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Transient asymptomatic bradycardia in patients on infusional 5-fluorouracil

ABSTRACT

The incidence of 5-fluorouracil (5-FU)-related cardiotoxicity seems to be dosage and schedule dependent. Although various other cardiac events have been reported in literature, a series of patients having transient asymptomatic bradycardia has not been reported in the literature as yet. We report such a series of patients who had transient asymptomatic bradycardia after being treated with continuous infusion 5-FU. We plan to do a Holter study during the period of bradycardia in subsequent patients and this may throw more light on the issue.

KEY WORDS: Bradycardia, 5-fluorouracil

That cardiotoxicity can occur with 5-fluorouracil (5-FU) has been known for long. The common events reported have been atrial fibrillation and ST–T changes, with chest pain being the commonest presenting symptom.[1] Cardiotoxicity due to 5-FU seems to be dosage and schedule dependent. With the earlier bolus regimens the incidence of cardiotoxicity was reported as being 1.6-3% but with the prolonged (4-5 days) infusion regimens this has increased to 7.6-18%.[2-4] Although various other cardiac events have been reported in literature, a series of patients having transient asymptomatic bradycardia has not been reported as yet. We report a series of six patients who developed asymptomatic bradycardia after treatment with continuous 5-FU infusion.

CASE SERIES

In the department of radiation oncology, at Christian Medical College, Vellore, 207 patients underwent chemotherapy with infusional 5-FU and cisplatin (dosage: cisplatin 75-100 mg/m² and infusional 5-fluorouracil 750-1000 mg/m²) from March 2004 to February 2005. Six patients developed asymptomatic transient bradycardia. Only patients who had a heart rate below 50/min were considered as having bradycardia and were included in this report. We present this series of patients who were treated with continuous infusion 5-FU and had transient asymptomatic bradycardia.

All the patients had their complete blood counts and blood biochemistry (including serum electrolytes) checked prior to chemotherapy and the reports were normal. All of them had a creatinine clearance of greater than 50. Apart from premedications and standard hydration, patients were given cisplatin and 5-FU as per the dosage range mentioned earlier; 5-FU was given as a continuous infusion from day 2 till day 5.

The age of the patients ranged from 38-59 years. There were two patients with carcinoma of the pyriform sinus and one each with carcinoma of the nasopharynx, oesophagus, alveolus, and larynx (supraglottis). None of the patients had any comorbid conditions, except for one patient who had hypertension.

In our series, all the patients had transient asymptomatic bradycardia, i.e., a heart rate below 50, and two patients had persistent bradycardia. There were no associated symptoms like chest pain, giddiness, and sweating at the time of bradycardia. Serum electrolytes were checked in all these patients during the episodes of bradycardia to rule out dyselectrolytemia and the reports were normal. ECG was done in all the patients except one at the time of the bradycardia and all were normal. ECG was done in all the patients except one at the time of the bradycardia and all were normal. Two of the patients (patients 1 and 6) had bradycardia persisting for more than 24 h and both experienced bradycardia during the first as well as the second cycle of chemotherapy; their chemotherapy regime was changed from the subsequent cycle. Repeated interruptions in treatment were necessary for two patients (patients 2 and 3) due to recurrence of bradycardia whenever the drug was resumed, but since the heart rate stabilized subsequently they were continued on the same chemotherapy regimen. The other two patients (patients 4 and

K Talapatra, I Rajesh, B Rajesh, B Selvamani, J Subhashini

Department of Radiation Oncology, Unit 2, Christian Medical College, Vellore - 430 002, India

For correspondence:
Dr. Subhashini John,
Department of Radiation Oncology, Christian Medical College, Vellore - 432 004, India.
E-mail: subha@cmcvellore.ac.in
5) had a short duration of bradycardia and reintroduction of the drug did not result in any major problem. The details of all the patients have been presented in Table 1.

**DISCUSSION**

The cardiovascular side effects of 5-FU was first documented by Gaveau in 1969 and, later, by Carpenter in 1972. The incidence of 5-FU-related cardiotoxicity appears to be dosage and schedule dependent. It was reported as 1.6-3% with the earlier bolus regimens but this has increased to 7.6-18% with the prolonged (4-5 days) infusion regimens. A study conducted on a series of 1350 patients found the incidence to be 1.2%. Another series of 1083 patients treated with 5-FU for various kinds of neoplasms identified 17 cases of 5-FU cardiopathy (1.6%). In our series, the incidence of asymptomatic bradycardia was 2.8%

The mechanism through which 5-FU exerts its cardiotoxic effects is unknown, although various hypotheses have been put forward, e.g., a coronary spasm directly induced by the drug or due to the release of a vasopressive substance, an immunoallergic reaction, or a direct toxic effect on the myocardium and pericardium. Adenosine analogues produce multiple hemodynamic effects, alterations in left ventricular contractility, and peripheral vasodilation or vasoconstriction, depending on the vascular bed.

In one study, the most common signs of cardiotoxicity were chest pain, ST–T wave changes, and atrial fibrillation. In that series, there was one case of ventricular fibrillation and another of sudden death. Eskilsson et al. also observed adverse cardiac effects in 14 patients (18%); he found that the incidence of cardiotoxicity was not higher in patients with signs of cardiovascular disease in the pretreatment evaluation than in those without. Another series found the main symptom to be unstable angina, which was responsive to cessation of 5-FU infusion and medical treatment (aspirin and nitrates), in five patients. One series reported that 19% of the patients developed reversible symptoms of angina pectoris during treatment, which lasted for up to 12 h after cessation of the infusion. Another series has reported five patients developing life-threatening toxicity consistent with coronary artery spasm. The acute events occurred on the third or fourth day of the 5-day infusion regimen and after the fourth intravenous bolus in the one patient on bolus therapy. All of the patients had ST elevation and ventricular arrhythmias, four had acute myocardial infarction, and two had cardiac arrests. Our series has shown only the occurrence of bradycardia from the third day of infusion.

In one series, the ECGs showed repolarization changes (ST segment deviation and T-wave inversion) in 65% and/or diffuse microvoltage in 22% of the patients who presented with cardiac events. Echocardiography showed partial or
global hypokinesia in 9 of the 16 patients who were examined, with one case showing prolonged akinesia.[3] In our series, ECG was done in five of the patients and all were normal. Cardiac enzymes were not evaluated in our series as none of the patients had chest pain.

Clavel et al., in their series, have reported that reintroduction of the drug in 28 patients resulted in myocardial necrosis in four cases and death due to cardiogenic shock in another four cases. The frequency of such side effects did not seem to be influenced by age, sex, route of administration, and previous pathology, including cardiovascular diseases.[7] In two of the patients the chemotherapy regime had to be changed due to persistent bradycardia even during the second cycle. Other patients in whom the drug was reintroduced in our series did not have major problems. In another reported series the frequency of bradycardia and ventricular extrasystoles increased significantly during treatment.[9]

Our series has shown a tendency for the development of asymptomatic bradycardia in patients undergoing treatment with infusional 5-FU. It may be argued that cisplatin and its hydration had a role to play in the bradycardia but this is unlikely, as cisplatin per se is not known to cause bradycardia and, moreover, the development of bradycardia was after the 3rd day in all the patients, making it all the more likely that 5-FU was the cause. We plan to do a Holter study during the period of bradycardia in subsequent patients and this may throw better light on the issue.

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