

## Brief Report

## PROTON-PUMP INHIBITION OF GASTRIC CHLORIDE SECRETION IN CONGENITAL CHLORIDORRHEA

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**I**N 1945 Gamble et al.<sup>1</sup> and Darrow<sup>2</sup> reported on two infants with severe congenital diarrhea, in back-to-back articles with identical titles. Both infants had very high stool chloride concentrations, low urinary chloride excretion, hypochloremia, metabolic alkalosis, and hypokalemia. Gamble et al. concluded that the disease was caused by abnormal secretion of chloride into the intestine, and they named it congenital alkalosis with diarrhea. Darrow believed that the primary defect was intestinal chloride malabsorption, but he gave much of the credit for characterizing the disorder to Gamble et al. and used the name they had chosen.

Subsequent studies supported Darrow's belief that the disease was caused by chloride malabsorption and that alkalosis was not a necessary manifestation. The disorder therefore became known as congenital chloridorrhea<sup>3</sup> or congenital chloride diarrhea.<sup>4</sup> Inherited as an autosomal recessive trait,<sup>5-7</sup> the disease causes intrauterine and lifelong diarrhea.<sup>4,8,9</sup> Excessive fecal losses lead to electrolyte and water deficits, which in turn cause volume depletion, hyperreninemia, hyperaldosteronism, renal potassium wasting, and sometimes nephropathy.<sup>8,10-12</sup> Intestinal perfusion studies have revealed a defect in the ileal and colonic chloride-bicarbonate exchange transporter that normally mediates active chloride absorption.<sup>13-17</sup>

Therapy consists of oral supplements of sodium and potassium chloride. Through passive diffusion, most patients can absorb enough chloride from these salts to prevent severe chloride depletion, but most of the supplemental chloride is not absorbed, which exacerbates the diarrhea. The dilemma was best expressed by Gamble et al.: "A small elevation can be sustained only under pressure of a large intake of chloride which is not quite offset by a greatly

increased outgo in the stools; even so the margin is narrow and uncertain."<sup>1</sup> No therapy improves net chloride absorption or reduces the severity of the diarrhea. Drugs that have been used to no avail include theophylline, acetazolamide, prednisone, spironolactone, cholestyramine, ketoprofen, indomethacin, and codeine.<sup>17-25</sup>

We report on a patient with congenital chloridorrhea whom we recently evaluated because of severe diarrhea and hypokalemia. Our studies were motivated by the hope of finding a way to reduce his diarrhea and to make him less dependent on intravenous fluid therapy. Both goals were realized by using a proton-pump inhibitor to reduce gastric chloride secretion.

### CASE REPORT

The patient was a 34-year-old man who had had severe diarrhea since birth. His parents and three siblings did not have diarrhea. In early childhood he had been hospitalized many times because of volume depletion and hypokalemia. At the age of two years, he was given the diagnosis of congenital alkalosis with diarrhea and was treated with oral salt supplements, as recommended by Darrow<sup>2</sup> and by Gamble et al.<sup>1</sup> His early growth and physical development were delayed. At 23 months, he could sit but not stand or talk. His siblings were highly antagonistic toward him, because he would have diarrhea at any time and smelled bad, and they could not invite guests to the home. After the age of four years, he was raised by foster parents. He graduated from high school in a special-education class.

The diarrhea and its management have been the focus of his life. As an adult, he has had great difficulty obtaining and keeping a job because of diarrhea, fecal incontinence, and the need for frequent hospitalizations. He had an average of 6 stools per day, with as many as 12 on some days. The stools were large in volume and liquid. Most bowel movements were associated with urgency and many with fecal incontinence. He had no abdominal pain or gastrointestinal bleeding. His treatment included oral supplements of potassium chloride, diphenoxylate with atropine, and a lactose-free diet. He was frequently admitted to the hospital or to an emergency department for intravenous fluid therapy to correct volume depletion and hypokalemia. He also had a manic-depressive disorder requiring treatment with paroxetine and amitriptyline.

Endoscopic and x-ray studies of the patient's gastrointestinal tract, performed on several occasions, were normal. In the most recent evaluation, performed just before his referral to Baylor University Medical Center, upper and lower endoscopic studies and biopsies of the duodenum and colon were normal, with no evidence of intestinal parasites, and the serum vasoactive intestinal polypeptide concentration was also normal. Except for moderate obesity (weight, 214 lb [97.3 kg]; height, 69 in. [1.8 m]), the patient's physical examination was normal.

### RESULTS

The patient was studied as an outpatient, except when hospitalized for the administration of intravenous fluids (so that stool output during a 48-hour fast could be measured). Paroxetine and amitriptyline were continued, except during the period of fasting. Our protocol for evaluating chronic diarrhea was approved by an institutional review committee, and informed consent was obtained from the patient.

While the patient was eating an unrestricted diet, the stool volume was 2.21 liters per day and the fe-

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**TABLE 1.** EXCRETION OF WATER AND ELECTROLYTES IN STOOL AND URINE IN A PATIENT WITH CONGENITAL CHLORIDORRHEA.

PERIOD OF STOOL AND URINE COLLECTION	VOLUME liters/day	pH	OSMOLALITY mOsm/kg	ELECTROLYTE CONCENTRATION				ELECTROLYTE OUTPUT			
				SODIUM	POTASSIUM	CHLORIDE	BICARBONATE	SODIUM	POTASSIUM	CHLORIDE	BICARBONATE
				mmol/liter				mmol/day			
During regular diet											
Stool*	2.21	6.43	293	90	37	139	1	199	82	308	2
Urine	0.96	6.07	685	146	66	0	42	141	64	0	41
During fast with intravenous fluids											
Stool*	1.31	6.53	297	106	35	155	3	139	46	204	4
During omeprazole therapy with regular diet											
Stool†	1.73	5.58	312	80	44	153	3	138	76	264	6
Urine	0.97	6.58	871	133	42	3	14	129	41	3	13

\*Stools were collected over a 48-hour period.

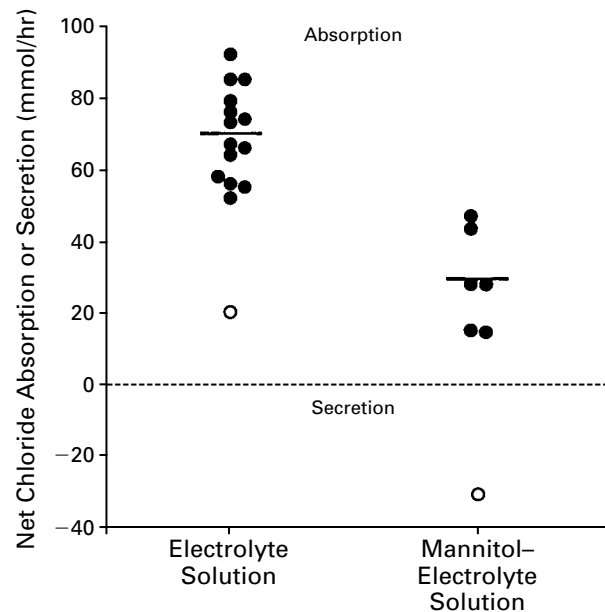
†Stools were collected over a 72-hour period.

cal chloride concentration (139 mmol per liter) was higher than the sum of the fecal sodium and potassium concentrations (Table 1), a typical finding in patients with congenital chloridorrhea. The fecal fat excretion was 7.8 g per day. The urinary chloride concentration was zero. During the fast, the stool volume and fecal chloride output were 59 and 66 percent, respectively, of the values obtained when the patient was not fasting.

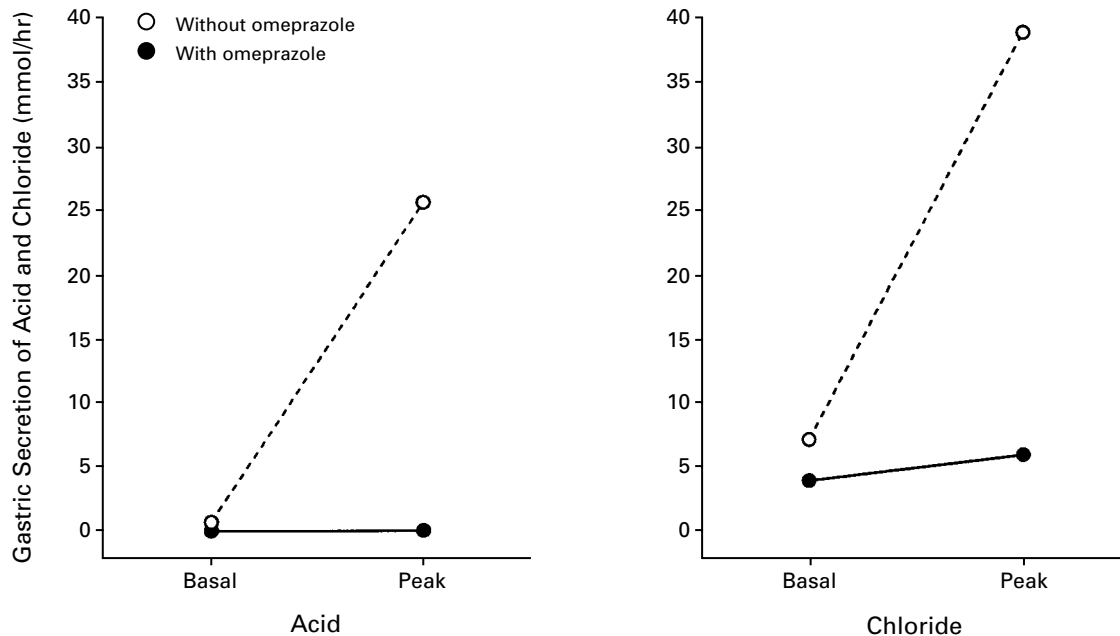
Intestinal chloride absorption was evaluated by total gut perfusion.<sup>26</sup> When the perfusion fluid was a balanced electrolyte solution, the rate of chloride absorption was low (Fig. 1). When the perfusion fluid contained mannitol, so that absorption had to take place against a concentration gradient, the intestine secreted chloride.

Gastric secretion was measured after an overnight fast. Gastric fluid was obtained for one hour before and one hour after the administration of pentagastrin in a dose that elicits maximal gastric acid secretion. Before treatment with omeprazole was initiated, gastric secretion of acid and chloride was within normal limits.<sup>27</sup> Treatment with omeprazole caused a marked inhibition of acid and chloride secretion (Fig. 2). Pentagastrin-stimulated chloride secretion was 39 mmol per hour before the administration of omeprazole and 6 mmol per hour after its administration. Assuming that parietal-cell secretion of chloride was completely inhibited by omeprazole, as was parietal-cell secretion of acid, the difference of 33 mmol per hour represents the rate of parietal-cell secretion of chloride after the administration of pentagastrin, when secretion was uninhibited. The residual output of 6 mmol of chloride per hour presumably represents chloride secreted by nonparietal gastric cells and chloride in swallowed saliva.

On the premise that omeprazole also inhibits gas-



**Figure 1.** Net Gastrointestinal Absorption or Secretion of Chloride during Perfusion of the Gastrointestinal Tract with Two Isotonic Solutions Containing a Nonabsorbable Marker in Normal Subjects (●) and a Patient with Congenital Chloridorrhea (○). The perfusion rate was 30 ml per minute. Unabsorbed fluid was collected by a rectal tube, and net absorption or secretion was calculated with standard equations.<sup>26</sup> The electrolyte concentrations in the balanced perfusion solution were as follows: sodium, 145 mmol per liter; potassium, 4 mmol per liter; chloride, 105 mmol per liter; and bicarbonate, 40 mmol per liter. In the mannitol-electrolyte solution, the concentrations were as follows: sodium, 110 mmol per liter; potassium, 4 mmol per liter; chloride, 75 mmol per liter; bicarbonate, 40 mmol per liter; and mannitol, 60 mmol per liter. The horizontal lines show the mean values for the normal subjects.



**Figure 2.** Effect of Treatment with Omeprazole (20 mg Twice Daily) on Gastric Secretion of Acid and Chloride in a Patient with Congenital Chloridorrhea.

Basal refers to the secretion rate without stimulation. Peak refers to the peak secretion rate after the subcutaneous injection of 6  $\mu$ g of pentagastrin per kilogram of body weight.

tric chloride secretion stimulated by food, the patient was treated with 20 mg of omeprazole twice daily. During omeprazole therapy with an unrestricted diet, the daily stool volume and fecal chloride secretion fell to 1.73 liters and 264 mmol, respectively (Table 1). Before omeprazole therapy, the fecal volume with an unrestricted diet exceeded the fasting fecal volume by 0.9 liter per day, whereas during omeprazole therapy, the fecal volume exceeded the fasting volume by only 0.4 liter per day. Urinary chloride output during treatment with omeprazole was 3 mmol per day, as compared with zero before treatment, indicating a positive chloride balance, with a high enough level of intestinal absorption to replace losses in sweat so that at least some chloride was excreted in the urine.

The patient returned to his home taking 20 mg of omeprazole twice daily, as well as oral potassium supplements. During eight months of follow-up, the number of stools decreased to two to four per day, with no fecal incontinence. He now has only occasional episodes of hypokalemia, at least one of which occurred after he had discontinued the potassium supplements. Serum electrolyte concentrations and renal function have remained normal, and the patient has returned to work.

#### DISCUSSION

The persistence of a high fecal chloride output during fasting in this patient indicated that substan-

tial amounts of fecal chloride were endogenous, as Gamble et al. suggested.<sup>1</sup> However, a high level of fecal excretion of endogenous chloride does not necessarily mean that chloride is secreted into the intestine at an abnormally high rate. In normal people, large amounts of chloride-containing fluids are secreted into the intestine, even during fasting<sup>28,29</sup>; the chloride and other ions in these fluids are completely reabsorbed in the ileum and colon, so that there is no fecal fluid output during fasting. Since our patient had severe intestinal chloride malabsorption, fecal excretion of chloride during fasting may have been due to a failure to reabsorb normal amounts of chloride secreted into the intestine. The same defect would cause malabsorption of dietary chloride and worsening of diarrhea when food is ingested.

These considerations led to the hypothesis that the patient might have less diarrhea if gastric chloride secretion were reduced. The gastric parietal cells are a rich source of secreted chloride. After the patient received pentagastrin, the parietal cells secreted chloride at a rate of approximately 33 mmol per hour. Although there are no methods for measuring gastric chloride secretion in response to food, it is probably similar to gastric acid secretion in response to food, which can be measured. Food stimulates nearly maximal rates of gastric acid secretion for about two hours after ingestion.<sup>30</sup> Assuming that parietal-cell secretion of chloride also occurs at maximal

rates for two hours after a meal, when the patient ate, the gastric parietal cells secreted about 66 mmol of chloride into his stomach. With three meals, the total parietal-cell chloride secretion would be 198 mmol per day — a substantial chloride load derived entirely from endogenous stores. We hypothesized that omeprazole would inhibit food-stimulated chloride secretion, as it inhibited chloride secretion stimulated by pentagastrin.

Treatment with omeprazole was associated with reductions in the volume and frequency of stools and the cessation of incontinence. It seems reasonable to propose that this improvement was due to the inhibition of gastric chloride secretion, which should not only protect endogenous chloride stores but also reduce the amount of chloride presented to the intestine, thereby reducing the amount of unabsorbed chloride in the stool and reducing the cations and water that need to be excreted to maintain electrical and osmotic equilibrium. Theoretically, the benefit of omeprazole could have been due in part to the inhibition of chloride secretion by the intestine. However, this is an unlikely explanation, since omeprazole is a prodrug that requires high acidity for localization and activation, and parietal cells, but not intestinal cells, provide such an environment.

In patients with congenital chloridorrhea, the oral intake of chloride, sodium, and potassium must exceed their fecal output (i.e., there must be a positive gastrointestinal balance) so that obligatory losses in sweat can be replaced. A positive balance can best be ensured by a high intake of chloride, even though it exacerbates diarrhea. We believe that the suppression of gastric chloride secretion by a proton-pump inhibitor reduces fecal electrolyte losses in patients with congenital chloridorrhea and thus promotes a positive gastrointestinal balance. However, this treatment does not reduce the need for careful monitoring of dietary intake, serum electrolyte concentrations, and urinary chloride excretion.

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