Acute Tubulointerstitial Nephritis With Eosinophiluria in a Dog

Mark K. Hadrick, Shelly L. Vaden, Frank J. Geoly, John M. Cullen, and James P. Douglass

A 2-year-old female intact Labrador Retriever was examined by its regular veterinarian for lethargy and vomiting of 4-days duration. The dog had whelped 4 apparently healthy puppies 4 weeks before presentation. The referring veterinarian had prescribed ormetoprim-sulfadimethoxine (Primor; Roche, Nutley, NJ) at 40 mg/kg PO sid for 10 days as treatment for canine acne 15 days earlier. Seven days earlier, she was seen by the same veterinarian for her yearly physical examination and vaccinations.

On a CBC, there were leukocytosis (29,200/μL) due to neutrophilia (25,100/μL) and eosinophilia (2,044/μL). Serum biochemical abnormalities included azotemia (blood urea nitrogen [BUN] concentration of 107 mg/dL; creatinine concentration of 8.3 mg/dL) and hyperphosphatemia (10.0 mg/dL). The dog was treated with 2.5 L of 0.9% NaCl administered IV overnight, but it resulted in minimal urine production (volume not recorded). The following day, BUN and creatinine concentrations had increased (BUN, 158 mg/dL; creatinine, 11.1 mg/dL). A presumptive diagnosis of oliguric acute renal failure was made and the dog was referred to the North Carolina State University Veterinary Teaching Hospital.

At the time of referral, the dog weighed 29.9 kg, was mildly depressed, and had a 1 $\times$ 0.5 cm^2 ulcer on its hard palate. She had a distended bladder, but an otherwise unremarkable physical examination. Blood and urine samples were submitted for evaluation, and indwelling jugular venous and urethral catheters were placed. During the next 12 hours, cimetidine (10 mg/kg IV bid; Smith Kline Beecham, Pittsburgh, PA), metoclopramide (0.15 mg/kg IV tid; Robbins, Richmond, VA), and 0.9% NaCl (6.5 mL/kg/h) were administered. Urine production was less than 1 mL/kg/h. Furosemide (2 to 3 mg/kg IV bolus; Hoechst-Russel, Somerville, NJ) was administered as needed to keep urine production $\geq$2 mL/kg/h.

Azotemia (BUN, 165 mg/dL; creatinine, 13.9 mg/dL) and hyperphosphatemia (11.0 mg/dL) were observed. Dilute urine (USG 1.016), proteinuria, glucosuria, and hematuria were observed on urinalysis, and urine pH was 6. Calcium oxalate crystals (moderate number), pyuria (>100/high power field [hpf]), hematuria (>50/hpf), and increased numbers of epithelial cells (15 to 20/hpf) were noted in the urine sediment. Urine culture yielded no bacterial growth.

On day 2, an infusion of furosemide (0.1 mg/kg/h) and dopamine (2 μg/kg/min; Abbott, North Chicago, IL) were initiated to maintain urine production above 2 mL/kg/h. Lactated Ringer's solution was administered IV at a rate equal to fluid losses. Vomiting was controlled by substituting chlorpromazine (0.15 mg/kg IV tid; Schein, Port Washington, NY) for the metoclopramide. Cimetidine administration was continued. Penicillin G (30,000 U/kg IV bid; Marsam, Cherry Hill, NJ) was begun pending leptospirosis serology results.

Leukocytosis (24,200/μL), consisted of neutrophilia (17,424/μL), eosinophilia (3,146/μL), and basophilia (242/μL). Azotemia (BUN 160 mg/dL; creatinine, 12.2 mg/dL) and hyperphosphatemia (9.4 mg/dL) persisted, and total carbon dioxide concentration was 17 mEq/L. Isosthenuria (USG 1.010), proteinuria, glucosuria, and hematuria still were present on urinalysis. The urine sediment had markedly increased white blood cells (>500/hpf), red blood cells (>50/hpf), and epithelial cells (15 to 20/hpf). Urine submitted for microbial culture resulted in growth of a resistant strain of *Escherichia coli* (6,800 colony-forming units [CFU]/mL), sensitive only to doxycycline, imipenem, amikacin, and cefotaxime. Doxycycline (10 mg/kg sid; UDL Labs, Rockford, IL) was administered. Cytological examination of the urine was performed because eosinophilia and basophilia were present in the CBC and marked leukocyturia was detected on urinalysis. The majority of urinary white blood cells were eosinophils (60%), with neutrophils accounting for the remainder. A heartworm antigen test, fecal flotation, and leptospirosis serology were negative. On ultrasonography, the kidneys were mildly enlarged, but normal in shape. The renal cortices were slightly hyperechoic relative to the liver, and corticomedullary contrast was distinct.

On day 3, BUN and serum creatinine concentrations were only slightly decreased (BUN, 145 mg/dL; creatinine, 12.1 mg/dL). Lactated Ringer's solution, dopamine, and furosemide infusions were continued, and urine production was between 2 and 3 mL/kg/h. Percutaneous ultrasound-guided renal biopsy was performed. Histological evaluation of renal cortical biopsies showed diffuse moderate interstitial inflammatory infiltrates composed predominantly of lymphocytes and plasma cells, with 10% to 20% eosinophils, and focally intense interstitial edema. Infiltrates of lymphocytes, plasma cells, and eosinophils were intensified multifocally, forming hypercellular nodules that surrounded and infiltrated groups of tubules, occasionally associated with disrupted tubular architecture. The lumina of many intact tubules and the apical cytoplasm of their epithelial cells contained droplets of proteinaceous material. No glomerular lesions were present. A diagnosis of severe, acute, lymphocytic, plasmacytic, eosinophilic, tubulointerstitial nephritis was made. Prednisone (1 mg/kg bid) was administered.

On day 4, the urinary catheter was removed because urine production was consistently greater than 6 mL/kg/h, and lactated Ringers was continued. Azotemia and hyperphosphatemia persisted.

Serum biochemical evaluation on day 7 (4 days after initiating prednisone) revealed a marked reduction in azotemia (BUN, 100 mg/dL; creatinine, 5.5 mg/dL). Serum phosphorus concentration was normal. A stress leukogram, consistent

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with corticosteroid administration, was observed. On urinalysis, there was trace proteinuria, isosthenuria (USG 1.010), but resolution of glucosuria.

On day 8, IV fluid administration was discontinued. Prednisone (1 mg/kg bid) and doxycycline were continued. Lactated Ringer's (20 mL/kg subcutaneously tid) was administered.

The dog was discharged on day 9 with instructions for the owners to continue administration of doxycycline for 7 days, to give a tapering dose of prednisone (1 mg/kg bid for 4 days, and then 1 mg/kg sid for 10 days followed by 1 mg/kg q/48 h for 10 days), and to continue administration of lactated Ringer's solution until reevaluation. On day 18, the BUN concentration was 118 mg/dL and the serum creatinine concentration was 3.9 mg/dL. The dog was clinically normal, except for polyuria and polydipsia. On day 34, the BUN concentration was 105 mg/dL and the serum creatinine concentration was 2.9 mg/dL. The owners reported continued polyuria and polydipsia, but no other abnormalities. The dog had 4 more litters of puppies over the following years without recurrence of illness, and was reported to be very polyuric and polydipsic when the owner was contacted 16 months after the initial episode of renal failure.

Discussion

Drug-induced acute tubulointerstitial nephritis (ATIN, acute interstitial nephritis, allergic interstitial nephritis) accounts for 1% to 14% of cases of acute renal failure (ARF) in people.[1-4] Only one case has been reported in the veterinary literature.[5] ATIN does not always cause acute renal failure in people, and subclinical renal disease also may occur.[2,6]

Various causes have been associated with ATIN in people. Before the advent of antibiotics, most ATIN cases were of infectious etiology (eg, leptospirosis, brucellosis, or other bacterial infection, or toxoplasmosis). More recently, drugs have emerged as the predominant cause of ATIN[7,8] and there are case reports involving almost every existing drug class.[9] Recently, ARF in dogs was reported after nafcillin administration.[10]

ATIN secondary to sulfonamides is well-recognized.[3,5,9,11-13] In 4 large biopsy-documented ATIN series, sulfonamides were implicated in 7% to 80% of human patients.[1,2,4,9] Trimethoprim-sulfadiazine was one of several possible causes of ATIN in a dog.[5] Ormetoprim-sulfadimethoxine, the potentiated sulfonamide used to treat the dog of the present report, previously has not been associated with ATIN or other renal disease in dogs.

The pathogenesis of drug-induced ATIN is unclear, but it is likely an immune-mediated process.[1-3,9] Allergic phenomena, including fever, skin rash, and arthralgia, often are present on presentation for renal failure,[6] and a rapid recurrence of renal dysfunction occurs in people re-exposed to the inciting drugs.[1,3] Complement and antibodies directed at the tubular basement membranes[3,9] are detected in the serum of some patients, and many have increased serum immunoglobulin (Ig) E concentrations, eosinophilia, and eosinophiluria.[2,6,8] Renal tubular secretion or reabsorption may increase the offending drug's renal concentration far above that of the serum.[3] The drug may bind to tubular basement membranes or interstitial proteins and act as a hapten, making them the preferential target of an allergic response.[2,3,9] The ensuing interstitial edema and inflammatory cell infiltration lead to renal insufficiency.

The diagnosis of ATIN requires a high index of suspicion. In animal patients, the primary differential diagnosis is acute tubular necrosis (ATN) secondary to toxicants, drugs, or ischemic renal damage.[14-17] Fever, skin rash, and arthralgia are variably present in human patients,[9] but were not present in the dog reported here. Affected human patients may be oliguric or nonoliguric.[6,8] In people, the interval between exposure to the implicated drug and the onset of clinical signs is variable, usually ranging from 1 to 30 days.[1-3,6] Ormetoprim-sulfadimethoxine was administered to the dog of this report beginning 15 days before and ending 5 days before presentation. Drug administration preceding a very abrupt decrease in renal function should increase clinical suspicion of ATIN, especially if no other inciting cause is found. Readministration of the drug to confirm hypersensitivity was not considered in the dog of the present report because of the life-threatening nature of the ATIN.

In people, differentiating ATIN from ATN without performing a renal biopsy is not possible because there are no definitive clinicopathological findings for ATIN.[4] Signs of ARF, including azotemia, isosthenuria, glucosuria, and proteinuria, generally are present.[2,4,6,8] Renomegaly has been noted in affected human patients[1,12] and was present in the dog of this report. The occurrence of eosinophilia and sterile eosinophiluria in the dog of this report are consistent with reports of ATIN in people, where eosinophilia and eosinophiluria often are prominent features.[1-3,6,18] Peripheral eosinophil counts in human patients with ATIN have ranged from 600 to 3,400/μL, and eosinophils have constituted 0% to 60% of the urine leukocytes.[2,6,18] Thus, neither of these findings is diagnostic.

Urinary eosinophils occur in human patients with a variety of conditions, including cystitis, pyelonephritis, acute glomerulonephritis, urinary tract neoplasia, and ATN.[19] Despite this, eosinophiluria in excess of 10% to 30% of the urine leukocytes is rare in human beings in conditions other than ATIN.[2,3,18] No clinical correlates of eosinophiluria in the dog have been published. In the dog of the present report, 60% of the urinary leukocytes were eosinophils. We have since evaluated 20 consecutive urine sediments from dogs with pyuria of various causes and found none with eosinophils. The use of routine urine sediment methods that identify eosinophils in veterinary medicine may clarify their clinical relevance. Other clinicopathologic abnormalities that may help distinguish between ATIN and ATN in people include increased serum IgE concentrations[2,6,8] and increased uptake of gallium citrate by the kidney during abdominal scintigraphy, as compared with ATN.[2] Neither of these tests were performed in the dog of the present report.

Definitive diagnosis of ATIN requires renal biopsy.[3,4] Typical biopsy findings include moderate to severe interstitial edema and patchy infiltrates consisting predominantly of lymphocytes and plasma cells. Interstitial infiltration with neutrophils, macrophages, and eosinophils is more variable, with eosinophilic infiltrates seen in only 50% of human patients with drug-induced ATIN.[1,2,6,8,9,19] Tubular degeneration

of varying severity also may be present,[2-4] but the glomeruli and renal vasculature usually are unaffected.[3]

In the dog of the present report, the biopsy results were consistent with ATIN. The dog had whelped 4 weeks before the onset of renal failure and both *Ancylostoma caninum* and *Toxocara canis* are reactivated in the bitch around parturition.[20] Both parasites are found in a variety of body tissues, predominantly skeletal muscle, and *T canis* larvae do encapsulate themselves in the kidney.[21] The possibility that the renal failure resulted from larval reactivation cannot be ruled out, but this would be an extremely unusual course of events. Furthermore, the dog subsequently had several litters without any clinical signs of renal disease. Given the history of sulfonamide exposure, the biopsy findings, and the clinical coarse, ATIN caused by drug exposure was considered most likely.

Treatment of ATIN in people consists of supporting renal function and discontinuing the offending drug. Up to 90% of affected patients will regain full renal function if supported through the acute or oliguric phase of renal failure, but up to 1 year may be required for complete recovery.[9]

Whether or not corticosteroids are indicated in the treatment of this disease is controversial.[9] There have been no randomized, controlled, or prospective studies, but several reports suggest corticosteroids are beneficial.[1,2,4,6] These reports suggest that corticosteroids may decrease the time needed for serum creatinine concentration to return to baseline,[6] eliminate or decrease the need for dialysis,[1,4] shorten hospital stay,[4] lower final serum creatinine concentration,[6] and decrease the chance of residual fibrosis and chronic renal failure.[2] Some authors suggest using corticosteroids only in patients whose renal function does not improve after the offending drug has been discontinued.[2,4]

In the dog of this report, the suspected drug had been discontinued before clinical evidence of renal failure occurred, and little improvement in renal function occurred with diuresis alone. An immunosuppressive dose of prednisone (1 mg/kg bid) was given for 10 days, after which the dose was decreased to 1 mg/kg sid for 10 days, and then to 1 mg/kg q/48 h for 10 days. Within 36 hours of corticosteroid administration, a profound diuresis occurred that eventually reached 12 mL/kg/h. Affected human patients develop a similarly profound diuresis 24 to 72 hours after initiation of corticosteroids.[1,2,4,6,13] Within 4 days of initiating prednisone, serum creatinine concentration had decreased to 50% of the pretreatment concentration.

In summary, we diagnosed a case of ATIN by clinical pathology and histopathology. Although not yet reported in dogs, ATIN in the dog of this report was thought to have been secondary to the administration of ormetoprim-sulfadimethoxine. Prednisone administration was accompanied by a marked reduction in serum creatinine concentration. Increased performance of renal biopsy in animals with ARF and urine sediment cytological examination in animals with ARF and pyuria may reveal more cases of ATIN in dogs.

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ERRATUM

In the November-December 1995 issue of *Journal of Veterinary Internal Medicine*, page 373, the heading should have read:

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On behalf of the College, the Editorial Board congratulates the following individuals for completing the Certifying Examination in 1995.

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Standard Paper

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Book

2. Ettinger SJ. Textbook of Veterinary Internal Medicine, 2nd ed. Philadelphia, PA: WB Saunders; 1983:55–57.

Chapter in a Book

3. Bonagura JD. Therapy of cardiac arrhythmias. In: Kirk RW, ed. Current Veterinary Therapy. Philadelphia, PA: WB Saunders; 1983:360–372.

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Gastrointestinal Motility and Disease in Large Animals

Christine B. Navarre and Allen J. Roussel

An understanding of the relationship between gastrointestinal (GI) motility and disease is imperative for the proper treatment of large animal patients, especially as new therapeutic agents become available. However, the abundance of information that has become available in the last 2 decades makes gaining this understanding a formidable task. This article summarizes the changes in GI motility caused by some common diseases and conditions encountered in large animal practice, such as GI obstruction, postoperative ileus, resection and anastomosis, diarrhea, endotoxemia, GI parasitism, hypocalcemia, and pregnancy.

J Vet Intern Med 1996;10:51–59.

The effects of disease on gastrointestinal (GI) motility have been investigated since the 19th century. However, there has been an explosion of information in the last 20 years, and it is no longer acceptable to describe changes in GI motility as simply increases or decreases in motility. GI motility can be evaluated by quantifying several different parameters. A better understanding of the relationship between GI motility and disease is imperative to proper patient care, especially as new therapeutic agents become available. This article focuses on the specific changes in GI motility caused by some common diseases and conditions encountered in large animal practice.

Until more studies specifically involving large animals are available, we must extrapolate from other species. However, in doing this, we must remember the extreme variation in the structure and function of the GI tract among species, particularly in the large intestine, and make extrapolations with caution. Data from human patients, small animals, and laboratory animals are included in this review; however, only those diseases and conditions affecting large animals are discussed. Also, only results of in vivo studies are included. More extensive reviews, including data from research in vitro, are available for most of these subjects. A brief discussion of normal motility patterns is included to familiarize the reader with terminology. For a more detailed description of normal motility, terminology, and recording methods, the reader is referred elsewhere.[1-3] Therapeutic options will not be discussed in this article, but several reviews on this subject are also available.[4,5]

Normal GI Motility

Three basic parameters of GI motility can be measured: myoelectric activity, mechanical activity, and transit of intraluminal contents.[1] Myoelectric and mechanical activities are closely coupled: as one increases, so does the other.[6,7] However, transit of gut contents does not always increase as myoelectric and mechanical activities increase.[8]

Two types of myoelectric activity, slow waves and spikes, are produced by the GI tract. Slow waves are subthreshold fluctuations in membrane potential that are not accompanied by muscle contraction (Fig 1),[7] and are continually propagated from the esophagus to the rectum. Spikes are membrane fluctuations that exceed the threshold, causing depolarization and muscle contraction (Fig 2).[7] They are usually superimposed on slow waves, and groups of spikes assume several different patterns depending on the species, the area of the GI tract, and the digestive state studied.

The migrating myoelectric complex (MMC) is the myoelectric pattern in the stomach and small intestine of fasted nonruminants, fed and fasted ruminants, and pigs and horses fed ad libitum.[2,3,9-11] There are 3 phases of the MMC: the quiescent phase, in which very little spike activity occurs; the irregular phase, characterized by intermittent spike activity; and the activity front, characterized by intense, continuous spike activity (Fig 3).[1-3,9,10] There is very little muscle contraction or transit of gut contents during the quiescent phase.[1,8] During the irregular phase, contractions mix the gut contents and propel them in an aboral direction.[1,8,10] The activity front is accompanied by intense muscular contraction that obliterates the lumen, preventing backflow of contents as it propagates, or "migrates" down the gut.[2,10] In nonruminants, and pigs and horses fed periodically, feeding abolishes the MMC pattern for several hours. The MMC pattern is replaced by the fed pattern, which is characterized by intermittent spike activity resembling the irregular phase.[2,3,9,10]

Normal cecal and colonic myoelectric activities, like those of the small intestine, are characterized by slow waves and spikes. However, unlike the small intestine, the patterns of spikes vary greatly with the species and the area of the large intestine studied. The two major spike patterns are the short spike burst (SSB) and the long spike burst (LSB).[1,2,12] SSBs cause segmental contractions and do not propagate; LSBs propagate both orally and aborally.[1,2,12]

There are many interchangeable terms for all of the patterns described. The terminology used here is preferred and will be used in the rest of the article.

Intestinal Obstruction

Obstruction of the small and large intestines may be intraluminal (eg, intussusceptions, impactions, enteroliths, foreign bodies) or extraluminal (eg, displacements and entrapments).[13] Both types are characterized by bowel distension

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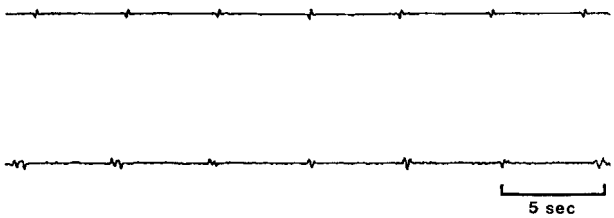

Fig 1. Slow waves recorded from the jejunum of a normal calf.

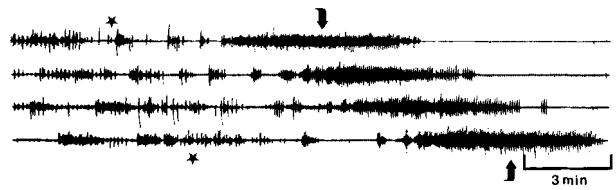

Fig 3. The phases of the migrating myoelectric complex recorded from a normal calf. Very little or no spike activity occurs in the quiescent phase intermittent spike activity occurs in the irregular phase (★) and intense, continuous spike activity occurs during an activity front (▲).[1]

and increased intraluminal pressure orally, and absence of intraluminal contents and decreased intraluminal pressure aborally. Most of the information on changes of motility after obstruction was derived from models of acute obstruction of the small intestine in horses and ponies,[14-17] cows,[18] sheep,[19] dogs,[20-21] and rats.[22] Human patients with spontaneous obstruction have also been studied.[23]

Despite differences in experimental design and species studied, the pattern of myoelectric activity of the segment oral to small intestinal obstruction was similar in most studies. Myoelectric and mechanical activity of the intestine after a complete obstruction consisted of alternating periods of contraction and quiescence.[20,23] The period of contraction was characterized by clusters of discrete spikes on consecutive slow waves, or prolonged, constant spike activity that lasted for several seconds (Fig 4).[14,15,18,20,22] The clusters of spikes were approximately 10 to 45 seconds in duration and occurred every 1 to 2 minutes.[14,22] The mechanical correlate of the clustered spikes were small groups of contractions of medium amplitude and duration, interrupted by short periods of inactivity.[16] When prolonged, constant spike complexes occurred, the mechanical activity consisted of single, high amplitude, contractions of long duration or spasms.[15]

Changes in small intestinal motility aboral to an obstruction were less consistent among studies. Total spike activity was significantly decreased aboral to small intestinal obstruction in dogs.[20,21] Long periods of quiescence, infrequent activity fronts, and periods of no irregular activity of the small intestine were described in a pony, in contrast to continuous irregular activity after an initial quiescent period in rats.[16,22] In sheep, total occlusion produced strong and prolonged bursts of activity aborally, whereas partial occlusion caused general inactivity.[19] These inconsistencies may be explained in part by species differences, experimental conditions, relationship of the recording period to feeding, and duration of the obstruction.

After relief of a small intestinal obstruction, the MMC was recognizable within 10 to 20 minutes, although duration of activity fronts is decreased and the quiescent phase was prolonged. Normalization of the MMC continued over time and was complete in 12 to 24 hours.[18,19,22]

The pathogenesis of the changes associated with small intestinal obstruction are not clearly understood. It is postulated that distention oral to an obstruction activates local myenteric receptors; activity is then stimulated orad to the obstruction via cholinergic pathways, and activity aborad is inhibited via noncholinergic, nonadrenergic pathways.[21]

The response of the large intestine to obstruction has not been studied extensively. Lowe et al[17] placed fistulas in the pelvic flexure of ponies and induced impactions by manipulating diet or creating intraluminal obstructions. Episodes of colic were accompanied by multiple high-amplitude, long-duration pressure peaks interpreted as contractions, oral and aboral to the pelvic flexure. Further research is needed before conclusions can be made about the effects of obstruction on large intestinal motility.

Postoperative Ileus

Veterinarians and physicians alike have long recognized postoperative ileus (POI) as a relevant clinical problem.[24,25] It is characterized by dilation and lack of propulsive contractions of the gut leading to accumulation of fluid and gas.[26] Its importance as a clinical disease is unmistakable. In a

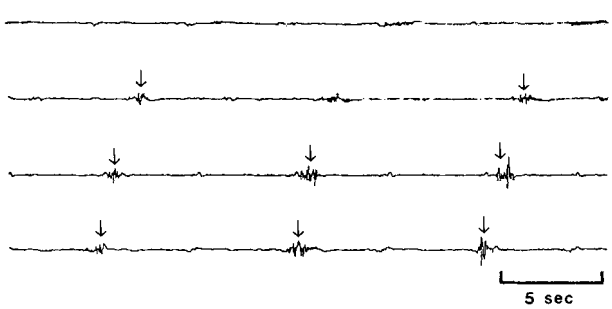

Fig 2. Spikes (arrows) superimposed on slow waves, recorded from the jejunum of a normal calf.

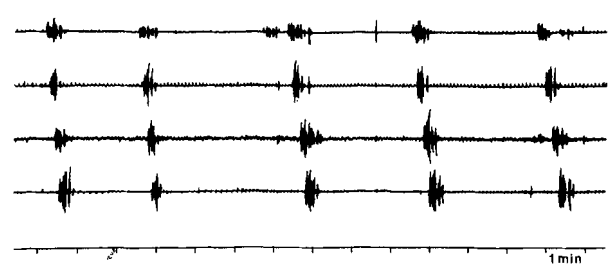

Fig 4. Clusters of spikes recorded from the jejunum of a calf during obstruction after administration of a psyllium-containing oral electrolyte supplement (Deliver [previously named Diaproof]; Miles Inc, Shawnee, KS).

retrospective study of postoperative complications of horses with colic, POI was the cause of death in 36 of 84 patients (42.9%).[25] In human patients, POI causes serious discomfort and prolongs hospitalization after surgery.[26]

Normal gastric and small intestinal motilities were altered in the postoperative period in several ways. In dogs and horses, an experimental model of POI was produced by rubbing a segment of small bowel with a dry sponge for 5 or 10 minutes, respectively, then leaving the same segment exposed to air for 30 minutes.[24,27,28] In dogs, this procedure abolished or greatly decreased the number and duration of activity fronts, and increased the duration of the irregular phase in the stomach and small intestine during the postoperative period.[24,27] The motility index (derived from the magnitude of contractile forces and the duration of myoelectric complexes) was also decreased.[27] In horses, the number of activity fronts was decreased and the normal synchrony of gastric and oral duodenal MMCs was disrupted.[28] As would be expected with a decrease in myoelectric activity, transit of plastic spheres and nonabsorbable markers was also delayed during the immediate postoperative period in dogs, horses, and rats.[24,28,29]

POI also occurs in the colon. In human patients undergoing various abdominal surgical procedures, only random, single, spike bursts were present initially.[26,30,31] Within 3 to 4 days, long, propagated, spike bursts resembling a normal pattern returned.[26,30,31] Mechanical activity and intraluminal pressures were decreased, and transit was delayed in the colon after various operative procedures.[26,32] Cecal impaction and rupture have been reported in the horse after various surgical procedures, including elective orthopedic surgery.[33-35] In those reports, the terms "ileus" and "intestinal hypomotility" were used but not defined.[33-35] It is not known if the authors were referring to gastric reflux, absence of borborygmi, or something else. Unfortunately, like equine duodenitis-proximal jejunitis, an experimental model mimicking the natural disease is not yet available so that more detailed studies can be performed.

Most researchers agree that normal motility returns first to the stomach, then to the small intestine, and finally to the large intestine.[26,28,30,36] Gastric and small intestinal motility returns within hours and colonic motility returns within a few days.[26,30,36] Surprisingly, neither the length nor the type of operative procedure affected the duration of postoperative changes of motility in monkeys and human patients.[31,32,36,37]

The pathophysiology of POI is incompletely understood at present. Depending on the anesthetic(s) used, general anesthesia alone has immediate variable effects on myoelectric activity, but there is no evidence to suggest that it significantly alters myoelectric activity of the GI tract in the postoperative period.[38-40] Disruption of gastroduodenal coordination is thought to be the principal lesion in equine postoperative ileus by some investigators.[28] Sympathetic and dopaminergic hyperactivity activity are proposed to play a role, but many other factors, such as other hormonal influences and the enteric nervous system, are probably also involved.[28]

Intestinal Resection and Anastomosis

Resection of devitalized small intestine and subsequent anastomosis is a common surgical procedure in large animal practice, particularly in horses. The effects of simply opening the abdomen and handling the bowel during surgery were discussed in the previous section. Now the effects of interruption of the continuity of the bowel wall on motility will be discussed.

Most of the information in this area was derived from studies of myoelectric activity of animals after a simple small intestinal resection and anastomosis or the creation of Thiry-Vella loops.[41-47] A Thiry-Vella loop is a section of small intestine that has been transected at both ends from the bowel, but its mesenteric attachments have been preserved.[41] The free ends of the isolated loop are passed through openings in the abdominal wall and sutured to the skin, forming 2 stomas, and the remaining bowel is anastomosed. Early studies of dogs and sheep suggested that propagation of MMCs was not interrupted by resection and anastomosis or Thiry-Vella loop preparation.[41,42] The complexes were said to start in the bowel orad to the anastomosis, migrate in sequence to the Thiry-Vella loop, and then to the aboral segment. Even though only a percentage of the complexes (60% in dogs, 30% in sheep) behaved in this manner, the authors suggested that continuity of the bowel was not needed for propagation of the MMC. However, in a similar study of dogs, Bueno et al[43] showed that approximately two-thirds of the MMCs appear to migrate directly across one anastomotic site, and only about one-third across a second anastomotic site. They also noted that the appearance and properties of these complexes were changed. This led them to the theory that MMCs do not propagate through anastomosis sites, but instead, new complexes are formed beyond the anastomosis. Thus, continuity of the bowel (ie, continuity of the enteric nerves and/or the musculature) is essential for normal propagation of the MMC.[43] This theory has since been supported by other studies.[44,45] The new MMCs arising aborad to an anastomosis occur with higher frequency, and the activity fronts of these complexes are increased in duration.[43,45,46] Coordination of propagation starts to return as the normal healing process begins. A closer association between the coordination of the oral and aboral segments was first noticed 8 weeks postoperatively, and normal coordination was completely restored by 10 to 12 weeks.[45-47]

The physiological relevance of interruption of the MMC after resection and anastomosis is unknown, but it does not appear to be clinically important. Without complications from strictures, animals can resume normal eating and defecating habits within 1 week, suggesting that aborad movement of ingesta is not considerably altered.

Diarrhea

The role of GI motility in the pathogenesis of diarrhea has been extensively researched. One might intuitively assume that diarrhea and an increase in propulsive motility go hand in hand. However, this is not necessarily the case. Thus, the changes that occur in the small and large intestines during diarrhea, and the effects of etiology on the pattern of motility will be discussed.

Three major myoelectric patterns of motility have been recognized in the small intestine in association with diarrhea; the migrating action potential complex (MAPC), the repeti-

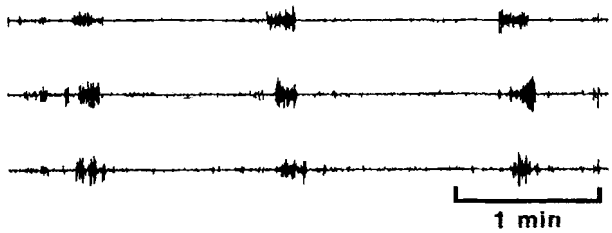

Fig 5. MAPCs propagating through 3 electrode sites, recorded from the jejunum of a calf after administration of *E coli* heat-stable enterotoxin.

tive bursts of action potentials (RBAP), and the minute rhythm. The MAPC and RBAP were first described and defined by Mathias et al, who introduced various preparations into an isolated loop of rabbit ileum.[48-58] The MAPC is characterized by action potential discharges (spikes) of 2.5 seconds or longer, that migrate aborally over at least 2 consecutive electrodes, and propel fluid (Fig 5).[48] The RBAP is an action potential discharge (spike) greater than 1.5 seconds in duration that is repeated on 3 or more successive slow waves on the same recording site (Fig 6).[49] RBAPs may or may not be propagated, and are less propulsive than MAPCs.[50,59] MAPCs are associated with noninvasive bacterial agents and their heat-labile toxins, such as *Vibrio cholerae, Escherichia coli* heat-labile enterotoxin, enteropathogenic *E coli,* and *Salmonella typhimurium.*[48,51-53,60] RBAPs are associated with invasive and cytotoxic organisms and their heat-stable toxins, such as enteroinvasive *E coli, E coli* heat-stable enterotoxin, *Shigella dysenteriae,* and *Campylobacter jejuni.*[48-50,54,61,62] It must be noted that these experiments were performed during anesthesia, and that the rabbit is not a natural host to all of the organisms studied.

In the rabbit ileum model, MAPCs were also recorded after gradual luminal distension of obstructed loops (but not of patent loops), exposure of the loops to castor oil and ricinoleic acid, and in the intestine orad to the ligated loop.[49,55,63] MAPCs also occurred in human patients after laxative abuse and secretory diarrhea of unknown etiology.[64] In contrast, pigs infected with coronavirus (transmissible gastroenteritis) had decreased numbers of MAPCs, and calves exposed to *E coli* heat-stable enterotoxin PO had no change in the numbers of MAPCs.[65,66] The definition of the

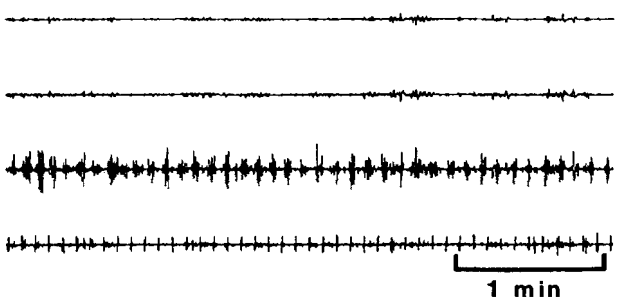

Fig 6. Intense spike activity representative of RBAPs on the third electrode site recorded from a calf infected with coronavirus.

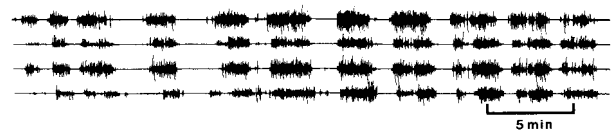

Fig 7. Minute rhythms recorded from the jejunum of a calf after administration of *E coli* heat-stable enterotoxin.[65]

MAPC (ie, propagated spikes longer than 2.5 seconds in duration) encompasses many patterns, including RBAPs and the long spike complexes described in response to obstruction. Also, although its frequency usually increases in patients with diarrheal diseases, the MAPC (also called a peristaltic rush) is a normal myoelectric pattern during the irregular phase in several species when flow of contents is greatest.[65-68] Therefore, the MAPC is thought to be a nonspecific motor pattern resulting from fluid distension, although it has also been induced by subunits of the enterotoxin molecules that do not induce secretion.[51]

The third and most frequently recorded myoelectric pattern from the small intestine during diarrhea is the minute rhythm,[59,69] which is characterized by propagating clusters of 3 to 10 spike bursts lasting 10 to 45 seconds, recurring at approximately 1-minute intervals, and separated by periods of quiescence (Fig 7).[59,70] Infusion of saline into the jejunum in pigs, and of D-mannitol into the duodenum of sheep resulted in well defined minute rhythms.[70] Grain overload in sheep, administration of *E coli* heat-stable enterotoxin to calves PO, and of ricinoleic acid and magnesium sulphate in dogs, all produced minute rhythms.[10,59,65] Minute rhythms are reported to be the most common myoelectric pattern recorded in humans with diarrhea, especially after laxative abuse.[69] Minute rhythms were also recorded in several species during normal fasting and fed states.[70] By definition, the minute rhythm also includes the clusters of discrete spikes described orad to an obstruction. Because the minute rhythm was recorded from normal animals during the irregular phase (when flow of digesta is greatest), during diarrheal states, and orad to obstructions, it is possible that this myoelectric pattern is a response to fluid distension.

The exact mechanisms leading to MAPCs, RBAPs, and minute rhythms are unclear. They may be a result of bacterial invasion or toxin production, or a reflex response to fluid distension. Prostaglandins are proposed to be involved in the pathophysiology of MAPCs, and tissue destruction is proposed to be important in the pathophysiology of RBAPs.[52,56-58] In vitro data suggest that nitric oxide is involved in the physiology and pathophysiology of intestinal motility.[71-73] Inhibitors of nitric oxide synthesis decreased the severity of castor oil-induced diarrhea in rats,[74] so nitric oxide may also be involved in the pathophysiology of these motility patterns. Research into the cellular mechanisms of these changes is already underway, and will be one of the major focuses of future studies.

The effects of diarrhea on small intestinal mechanical activity and transit are less well studied compared to the myoelectric activity. Ring-like contractions occurred simultaneously with RBAPs, and similar contractions that propagated

rapidly were observed simultaneously with MAPCs.[48,53] Prolonged, propagated contractions and giant migrating contractions recorded in normal dogs and after exposure to cholera toxin may be the motor correlates of the MAPC.[75-77] Also, discrete clustered contractions and migrating clustered contractions recorded from the same dogs may be the motor correlates of the minute rhythm.

Lack of uniformity in the terminology used to describe colonic patterns of motility during diarrhea makes correlation of information from different studies difficult. Colonic motility was altered in human patients with irritable bowel syndrome (IBS),[78] human patients and dogs with laxative-induced (castor oil, senna extract, magnesium citrate, oleic acid) diarrhea,[78-80] and human patients and dogs with ulcerative colitis.[81-83] Gross and histopathologic lesions are absent in IBS and laxative-induced diarrhea, but occur in those with ulcerative colitis.[55,83] Despite this difference, the changes in motility are similar for both. Myoelectric activity was altered by a decrease in the frequency of SSBs and LSBs, and a decrease in the duration of total spiking activity.[78,81] Mechanical activity was altered by an increase in the duration of colonic migrating motor complexes, and the occurrence of giant migrating contractions (GMCs).[79,80,83] GMCs are distinct, high-amplitude contractions that rapidly migrate aborally, and are frequently followed by expulsion of feces or gas. As would be expected with the occurrence of GMCs, colonic transit is increased.[80,82]

The pathophysiology of changes in colonic motility during diarrhea are unclear. Because the changes are similar regardless of whether morphological changes in the colon occur, it is difficult to attribute these changes to a structural change in the gut wall. As is suspected in the small intestine, prostaglandins are also proposed by some to play a role in these changes.[84,85]

Endotoxemia

Endotoxemia is a contributing factor in the pathogenesis of many diseases, including diseases of the GI tract.[38] Changes in GI motility induced by endotoxin may contribute to the pathogenesis of GI diseases. In addition, the magnitude and duration of effects of endotoxin on motility, like those on clinical signs are dose-dependent.[86-89] It should be noted that in the studies subsequently cited in this section, diarrhea was not induced by any of the doses of endotoxin administered.

The myoelectric and mechanical activities of the ruminant forestomach and abomasum, and of the monogastric stomach were decreased in response to IV administered endotoxin.[86,87,90-92] Decreased frequency and amplitude of ruminal contractions at low doses, and complete inhibition of reticular and abomasal spikes at higher doses were recorded in sheep and goats.[86,87] In the stomach of ponies and pigs, total spike activity, and the amplitude and rate of contractions were also decreased.[87,91-92]

The effects of endotoxin on small intestinal activity were not as consistent. During myoelectric and mechanical recordings in sheep, rats, pigs, and horses, the MMC was disrupted and replaced by short periods of intense activity that resembled activity fronts, but were shorter in duration and more frequent.[87-92] This occurred with low doses of endotoxin in horses and pigs, and relatively high doses in sheep and rats. In these studies, the authors compared these complexes with MAPCs, RBAPs, and minute rhythms, but evaluation of these comparisons cannot be made without more detailed descriptions of the complexes than those published in the texts.

The myoelectric and mechanical activities of the large intestine were evaluated in horses.[92,93] The number of contractions of the cecum and right ventral colon, the contractile product of the left dorsal colon, and the spike rate of the small colon were decreased.[92,93]

The IV administration of endotoxin induced alterations in GI motility very rapidly. The inhibition of reticular contractions and MMCs in sheep, and the decrease in the amplitude and rate of gastric contractions in ponies occurred within minutes of endotoxin administration[80,84]; normal motility was reestablished within hours.[90,92]

The pathophysiology of these changes is still being investigated. Some of the proposed mechanisms include increases in concentrations of platelet-activating factor, free radicals, and inflammatory mediators (in particular prostaglandins); interference with blood flow to the bowel; increased sympathetic innervation; a central opioid effect; or a combination of these.[87,88,90,93] Other inflammatory mediators like nitric oxide and tumor necrosis factor are important in the systemic and GI effects of endotoxemia,[94-96] and although there are no studies of intestinal motility specifically, these mediators may also play a role in the effects of endotoxin on gastrointestinal motility.

Gastrointestinal Parasitism

The pathogenic mechanisms of parasites, like bacteria, vary with the species. Despite these variations, changes in motility in different animal species with different parasites are somewhat consistent.

The myoelectric activity of the nematode-infested small intestine was studied in dogs and rats infested with *Trichinella spiralis,* dogs with hookworm infestations, horses with mixed small and large strongyle infestations, and sheep infested with *Haemonchus contortus.*[97-102] Similar changes were found in all cases. The cycle length of the MMC was increased, and therefore the number of MMCs per unit time was decreased in all cases, except sheep with *H contortus,* in which the opposite occurred.[98-102] Various rapidly propagating, intense, spike complexes were also recorded.[97,99,100,103] One author described these as MAPCs, but without more detailed descriptions of these complexes, it is not possible to know if these complexes are synonymous with the MAPCs described previously in this article.[99] In another study, both live and dead strongyle larvae disrupted the MMC pattern in ponies.[67]

The mechanical activity of the small intestine was recorded from dogs infested with *T spiralis.* The frequency and amplitude of contractions, and the distance of propagation of contractions were all decreased.[98,104] An increased number of GMCs, like those described in the colon during diarrhea, were recorded in these dogs.[98,104] It is possible that GMCs are the motor correlate of the rapidly propagating spike com-

plexes described previously. Diarrhea was a consistent finding in these animals and the decrease in numbers of GMCs to normal coincided with cessation of diarrhea.

Small intestinal transit time was increased in dogs infested with *T spiralis,* and in rabbits infested with *Eimeria magna.*[103,104] In rats infested with *T spiralis,* however, the transit time was decreased.[105] In the case of the dogs with *T spiralis,* this discrepancy may be due to the fact that transit time was measured only during periods when no GMCs were present.[104]

Cecal motility was not changed in fasted ponies with mixed strongyle infestations, but cecal spike bursts were more frequent in foals infested with *Strongylus vulgaris* and in rabbits with *E magna.*[102,103,106] Opposing results were also found in the colon. The cranial colon showed a decrease in spike frequency in ponies, but no change in rabbits, whereas the spike frequency of the colonic pelvic flexure in foals was increased.[102,103,106] These discrepancies could be due to species differences or differences in experimental design.

Hypocalcemia

Calcium is of vital importance to the proper functioning of smooth muscle and nervous tissue, both of which are abundant in the GI tract. Hypocalcemia, a clinical problem in postparturient dairy cattle, would therefore be expected to cause changes in GI motility. Indeed, decreased ruminal contractions and ruminal tympany often accompany clinical signs of postparturient paresis.[107] Hypocalcemia is also believed to be a predisposing factor in abomasal displacement in postparturient dairy cattle.[108,109] These facts prompted the investigations[110-112] of the effects of hypocalcemia on ruminal and abomasal motility.

Experimentally induced hypocalcemia in sheep and cows was accompanied by changes in intestinal mechanical activity; more specifically, there was a decrease in the rate and amplitude of ruminal and abomasal contractions.[110-112] Two studies showed that as blood calcium concentrations decreased, ruminal and abomasal mechanical activity decreased in a positive linear relationship.[110,111] In some instances, the mechanical activity decreased until stasis occurred (rumen of sheep, abomasum in some cows).[110,111] However, a third study showed no linear relationship for the abomasum, but an "all or none" response, where mechanical activity remained unchanged despite decreasing calcium concentrations, until a threshold was reached and stasis occurred.[112] Different conclusions were reached with these experiments. In the first, Huber et al[110] concluded that rumen stasis occurred because of a failure of neuromuscular transmission. Daniel[111] concluded that the changes in motility were caused by the generalized effects of calcium on smooth muscle contractility. Both agreed that subclinical hypocalcemia may play a role in the pathogenesis of abomasal displacement because abomasal motility is decreased before clinical signs of postparturient paresis occur. Because Madison and Troutt[112] found that decreased abomasal motility occurred in an "all or none" response, and only at serum calcium concentrations corresponding to clinical stage 3 postparturient paresis, they disagreed and concluded that subclinical hypocalcemia is not a predisposing factor in abomasal displacement. Differences in experimental design, species differences, low numbers of animals, and inferences drawn from data that are not statistically significant make it difficult to draw a conclusion regarding the importance of blood calcium concentrations in motility.

Pregnancy

GI disturbances such as constipation, heartburn and nausea, are frequent complaints of pregnant women.[113] In animals, the only clinically recognized GI disturbance associated with pregnancy is vagal indigestion in cattle.[114] Studies of GI motility have not been performed in pregnant cattle, but have been performed in pregnant women and laboratory animals.[114-119]

Gastric emptying is delayed, and small intestinal and colonic transit times are increased in humans, guinea pigs, and rats, especially in late gestation.[115-118] There is also more variation in MMC cycle length due to prolongation of some, but not all MMC cycles in rats in late gestation.[119] Gastric emptying increased and the MMC cycle length returned to normal within a few days after parturition in guinea pigs and rats.[116,119]

These changes are thought to be caused by hormonal changes, particularly increases in progesterone concentrations.[118] Although vagal indigestion in late pregnancy is presumed by some to be caused by the large gravid uterus compressing the abomasum and/or the cranial small intestine, hormonal influences should not be discounted.[114]

Conclusion

As investigations continue and information accumulates, we will gradually learn more about the diseases just discussed and their effects on GI motility. However, there are other diseases, such as equine duodenitis-proximal jejunitis, postoperative cecal impaction, and enteric neuropathy (grass sickness), about which very little information is known in regard to their relationship to GI motility. As large animal practitioners, we must continue to seek knowledge about these diseases, and we must support and encourage clinical and experimental investigations into these diseases.

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