CASE REPORT

Sorbitol-Induced Diarrhea In A Tube-Fed Patient

Jan Greenwood and Glen Brown

INTRODUCTION

Enteral administration of nutrition support is the route of choice in the critically ill patient with a functional gastrointestinal tract (GI tract).[1] When compared to parenteral nutrition, enteral nutrition is more economical, has fewer technical difficulties, and less metabolic risk. By delivering nutrients directly into the GI tract, substrate utilization is enhanced and maintenance of gut integrity promoted.[1] Diarrhea can potentially interfere with the delivery of optimum nutrition via the enteral route. Immediate identification and rectification of the precipitating cause is key to continued delivery of optimum enteral nutrition. All patient and treatment factors must be considered when investigating the cause of diarrhea. Osmotic diarrhea can be a direct result from the enteral feeding, but consideration should also be given to concurrently administered, osmotically-active medications. Since osmotic diarrhea is a common cause of diarrhea in the hospitalized population,[2] the least invasive first step to the identification of the precipitating cause should be a review of those factors which may give rise to osmotic diarrhea. The following case report demonstrates the potential for pharmaceutical excipients, specifically sorbitol, to contribute to the development of osmotic diarrhea in the critically ill patient.

CASE REPORT

A 61 year-old, male was admitted in acute respiratory distress. A two-month history of anorexia, weight loss, vomiting, diarrhea, cough, increased sputum production, and shortness of breath on exertion was obtained. An initial impression was of adult respiratory distress syndrome secondary to pneumonia necessitating mechanical ventilation. A nasogastric feeding tube was placed and enteral feeding initiated on day two. A hypertonic, polymeric, enteral feeding product (Resource Plus®, Sandoz) was provided full strength at a rate of 25 mL/hour. The delivery rate was limited by consistently large volumes of gastric residuals upon aspiration of the nasogastric tube. Despite broad spectrum antibiotic therapy, the patient's condition did not improve and he continued to require mechanical ventilation. Parenteral nutrition was initiated on day five and continued through to day 12. Re-introduction of nasogastic feeding on day 11 using Resource Plus® at 25 mL/hr and increased to 55 mL/hr was well tolerated with minimal residual gastric contents with aspiration. On day 13 a HIV test returned positive. Repeat bronchoscopy was positive for *Pneumocytis carinii* and therapy with cotrimoxazole and hydrocortisone was initiated. On day 18 the feeding formula was changed to an isotonic polymeric enteral feeding product (Osmolite HN®, Ross Laboratories), full strength at 85 mL/hr as the patient was requiring a higher protein intake. On day 22 of hospitalization, (day eight of cotrimoxazole therapy), continuous stooling began and progressed over the following 24 hours to profuse diarrhea necessitating the insertion of a rectal tube. Stools were collected and subsequently found to be negative for *Clostridium difficile, Salmonella, Shigella,* and *Campylobacter.* A review of the enteral nutrition support revealed that the feeding formula and the rate of delivery had remained constant prior to the development of diarrhea. A review of the medications revealed no alteration in drug therapy other than the delivery route of potassium chloride. Immediately prior to the onset of the diarrhea, potassium chloride supplementation had been converted from the parenteral to the enteral route. Over the 12-hour period (early Day 22) prior to the initiation of the diarrhea, 100 mEq of potassium chloride had been administered (5 × 20 mEq doses) as

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an elixir (Kay-Ciel®, Berlex) via the nasogastric tube. The possibility that the elixir was the cause of the diarrhea was entertained as it remained the only altered factor in the patient's care. Potassium supplementation was subsequently provided via the parenteral route and antidiarrheal therapy (camphorated tincture of opium, Paregoric) was initiated. Nasogastric feeding was maintained throughout the course of the diarrhea, but was manipulated in an attempt to resolve the diarrhea. On day 22, the feeding formula was changed to an elemental product (Flexical®, Mead Johnson) and initiated full strength at 25 mL/hr and slowly increased to a final rate of 80 mL/hr. The patient also received a single dose of acetaminophen 640 mg as an elixir (Tylenol®, McNeil) during the late evening of Day 22 which may have further exacerbated the diarrhea. Since the diarrhea did not completely resolve by day 23 the formula was further manipulated by a change to full strength fiber-containing polymeric product (Jevity®, Ross) at 25 mL/hr and slowly increased to a final rate of 85 mL/hr. The diarrhea resolved on day 24 and antidiarrheal therapy was tapered and discontinued. No episodes of diarrhea were noted for the duration of hospitalization. The polymeric product (Jevity®, Ross) was continued for the duration of hospitalization at a rate of 85 mL/hr. Despite 14 days of cotrimoxazole therapy and 25 days of mechanical support, respiratory function did not improve and the patient expired.

DISCUSSION

Diarrhea is a common complication of enteral nutrition support in the critically ill patient as demonstrated by reports of a 41% incidence in patients in the ICU setting.[3] A higher incidence has been noted in patients receiving nasogastric feedings.[3] A valid determination of the prevalence of diarrhea is hindered by the lack of a uniform definition of the symptom. Various definitions of diarrhea have been proposed ranging from "the presence of loose stools noted by the patient or staff",[4] "soft or liquid stool in excess of 500 mL a day"[5], to "the passage of three or more liquid stools a day".[3] Diarrhea is generally recognized as an excessive frequency or liquidity of fecal discharge relative to an individual's usual bowel habits. By any definition, diarrhea is not benign and can significantly interfere with patient well-being and care. From a nutritional perspective, diarrhea may directly interfere with fluid and electrolyte balance, contribute to a loss of nutrients such as magnesium and zinc, and negatively impact on the ability to deliver adequate nutrition via the enteral route.[1] The presence of diarrhea in a tube-fed patient frequently results in the tube feeding being initially labelled as the cause. In an attempt to resolve the diarrhea, various adjustments to the enteral feeding are often carried out. These include diluting the formula, reducing the rate of delivery, holding the feed for 24 hours, changing to another product, or discontinuing enteral nutrition in favor of parenteral nutrition. These alterations inevitably interfere with the provision of enteral nutrition and, if allowed to continue for any length of time, can delay the achievement of positive nitrogen balance and optimal nutritional status. Uncontrolled diarrhea can result in painful excoriations of the perineum and contamination of adjacent wound sites. These complications increase the nutritional needs of the patient since additional requirements are necessary for wound healing.[6] Diarrhea also impacts negatively on the efficiency of nursing care. Constant stooling results in soilage that necessitates frequent linen and dressing changes, both of which are time consuming. For the patient and the family members, the inability to control bowel movements and the frequent foul smell associated with diarrhea can be humiliating.[7] All health care team members have a vested interest in identifying the cause of diarrhea and implementing the appropriate steps for prompt resolution.

There are many causes of diarrhea in the critically ill tube-fed population and identifying the source can be a difficult task. Of the various mechanisms resulting in diarrhea, a relatively common cause is the ingestion of a poorly absorbed solute,[2] usually an indigestible or nonabsorbable sugar, such as lactose, lactulose, mannitol, sorbitol, or a divalent ion, such as magnesium. When such solutes enter the GI tract, fluid moves across the permeable intestinal epithelium causing an increase in the intraluminal water content. If the absorptive capacity of the distal GI tract is subsequently exceeded, diarrhea results. Osmotic diarrhea can be identified clinically by the termination of the diarrhea with fasting. Objective assessment by stool testing will reveal an elevated osmotic gap.[8] The tube feed is often initially suspected as the cause of diarrhea based on the popular beliefs that feeding formulae are hyperosmolar, lactose-containing, or are being delivered too rapidly. These beliefs are now being questioned as many enteral products on the market are iso-osmolar with plasma, lactose-free, and can be delivered at an appropriate rate through the use of enteral feeding pumps.[7,9] Even if the product selected is hyperosmolar, little information exists to support the belief of associated GI intolerance and the need to initiate the feed at dilute strengths.[9,10]

Many events occur concurrently with the initiation of tube feeding. Often this procedure prompts the conversion of medication adminis-

tration from the parenteral to the enteral route. In addition, other medications may be added to the drug regimen. Consideration of these changes is needed when attempting to identify the cause of diarrhea. An evaluation of the patient's drug therapy is necessary and should not be limited to a review of the active ingredients of drug products. The excipients and vehicle for various drug formulations must also be considered.

A frequent component of liquid dosage forms for enteral administration is sorbitol. The literature is scattered with case reports of sorbitol-induced diarrhea in the hospitalized individual.[2,5,11,12] One report identifies the sorbitol content of an oral theophylline solution as the cause of the diarrhea in a tube-fed patient.[2] An analysis of this case indicates that sorbitol in the potassium chloride solution was the most likely cause of diarrhea. Over the 12 hours spanning the initiation of diarrhea, the patient had been administered medications containing a total of 37 grams of sorbitol; a quantity sufficient to cause diarrhea.[13] Since no other precipitating factor (infection, prokinetic agent) could be identified, and the diarrhea subsided with the discontinuation of the sorbitol-containing medication, this pharmaceutical excipient appears to be the cause. Alterations in the enteral feeding product selection and rate were not implicated since these manipulations occurred after the onset of diarrhea. The possibility of underlying HIV disease or cotrimoxazole therapy causing diarrhea is remote since the diarrhea resolved within two days despite lack of treatment of HIV and continued therapy with cotrimoxazole. Since the patient had not demonstrated any GI intolerance to the enteral product or administration rate for considerable time prior to the initiation of diarrhea, the enteral nutrition was not considered causative. The time course of diarrhea is consistent with an osmotic diarrhea resulting from repetitive administration of an osmotic agent (sorbitol). The onset of diarrhea is confounded by manipulations in enteral feeding product selection and rate, and by the initiation of antidiarrheal therapy. The absence of diarrhea following the discontinuation of camphorated tincture of opium supports a minimal contribution of antidiarrheal therapy to the resolution of the diarrhea.

Sorbitol is a polyalcohol sugar that is found naturally in certain fruits and plants. For pharmaceutical purposes, it is synthesized for use as a sweetener to enhance the palatability of oral dosage formulations. Sorbitol is also used as a stabilizer and suspending agent to evenly distribute active ingredients in oral liquid formulations.[11] Sorbitol is absorbed slowly and incompletely by passive diffusion in the small intestine.[14,15] When ingested in sufficient amounts, sorbitol readily acts as a cathartic.[14,15] The adult cathartic threshold has been identified as approximately 20 to 50 g in the normal adult[13] with some individuals experiencing symptoms of gastrointestinal distress with as little as 5 to 10 g.[13,16,17] The concentration of sorbitol does not appear to be a factor in gastrointestinal intolerance.[15] The onset and resolution of sorbitol-induced diarrhea varies with the dose, frequency of administration, time interval between dosages, and with the individual. In general, ingestion of a cathartic dose of sorbitol results in diarrhea within three hours and lasts for two to three hours. With several doses six hours apart, constant stooling may result and continue for eight to sixteen hours.[18] An individual receiving single or multiple sorbitol-containing medications in normal therapeutic doses could readily exceed the cathartic threshold and experience diarrhea. Individuals with untreated celiac disease have a reduced tolerance to both the total quantity and concentration of sorbitol, a direct consequence of villous atrophy and a subsequent reduced absorption of hydrophilic solutes of low molecular weight.[15] If gastrointestinal tract changes which may occur with critical illness such as GI mucosal edema or villous atrophy[19] promote similar pharmacodynamic effects with the ingestion of sorbitol, diarrhea may be expected with smaller doses in this population than in healthy individuals. We suggest that the diarrhea reported in this case study was a direct consequence of the frequent administration of a cathartic dose of sorbitol in the form of a potassium chloride elixir. With the removal of the cathartic agent, the diarrhea abated.

Identifying the sorbitol content of pharmaceutical products can be difficult. Any liquid, oral dosage form should be considered a possible source of sorbitol whether it be labelled an elixir, solution or suspension. Presently, no regulations exist that require pharmaceutical manufacturers to identify the sorbitol content of drug products. The sorbitol content of selected pharmaceutical dosage formulations is listed in Table I. Most pharmaceutical manufacturers will disclose the sorbitol content when contacted directly and the address and phone number of Canadian pharmaceutical manufacturers are listed in the yellow pages of the *Compendium of Pharmaceuticals and Specialties (CPS).*[20] In addition, a publication entitled, *Caloric and Carbohydrate Content of Oral Pharmaceutical Products in Canada,*[21] provides the sorbitol content of selected products. Most hospital pharmacies will have a copy of this publication. Unfortunately, it is not published regularly so recently released products will not be listed.

In conclusion, nutritional support provided via enteral feeding tube is

Table I: Sorbitol Content of Selected Oral, Liquid Pharmaceutical Products*

Active Ingredient	Concentration (per 5 ml)	Manufacturer	Sorbitol (per 5ml)
Acetaminophen	80mg	Sterling	2mg
Acetaminophen	80mg	Horner	2932mg
Acetaminophen	160mg	McNeil	900mg
Aminophylline	105mg	Fisons	0mg
Amitriptyline	10mg	Merck, Sharpe & Dohme	3460mg
Chlorpromazine	25mg	Rhone-Poûlenc	0mg
Cimetidine	300mg	Smith Kline & French	2800mg
Cotrimoxazole	TMP40/SMX200	Roche	350mg
Digoxin	0.25mg	Burroughs-Wellcome	0mg
Dimenhydrinate	15mg	Horner	260mg
Diphenhydramine	12.5mg	Parke-Davis	0mg
Ferrous Sulfate	625mg	Mead Johnson	1545mg
Furosemide	20mg	Hoechst	3500mg
Metoclopramide	5mg	Nordic	0mg
Oxtriphylline	100mg	Parke-Davis	965mg
Phenytoin	125mg	Parke-Davis	0mg
Potassium Chloride	6.6mEq	Berlex	2500mg
Prochlorperazine	5mg	Rhone-Poûlenc	0mg
Ranitidine	75mg	Glaxo	350mg
Multivitamin (Pardec®)	Various	Parke-Davis	0mg
Multivitamin (Maltevol-12®)	Various	Horner	1025mg
Multivitamin (Infantol®)	Various	Horner	1300mg

* Sorbitol content obtained through communication with manufacturer (July, 1990) or from references 21 and 22.

an essential cornerstone of patient care in the critical care setting. The presence of diarrhea can significantly interfere with the provision of optimal nutrition support via the enteral route. Although the tube feeding itself is often initially suspected as the cause of diarrhea, this is often without justification. As demonstrated by this case report, consideration needs to be given to the sorbitol content of various liquid pharmaceuticals used in the treatment of critically ill patients. By quickly identifying and discontinuing the offending pharmaceutical product, unnecessary prolonged courses of diarrhea and the corresponding adverse nutritional consequences can be avoided.

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