OBSERVATIONS

Serotonin 5-HT3 Receptor Antagonist for Treatment of Severe Diabetic Diarrhea

Diabetic diarrhea is a troublesome gastrointestinal complication of diabetes. This condition persists for several weeks to months, and it frequently accompanies fecal incontinence. The cause of diabetic diarrhea is not fully understood, but autonomic neuropathy is thought to be an underlying mechanism (1). Parenteral somatostatin analog octreotide has been shown to be useful in the treatment of severe long-standing diabetic diarrhea (1). Selective serotonin 5-hydroxy tryptamine type 3 (HT3) receptor antagonist, which was developed as an antiemetic in cancer chemotherapy, prolongs colonic transit, inhibits small bowel secretion, and decreases colonic compliance (2). Here, we report the underlying mechanism of ramosetron (2), a selective serotonin 5-HT3 receptor antagonist, for the treatment of severe diabetic diarrhea.

A 37-year-old man, who developed type 2 diabetes at 30 years of age, presented with watery diarrhea in late February 2009. Diarrhea occurred at a frequency of >15 bowel movements in 24 h, with a high nocturnal frequency and fecal incontinence. After 2–3 days with diarrhea, the patient developed constipation for 4–5 days. His A1C level had remained at ~10% for the previous 4 years. He had simple diabetic retinopathy, numbness, and dull pain in the lower limbs but no microalbuminuria. The coefficient of variation of the R-R interval was reduced to 1.24%. He also presented with retrograde ejaculation. Steatorrhea was absent, and the bacterial culture of his stool revealed normal flora. Abdominal computed tomography revealed no abnormal lesions in the liver or the pancreas. The patient did not report abdominal pain or any other abdominal symptoms and had no signs of infectious disease. His body weight did not change after the development of diarrhea. He was prescribed conventional antidiarrheal drugs, including pancreatic enzyme supplementation and loperamide, but these were ineffective. Because severe watery diarrhea persisted, he was administered ramosetron (5 μg/day). The watery diarrhea and fecal incontinence had completely disappeared after 1 week of ramosetron treatment. To date, he has a bowel movement frequency of 4–5 soft stools per day followed by constipation for 4 days.

In addition to the classic sympathetic and parasympathetic autonomous nervous system, the enteric nervous system (ENS) is important for the regulation of enteric function (3). Diabetes results in abnormalities of the ENS (4), such as loss of neurons containing nitric oxide synthase, which mediates gastrointestinal tract relaxation, and an increase in the enteric serotonin content, which regulates gastrointestinal tract contraction. An imbalance between the inhibitory and excitatory ENS could be one of the causes of diabetic diarrhea. Serotonin 5-HT3 receptor antagonist inhibits the excitatory neurons of ENS and thus plays a role in establishing a balance between the components of the ENS of diabetic patients. The usefulness of the serotonin 5-HT3 receptor antagonist ondansetron in the treatment of diabetic diarrhea has also been reported (5). In conclusion, absolute or relative change in the ENS expression level of serotonin or its receptor may be involved in the pathogenesis of diabetic diarrhea, and an oral serotonin 5-HT3 receptor antagonist should be considered for its treatment.

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