Case Report Rapport de cas

Botulinum toxin A as a treatment for delayed gastric emptying in a dog

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Abstract — A toy Australian shepherd dog was referred for bile peritonitis following excision of a biliary mucocele. Subsequent delayed gastric emptying was refractory to prokinetic therapy but responded to injection of botulinum toxin A into the muscularis layer of the pylorus; a novel therapy for delayed gastric emptying in dogs.

Résumé — Toxine botulinique : Traitement de la vidange gastrique retardée chez un chien. Un chien Berger australien miniature a été référé pour une péritonite biliaire après l'excision d'une mucocèle biliaire. La vidange gastrique retardée subséquente a été réfractaire au traitement stimulant la motilité gastrique mais a répondu à l'injection de la toxine botulinique A dans la couche musculeuse du pylore; un traitement innovateur pour la vidange gastrique retardée chez les chiens.

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A 5-year-old, 4.4 kg, spayed female toy Australian shepherd dog had a 4-day history of intermittent vomiting, culminating in anorexia and lethargy the day of presentation. The referring veterinarian performed an ultrasonographic examination and the findings were consistent with a biliary mucocele. The patient had a cholecystectomy the following day. There was a small volume of bile in the abdomen but no leakage. Histopathology confirmed the diagnosis of a biliary mucocele. Blood chemistry showed that alanine transaminase and alkaline phosphatase were elevated [7943 U/L; reference interval (RI): 20 to 200 U/L and 11 323 U/L; RI: 10 to 70 U/L, respectively] and there was hyperbilirubinemia (73.5 μmol/L; RI: 0 to 6.8 μmol/L). Recovery from surgery was rapid but the dog's condition deteriorated 3 d later and she was presented for abdominal effusion with respiratory difficulty that was presumed to be secondary to the effusion.

Abdominocentesis and cytology identified a dark brown exudate with Gram-negative rods. Culture was positive for *Pseudomonas aeruginosa.* The dog was taken to surgery and her abdomen was lavaged. No bile leakage was detected. The patient was transferred to our institution for further evaluation and treatment. At the time of referral, the referring veterinarian had been treating the dog with enrofloxacin, 2.3 mg/kg body weight (BW), IV, q12h, ampicillin, 45.5 mg/kg BW, IV, q12h, and buprenorphine, 0.02 mg/kg BW, SC, q8h.

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Case description

On physical examination, vital parameters were unremarkable (heart rate: 120 beats/min; respiratory rate: 44 breaths/min; temperature: 38°C, blood pressure: 100 mmHg). Abdominal palpation did not identify any abnormality. The patient was alert and responsive during examination and there was no respiratory difficulty. Gastrointestinal sounds were markedly decreased and pain was mild. Serum chemistry revealed elevated alanine transaminase (1283 U/L; RI: 0 to 113 U/L) and alkaline phosphatase (5157 U/L; RI: 4 to 113 U/L), consistent with bile peritonitis. Total protein (40 g/L; RI: 54 to 71 g/L) and serum albumin (17 g/L; RI: 31 to 42 g/L) were decreased. No protein was detected in the urine, leaving a protein losing enteropathy or decreased albumin production secondary to hepatopathy as the most likely explanations for the hypoalbuminemia. Blood urea nitrogen was low (2.1 mmol/L; RI: 3.2 to 9.3 mmol/L) and total bilirubin was elevated (41.0 μmol/L). Blood glucose was normal (4.8 mmol/L; RI: 3.0 to 6.6 mmol/L). These findings were consistent with cholestasis and possible decreased liver function.

Cholesterol was normal at the referring veterinarian, but was low at the time of presentation (2.6 mmol/L; RI: 3.5 to 9.3 mmol/L), presumed to be associated with the marked inflammation. Prothrombin time (8.7 s; RI: 6.4 to 8.2 s) and activated partial thromboplastin time (15.6 s RI: 8.4 to 14.8 s) were elevated. A complete blood (cell) count (CBC) revealed an inflammatory leukogram (segmented neutrophils: 25 × 10^3/μL; RI: 2.6 to 11.0 × 10^3/μL; band neutrophils: 0.6 × 10^3/μL; RI: 0 to 0.2 × 10^3/μL; lymphocytes 4.4 × 10^3/μL; RI: 1 to 4.8 × 10^3/μL). A normocytic, normochromic anemia was noted [packed cell volume 30%; 40 to 55%; mean corpuscular volume (MCV) 66 fL; RI: 62 to 73 fL; mean corpuscular hemoglobulin concentration 370 g/L; RI: 330 to 370 g/L; mean corpuscular hemoglobulin 24 pg; RI: 22 to 26 pg]. Abdominal ultrasound showed a small peritoneal fluid pocket which was aspirated; the fluid was neutrophilic [total nucleated cells: 43.1 × 10^3/μL;

87% neutrophils (some mild degeneration, occasional hypersegmentation); 7% macrophages; 3% small lymphocytes; 3% mesothelial cells] with no microorganisms or bilirubin crystals.

The patient was admitted to our intensive care unit and received intravenous crystalloid fluids (Normosol-R, Hospira, Lake Forest, Illinois, USA), 81.8 mL/kg per day and colloid support (6% Hetastarch in 0.9% NaCl; B. Braun Medical, Irvine, California, USA), 20 mL, IV, over 5 h. The dose of enrofloxacin was increased to 10 mg/kg BW, IV, q24h and the ampicillin dose was decreased to 22.7 mg/kg BW, IV, q8h. The patient's increased coagulation times were suspected to be secondary to decreased vitamin K absorption so vitamin K, 1.1 mg/kg BW, SC, q24h, was administered. Buprenorphine (0.3 mg/mL, Reckitt Benckiser Pharmaceuticals; Richmond, Virginia, USA) was continued at the dose prescribed by the referring veterinarian. In light of her hypoproteinemia and hypoalbuminemia, the patient received a plasma transfusion (60 mL) through the night in preparation for surgery the following day.

The day following admission the patient was taken to surgery for suspected bile peritonitis. Premedication was achieved with hydromorphone (2 mg/mL, West Ward; Eatontown, New Jersey, USA), 0.14 mg/kg BW, IV, and the patient was maintained on isoflurane. During the procedure the dog received remifentanil (1 mg for IV use, Mylan Institutional; Rockford, Illinois, USA), 0.1 μg/kg BW/min as a continuous rate infusion (CRI). Extensive bile staining was present on the diaphragm and multiple pieces of mucocele debris were identified in the cranial abdomen. A region of necrosis was identified around 1 branch of the biliary tree but a full exploration of the tree was not possible. After duodenotomy and catheterization of the common bile duct, 2 defects were identified in the biliary tree, resulting in bile leakage, which necessitated re-ligation of the remnant of the cystic bile duct as well as ligation of the hepatic duct from the right medial liver lobe. Samples of the liver were taken for histopathology and culture. A Jackson-Pratt closed suction drain (Cardinal Health, McGaw Park, Illinois, USA) was placed into the peritoneal cavity prior to closure. Histopathology revealed chronic, diffuse centrilobular hepatocyte necrosis and acute, severe fibrinosuppurative peritonitis. No bacteria were detected. After surgery, the patient was started on a fentanyl (0.05 mg/mL, Hospira) CRI at 2.7 μg/kg BW/h for pain control and on sucralfate (Teva Pharmaceuticals, Sellersville, Pennsylvania, USA), 500 mg, PO, q6h and famotidine (10 mg/mL; West-Ward), 0.5 mg/kg BW, IV, q12h, as preventative against gastric ulceration.

The day following surgery (day 3), the patient's appetite was poor and she was suspected to be nauseated. She was started on maropitant citrate, (Cerenia 10 mg/mL; Pfizer Animal Health, New York, New York, USA), 1 mg/kg BW, SC, q24h, for nausea and she received a metoclopramide (5 mg/mL injection, Hospira), CRI at 1 mg/kg BW per day to stimulate gastrointestinal motility. For the next 2 d, the metoclopramide was increased by 0.5 mg/kg BW per day to a total of 2 mg/kg BW per day due to poor appetite and occasional vomiting. The dog was also transitioned from fentanyl CRI back to buprenorphine, 0.02 mg/kg BW, SC, q8h as her pain appeared well controlled. The patient's energy level increased and she was judged as recovering well from surgery.

On day 6, the patient's appetite decreased and she became nauseated. Through the day, she regurgitated clear, foamy liquid several times. Regurgitation continued through the following day and her buprenorphine was discontinued in order to resolve potential opioid-induced nausea. The maropitant citrate was discontinued as well and ondansetron (Wockhardt, Parsippany, New Jersey, USA), 0.2 mg/kg BW, IV, q12h and ranitidine (Zantac; Smith-Kline-Glaxo, North Carolina, Triangle Park, USA), 1.6 mg/kg BW, SC, q12h were started for their antiemetic and prokinetic effects, respectively. Abdominal radiographs showed a fluid distended stomach.

On day 7, a nasogastric tube was placed to support enteral nutrition (CliniCare; Pfizer Animal Health), 10 mL, q3h. At the time of placement, a large volume of clear, greenish fluid was recovered from the stomach. The patient's attitude improved over the next 2 d and her regurgitation decreased, although a moderate amount of fluid was being removed from the nasogastric tube. Erythromycin (Hospira) was started at 1 mg/kg BW, every 8 h via the nasogastric tube in an effort to stimulate gastric emptying.

Ten days following admission, the patient's regurgitation increased in volume and an upper gastrointestinal (GI) endoscopy was performed. The anesthetic protocol was similar to the first procedure, except that the patient was maintained on sevoflurane rather than isoflurane. There was moderate esophagitis and esophageal mucosal ulceration with a diffusely mildly erythematous stomach and no evidence of ulceration, consistent with gastritis. No anatomic causes for delayed gastric emptying were identified. The nasogastric tube was replaced with an esophagostomy tube (16 Fr 16 inch red rubber catheter; Covidien; Mansfield, Massachusetts, USA), to allow aspiration of stomach contents. Cisapride (compounded by Wedgewood Pharmacy, Swedesboro, New Jersey, USA) was started at 0.5 mg/kg BW, PO, q8h as an additional prokinetic agent.

Regurgitation continued and a large volume of fluid was still being removed from the esophagostomy tube so an abdominal ultrasound was performed on day 11. A moderate volume of hypoechoic fluid was identified between the liver and the pylorus. The fluid was aspirated and was consistent with bile effusion (protein: 25 g/L; nucleated cells: 880/μL; bilirubin: 152.2 μmol/L); no growth was detected on aerobic culture. The abdominal ultrasound was repeated 2 days later and no significant change was noted. The patient was taken to surgery on day 14 to explore possible reasons for gastric stasis. The anesthetic protocol was similar to that used for the gastroscopy. A pocket of bilious fluid was identified adjacent to the liver and a duodenotomy was again performed to facilitate catheterization of the major duodenal papilla and an intraoperative contrast cholangiogram was performed by use of a C-arm fluoroscope (BV 29 C-arm Fluoroscope; Philips Healthcare, Andover, Massachusetts, USA). No leakage was identified from the biliary tree so bile leakage was suspected to originate from the right medial liver lobe in the area of the previously dissected hepatic fossa. This lobe was removed and a jejunostomy tube (8 Fr, 36 in Corflo®-Ultra Jejunal Tube; MILA International,

Erlanger, Kentucky, USA) was placed to facilitate enteral nutrition by bypassing the stomach, thus decreasing ingesta available for reflux. Histopathology of the liver lobe revealed midzonal hepatocellular degeneration, moderate to severe periportal fibrosis, and severe multifocal thrombosis and infarction. These findings were consistent with previous ligation of the right medial lobar biliary duct. The dog was restarted on a fentanyl CRI at 3 μg/kg BW per hour after surgery.

The patient appeared to improve for several days following the second surgery; however, a large volume of fluid was still removed from the esophagostomy tube during this time. A presumptive diagnosis of postsurgical gastroparesis was made and on day 17 the patient underwent a barium contrast study to evaluate her gastrointestinal motility. At this time, she was receiving ranitidine (Smith-Kline-Glaxo), ondansetron (Wockhardt), and cisapride (Wedgewood Pharmacy) to stimulate gastrointestinal motility and decrease vomiting. Barium suspension (26 mL) was administered via the esophagostomy tube under fluoroscopy. Two gastric contractions were noted during the following 5 min but no barium was observed to exit the stomach through the pylorus. Serial abdominal radiographs at 1, 2, and 4 h following barium administration showed a small amount of contrast material passing into the duodenum; the majority of the barium remained in the stomach. There was no evidence of mechanical obstruction so the patient was diagnosed with a functional gastric outflow obstruction. Following the procedure, ranitidine, buprenorphine, and ampicillin were discontinued and the patient was started on domperidone (Dechra Veterinary Products, Overland Park, Kansas, USA), 1 mg/kg BW, q12h via the esophagostomy tube.

A large volume of fluid continued to be aspirated from the esophagostomy tube and there was no improvement with domperidone therapy. On day 19, the patient was anesthetized in order to facilitate injection of botulinum toxin A (BoTN; Allergan, Irvine, California, USA) into the pylorus. The patient was premedicated with dexmedetomidine (Pfizer) 10 μg/kg BW and maintained on sevoflurane. Ultrasound-guided percutaneous injection was attempted but we were unable to identify the pylorus. An endoscope was passed into the stomach but we were still unable to identify the correct region for injection. The patient was surgically prepared and a laparoscopy-assisted pyloric injection was performed. The pyloric antrum and proximal duodenum were exteriorized through a 4 cm right-sided paramedian incision. A 400 U dose of BoTN was reconstituted into 3 mL sterile 0.9% saline solution and the full volume was injected in a four-quarter circumferential pattern in the muscularis and submucosal layers of the pylorus. A dose of 100 U of BoTN was deposited at each quarter (12 o'clock, 3 o'clock, 6 o'clock, and 9 o'clock) before returning the stomach to the abdomen. Severe esophagitis had been identified during endoscopy and so a gastrostomy tube was placed and the esophagostomy tube was removed.

Three days following administration of BoTN (day 22), a barium contrast study was repeated. The patient was still receiving domperidone, cisapride, and ondansetron at the doses previously described. Barium contrast (40 mL) was administered through the gastrostomy tube under fluoroscopy and serial abdominal radiographs were taken at 20 min, 1 h, and 4 h following administration. Barium began to leave the stomach within 20 min and no contrast remained in the stomach at 4 h post-administration. A moderate amount of fluid continued to be removed from the gastrostomy tube for the next few days but the dog's attitude continued to improve and she began to eat a small amount of critical care diet (Prescription Diet a/d; Hill's Pet Nutrition, Topeka, Kansas, USA).

On day 25, the patient had 1 episode of vomiting following feeding through the gastrostomy tube and there was a small amount of regurgitation. She was continuing to receive ondansetron and domperidone and metoclopramide was now at 0.4 mg/kg BW, SC, q6h. A barium contrast study was repeated using the same protocol as on day 22. Findings were similar to those previously noted: gastric and pyloric motility was decreased but contrast material was witnessed to enter the duodenum. Gas was present in the stomach but there was no distension. Some retrograde movement of contrast was noted in the duodenum but no duodenogastric reflux or gastroesophageal reflux was observed.

The patient continued to retch and vomit over the next 2 d; however, her attitude and appetite continued to improve. On day 30 the patient became febrile (39.5°C) and was markedly lethargic. A SNAP cPL (IDEXX Laboratories, Westbrook, Maine, USA) was performed and exceeded 400 μg/L, consistent with pancreatitis. A CBC revealed an inflammatory leukogram (segmented neutrophils: $15.6 \times 10^3/\mu L$; band neutrophils: $12.2 \times 10^3/\mu L$; lymphocytes: $1.9 \times 10^3/\mu L$). In light of her acute deterioration the owners declined further diagnostics and elected euthanasia. No necropsy was performed.

Discussion

We describe a case of refractory delayed gastric emptying subsequent to surgical treatment of bile peritonitis. Delayed gastric emptying is common in dogs and can be due to anatomic or functional outflow obstruction. Anatomic obstruction occurs as a result of foreign bodies or masses (neoplasia or hyperplasia) which physically inhibit flow of ingesta through the pylorus into the duodenum.

In the absence of an anatomic cause for delayed gastric emptying, as in this case, the patient may be presumptively diagnosed with a functional outflow obstruction (1,2). Functional gastric outflow obstruction can occur secondary to a variety of etiologies including inflammation or infection, or may be idiopathic (1,2). In addition, concurrent drug usage, electrolyte disorders, metabolic diseases, and stress can contribute to decreased gastric motility (1,2). In the case presented here, multiple factors potentially contributed to delayed gastric emptying. Abdominal inflammation secondary to prolonged bile peritonitis and repeated surgical manipulation were compounded by long-term opioid administration, gastritis, intermittent hypokalemia, pain, and stress, all of which could have contributed to the refractory delayed gastric emptying.

Definitive diagnosis of functional outflow obstruction can be challenging as it results from pathology within the enteric nervous system and smooth muscle and/or asynchrony between the stomach and duodenum. In most practices, diagnosis relies on contrast radiography (3,4). It should be noted that, while liquid

typically passes from the stomach after 4 h, solid ingesta may persist for longer and a liquid contrast study may not necessarily predict how the stomach will handle a heterogenous mixture of solid and liquid ingesta (3,4). Radionuclide scintigraphic techniques have also been described for evaluation of gastric emptying, but these have limited use in most small animal practices (3,5). A third diagnostic modality has been described in which particle contrast agents such as barium impregnated spheres are administered orally and may be used to evaluate how the stomach handles particulate matter (3,4). While this technique is relatively simple, it is unclear how effective it is in predicting the emptying of digestible food from the stomach and correlation with scintigraphic techniques has not been well established (3–5).

Multiple treatments for functional gastric outflow obstruction have been described. Composition, quantity, and particle size of the diet play a role in the rate of gastric emptying (6) and so diet change alone may resolve clinical signs in mild cases. Prokinetic agents such as serotonergic agents (cisapride, metoclopramide), acetylcholinesterase inhibitors (ranitidine, nizatidine), and dopamine D_2 receptor antagonists (metoclopramide, domperidone), and low dose erythromycin (1,2) may be useful. In this patient, cisapride, metoclopramide, ranitidine, low dose erythromycin, and domperidone were used with little success.

Botulinum toxin A produced by *Clostridium botulinum* irreversibly inhibits exocytosis of acetylcholine at presynaptic nerve terminals, thereby preventing muscle contraction. Function is regained by reinnervation of the motor unit and may take several months (7). Botulinum toxin A has been approved by the FDA for use in humans for the treatment of detrusor overactivity, chronic migraine, upper limb spasticity, cervical dystonia, and primary axillary hyperhidrosis. There is no approval for the use of this drug in veterinary patients; however, canine models are often used experimentally to evaluate the efficacy of BoTN for human applications (8–10). While there is no label indication, the use of BoTN in the treatment of delayed gastric emptying has been evaluated over the last decade in human patients. Open-label studies have been performed and, in patients refractory to traditional medical management, endoscopic injection of BoTN has shown promise (7,11–21). One open label study involved a cohort of patients who had developed gastroparesis following iatrogenic vagotomy. A significant reduction in symptoms was noted at 1 and 3 mo following treatment, with a return of symptoms by 6 mo (21). Reported side effects have been minimal and have included a rare occurrence of hypersensitivity to the toxin. While no adverse events have been specifically noted with injection of BoTN into the pylorus, the authors note that diffusion of the drug into the pyloric antrum is theoretically possible and may further decrease gastric emptying (12).

While most uncontrolled studies have supported the use of BoTN for the treatment of delayed gastric emptying, 2 double-blinded studies have found that, while patients showed improvement with BoTN treatment, there was no significant difference from the improvement seen with a placebo alone (22,23). While the study design makes these results the most compelling, differences in etiology between canine and human patients make it difficult to determine to what extent these findings can be extrapolated to dogs. Most cases of delayed gastric emptying in human patients are idiopathic or secondary to diabetes mellitus or iatrogenic surgical damage to the vagal innervation to the stomach (15). In the case presented here, multiple factors were suspected as the cause of the delayed emptying and all were distinct from those most often implicated in humans. In addition, while delayed gastric emptying is most often a transient phenomenon in dogs, it is often a chronic disease in humans that requires long-term palliative therapy. It is not known, therefore, what role BoTN can play in the treatment of refractory delayed gastric emptying in veterinary patients. If the patients do show resolution of clinical signs due to BoTN injection, it is uncertain whether this resolution will persist indefinitely once the underlying cause has resolved. Unfortunately, euthanasia of the patient and an absence of necropsy findings in this case made it impossible to determine the long-term effects of BoTN in this dog and so this question remains unanswered.

A barium contrast study performed several days following administration of BoTN showed marked improvement from one performed prior to administration and there was a noted improvement in clinical signs. However, barium contrast studies are not an ideal metric for evaluation of delayed gastric emptying. Furthermore, the patient was receiving prokinetic therapy and it is not known how that contributed to the improvement. The patient was on the prokinetics for 10 d with continuing signs of gastric stasis, making prokinetic treatment response a less likely explanation for the improvement noted.

All reports of BoTN therapy for delayed gastric emptying in humans involved endoscopic injection into the pylorus. In this case BoTN was injected via a laparoscopic incision. It is uncertain whether this has any bearing on its efficacy in treating delayed gastric emptying. However, the ability to identify the layers of the pylorus and inject BoTN accordingly allowed greater accuracy in the choice of injection site and the administration of BoTN. It is unknown whether the decreased ability to identify the layers of the stomach by endoscopy may contribute to the poor performance of BoTN noted in controlled human trials (21,22). On the other hand, the technique described here necessitated surgical entry into the abdominal cavity and thus greater morbidity to the patient.

While we didn't identify any adverse effects directly linked to the administration of BoTN in this case, the possible development of pancreatitis is worth noting. Pancreatitis was a potential sequela to the primary disease in this patient; however, the proximity of the injection site to the pancreas leaves open the possibility for diffusion of BoTN into the pancreas. BoTN has been used in dogs in an experimental model for sphincter of Oddi dysfunction (9) and has been described as a treatment for sphincter of Oddi dysfunction in humans (24); because of this we suspect that, if the presumptive diagnosis of pancreatitis was correct, BoTN played little to no role in its development.

In conclusion, we describe a case in which a toy Australian shepherd dog developed delayed gastric emptying following repeated surgical treatment for bile peritonitis. The delayed gastric emptying was refractory to traditional prokinetic therapy but resolved following administration of BoTN. To the authors' knowledge, this is the first report of the use of BoTN in this

manner. Based on the results of this case, we believe the use of BoTN for treatment of delayed gastric emptying in dogs warrants further examination. CVJ

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