Paralytic Ileus Accompanied by Pneumatosis Cystoides Intestinalis after Acarbose Treatment in an Elderly Diabetic Patient with a History of Heavy Intake of Maltitol

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Abstract

An 87-year-old woman, diagnosed with diabetes mellitus at age 73, exhibited abdominal distention and appetite loss in March 1998. She had received acarbose as well as 5 mg per day of glibenclamide and had habitually used about 100 g of maltitol daily from 1997. She was diagnosed as having paralytic ileus accompanied by pneumatosis cystoides intestinalis (PCI). This condition subsided quickly with discontinuation of diet or cessation of acarbose and maltitol usage. The patient's condition appears to be attributable to increased gas levels produced by fermentation of disaccharides and maltitol. Decreased intestinal motility may be a result of pre-existing diabetic autonomic neuropathy and hypothyroidism. The patient's clinical course suggests that paralytic ileus and PCI should be listed as rare side effects of alpha-glucosidase inhibitors and that the drug should be used with great caution for those who consume non-digestive sugar substitutes. (Internal Medicine 39: 826–829, 2000)

Key words: alpha-glucosidase inhibitors, non-digestive sugar substitutes, bacterial fermentation

Introduction

Acarbose is a new hypoglycemic agent that can suppress postprandial hyperglycemia by delaying absorption of carbohydrates in the small intestine through antagonistic as well as dose-dependent suppression of alpha-glucosidase (1). The hypoglycemic agent's side effects are abdominal distention and increased flatus due to the increased levels of intestinal gas (2). This mechanism is attributed to fermentation of intestinal bacteria that forms metabolites like carbon dioxide, methane and hydrogen from undigested carbohydrates (3). Some diabetic patients use sugar substitutes in cooking and thus consume these artificial products instead of digesting sweets with

glucose. Maltitol is a sugar substitute that is a kind of disaccharide and is considered more difficult to digest and absorb than sucrose, and produces a less-marked blood glucose response than sucrose (Fig. 1). Non-digestive sugar substitutes like maltitol are metabolized by fermentation of intestinal bacteria into carbon dioxide and hydrogen (4). In the recent case of an elderly diabetic patient with a history of heavy maltitol intake, paralytic ileus was found accompanied by PCI after acarbose treatment.

Case Report

An 87-year-old Japanese female had been diagnosed as non-insulin-dependent diabetes mellitus in 1984. Family history indicated a brother with the same disorder.

At 58 years of age, the patient had gastric ulcer that was treated by doctors at another hospital; a partial gastrectomy was performed using the Billroth-I method. Starting in 1996, the patient had received 5 mg per day of glibenclamide, but the patient's postprandial blood glucose level after two hours remained as high as 306 mg/dl. The patient had received 150 mg per day of acarbose in addition to glibenclamide dosage; in 1997, the patient also began habitually using about 100 g per day of maltitol. The patient's diabetic complication was compounded with background diabetic retinopathy and an atonic bladder, and she received a cholinergic agent, bethanechol chloride, starting in 1996. She had previous complications of severe constipation.

The patient had experienced occasional abdominal distention in January 1998 and was hospitalized on March 9th because of abdominal distention and loss of appetite that lasted for 3 days. On admission, the patient's height, weight, and body temperature was recorded as 142.0 cm, 31.0 kg, and 35.0°C, respectively. The patient's blood pressure was 120/70 mmHg; her heart rate was regular and 60 beats per minute. The patient was conscious and coherent. Upon physical examination, no goiter was present. Heart sounds were clear and the rhythm was regular without audible murmurs; breath sounds were normal without rales or bronchial obstruction. The abdomen

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Figure 1. Structural formula of maltitol.

Table 1. Laboratory Data on Admission

Urinalysis		Na	144 mEq/l
protein	(-)	K	3.8 mEq/l
glucose	(-)	Cl	104 mEq/l
ketone body	(-)	Ca	7.8 mg/ml
WBC	4,360/ μ l	IP	2.4 mg/ml
RBC	329 $\times 10^4$ / μ l	BUN	22 mg/dl
Hb	10.2 g/dl	Cr.	0.6 mg/dl
Ht	30.6%	U.A.	5.3 mg/dl
MCV	93 fl	T.P.	5.4 g/dl
Plt.	15.7 $\times 10^4$ / μ l	ZTT	0.5 U
ESR	15 mm/h	TTT	0.8 U
CRP	0.30>mg/dl	GOT	29 IU/l
BG	270 mg/dl	GPT	17 IU/l
HbA _{1c}	8.0%	LDH	654 IU/l
		ALP	303 IU/l
		γ -GTP	26 IU/l
		T.chol.	152 mg/dl
		HDL-chol.	43 mg/dl
		T.G.	65 mg/dl
		Amy.	90 IU/l
		CPK	75 IU/l

showed a noticeable generalized distention; the contour of distended intestinal loops were observed and bowel sounds were absent. On palpation, crepitation was audible without tenderness and muscular defense in the area. Neurological examination revealed diminished vibratory sensation in the lower extremities. Deep tendon reflexes of the lower extremities were diminished. Routine laboratory tests indicated that the white blood cell count was normal and CRP was negative (Table 1). Thyroid function fit that of a typical primary hypothyroid pattern (Table 2). An X-ray film of the abdomen revealed noticeable gaseous distension of the small intestine (Fig. 2). Computerized tomography of the abdomen revealed noticeable gas-

Table 2. Endocrinological Data

	9/3	19/3	6/4	7/5
TSH (0.40-4.45 mU/ml)	9.13	12.23	1.43	0.65
fT ₄ (0.95-1.53 ng/dl)	0.79	0.79	1.25	1.32
fT ₃ (3.7-5.5 pg/ml)	2.0	2.4	2.4	2.2
Thyroid test			100>	
Microsome test			100>	
TRAb (10%>)			4.1%

Figure 2. X-ray film of the abdomen showing noticeable gaseous distension of the small intestine.

eous distension of the small intestine with pockets of small gas bubbles in the submucosal space (Fig. 3). Barium enema examination revealed no constriction in the sigmoid or lower descending colon. The endoscopy showed no narrowing of the upper gastrointestinal tract.

The patient was diagnosed as having paralytic ileus accompanied by PCI. Diet was discontinued and use of maltitol and other medications, including acarbose, halted. Along with these measures, drip infusion of 500 ml Ringers solution and 1,500 ml Solita T₃ solution were administered for one day. The symptoms subsided and radiological indications of the ileus disappeared on the 5th hospital day (Fig. 4). The condition did not reappear during the period of hospitalization. On the 13th day, levothyroxine sodium 25 μ g per day was initiated; on the 27th day, measurements of thyroid functions returned to normal lev-

Figure 3. Computerized tomography of the abdomen showing noticeable gaseous distention of the small intestine with pockets of small gas bubbles in submucosal space (arrows).

Figure 4. Computerized tomography of the abdomen showing disappearance of gaseous distention of the small intestine.

els (Table 2).

Discussion

It has been reported that diabetic autonomic neuropathy and hypothyroidism decrease intestinal motility (5, 6). Although it is assumed that the patient's diabetic autonomic neuropathy caused atonia in the bladder, diabetics have rarely suffered from paralytic ileus. In the present case, prior to receiving the levothyroxine sodium, the paralytic ileus had begun to improve. Thus, this clinical course suggests that other factors in addition to diabetic autonomic neuropathy and hypothyroidism were responsible for the decrease in intestinal motility.

Previous research has shown that the development of ileus is affected by acarbose (7). An ileus is not only mechanical, but also paralytic (8). Causes for these conditions are related to fermentation processes of intestinal bacteria that produce carbon dioxide, methane and hydrogen from undigested carbohydrates. However, the possibility remains that other factors cause paralytic ileus, since only a single case exists with paralytic ileus after taking acarbose. The patient had from 1997 habitu-

ally used about 100 g per day of maltitol instead of consuming sweets. Maltitol is metabolized into carbon dioxide and hydrogen by fermentation. General guidance in patient consumption of maltitol is for a maximum daily intake of 10 g–30 g per day. In this case study, the patient suffered from two conditions: decreased intestinal motility due to diabetic autonomic neuropathy and hypothyroidism, as well as paralytic ileus due to intestinal bacteriological fermentation of administered acarbose and large amounts of maltitol that formed excess gas from undigested disaccharides.

In this case study, paralytic ileus was accompanied by PCI. Etiology for PCI has been categorized by either mechanical or bacterial theories (9). Neonatal necrotizing enterocolitis and jejunoileal bypass operations for obesity have provided observation of bacterially-attributed PCI due to bacterial overgrowth and gas formation in the intestine with increased permeability of intestinal mucosa to gas-forming bacteria (10, 11). It has been reported that lactulose, a disaccharide which is more difficult to digest, and is fermented by intestinal bacteria, may aggravate PCI symptoms (12). Recently, researchers reported that an alpha-glucosidase inhibitor, voglibose, may be a causative factor for PCI (13). In the present case, it is thought that disaccharides or maltitol were fermented by intestinal bacterial to generate a large volume of gas and intestinal functions were decreased due to diabetic autonomic neuropathy and hypothyroidism. Apparently, the increased gas volume and decreased intestinal functions resulted in elevation of the inner pressure of the intestine to increase the permeability of the intestinal mucosa to gas-forming bacteria. The degree of involvement of both alpha-glucosidase inhibitor and maltitol in the onset of PCI has not been clarified, however. Furthermore, abdominal palpation during admission revealed audible crepitation caused by pockets of small gas bubbles in intestinal submucosal space; this finding was confirmed by computerized tomography of the abdomen.

Medical personnel should closely observe patients for the onset of paralytic ileus and PCI whenever diabetic patients receive alpha-glucosidase inhibitors. Furthermore, it is important to examine for symptoms of these conditions, such as abdominal distention and increased flatus, when diabetic patients receive alpha-glucosidase inhibitors and have been consuming non-digestive sugar substitutes like maltitol.

References

- 1) Joubert PH, Venter HL, Foukaridis GN. The effect of miglitol and acarbose after an oral glucose load: A novel hypoglycemic mechanism? *Br J Clin Pharmacol* **30**: 391–396, 1990.
- 2) Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. *Ann Intern Med* **121**: 928–935, 1994 (see comments).
- 3) Coniff RF, Shapiro JA, Seaton TB, Hoogwerf BJ, Hunt JA. A double-blind placebo-controlled trial evaluating the safety and efficacy of acarbose for the treatment of patients with insulin-requiring type II diabetes. *Diabetes Care* **18**: 928–932, 1995.
- 4) Oku T, Akiba M, Lee MH, Moon SJ, Hosoya N. Metabolic fate of ingested [^{14}C]-maltitol in man. *J Nutr Sci Vitaminol (Tokyo)* **37**: 529–544, 1991.

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- 5) McNally EF, Reinhard AE, Schwartz PE. Small bowel motility in diabetics. *Am J Dig Dis* **14**: 163–169, 1969.
 - 6) Faulk DL, Anuras S, Christensen J. Chronic intestinal pseudoobstruction. *Gastroenterology* **74**: 922–931, 1978.
 - 7) Nishii Y, Aizawa T, Hashizume K. Ileus: a rare side effect of acarbose. *Diabetes Care* **19**: 1033, 1996 (letter).
 - 8) Odawara M, Bannai C, Saitoh T, Kawakami Y, Yamashita K. Potentially lethal ileus associated with acarbose treatment for NIDDM. *Diabetes Care* **20**: 1210–1211, 1997 (letter).
 - 9) Priest RJ, Goldstein F. Pneumatosis cystoides intestinalis. in: *Gastroenterology*. 4th ed. W.B. Saunders Co., Philadelphia, 1985: 2474–2483.
 - 10) Seaman WB, Fleming RJ, Baker DH. Pneumatosis intestinalis of the small bowel. *Semin. Roentgenol* **1**: 234–242, 1966.
 - 11) Sicard GA, Vaughan R, Wise L. Pneumatosis cystoides intestinalis: An unusual complication of jejunoileal bypass. *Surgery* **79**: 480–484, 1976.
 - 12) Ellis BW. Symptomatic treatment of primary pneumatosis coli with metronidazole. *Br Med J* **280**: 763–764, 1980.
 - 13) Hayakawa T, Yoneshima M, Abe T, Nomura G. Pneumatosis cystoides intestinalis after treatment with an α -glucosidase inhibitor. *Diabetes Care* **22**: 366–367, 1999 (letter).
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