Kayexalate (sodium polystyrene sulphonate) in sorbitol associated with intestinal necrosis in uremic patients

Geoffrey W Gardiner MD FRCPC

BACKGROUND: Kayexalate (sodium polystyrene sulphonate) in sorbitol is commonly used to treat hyperkalemia in patients with renal insufficiency. Isolated case reports and one recent large series have documented intestinal necrosis following administration of kayexalate in sorbitol.

METHODS: Two patients with luminal kayexalate crystals associated with intestinal pathology were first identified in the pathology department, and clinicopathological correlation was carried out.

RESULTS: Both patients were seriously ill, had prior cardiac surgery and were in renal failure (uremic). Examination of autopsy and colonic resection showed luminal kayexalate crystals associated with underlying mucosal necrosis, submucosal edema and transmural inflammation.

CONCLUSION: Although occurring in complex clinical settings, the pathological findings provide additional evidence that kayexalate in sorbitol may be associated with intestinal necrosis and inflammation in uremic patients and that this may be a clinically and pathologically under-recognized iatrogenic bowel injury.

Key Words: Intestinal necrosis, Kayexalate, Renal failure, Sodium polystyrene sulphonate, Sorbitol, Uremia
Kayexalate is a powdered form of sodium polystyrene sulphonate that is usually suspended in sorbitol solution and given orally or as a retention enema for the treatment of hyperkalemia in patients with renal insufficiency (uremia) (1). Kayexalate acts as a cation exchange resin in which sodium ions are released and replaced with potassium ions with subsequent loss in the stool lowering serum potassium. Sorbitol is a poorly absorbed sugar that is primarily degraded by colonic bacteria and acts as an osmotic laxative to prevent constipation and fecal impaction.

Lillimoe et al (2) first reported colonic necrosis after administration of kayexalate sorbitol enemas in uremic patients. This was followed by isolated case reports (3,4). Recently Rashid and Hamilton (5) reported pathological findings in a series of 15 cases and concluded that this condition is under-recognized by both clinicians and pathologists. This report confirms and illustrates these findings with two cases, neither of which were suspected clinically.

**CASE PRESENTATIONS**

Case 1: A 66-year-old man underwent an aortic valve replacement with uncomplicated surgery and immediate postoperative period. On the fourth postoperative day he developed a sudden heart block with cardiogenic shock and was successfully resuscitated but became acidotic and hypoglycemic after return to the intensive care unit. Acute liver failure (ischemic hepatitis and shock liver) developed with aspartate aminotransferase rising to 8129 U/L (normal less than 40 U/L) and alanine aminotransferase rising to 4587 U/L (normal less than 35 U/L). Simultaneously, renal failure ensued with creatinine rising to 415 µmol/L (normal less than 120 µmol/L) and urea rising to 23 mmol/L (normal 3 to 7 mmol/L). A presumed metabolic neurological coma also developed. Postresuscitative blood pressure remained stable, and no gastrointestinal bleeding or peritoneal signs developed. Marked hyperkalemia with potassium rising to 6.8 mmol/L (normal 3.5 to 5 mmol/L) necessitated the vigorous use of kayexalate enemas and large doses of kayexalate sorbitol solutions (240 g over two days) through a nasogastric tube. The patient died on the 10th postoperative day, six days after the episode of cardiogenic shock.

Necropsy confirmed shock liver (ischemic hepatitis) with coagulative necrosis in zones II and III of the microcirculatory acinus, and kidneys showed diffuse ischemic tubular damage. Examination of the gastrointestinal tract found patchy hemorrhagic mucosal erosions of the stomach, ileum and colon (Figure 1). Light microscopy showed coagulative necrosis of the mucosa with overlying purple rhomboid kayexalate crystals, submucosal edema and acute transmural inflammation (Figures 2,3). The muscularis propria showed acute inflammation and myocytolysis but no frank coagulative necrosis. The aortic ostia of the mesenteric arteries were patent with no evidence of atherosclerotic occlusion or venous thrombosis.

Case 2: A 71-year-old woman was transferred to hospital because of chronic lower gastrointestinal bleeding (hemoglobin 76 g/L requiring transfusion of 8 U of blood over two weeks. Two years previously she had undergone an aortic and mitral valve replacement with a difficult postoperative course followed by chronic renal failure with unstable serum potassium. In addition, she had mild insulin-dependent diabetes that was well controlled. The patient was receiving digitoxin, furosemide, warfarin sodium and kayexalate 15 g/day orally. Blood urea nitrogen was 25.7 mmol/L and creatinine 238 µmol/L. Mesenteric angiogram showed changes suggestive of angiodysplasia but with no well developed vascular
tuft or active bleeding. A right hemicolectomy was performed. Postoperatively, the patient’s course was unstable requiring hemodialysis, and she died on the 18th postoperative day.

The right hemicolecotomy consisted of 45 cm of colon with a short length of ileum. Examination of the mucosa revealed focal mucosal hemorrhage with erosion and underlying edematous bowel wall (Figure 4). Histological examination showed hemorrhagic mucosal necrosis associated with kayexalate crystals, submucosal edema and acute trans-
mural inflammation (Figures 5,6). Coagulative necrosis of muscle was not evident. Submucosal blood vessels were within normal limits for her age, and no dilated or thrombosed vessels transversing the muscularis mucosae at sites of erosion were identified.

DISCUSSION

Many gastrointestinal complications in patients with renal failure are reported and include peptic ulcers (6), bleeding or perforated colonic ulcers (7-9), and complications of pre-existing disease such as perforated diverticula (9). Ischemic colitis is the most common colonic complication in renal transplant patients, occurring in about 1% of patients (10). Electrolyte imbalance, particularly hyperkalemia, is a frequent complication of renal failure and its treatment with kayexalate in sorbitol may rarely result in intestinal necrosis.

In an epidemiological study estimating intestinal necrosis in postoperative patients receiving sodium polystyrene sulphonate, Gerstman et al (11) found an incidence of 1.8% and concluded that sorbitol-associated complications may be a not uncommon occurrence in postoperative patients. Furthermore, it has been suggested that some cases of idiopathic colonic ulcers in patients with renal failure represent kayexalate in sorbitol-induced injury (5).

Although the precise mechanism of kayexalate in sorbitol necrosis is uncertain, contributing factors may include uremia, hypovolemia and hypotension after dialysis or surgery. Indeed, elevated renin levels in uremic patients may predispose to angiotension-mediated mesenteric vasoconstriction with resulting intestinal ischemia (12). Certainly the major clinical and morphological differential diagnoses include ischemic injury of the bowel in uremic patients.

Lillimoe et al (2) first reported five patients presenting with extensive mucosal necrosis and transmural infarction of the colon following kayexalate and sorbitol enemas to treat hyperkalemia in uremic patients. They further investigated the effects of kayexalate sorbitol enemas in normal and uremic rats and concluded that sorbitol is the agent responsible for colonic damage and that the injury was potentiated in uremic rats. In this study, when sorbitol alone or kayexalate sorbitol was given, extensive transmural necrosis developed in 80% of normal rats and all uremic rats. The pathogenesis is unclear but it was speculated that the osmotic load could cause vascular shunting, resulting in intestinal ischemia, or that the osmotic load from sorbitol could cause direct toxic damage by disrupting mechanisms that regulate cell volume. While administered as a poorly absorbed sugar, sorbitol is also an organic osmolyte (polyol) found in high concentration in cell cytosol with a key role in cell volume homeostasis (13). Cellular membrane transport systems involving potassium and sodium are also integral parts of cell volume regulatory control (13).

While kayexalate crystals can be an incidental finding and are not known to cause injury, the purple irregular jagged crystals are a helpful histological clue to the possibility that sorbitol, the agent responsible for colonic necrosis, has been administered. The presence of crystals should alert the pathologist to discuss the patient’s case with the clinician. It must be remembered that kayexalate crystals can be found over normal mucosa and the differential diagnosis would include cholestyramine resin used in the treatment of hypercholesterolemia, bile-acid induced diarrhea or Clostridium difficile colitis. Kayexalate crystals are reported to be less basophilic and opaque than cholestyramine crystals and stain red with acid-fast stain (5).

Although varying in degree, the histopathological pattern of injury was similar in both patients, with mucosal necrosis and ulceration with overlying crystals and submucosal edema and transmural inflammation. The muscularis propria showed edema and acute inflammation with myocytolysis and was reminiscent of changes seen in toxic megacolon. The presence of spreading submucosal inflammation and edema also warrants the consideration of phlegmonous colitis (14) and other types of infectious enterocolitis including Eschericia coli O157:H7 that could be diagnosed by appropriate stool cultures. Kayexalate crystals are the distinguishing clue to etiology.

In case 1, because of a time interval of six days after transient cardiogenic shock and absence of signs of acute ischemic bowel injury, superficial intestinal necrosis was attributed to kayexalate in sorbitol etiology. Large doses of kayexalate in sorbitol were given through a nasogastric tube, and autopsy revealed patchy gastric mucosal necrosis (Figure 3) with overlying kayexalate crystals. This finding supports the recent series from Johns Hopkins University (5) with the first recorded observation that gastrointestinal injury may occur in the stomach and small intestine, and not exclusively in the colon. Although it could be argued that this change is incidental, because patients with uremia have a higher incidence of gastritis, and gastric and duodenal erosions (15-17), crystals and underlying mucosal necrosis could be attributed to a kayexalate in sorbitol etiology. Our hospital pharmacy restricted the use of sorbitol in enemas based on earlier adverse reports (2-4), but the findings in case 1 confirm the presence of gastric and small intestinal injury as a possible adverse drug effect, and the restriction of oral sorbitol administration should be considered.

Case 2 presented with intermittent lower gastrointestinal bleeding. Right-sided diverticula and angiodysplasia are common causes of bleeding in uremic patients (18), and thrombocytopenia and coagulation defects frequently present in uremia may also contribute to a bleeding diathesis (19). Angiodysplasia is an extremely difficult lesion for the pathologist to identify in a colectomy specimen, and intravascular injection techniques are often required for diagnosis (20). More practical alternative methods have also been reported (21). Although it is difficult to totally exclude this lesion, no dilated venules were found traversing the muscularis mucosae in the erosions, and colonic bleeding was attributed to kayexalate in sorbitol necrosis. Kayexalate in sorbitol was given for chronic hyperkalemia in small doses orally.

It is unclear whether toxic effects are dose-related or whether delayed peristalsis enhances toxicity. Chronic constipation is a common problem relating to medication use in
chronic renal failure. Furthermore, the precise details of kayexalate in sorbitol administration are often difficult to assess or not available.

CONCLUSION
These two cases serve to illustrate that nephrologists, gastroenterologists and pathologists must be alerted to the fact that routine therapy for hyperkalemia rarely results in significant iatrogenic bowel injury in uremic patients.

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REFERENCES