95% fluid (Wittek et al. 2005c). Monitoring of abomasal luminal pH in milk fed calves can also give an estimate of the rate of emptying via measuring the time taken for luminal pH to return to within 1.0 pH units of the preprandial value (Marshall et al. 2004) (Figure 1). This is because an increase in luminal pH in suckling calves is associated with the presence of ingesta in the stomach, and a return to preprandial pH occurs when most of the ingesta have emptied from the stomach.

5.1 Acetaminophen absorption pharmacokinetics

Acetaminophen is a widely used oral analgesic and antipyretic drug in humans. When administered orally, acetaminophen is absorbed in the small intestine, with the rate-limiting step for absorption being the rate of gastric emptying in animals with normal small intestinal function. Because the apparent rate of absorption is much faster than the rate of elimination in suckling calves, the maximal acetaminophen concentration (C_max) and time to maximal acetaminophen concentration (T_max) after oral ingestion are primarily dependent on the rate of abomasal emptying.
Acetaminophen absorption has been validated as a measure of abomasal emptying rate in suckling calves (Marshall et al. 2005) with $T_{\text{max}}$ providing the most accurate measure of emptying rate using scintigraphic half emptying time as the gold standard (Figure 3). However, Schaer et al recently suggested that the $T_{\text{max}}/C_{\text{max}}$ may be a more appropriate index of emptying rate than $T_{\text{max}}$ in suckling calves (Schaer et al. 2005). In order to confirm this impression, we regressed the $T_{\text{max}}/C_{\text{max}}$ values for 32 studies against the scintigraphic half emptying time (the gold standard measure) for the calves in our study (Marshall et al. 2005). Regression analysis indicated a linear relationship between the 2 indices (Figure 4), with a high $R^2$ value (0.88). However, the $R^2$ value for $T_{\text{max}}/C_{\text{max}}$ was numerically lower than that for $T_{\text{max}}$ ($R^2 = 0.91$), indicating that $T_{\text{max}}$ remains the preferred index of emptying rate. Schaer et al also emphasized that when acetaminophen is added to milk replacer, that oroduodenal transit may be a more accurate term for the acetaminophen absorption test, because esophageal groove closure may be incomplete in some calves and absorption of acetaminophen from the reticulorumen appears minimal (Schaer et al. 2005).

Figure 3. Change in plasma acetaminophen concentration in a week old Holstein-Friesian calf after suckling 2 L of milk replacer containing acetaminophen (50 mg/kg body weight) at time = 0 minute

The calf was given an injection of 2 ml of 0.9% NaCl (control) or 8.8 mg of erythromycin/kg body weight 30 minutes before the start of suckling. The time to maximal acetaminophen concentration ($T_{\text{max}}$) is shorter after erythromycin administration.

Figure 4. Scatterplot and linear regression line relating the ratio of time to maximal acetaminophen concentration ($T_{\text{max}}$) to maximal plasma concentration ($C_{\text{max}}$) (ie $T_{\text{max}}/C_{\text{max}}$) to scintigraphically determined half emptying time in 32 Holstein-Friesian calves
Animals suckled 2 L of milk replacer containing acetaminophen (50 mg/kg body weight) at time = 0 minutes.

Jugular venous blood samples for determination of plasma acetaminophen concentrations are obtained periodically after the start of suckling the test solution containing acetaminophen at 20-50 mg/kg body weight. Different sampling times are selected in an attempt to have at least 6 data points before and after the time of maximal acetaminophen concentration in order to facilitate nonlinear regression analysis. Values for C_max and T_max are obtained from a plot of the plasma acetaminophen concentration-time data. More precise estimates of emptying rate can be obtained by using the first derivative of a modified power exponential formula to model the acetaminophen concentration-time curve; this approach is based on the fact that the acetaminophen concentration-time relationship represented as a cumulative dose curve is an inverse analogue of the scintigraphic emptying curve. The equation is: 

\[ C(t) = m \cdot k \cdot e^{k \cdot t} \cdot (1 - e^{-k \cdot t})^{\beta-1} \]

where \( C(t) \) is the plasma acetaminophen concentration in µg/ml at time \( t \) in min, and \( m \), \( k \), and \( \beta \) are constants; \( m \) is the total cumulative recovery of acetaminophen when time is infinite, \( k \) is an estimate of the rate constant for abomasal emptying, and \( \beta \) provides an estimate of the duration of the lag phase before an exponential rate of emptying is reached. Nonlinear regression is used to estimate values for \( m \), \( k \), and \( \beta \) from the known values for acetaminophen concentration and time. The time to calculated \( C_{\text{max}} \) (Model \( T_{\text{max}} \)) is obtained as: \( \text{Model } T_{\text{max}} = \ln(\beta)/k \), and the calculated value for Model \( C_{\text{max}} \) is determined by applying the values for \( m \), \( k \), \( \beta \), and \( t = \text{Model } T_{\text{max}} \) to the cumulative dose curve (Marshall et al. 2005).

The first derivative of a modified power exponential model focuses on gastric emptying and subsequent small intestinal absorption of a marker substance and therefore provides a conceptually appropriate model for assessing abomasal emptying rate. For comparison, the traditional one compartment open model that is used to describe oral absorption pharmacokinetics simultaneously considers gastric emptying, small intestinal absorption, and systemic clearance, and therefore provides a less precise estimate of abomasal emptying rate (Marshall et al. 2005).

5.2 D-xylose absorption pharmacokinetics

D-xylose, a natural pentose sugar, can be used instead of acetaminophen to measure abomasal emptying rate in countries that do not permit the use of acetaminophen in food producing animals (Wittek et al. 2005c). The rate of D-xylose absorption is influenced primarily by gastric emptying rate, although small intestinal motility, the surface area available for absorption, and bacterial flora of the small intestine also influence the D-xylose concentration-time relationship.

The D-xylose absorption test originally was introduced as diagnostic procedure for malabsorption syndrome in humans. The test has been used as a malabsorption test in adult cattle (Pearson and Baldwin, 1981) and suckling calves (Seegarber & Morrill, 1979; Nappert et al. 1993; Mir et al. 1993), and we have adapted this test using a pharmacokinetic modeling approach to accurately estimate \( T_{\text{max}} \) as an index of abomasal emptying rate (Wittek et al. 2005c) (Figure 4). Like other sugars, D-xylose is absorbed by active and passive transport mechanisms in the duodenum and proximal jejunum with a low efficiency of absorption in cattle. Ten to 20% of orally administered D-xylose is typically absorbed in suckling calves and lactating dairy cattle; although the absorption efficiency is higher in adult cattle immediately after surgical correction of abomasal volvulus and left displaced abomasum (Wittek et al. 2005c).

The D-xylose test in adult cattle requires intra-abomasal injection of 0.5 g D-xylose/kg body weight as a 50% solution (3330 mmol/l). Maximal plasma D-xylose concentrations occur at 90-120 minutes after intra-abomasal injection in healthy lactating Holstein-Friesian cattle (Wittek et al. 2005c; Figure 5). A high osmolarity of the D-xylose solution is required because the absorption
efficiency is low and the injection volume must be as small as possible (< 600 ml). However, injection of up to 600 ml of the D-xylose solution in adult cattle might directly increase the rate of abomasal emptying because this increases abomasal volume by approximately 25%, and gastric volume is an important determinant of emptying rate. The intra-abomasal injection of 50% D-xylose solution also causes a marked increase in abomasal luminal osmolarity to over 1000 mOsm/l in adult cattle (Wittek et al. 2005c); this increase would be expected to directly decrease abomasal emptying rate. Because intraluminal injection of acetaminophen does not increase abomasal volume or osmolality, acetaminophen is preferred over D-xylose absorption as a pharmacokinetic measure of abomasal emptying rate in adult cattle.

The D-xylose test in suckling calves is typically performed by allowing calves to suckle 0.5-1.3 g D-xylose/kg body weight as a 4.6% to 10% solution alone or added to milk. Maximal plasma D-xylose concentrations occur at 150 min in 1- to 6-week old dairy calves when D-xylose (0.5 g/kg BW) was added to milk (Seegraber & Morrill, 1979), at 180 to 240 min in 8-day old calves fed D-xylose (1.3 g/kg BW) in water as a 4.6% solution (Nappert et al. 1993), and at 90 min in 1- to 6-week old calves fed D-xylose (0.5 g/kg BW) as a 10% solution (Mir et al. 1993).

The time to maximal D-xylose concentration (T_max) is longer in cows with left displaced abomasum, indicating a slower rate of abomasal emptying.

5.3 Ultrasonographic measurement of abomasal dimensions and volume

Ultrasonographic measurement of abomasal dimensions provides an accurate method of determining abomasal volume and location in suckling calves (Wittek et al. 2005a). Evaluation of the change in calculated abomasal volume after ingestion of a standardized meal provides an accurate method for determining the abomasal emptying rate in suckling calves.

For ultrasonographic measurement of abomasal emptying rate, the hair on the ventral aspect of the abdomen of each calf is clipped. The calf is then gently restrained in a standing position and a 3.5-MHz ultrasound sector probe applied to the ventral aspect of the abdomen in transverse and sagittal planes to determine the maximal ultrasonographically visible abomasal dimensions (length, width, and height). Ultrasonographic measurements are obtained immediately before the start of suckling, and periodically after the start of suckling. Abomasal volume is calculated from the ultrasonographically determined measurements by use of the equation for the volume of an ellipsoid (volume = width X length X height X π/6, where π = 3.142). This method has been validated in our
laboratory for use in calves (Wittek et al. 2005a). A modified power exponential equation is used to calculate the half time of abomasal emptying (t\textsubscript{1/2}) from the abomasal volume using nonlinear regression. Briefly, a volume-vs-time curve is generated for each experiment by use of the following equation: \( y(t) = 1 - (1 - e^{-k \cdot t})^{\beta} \), where \( y(t) \) is the proportion of peak volume after suckling at time \( t \) (the time interval from start of suckling in minutes), \( k \) is the slope of the terminal portion of the emptying curve (units of min\textsuperscript{-1}), and \( \beta \) is the extrapolated y-intercept for the terminal portion of the curve. Values for \( k \) and \( \beta \) obtained from nonlinear regression analysis of experimental data are applied in the calculation of abomasal half emptying time (t\textsubscript{1/2}) as follows: 
\[
t_{1/2} = \frac{-1}{k} \cdot \log(1 - 2^{-1/\beta}).
\]

5.4 Dilution half time of nonabsorbed markers

The dilution half time of a nonabsorbed marker substance is equivalent to the abomasal emptying rate if reticuloruminal outflow is equivalent to abomasal outflow, and abomasal fluid secretion rate is zero. The first assumption appears reasonable in an animal at steady state; however, because abomasal fluid secretion rates are greater than zero, the true abomasal emptying half time will be slower than that estimated by marker dilution techniques. We estimated the D-xylose dilution half time to be 20 min in late lactation dairy cows (Wittek et al. 2005c). Other estimates of dilution half time using Cobalt-EDTA were 15 min in Swedish Red and White cattle (Holtenius et al. 1998), and 30 to 45 min in adult dairy cattle using phenol red (Pearson & Baldwin, 1981).

6. EFFECT OF THERAPEUTIC AGENTS ON ABOMASAL EMPTYING RATE

Medical treatment of cattle suspected to have abomasal hypomotility is widely practiced, but until recently, little data was available on treatment efficacy. Because abomasal hypomotility has been associated with hypocalcaemia, endotoxemia, alkalemia, hyperinsulinemia, and hyperglycemia, the current focus in treating adult cattle and calves suspected to have abomasal hypomotility is correcting acid-base, electrolyte, and metabolic abnormalities, combating the effects of endotoxemia, and eliminating gram-negative bacterial infections. Some clinicians have also administered bethanechol, neostigmine, metoclopramide, or erythromycin to ruminants suspected to have abomasal hypomotility, based on evidence of a prokinetic effect in neonatal and adult humans and domestic monogastric animals and the results of a study using bethanechol in yearling cattle (Roussel et al. 1994).

Prokinetic agents have the ability to stimulate, coordinate, and restore gastric, pyloric, and small intestinal motility (Steiner and Roussel, 1995). We have recently examined whether neostigmine, metoclopramide, and erythromycin exert a clinically useful prokinetic effect in suckling calves (Wittek et al. 2005b). Six male Holstein calves 15 to 40 days of age were monitored for 1 h before being fed milk replacer (60 ml/kg) at time = 0 min, and then monitored for another 3 h. Calves received the following treatments: metoclopramide (0.1 mg/kg, IM, at -30 and 90 min), neostigmine (0.02 mg/kg, SC, at -30 and 90 min), erythromycin (8.8 mg/kg, IM, at -30 min), low dose erythromycin (0.88 mg/kg, IM, at -30 min), combination of erythromycin (8.8 mg/kg IM) and neostigmine (0.02 mg/kg SC) or placebo as control. Abomasal motility and emptying rate were assessed by measuring luminal pressure and change in abomasal volume over time. Erythromycin (8.8 mg/kg) had an immediate and marked prokinetic effect, as it increased the frequency of abomasal luminal pressure waves and the mean abomasal luminal pressure, and decreased the abomasal half emptying time by 37%. Metoclopramide, neostigmine, and low dose erythromycin (0.88 mg/kg) did not alter abomasal motility, mean luminal pressure, or emptying rate. We concluded that erythromycin, when administered at the labelled antimicrobial dose (8.8 mg/kg, IM), exerted a marked prokinetic effect in healthy suckling calves, whereas metoclopramide and neostigmine did not alter abomasal motility or emptying rate.
In a preliminary study in lactating dairy cows, erythromycin lactobionate (0.1 mg/kg, IV; 1 mg/kg, IV or IM) and erythromycin base (10 mg/kg, IM) in polyethylene glycol caused a large and sustained increase in the myoelectrical activity in the abomasal body, pyloric antrum, and duodenum, and increased the luminal pressure in the abomasal body (Huhn et al. 1998). These effects were accompanied by an increased rate of abomasal emptying, as assessed by change in duodenal pH.

Erythromycin is the most effective widely available prokinetic agent in adult cattle (Huhn et al. 1998) and calves (Wittek et al. 2005b; Constable & Nouri, 2006). Erythromycin exerts its effect on accelerating gastric emptying by acting as a motilin agonist via binding to motilin receptors in the pyloric antrum and proximal small intestine (Itoh, 1997). Motilin is a 22 amino acid peptide that is periodically released from endocrine cells in the duodeno-jejunal mucosa, thereby initiating the migrating motor complex of the mammalian gut during the interdigestive period. There is considerable interest in the group of nonpeptide motilin agonists, called the motilides (motilin-like macrolides) that interact with the motilin receptor and promote gastric emptying (Itoh, 1997).

We have recently compared the effect of parenteral administration of erythromycin and 2 structurally different macrolides (tilmicosin and tylosin) on abomasal emptying rate (Nouri & Constable, 2006). The 3 macrolides were administered once using the recommended dose and route of administration. Eight male Holstein-Friesian calves (5-35 days of age) were given each of the following treatments in random order; control (2 ml of 0.9% NaCl IM); erythromycin (8.8 mg/kg IM); tilmicosin (10 mg/kg SC); tylosin (17.6 mg/kg IM). Abomasal emptying rate was assessed by the time to maximal plasma acetaminophen concentration (Tmax) and ultrasonographic determination of the half time of abomasal emptying. Acetaminophen absorption indicated that erythromycin, tilmicosin, and tylosin increased the rate of abomasal emptying, when compared to control. Ultrasonography indicated that erythromycin increased and tylosin and tilmicosin tended to increase abomasal emptying rate compared to control. We concluded that a beneficial side effect of erythromycin, tilmicosin, and tylosin administration in sick cattle may be an increase in abomasal emptying rate (erythromycin > tylosin > tilmicosin), although the clinical significance of this effect needs to be determined.

7. SUMMARY

Continuous measurement of abomasal luminal pH is most accurately performed by placing a flexible glass pH electrode through an abomasal cannula. Abomasal pH can be increased by dietary changes, oral administration of antacids such as Al(OH)$_3$/Mg(OH)$_2$ that neutralize secreted acid, and oral or parenteral administration of histamine type-2 receptor antagonists (H$_2$-blockers) and proton pump inhibitors that inhibit acid secretion. Oral ranitidine (50 mg/kg body weight every 8 h) or omeprazole (4 mg/kg body weight every 24 h) are effective at increasing luminal pH in suckling calves, but ensuring the animal eats should be the primary focus of treatment in animals suspected to have abomasal ulceration. Abomasal hypomotility and a decreased rate of abomasal emptying are believed to play important roles in the etiopathogenesis of abomasal disorders in adult cattle and calves. The primary focus of treatment in cattle with abomasal hypomotility should be correction of electrolyte, acid-base, and metabolic abnormalities. Erythromycin (8.8 mg/kg body weight IM) provides the most effective treatment for abomasal hypomotility, and shows promise for the medical treatment of cattle with left displaced abomasum.

8. KEY WORDS

Abomasal emptying rate, left displaced abomasum, abomasal ulcer, abomasal pH, erythromycin, tilmicosin, tylosin.
La mesure en continu du pH intraluminal de la caillette est plus précise lorsqu’elle est réalisée à l’aide d’une électrode en verre flexible, qui est introduite à travers une canule. L’augmentation du pH abomasal peut être associée aux changements alimentaires, à l’administration orale d’anti-acides tels que Al(OH)3/Mg(OH)2 qui neutralisent les sécrétions acides, et à l’administration orale ou parentérale d’antagonistes aux récepteurs histaminiques de type 2 (antagonistes H2) et des inhibiteurs de la pompe à protons qui inhibent la production d’acides. La ranitidine (50 mg/kg PV toutes les 8 heures) ou l’oméprazole (4 mg/kg PV, toutes les 24 heures) par voie orale sont efficaces pour augmenter le pH intraluminal chez le veau à la mamelle, mais la gestion de la prise alimentaire doit être la première cible du traitement pour les animaux chez lesquels une ulcération abomasale est suspectée. La diminution de la motricité de la caillette, et de sa vitesse de vidange sont supposés jouer des rôles essentiels dans l’étiopathogénie des désordres abomasaux chez la vache et le veau. L’objectif premier du traitement de l’hypomotilité abomasale chez les bovins devrait être la correction des anomalies électrolytiques, acido-basiques et métaboliques. L’érythromycine (8.8 mg/kg PV, IM) est le traitement le plus efficace de l’hypomotricité de la caillette, et présente des perspectives intéressantes pour le traitement médical du déplacement de la caillette à gauche.

10. MOTS CLES

Vitesse de vidange abomasale, déplacement à gauche de la caillette, ulcères, pH abomasal, erythromycine, tilmicosine, tylosine.

11. REFERENCES


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