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Treatment of Medication Intolerance with Lactase in a Complex Palliative Care Patient

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INTRODUCTION

Lactose intolerance is a clinical deficiency of the intestinal enzyme lactase, which is responsible for hydrolyzing the milk sugar lactose into glucose and galactose for absorption. Such a deficiency results in abdominal pain, distention, borborygmi, flatulence, diarrhea, or, occasionally, systemic symptoms such as muscle and joint pain, fatigue, eczema, and mouth ulcers upon ingestion of disaccharide (1). In children, symptoms can become severe and prolonged, and may also be associated with complications such as bacterial proliferation, dehydration, and metabolic acidosis. Infants with galactosemia, a condition in which galactose cannot be converted to the metabolically useful sugar glucose, experience similar illness with lactose ingestion (2). Lactose intolerance affects 33 to 50 percent of the world's population and becomes increasingly common with age, as most mammals lose 70 to 90 percent of their lactase enzyme within a few years of weaning (3, 4). Lactase deficiency varies widely with race: African American, Native American, Middle Eastern, and Asian populations have the highest incidence (60 to 90 percent), whereas only 10 percent of Scandinavian or European descendents are affected (5). While there is patient variation in tolerance, the majority experience gastrointestinal symptoms after the ingestion of approximately 10 g of lactose, equivalent to one glass of milk (5). Currently, diagnostic tests employ loads of 50 to 100 g of lactose, but the use of such high quantities has been questioned since sensitivity to lactose levels of 3 g or less has been demonstrated (5, 6). In fact, the modest presence of lactose as a bulking agent in pharmaceutical products has been the source of medication intolerance in several instances. We report the case of a complex pediatric patient who experienced such a reaction, and in whom treatment with exogenous lactase provided significant relief.

CASE REPORT

C.H., a three-and-a-half-year-old Caucasian boy, was admitted for a routine respite stay at a pediatric palliative care hospice in the fall of 2006. C.H. was born with complex congenital anomalies including pontine dysplasia, optic pituitary dysplasia, central diabetes insipidus, adrenal insufficiency, hypothyroidism, epilepsy, and gastric dumping syndrome associated with hypoglycemia. In 2004, a fundoplication procedure had been performed to manage his severe gastroesophageal reflux disease. Although there was no prior history of lactose intolerance, he was on an enteral lactose-free feed with a strict volume intake of 1,845 ml daily. In the summer of 2006, a dietary switch from the formula Peptamen Jr. (Nestlé Inc.) to Nutren Jr. (Nestlé Inc.) was concurrent with resolution of his dumping syndrome and hypoglycemia, as well as his seizures. Although these symptoms had resolved, C.H. continued to suffer from gastrointestinal discomfort and intense pain, manifested as sporadic screaming episodes and abdominal distention. C.H. communicated only via touch, since he could not see, hear or speak. C.H.'s mother described his symptoms as "neurological screeching;" his bloating was so intense that venting of his gastric tube using a syringe yielded 1,000 ml of gas at a time. C.H. was on a complex medication regimen that included desmopressin (Ferring Pharmaceuticals, 0.025 mg p.o bid, 0.05 mg p.o qhs), clonidine (Novopharm Ltd., 0.05 mg p.o qhs), hydrocortisone (Pfizer Inc., 3.5 mg p.o bid), clobazam (Novopharm Inc., 5 mg p.o daily), levothyroxine (Abbott Laboratories., 0.025 mg p.o daily), omeprazole (AstraZeneca Inc., 10 mg p.o bid), metronidazole (Apotex Inc., 180 mg p.o bid), morphine hydrochloride (ICN Pharmaceuticals, 1 mg p.o. q3h prn) and Microlax enemas (Pharmacia Inc., prn). Small bowel bacterial overgrowth was the working diagnosis for his gastrointestinal symptoms, and a formulation of *L. acidophilus* & *L. casei* (Bio-K+ International Inc., 30 ml p.o qid)

was given in addition to the metronidazole for this purpose. C.H.'s mother and the palliative care team finally resorted to morphine to alleviate his pain (1 mg three to four times daily), which calmed him down and induced sleep, but did not manage the gas and pain.

In September 2006, the pharmacist suspected lactose intolerance after discerning the number of tablets containing lactose as a binding agent, as per their drug monographs in the Compendium of Pharmaceuticals and Specialties (CPS) (7). Exogenous β -galactosidase with 3000 units of lactase activity (known under the generic name of lactase, Life Brand, 3000 Units) was initiated with C.H.'s medications and feeds, and he improved drastically. His screaming abated, his abdominal swelling decreased, and he was able to discontinue the morphine within three weeks. Metronidazole was also removed from his regimen within one month. C.H.'s abdominal girth also improved over subsequent weeks; according to his mother he eventually decreased by two pant sizes. Most notably, C.H. began to grow. For a full year prior to starting the lactase supplements he weighed 11 kg; within nine months after the lactase, he gained more than three kilograms. C.H. has since remained a more content boy, and the effect on his family has been equally positive.

DISCUSSION

Lactase deficiency varies widely in severity but the majority of patients can tolerate a dose of 12 to 18 g of lactose (8). Certain patients, however, have been noted to experience gastrointestinal symptoms after exposure to much lower quantities (6), and there appears to be no minimal threshold of lactose consumption required for inducing sensitivity. There have been documented cases of lactose intolerant individuals experiencing adverse reactions to the lactose filler in their medications (9-17). In one report, the onset of diarrhea, borborygmi, flatulence, and abdominal discomfort

followed the ingestion of flutamide capsules, which contain at least 210 mg of lactose each (11). In another case, inhalation of cromolyn sodium capsules containing only 20 mg of lactose each induced similar symptoms (10). It should be noted that up to 80 percent of the cromolyn dose inhaled from a turbuhaler can be swallowed, indicating that the patient reacted to an exposure of less than 16 mg of lactose.

Among the 10 medications that C.H. was taking, five contained lactose. The quantity of lactose in each of those medications is outlined in Table 1. C.H. had a total intake of approximately 360 mg of lactose per day. Consistent with previous case reports, this quantity is sufficient to induce medication intolerance in a highly sensitive lactase-deficient patient.

Symptoms of lactose intolerance occur when undigested lactose reaches the large intestine, osmotically draws in fluid, and is fermented by colonic bacteria (12). The precise pathogenesis of C.H.'s symptoms may not be entirely explained by this mechanism, since the quantity of lactose he consumed was so small relative to the symptoms he experienced. Petrini et al. have proposed a mucosal hypersensitivity, perhaps immune-mediated etiology for this type of reaction (9). It is clear, however, that lactase deficiency was the source of C.H.'s medication intolerance. A temporal relationship between lactase supplementation and clinical improvement supports this finding. Following the administration of lactase, three significant changes occurred: (1) the resolution of C.H.'s screaming and a drastic reduction in gastrointestinal distention, (2) the successful discontinuation of gastrointestinal and pain medications, and (3) an increased rate of weight gain. Although no hydrogen breath test or intestinal biopsy was performed to definitively diagnose lactose intolerance, C.H.'s case provides indirect but strong evidence that medication intolerance can occur due to the presence of lactose therein.

Table 1 / Lactose content of C.H.'s medications

Medication	Quantity of lactose per tablet (mg/tab) ^a	Daily dose (no. of tablets/day)	Daily lactose ingestion (mg/day)
DDAVP	unavailable ^b	1.0	unavailable
Novo-clonidine	89.0	0.5	44.5
Novo-clobazam	80.0	0.5	40.0
Synthroid	62.8	1.0	62.8
Cortef	300.0	0.7	210.0
Total			>357.3 mg/day

^a Obtained from contacting respective manufacturers

^b Not disclosed by manufacturer

CONCLUSION

After months of discomfort, treatment with exogenous lactase supplements alleviated the distress and pain in a complex palliative care patient. Many drug formulations contain lactose, owing to its useful physical and chemical properties as a diluent or filler in solid oral dosage forms. In the CPS alone, 795 drug monographs list lactose as a non-medicinal ingredient (a quick reference list can be found in the lilac pages of the CPS) (7). The lactose base in medications may cause a range of gastrointestinal symptoms, especially in sensitive lactose intolerant patients. Those who experience such symptoms should be evaluated for lactase deficiency and have their medications reconsidered, or receive appropriate treatment. Health care professionals should be aware of the potential harm that lactose fillers can cause, and lactose-free alternatives should be sought when possible.

Testimonial

"When the palliative team first approached us and suggested giving our son a lactase supplement with his meds we were very skeptical. With the amount of pain that our son suffered, including frequent hospitalizations due to feeding issues, it was difficult for us to understand that Lactaid could make such a difference. But when we did start it, it was not long before we saw a difference. He became a much happier little boy, caring for him was easier, the level of pain decreased, his abdomen decreased in size, hospitalizations decreased and he started growing developmentally. Sometimes the simpler things must be considered even in complex patients, and they can have a huge impact. Lactaid has changed our life."

– C.H.'s mother

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Conferences

July 19-22, 2009 – The 5th International Aids Society Conference on HIV Pathogenesis, Treatment and Prevention is being held at the International Convention Centre in Cape Town, South Africa. www.ais2009.org

September 10-11, 2009 – *Multiculturalism, Religions and Bioethics* is the theme of the European Association of Centres of Medical Ethics annual conference, being held in Venice, Italy, co-hosted by the University of Venice and Fondazione Lanza in Padua. <http://www.webethics.net/eacme2009/>

September 24-27, 2009 – *Together!* is the theme of the combined 10th Australian Palliative Care Conference and 8th Asia Pacific Hospice Conference at the Perth Convention Exhibition Centre in Perth, Australia. <http://www.conlog.com.au/palliativecare2009/> For information write to: conference@conlog.com.au

October 18-21, 2009 – *Voyages in Care and Understanding* is the theme of The Canadian Hospice Palliative Care Association conference being held at the Winnipeg Convention Centre, Winnipeg, Manitoba, Canada. <http://conference.chpca.net/> For information contact the national conference coordinator Michael Peterson at 1-800-668-2785 ext.225 or mpeterson@bruyere.org

October 28-29, 2009 – *The Space Between 2* is the name of the 2nd palliative care conference organized by Highland Hospice being held at Drumossie Hotel, Inverness, Scotland. For more information visit www.highlandhospice.org or call 01463 243132.

November 24-26, 2009 – *Making Life before Death Matter* is the theme of the Help the Hospices Conference being held at the Harrogate International Conference Centre, Harrogate, England. www.helpthehospices.org.uk/2009conference/ For more information, call Salma Masters 020 7520 2911 or write to conference@helpthehospices.org.uk