Sinus Bradycardia Associated With Daclizumab in Liver Transplant Recipients: Report of 3 Cases

Adel Bassily-Marcus,[1] Roopa Kohli-Seth,[1] Andrew Leibowitz,[2] Victor Murgolo,[3] John Oropello,[1] Anthony Manasia,[1] Ernest Benjamin[1]

Abstract

Daclizumab is a commonly used immunosuppressive agent for prophylaxis of solid organ rejection. Although rare, the cardiovascular adverse effects of daclizumab include sinus tachycardia, hypotension, and hypertension. Here, we report 3 patients who developed significant and prolonged sinus bradycardia after receiving daclizumab following orthotopic liver transplant. Daclizumab should be considered a possible cause of bradycardia following its administration in orthotopic liver transplant.

Key words: *Bradyarrhythmias, Zenapax, Drug-induced, Famotidine, Transplantation*

Because of the safety profile of daclizumab, use of this immunosuppressive agent for prophylaxis against solid organ rejection has increased. An anti–interleukin-2 receptor monoclonal antibody, daclizumab specifically binds to the alpha subunit of the interleukin-2 receptor that is expressed only on the surface of activated lymphocytes, thereby reducing interleukin-2–mediated activation of T cells. Thus, daclizumab reduces the frequency of acute rejection episodes and improves patient outcomes without significant toxicity or increased susceptibility to infection (1-4).

Few cardiovascular adverse effects have been associated with this agent. As listed on the package insert, these cardiovascular adverse effects include hypotension, aggravated hypertension, pulmonary edema, and tachycardia. To our knowledge, there has been no reported case of bradycardia in patients treated with daclizumab. Here, we report 3 patients who developed significant and prolonged sinus bradycardia after receiving daclizumab following orthotopic liver transplant.

From the Departments of [1]Surgery, Division of Critical Care Medicine; [2]Anesthesiology; and [3]Nursing Mount Sinai Medical Center, The Mount Sinai School of Medicine, New York, NY, USA
Address reprint requests to: *Adel Bassily-Marcus, MD, The Mount Sinai Hospital, One Gustave L. Levy Place, Box # 1264, New York, NY 10029*
***Phone**: +(212) 241-8867 **Fax:** +212 860-3669 **E-mail:** adel.bassily-marcus@mssm.edu*

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Case 1

A 32-year-old man underwent an uneventful orthotopic liver transplant for primary sclerosing cholangitis. During the immediate postoperative period, the patient was hemodynamically stable, in sinus rhythm at 94 bpm, with a P-R interval of 184 msec, and a corrected QT (QTc) interval of 480 msec. The first dose of daclizumab (1 mg/kg IV) was given on the day of the procedure. Thirty hours later, the patient developed sinus bradycardia at 58 bpm. His P-R interval was 124 msec and his QTc interval was 464 msec. Medications at that time included famotidine, dexamethasone, clotrimazole, trimethoprim/sulfamethoxazole, valganciclovir, sevelamer, ursodiol, and calcium carbonate.

The patient was still in sinus bradycardia when he received the second dose of daclizumab (1 mg/kg IV) on the fourth day after surgery. Despite a transient fever of 39.2°C, asymptomatic sinus bradycardia as low as 47 bpm continued until the 10th day after surgery. The patient's renal function remained stable (creatinine level, 123.7 μmol/L [1.4 mg/dL]), and his electrolyte levels were in the normal range. Tacrolimus was started on the fourth day after surgery, and the trough serum level was 4.5 ng/mL on the fifth postoperative day. Because the patient developed biopsy-proven acute graft rejection 6 days after the transplant, antithymocyte globulin was added to the immunosuppressive regimen (which also included mycophenolate mofetil). No further episodes of bradyarrhythmia were documented, and the patient was discharged 15 days after surgery (Figure 1).

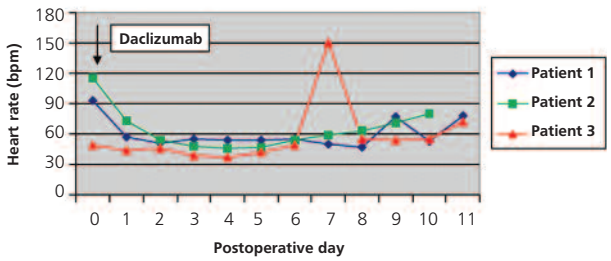

Figure 1. Heart rate recorded in all 3 patients starting from admission until discharge from the ICU following liver transplant.

Case 2

A 41-year-old man with a 10-year history of hepatitis B cirrhosis received a deceased-donor orthotopic liver transplant because of fulminant hepatic failure with grade-3 hepatic encephalopathy and oliguric acute renal failure. Postoperatively, the patient's pulse rate was 101 bpm, and an echocardiogram showed a P-R interval of 144 msec and a QTc interval of 395 msec. Forty-four hours after receiving the first dose of daclizumab (1 mg/kg IV), the patient developed sinus bradycardia at 54 bpm with a normal blood pressure of 118/71 mm Hg.

The patient remained in sinus bradycardia at approximately 40 bpm until the seventh day after surgery. The P-R interval was 168 msec and the QTc interval was 452 msec. Serum electrolyte levels were in their normal ranges, and the total bilirubin level decreased from 482.2 μmol/L (28.2 mg/dL) before the transplant to 205.2 μmol/L (12 mg/dL). The patient's renal function worsened, with a peak creatinine level of 194.4 μmol/L (2.2 mg/dL) on the first day after surgery. Medications included lamivudine, dexamethasone, trimethoprim/sulfamethoxazole, clotrimazole, calcium carbonate, ursodiol, famotidine, valganciclovir, aspirin, regular insulin, fentanyl, midazolam, hepatitis B immune globulin, and mycophenolate mofetil. The patient received a second dose of daclizumab (1 mg/kg IV) on the fourth day after surgery while his pulse rate was between 46 and 56 bpm. The patient remained in sinus bradycardia until the eighth day after transplant, at which time his heart returned to sinus rhythm.

Case 3

A 65-year-old woman received a deceased-donor orthotopic liver transplant for end-stage liver disease and hepatocellular carcinoma associated with hepatitis C virus. She had history of hypothyroidism, septal myocardial infarction, insulin-dependent diabetes mellitus, and chronic renal insufficiency with a baseline creatinine level of 291.7 μmol/L (3.3 mg/dL).

Sinus bradycardia at 48 bpm was observed 12 hours after a daclizumab (1 mg/kg IV) injection. Serum electrolyte levels were within the normal range, and the total bilirubin level was 83.7 μmol/L (4.9 mg/dL). Other medications included midazolam, fentanyl, famotidine, cefotaxime, fluconazole, methylprednisolone, insulin, valganciclovir, trimethoprim/sulfamethoxazole, clotrimazole, lamivudine, aspirin, and levothyroxine. Famotidine was discontinued on the fourth day after transplant, and sucralfate was started for stress ulcer prophylaxis. Tacrolimus (1 mg bid) was started on the fourth day after transplant and its level was 3.2 ng/mL on postoperative day number 6. A second dose of daclizumab (1 mg/kg) was also given on postoperative day number 4.

The patient remained in sinus bradycardia until 6 days after transplant, at which time her pulse rate decreased to 38 bpm. Other values included a BP range of 120/49 to 125/54 mm Hg, a P-R interval of 184 msec, and a prolonged QTc interval of 607 ms. Several doses of atropine were given (total, 2.4 mg IV) with no improvement in pulse rate. A transcutaneous pacemaker was placed and set on demand mode. A 2-dimensional echocardiogram showed normal left ventricular function and size. The level of thyroid stimulating hormone was within the normal range. While the patient remained in sinus bradycardia, all electrolyte levels were within their normal ranges except for a magnesium level of 1.19 mmol/L (2.9 mg/dL). Her peak total bilirubin level was 68.4 μmol/L (4.0 mg/dL). Six days after the transplant, the patient developed an episode of paroxysmal atrial fibrillation with a rapid ventricular response, which lasted for 48 hours, and was treated with diltiazem. On the eighth day after transplant, the patient' heart rate returned to sinus bradycardia until approximately the 10th day after transplant, at which time it returned to sinus rhythm.

Discussion

We have discussed 3 patients who underwent orthotopic liver transplant who developed an episode of clinically significant postoperative sinus bradycardia 12 to 44 hours after their first injection

of daclizumab. The bradycardia lasted 6 to 9 days. All 3 patients had no known history of bradycardia. In our third patient, when the heart rate decreased to 38 bpm, an unsuccessful attempt was made to correct the bradycardia using 2.4 mg of atropine; this failed, and a transcutaneous pacemaker eventually was used.

Daclizumab is an effective agent for inducing immunosuppression in kidney (4-6) and liver transplant (7-9). Unlike OKT3 or calcineurin inhibitors, it has no neurotoxicity or nephrotoxicity and does not cause cytokine release. Daclizumab is not associated with cardiovascular toxicity. Occasional instances of hypotension, sinus tachycardia, hypertension, and pulmonary edema have been reported, but no instances of significant sinus bradycardia have been reported until now.

In liver transplant recipients, perioperative bradyarrhythmias have been observed preoperatively, intraoperatively, and postoperatively. Sinus bradycardia often complicates severe hyperbilirubinemia (typically above 342 μmol/L [20 mg/dL]), possibly due to bile salt deposition in the SA node (10-12). The patients reported here did not have severe hyperbilirubinemia, and bilirubinemia at the time of the bradycardic event was declining.

During surgery, sinus bradycardia can be observed as a component of the postreperfusion syndrome (13). These patients did not have reperfusion syndromes, and the bradycardia occurred several hours after completion of the transplant. Postoperative sinus bradycardia may be seen after IV administration of certain immunosuppressive agents such as tacrolimus (14, 15), cyclosporine (16), or FTY720 (17, 18).

Other possible causes of sinus bradycardia include pre-existing autonomic neuropathy, increased vagal tone, myocardial ischemia with A-V node ischemia and electrolyte imbalance, drug toxicity, and drug interactions. Autonomic neuropathy may complicate end-stage liver disease irrespective of its cause. The severity of the neuropathy correlates with the degree of liver failure (19) and improves rapidly following liver transplant (20, 21). Our patients presented no evidence of dysautonomia, myocardial ischemia, or increased vagal tone.

A direct cardiotoxic effect of daclizumab causing sinus bradycardia, such as that associated with cyclosporine and tacrolimus, although possible, appears unlikely. In this series of patients, an adverse drug-drug interaction appears to be the most likely cause of sinus bradycardia. Among the medications that these patients were concomitantly receiving with daclizumab, the histamine-2 receptor blocker, famotidine, deserves special consideration. All 3 patients were receiving famotidine for stress ulcer prophylaxis.

The chronotropic adverse effects of histamine-2 receptor blockers have been described since 1977 (22-25), especially with ranitidine (26-30). The effect of famotidine on heart rate is controversial. In addition to sinus bradycardia, transient atrioventricular blockade, especially after rapid IV administration, has been described (31, 32). The mechanism of this bradycardia is unknown. The proposed hypotheses include unopposed histamine-1 receptor activity causing prolongation of AV conduction time, reversal of histamine-induced positive chronotropic activity, blockage of the histamine-2–mediated coronary artery dilation, and increased secretion of prolactin causing dysrhythmias (33, 34). However, in a study evaluating the cardiovascular effects of IV administration of famotidine in critically ill persons, 2047 doses of IV famotidine were administered with close cardiovascular monitoring. There were no clinically significant cardiovascular abnormalities related to famotidine, whether the drug was administered by rapid IV injection or slow IV infusion (35).

Another possible drug-drug interaction involves the opioid analgesic, fentanyl, which can induce a vagally mediated sinus bradycardia. Two of our patients had been receiving fentanyl at the time the bradycardia started. However, these episodes persisted for 10 days despite discontinuation of the fentanyl.

The potential association of daclizumab with bradycardia may be important when selecting immunosuppressive agents in the posttransplant setting. Patients with underlying cardiac dysfunction or pre-existing bradycardia may not tolerate this drug well, and other agents should be considered.

In conclusion, each patient presented here underwent an orthotopic liver transplant and had a subsequent episode of prolonged sinus bradycardia 12 to 44 hours after receiving the first dose of daclizumab. The bradycardia episode lasted 6 to 8 days. The mechanism of this arrhythmia is unclear. We postulate that it might have been due to an as yet undefined direct cardiotoxic effect of the drug, or more likely, to a drug-drug interaction between daclizumab and

another medication that these patients routinely were given in the early postoperative period. Among the suspected medications, famotidine, and to a lesser degree, fentanyl, deserve special consideration.

We hope to foster awareness that combining daclizumab with some other medications might not be prudent in patients who would be unlikely to tolerate significant bradycardia. Prospective studies are needed to determine the incidence and the significance of this observation as well as its mechanism.

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