Communications

Bradycardia Associated with Cimetidine

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Cimetidine, a recently marketed histamine H_2-receptor antagonist, is valuable for treating patients with duodenal ulcer, Zollinger-Ellison syndrome, and other conditions associated with excessive gastric acid secretion. Side effects from cimetidine have been infrequent, but mild diarrhea, muscular pain, dizziness, rash, gynecomastia, and acute confusional states in elderly patients have been reported.[1] Since histamine H_2-receptors have been identified in the cardiovascular system, cimetidine may also affect cardiac function.

Case Report

A 78-year-old man was hospitalized with acute upper gastrointestinal (GI) bleeding. His first episode of GI bleeding was in 1932, when duodenal ulcer was diagnosed, and in 1937 he had a gastroenterostomy for ulcer disease. He did well until November 1974, when he developed acute GI bleeding from a marginal ulcer. He was again hospitalized in November 1976 for a bleeding marginal ulcer. He did well with oral antacids until February 15, 1978, when he had three black, tarry stools and complained of mild epigastric pain and slight "fuzziness." His hematocrit was 42, pulse rate was 70 beats per minute, and cimetidine, 300 mg every six hours, was started. The next day he continued to feel lightheaded and was hospitalized. Admission work-up revealed an elderly white man in no acute distress; pulse 55 beats per minute and irregular; blood pressure 116/60 mmHg supine, 120/60 mmHg standing; bowel sounds were hyperactive and stool guaiac positive; gastric aspirate produced guaiac positive "coffee-grounds" material; hematocrit value, 36%, white blood cell count, 7,100/cu mm with normal differential: protime 11 sec patient/12 sec control; chest roentgenogram results were normal; and electrocardiogram showed sinus bradycardia with rare atrial premature beats, first degree heart block, and right bundle branch block. Except for the sinus bradycardia, the electrocardiogram abnormalities had been present for over five years.

Cimetidine and antacids were continued, but gastrointestinal bleeding persisted. By February 18, his hematocrit value had fallen to 27%, he had orthostatic changes in blood pressure (104/64 mmHg supine, 86/40 mmHg sitting) and heart rate (60 beats/min supine, 72 beats/min sitting), and he was transfused with two units of packed cells. Despite the falling hematocrit and orthostatic blood pressure changes, sinus bradycardia persisted (Figure 1). Electrocardiograms on February 20 and 26 demonstrated persistent sinus bradycardia (heart rates of 43 beats/min and 55 beats/min, respectively), first degree heart block, and right bundle branch block; the PR interval was unchanged from admission, but atrial premature beats were no longer seen. Endoscopy revealed two recurrent marginal ulcers on the pyloric side of the anastomosis. When bleeding continued despite antacid and cimetidine therapy, a gastrojejunostomy and highly selective vagotomy was performed on February 27, and the GI bleeding resolved.

During cimetidine treatment sinus bradycardia persisted, with heart rates less than 50 beats/min on several occasions. The patient tolerated the bradycardia without complaints. When the cimetidine was stopped, normal sinus rhythm returned within 24 hours, and the patient's heart rate varied between 60 and 92 beats/min during the remainder of the hospitalization. Four days after stopping cimetidine, his ECG showed normal sinus rhythm, first degree heart block (PR interval unchanged from admission), and right bundle branch block; there were no atrial premature beats. At a follow-up examination three months later his pulse rate was 68 beats/min and regular (Figure 1).

Discussion

Histamine H_2-receptors have been identified in human cardiac tissue,[2] and H_2-receptor blockade with cimetidine prevents histamine induced in-

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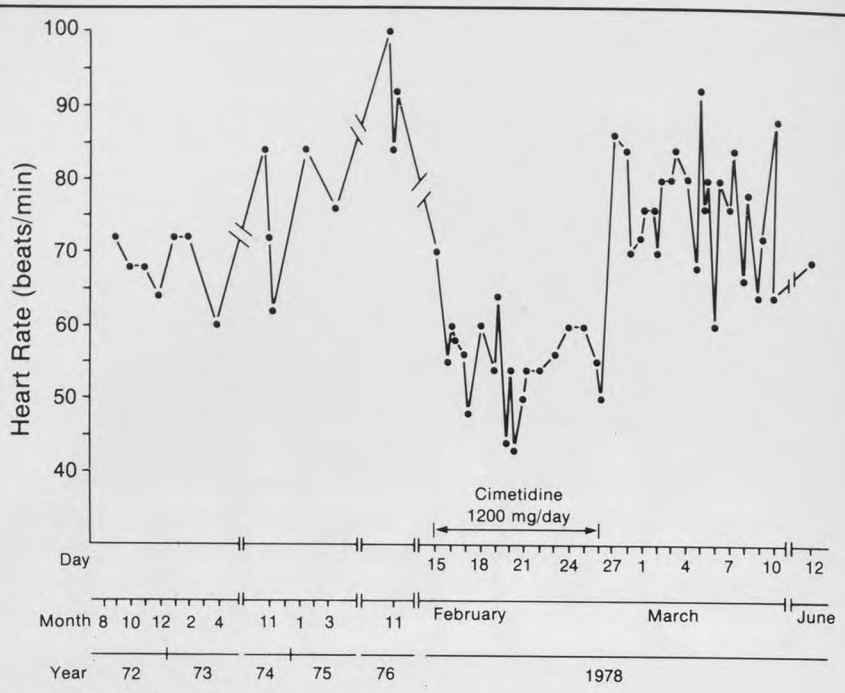

Figure 1. Heart rate of a 78-year-old man before, during, and after a course of cimetidine, 300 mg every 6 hours

creases in heart rate.[3,4] A physiologic role for histamine in the normal control of heart rate has been suggested[5] but has not been established.

Despite the presence of H_2-receptors in the heart, cimetidine has little effect on normal cardiac function. However, a few cases of bradycardia associated with cimetidine therapy have been reported.[6-10] Most of these patients had no previous cardiovascular disease, and bradycardia developed three hours to two weeks after starting cimetidine. The bradycardias in these patients were generally sinus rhythms of 42 to 50 beats/min; however, idioventricular[6] and junctional[9] rhythms have been reported. Normal heart rate returned in less than 24 hours after stopping cimetidine. A 39-year-old man developed dizziness and malaise along with the bradycardia,[7] but the other patients apparently tolerated the bradycardia without complaints.

This patient's bradycardia began within 24 hours of starting cimetidine and resolved within 24 hours after stopping the drug. He tolerated the bradycardia well. Despite the bradycardia his heart rate increased 12 beats/min when his systolic blood pressure fell 18 mmHg in response to sitting up. He had had cardiac conduction abnormalities (first degree heart block, right bundle branch block) for several years, and cimetidine therapy was not associated with any ECG abnormalities other than bradycardia.

Considering the large number of patients who have received cimetidine since its introduction, bradycardia is apparently a rare occurrence. However, patients who might not tolerate bradycardia should be followed carefully when cimetidine is first prescribed.

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