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Calcium ameliorates diarrhea in immune compromised children

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Abstract

Treatment of infectious diarrheas remains a challenge, particularly in immunocompromised patients in whom infections usually persist and resultant diarrhea is often severe and protracted. Children with infectious diarrhea who become dehydrated are normally treated with oral or intravenous rehydration therapy. Although rehydration therapy can replace the loss of fluid, it does not ameliorate diarrhea. Thus, over the past decades, there has been continuous effort to search for ways to safely stop diarrhea. Herein, we report three cases of immunocompromised children who developed severe and/or protracted infectious diarrhea. Their diarrheas were successfully “halted” within 1-2 days following the administration of calcium.

Keywords

calcium supplementation; diarrhea; Norovirus infection; Cryptosporidium infection; calcium-sensing receptor

Introduction

Acute infectious diarrhea remains a potentially lethal worldwide problem, particularly in infants, young children and immune compromised patients (1-2). While oral rehydration therapy is often used and is valuable for correcting dehydration, it does not “halt” the underlying intestinal fluid loss; its use in treating diarrhea has dropped significantly both by parents and practitioners (3). On the other hand, although there are a few anti-diarrheal therapies available or in development (4), they are limited by their expense, lack of availability and/or safety concerns. Thus, simple, safe and inexpensive novel anti-diarrheal therapies are needed. Based on our work on the role of CaSR (5-9), we assessed the effect of calcium supplementation to activate CaSR to treat infectious diarrhea in three immunocompromised children. Infectious diarrhea in these patients ceased within 1-2 days of oral/intravenous calcium administration.

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Case reports

Case 1

AB is an 8 month old boy with severe malnutrition and hypocalcemia who was referred for two weeks of worsening non-bloody watery diarrhea due to Norovirus gastroenteritis that had been unresponsive to nil per os, intravenous bicarbonate and rehydration therapy. His past medical history was significant for Hirschsprung's disease, intestinal lymphangiectasia and feeding difficulty. Findings on the initial physical examination revealed a malnourished and thin child with tachycardia, tachypnea, dry mucus membrane and a benign abdomen. His laboratory values and stool electrolyte analysis are shown in Table 1. Given the presence of severe hypocalcemia, he received daily intravenous calcium gluconate (1 meq/kg/day) replacement. Remarkably, as his serum ionized Ca^{2+} increased, his daily colostomy output decreased steadily (Fig. 1).

Case 2

CD is a 13 year old girl with pontine glioma receiving chemotherapy (irinotecan and avastin) complicated with CMV colitis who presented with one month of severe non-bloody watery diarrhea unresponsive to intravenous fluid replacement and high-dose loperamide. Given her low serum ionized calcium (Table 1), an intravenous calcium acetate (1 meq/kg/day, via total parenteral nutrition) replacement therapy was initiated. Two days after calcium was replaced and her hypocalcemia improved, her diarrhea stopped (Fig. 2).

Case 3

EF is a 10 year old Caucasian boy who presented with protracted diarrhea for three months due to Norovirus and cryptosporidium infections. His past medical history was significant for Down syndrome and posterior urethral valves leading to obstructive uropathy and end-stage renal disease, for which he underwent renal transplantation in 2004. Since then, he had been on maintenance mycophenolate mofetil, tacrolimus and low dose prednisone. Findings on initial physical examination revealed an obese but short child with tachycardia, dehydration and a benign abdomen. The diarrhea was watery and non-foul-smelling. Initially, the diarrhea was mild and intermittent. Within two months, it progressed to become daily and copious. His laboratory values are shown in Table 1.

He was initially treated with oral nitazoxanide (200 mg twice daily for seven days) and intravenous fluid rehydration. Diarrhea and metabolic acidosis worsened (Fig. 3). A decision was made to withhold all enteral intake, intravenous fluid administration was re-adjusted, and a sodium bicarbonate drip initiated. However, his diarrhea persisted (Fig. 3A). There were no abnormalities noted on esophagogastroduodenoscopy and colonoscopy.

Given his diarrhea worsened with nil per os, a diagnosis of secretory diarrhea was made, oral feeds resumed and a trial of oral calcium carbonate (650 mg trice daily, 1 meq/kg/day) started. The child's daily stool output before and after calcium administration is shown in Fig. 3A. Following calcium administration, diarrhea dropped significantly at day 1 and normalized at day 3 (Fig. 3A). Ten days later, the patient was discharged and calcium carbonate discontinued. Twelve days after discontinuation of calcium carbonate, diarrhea

recurred (Fig. 3A). Calcium therapy was restarted. One day after re-initiation of calcium therapy diarrhea stopped. Two days later, constipation developed. As a result, calcium carbonate was discontinued and constipation subsequently resolved. One week after discontinuation of calcium carbonate, diarrhea recurred again for the 3rd time, although it was less severe than the previous two episodes. Subsequent review of histology revealed positive cryptosporidium. Stool studies were positive for cryptosporidium. A 2nd course of nitazoxanide was given. To avoid constipation, calcium carbonate was not given this time; instead, he was given calcium-enriched dairy products. Two weeks later, his diarrhea resolved (data not shown). During the entire period of calcium treatment, the serum calcium levels were monitored and were within the normal range (ionized Ca^{2+} = 4.55-5.25 mg/dl) without evidence of hypercalcemia (Fig. 3B).

Discussion

This case series demonstrated that calcium administration might be effective in “halting” viral and parasitic diarrhea in immune compromised children. Complementing to our observations, Bovee-Oudenhoven et al have shown that calcium supplementation can reduce the severity and duration of bacterial diarrhea caused by *Escherichia coli* in human adult volunteers (10). Thus, calcium might be a general anti-diarrheal agent. Indeed, people taking high calcium diets are often constipated as are patients with hypercalcemia.

It is noteworthy that the calcium therapy can be re-used and its anti-diarrheal effect can be reproduced in the same patient multiple times without reduction of efficacy or development of resistance; it might even enhance the sensitivity to the therapy (patient 3; Fig. 3). While this seems unusual, it does go along with the known property of the calcium-sensing receptor (CaSR), the primary sensing mechanism of extracellular calcium (11). Unlike most of the G protein-coupled cell surface receptors where prior drug exposure induces “desensitization”, the CaSR is equipped with an unusual intracellular mechanism that enables to “refuse” agonist-induced receptor internalization (12). Nonetheless, it is important to note that the more rapid response to the second treatment seen in case 3 might also be simply related to diarrhea being less severe than it was at the time of the first treatment.

Figure 1 suggests a strong correlation between serum ionized calcium and stool output in patient 1. However, in patient 3, stool output was unrelated to serum calcium, and diarrhea was seen at serum calcium levels that were associated with little or no diarrhea in the first patient (Figure 1C). The reason for the discrepancy is unknown, but might be related to the differences between the two patients. For example, the level of serum calcium prior to therapy and the route of calcium supplementation were different between the two patients. Whereas patient 1 had hypocalcemia patient 3 did not; the latter's serum calcium levels prior to calcium supplementation were within normal ranges. Similarly, whereas patient 1 received intravenous calcium supplementation patient 3 did not; the latter received only oral calcium supplementation. Had luminal calcium levels been measured in patient 3, a correlation between luminal calcium and stool output might be existing as well.

Both direct and indirect mechanisms have been proposed to explain the calcium anti-diarrheal effect. First, calcium acts via specific interaction with the cell surface sensing

receptor CaSR in the gut (6-9). Second, calcium functions via nonspecific binding to pathogens, bile acids or fatty acids (10). Since calcium can achieve similar anti-diarrheal effect via a non mucosal route (patient 1 and patient 2), the nonspecific mechanisms seem less explanatory in this study.

In summary, our small case series suggests that the simple nutrient calcium might be useful in rapidly "halting" infectious diarrhea. Given its rapid action, its simplicity and its wide availability, this simple nutrient-based anti-diarrheal therapy would be particularly attractive as a treatment for diarrhea in infants and young children in the developing nations, both immune compromised and non compromised. Clearly, large-scale trials are needed to verify its efficacy and safety.

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Figure 1.

Colostomy output (**A**) and serum ionized Ca^{2+} (**B**) association with intravenous calcium replacement therapy in case 1. Note that the colostomy output response data appear to best fit to a two-phase response model (i.e., a rapid initial phase followed by a slow delayed phase). Initially, colostomy output is rapidly reduced as decreased serum Ca^{2+} increases. However, diarrhea does not completely stop as hypocalcemia is normalized; a near complete resolution of diarrhea is achieved only 4 days later when 7-day calcium therapy has completed. Nonetheless, the change in stool output is overall correlated negatively with the change in ionized Ca^{2+} (**C**). $r = -0.9087$, $P = 0.0007$.

Figure 2.
Stool volume association with intravenous calcium replacement therapy in case 2.

Figure 3.

Diarrhea response to oral calcium therapy in case 3. Calcium therapy can be repeated with neither reduction of efficacy or development of resistance (**A**) nor evidence of hypercalcemia (**B**). It seems that prior exposure to calcium sensitizes subsequent responses to calcium therapy; when diarrhea recurred, it was normalized within the same day when same dose of calcium was given.

Table 1

Baseline characteristics and diarrhea responses to calcium therapy

	Case 1	Case 2	Case 3
Age	8 mo	13 yr	10 yr
Sex	male	female	male
Predisposing condition	Malnutrition due to intestinal lymphangiectasia	Brain tumor on chemotherapy	Post transplantation on immunosuppressants
Type of enteral infection	Norovirus	CMV	Norovirus/cryptosporidium
	Acute	Sub-acute	Chronic
Type of diarrhea	Secretory	Secretory	Secretory & inflammatory
Labs at presentation			
Serum	Na, mM	129 (↓)	134
	K, mM	4.3	4.2
	Cl, mM	120 (↑)	103
	HCO ₃ , mM	6 (↓)	13.6 (↓)
	Ca (ionized) mg/dl	2.32 (↓)	2.9 (↓)
	Mg, mg/dl	1.1 (↓)	1.4 (↓)
	P, mg/dl	1.2 (↓)	3.0
	25-OH Vit D ₃ nl/ml	<5 (↓)	
	PTH,nLeq/ml	77 (↑)	
			18
Stool	Na, mM	131	
	K, mM	8.8	
	Cl, mM	122	
	Osmotic gap mOsm	10	
			29
Calcium therapy			
Form	Ca gluconate	Ca acetate	Ca carbonate
	Dose	1 meq/kg/day	1 meq/kg/day
	Route	IV drip	via TPN
Diarrhea response			
Onset @	day 1	day 1	day 1
	Cessation @	day 2	day 3**
Adverse effect of calcium	none	none	mild constipation

* The diarrhea response curve (Fig. 1) suggests a partial or two-phase (rapid and delayed) response.

** Prior exposure to calcium appears to sensitize subsequent responses to calcium therapy. Thus, when diarrhea recurred, it was normalized within the same day (24 hours) when same dose of calcium was given (see Fig. 3).