—**Report on Experiments and Clinical Cases**—

Ileus After Administration of Cold Remedy in an Elderly Diabetic Patient Treated with Acarbose

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Abstract

A 69-year-old type 2 diabetic man was admitted due to diabetic gangrane. He had a history of subtotal gastrectomy. During hospitalization, he was treated with regular insulin and 300 mg/day of acarbose. He developed a low grade fever, cough and nasal discharge, and was given a compound "cold" remedy with anticholenergic properties. The next day, he suffered from a paralytic ileus. Oral intake and acarbose were withheld and the ileus spontaneously resolved after 2 days. These finding indicate the possibility that the ileus was triggered by drugs with anticholinergic properties in this elderly diabetic patient treated with α-glucosidase inhibitors. (J Nippon Med Sch 2001; 68: 61—64).

Key words: acarbose, α-glucosidase inhibitor, elderly, diabetes mellitus, ileus

Introduction

Acarbose, an α-glucosidase inhibitor, interferes with the degradation of starches, dextrins, maltose, and sucrose into monosaccharides, and its hypoglycemic effect in patients with type 2 diabetes mellitus is well established[1-3]. Acarbose are believed to be a safe agent, and severe side effects have rarely been reported. However, recent reports reveal the existence of a potential risk of developing ileus from α-glucosidase inhibitors[4-7].

We encountered an elderly diabetic patient treated with acarbose who developed ileus which was triggered by administration of drugs with anticholinergic properties for the common cold.

Case Report

A 69-year-old type 2 diabetic man was admitted due to diabetic gangrane on 19 February 1999. He underwent a subtotal gastrectomy for gastric cancer in 1988. Type 2 diabetes mellitus was also diagnosed at that time. He had been treated with insulin for diabetes mellitus in our outpatient department. His blood glucose control was poor. Bilateral foot numbness was noted at age 67. He started 300 mg/day of acarbose t.i.d. before each meal on 11 November 1997. His family history revealed that his mother had type 2 diabetes mellitus. He had a smoking history from age of 20 to 50 years old (50 cigarettes/day) and used to drink 360 cc of sake every evening.

On admission, he was 160 cm in height and 52 kg in weight (body mass index 20.3). He had a temperature of 37.0℃, a heart rate of 80 beats/min (regular), and a blood pressure of 138/78 mmHg. He had diabetic retinopathy (Scott III_a) on funduscopic examination. There was no abnormality in his chest or abdomen and there was no lymphadenopathy. Arteria pedia dorsalis pulse was palpable on both sides. The tendon

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reflexes were symmetrically diminished in the lower limbs. There was paresthesia and diminished vibration sense in the lower limbs.

Urinalysis showed glycosuria (+) and proteinuria (2+). Liver function and electrolyte levels were normal. C-reactive protein (CRP) was 0.5 mg/dl, fasting plasma glucose: 193 mg/dl, HbA1C: 10.3%, total cholesterol: 203 mg/dl, high density lipoprotein (HDL)-cholesterol: 71 mg/dl, triglyceride: 63 mg/dl, BUN: 25.9 mg/dl and serum creatinine 1.66 mg/dl. The urinary albumin excretion rate was 479 mg/day. His creatinine clearance was 38.8 l/day. Chest X-ray and abdominal X-ray revealed no abnormality, and an electrocardiogram showed a normal range. An abdominal echogram and computed tomography (CT) scan showed no abnormality in the pancreas or spleen.

During hospitalization, he was treated with 24 units of regular insulin and 300 mg/day of acarbose. On February 25,1999, the patient developed a low grade fever, cough, nasal discharge and was given 3.0 g/day of PL® granule (Sankyo Co. Ltd., Tokyo). The next day, he suffered from sudden abdominal pain, nausea and vomiting. His abdomen was distended and tympanitic with diffuse tenderness and absent bowel sounds. Abdominal X ray showed abnormal accumulation of gas in the intestines with niveau (**Fig. 1**), indicating a paralytic ileus. At this time, the leukocyte count was 5,300/mm^3 with granulocytosis, and C-reactive protein was 0.4 mg/dl. Random sample plasma glucose was 186 mg/dl, and urinary ketone bodies were negative. The laboratory data were otherwise unremarkable. Fluid and antibiotics (piperacillin sodium of 2 g/day) were given, and oral intake and acarbose were withheld. After 2 days, the ileus spon-

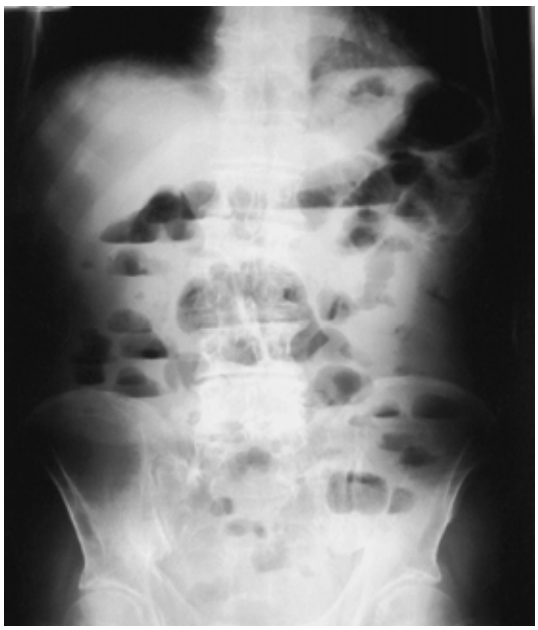

Fig. 1 Abdominal X-ray showing abnormal accumulation of gas in the intestines with niveau, indicating a paralytic ileus.

Table 1 The clinical characteristics of cases of ileus associated with α-glucosidase inhibitors treatment

No	Author	Age/ Sex	Medicine	Dose (mg/day)	Period	Therapy/ Prognosis	Past history
1	Ohno T[6] (1995)	75/M	Acarbose	100 → 200	1M	Conserv.	
2		68/M	Acarbose	150	12D	Died	Ilus operated
3		63/M	Acarbose	150 → 300	3M	Conserv.	Appe.
4		75/F	Acarbose	300	2M	Conserv.	
5		71/F	Acarbose	150	1M	Operated	Appe.
6		70/F	Acarbose	150	2M	Operated	Hystere.
7		66/M	Voglibose	0.6 → 0.9	1M	Conserv.	Appe. Gastrec.
8		62/F	Voglibose	0.6	6D	Conserv.	Appe. Hystere.
9	Hayashi R[7] (1996)	63/F	Voglibose	0.6	15D	Conserv.	
10	Nishii Y[5] (1996)	39/F	Acarbose	150 → 300	1M	Conserv.	
11	Odawara M[4] (1997)	49/F	Acarbose	100 → 150	1M	Conserv.	
12	Present case	69/M	Acarbose	300	15M	Conserv.	Appe. Chole.

→: increased dosage, M: month(s), D: days, Conserv.: conservative therapy, Appe.: appendectomy, Hystere.: hysterectomy, Gastre.: gastrectomy, Chole.: cholecystectomy

taneously resolved. Ileus did not recur and he has been free from any gastrointestinal symptoms since then. Upper and lower gastrointesinal investigations showed no abnormalities without any obstruction.

Discussion

We report here an elderly diabetic patient taking acarbose, an α-glucosidase inhibitor, who developed ileus after administration of a compound "cold" remedy with anticholenergic properties.

Acarbose, a pseudotetrasaccharide of microbial origin, reversibly inhibits α-glucosidases of the brush border membrane of the small intestine, which are essential for the degradation of starch, dextrins, maltose, and sucrose to absorbable monosaccharides. The side effects of acarbose consist primarily of gastrointestinal symptoms related to complex carbohydrates delivered to the large colon. Fermentation of undigested carbohydrates by colonic bacteria is known to cause increased flatulence, soft stools, and abdominal discomfort but these symptoms are mostly of mild to moderate intensity[2]. However, ileus has been reported recently in Japan[4-7].

The clinical characteristics of 11 previously reported cases of ileus associated with α-glucosidase inhibitors treatment as well as the characteristics of the present patient are listed in **Table 1**[4-7]. Their ages ranged from 39 to 75 years. There were 5 male and 7 female patients. Ten of the 12 cases were over 60 years of age and 7 had history of abdominal surgery. Two non-elderly diabetic patients without any history of abdominal operation or gastroenteropathy have been reported in Japan[4,5]. However, in 5 cases, including these two non-elderly cases, ileus developed rapidly after the increase of α-glucosidase inhibitor dosage[4-6]. Two were operated on. The prognosis was good, except for one case who died. In all patients except our case, the duration of α-glucosidase inhibitor treatment until ileus occurred ranged from several days to three months. Fifteen months elapsed before the development of ileus in the present case. In contrast to the majority of previously reported cases, our case had a long-standing history of treatment with acarbose. The present patient had diabetic triopathy. Therefore the paralytic ileus may have been due to gastrointestinal dysfunction (gastroparesis) caused by diabetic neuropathy. Gastroparesis is a well recognized complication of diabetic patients with autonomic neuropathy[9] or with a history of gastrectomy[10]. Gastroparesis can cause nausea, vomiting, anorexia, early satiety, chaotic glycaemic control and unexplained weight loss[9], and also may be a feature of intestinal pseudo-obstruction[11]. However, there were no symptoms such as chronic nausea, vomiting, anorexia or early satiety in our case.

We speculate that topical use of PL® granules might have contributed to the development of ileus in this case. It is a well known fact that elderly people who are troubled with constipation may notice a worsening of symptoms when taking a drug with anticholinergic properties[12]. PL® granules are a compound "cold" remedy and consist of salicylamide, acetaminophen, anhydrous caffeine and promethazine methylenedisalicylate. Promethazine hydrochloride is one of the first-generation H_1 antagonists and possesses cosiderable anticholinergic activity[13]. Drugs with anticholinergic effects are used extensively in elderly persons[12]. Major classes of drugs with anticholinergic effects are belladonna alkaloids, antiparkinson drugs, tricyclic antidepressants, antipsychotics, antihistamines, and some antiarrhythmics.

An interesting fact is that ileus has not been documented as a side effect of α-glucosidase inhibitors in Caucasians. The cause of this discrepancy is unknown. Nishii et al[5] speculate that this difference may be due at least in part to the abundance of carbohydrates and fiber in the Japanese diet compared with the Western diet. Hara et al[14] revealed that the percentage of carbohydrates in all calorie sources was an important factor for the expression of the effects of α-glucosidase inhibitors.

Previous reports[6,7] and our case indicate that history of an abdominal operation and relatively old age are important risk factors for ileus due to α-glucosidase inhibitors. In addition, when increasing α-glucosidase inhibitor dosage or administering drugs with anticholinergic effect, doctors should monitor the patient's status closely and, if severe abdominal symptoms develop, must consider discontinuing treatment with α-glucosidase inhibitors.

References

1. Chiasson J-L, Josse RG, Hunt JA, Palmason C, Rodger NW, Ross SA, Ryan EA, Tan MH, Wolever TMS: The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. Ann Intern Med 1994; 121: 928–935.
2. Coniff RF, Shapiro JN, Seaton TB, Bray GA: Multicenter, placebo-controlled trial comparing acarbose (BAYg 5421) with placebo, tolbutamide, and tolbutamide-plus-acarbose in non-insulin-dependent diabetes mellitus. Am J Med 1995; 98: 443–451.
3. Joubert PH, Venter HL, Foukardis GN: The effect of miglitol and acarbose after an oral glucose load: A novel hypoglycaemic mechanism. Br J Clin Pharmac 1990; 30: 391–396.
4. Odawara M, Bannai C, Saitoh T, Kawakami Y, Yamashita K: Potentially lethal ileus associated with acarbose treatment for NIDDM. Diabetes Care 1997; 20: 1210–1211.
5. Nishii Y, Aizawa T, Hashizume K: Ileus: A rare side effect of acabose. Diabetes Care 1996; 19: 1033.
6. Ohno T: Gastrointestinal side effects of alpha-glucosidase inhibitors with special reference to ileus. Shinyaku to Rinsho 1995; 44: 144–146. (in Japanese)
7. Hayashi R, Wada M, Imano E, Kanda T: Occurrence of ileus after voglibose treatment in an elderly diabetic patient with gait disturbance caused by cerebral hemorrhage. Jpn J Geriat 1996; 33: 607–612. (in Japanese; Abstract in English)
8. Puls W, Keup U, Krause HP, Thomas G, Hoffmeister F: Glucosidase inhibition: A new approach to the treatment of diabetes, obesity, and hyperlipoproteinaemia. Naturwissenschaften 1977; 66: 536–537.
9. Barkin JS, Robbins EG, Stein B: Diabetes and the GI system. "In Ellenberg & Rifkin's Diabetes Mellitus" Porte D Jr., Sherwin RS, eds. 1997; pp 1183–1205, Appleton & Lange, Stamford.
10. Smale BF, Copeland JG, Reber HA: Delayed gastric emptying after operation for obstructing peptic ulcer disease: The influence of cimetidine. Surgery 1984; 96: 592–598.
11. Faulk DL, Anuras S, Christensen J: Chronic intestinal pseudo-obstruction. Gastroenterology 1978; 74: 922–931.
12. Myers M, Meier DE, Walsh JR: General principles. "In Geriatric Medicine, Volume 1, Medical Psychiatric and Pharmacological Topics" Cassel CK, Walsh JR, eds. 1984; pp 605–617, Spring–Verlag, New York.
13. Babe KS, Srafin WE: Histamine, bradykinin, and their antagonists. "In Goodman and Gilman's The Pharmacological Basis of Therapeutics" Hardman JG, Limbird KE, eds. 1996; pp 581–600, McGraw–Hill, New York.
14. Hara T, Sakakibara F, Nakamura J, Takeuchi N, Koh N, Hotta N: An importance of carbohydrate ingestion for the expression of the effect of α-glucosidase inhibitor in NIDDM. Diabetes Care 1996; 19: 642–647.

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