FAILURE OF DANAPAROID ANTICOAGULATION FOR CARDIOPULMONARY BYPASS

Robert E. Ariano, PharmD, BCPS,^a Samir K. Bhattacharya, FRCS(C), FACS,^b Michael Moon, MD,^b and Laurence G. Brownell, FRCPC,^c *Winnipeg, Manitoba, Canada*

Danaparoid has recently received attention as probably the best available alternative to heparin for patients with heparin-induced thrombocytopenia and thrombosis (HITT). Danaparoid anticoagulation for operations performed with cardiopulmonary bypass (CPB), however, is not without its problems. In this case report we describe the failure of danaparoid anticoagulation for a patient scheduled to undergo redo coronary artery revascularization and aortic valve replacement.

Clinical summary. A 68-year-old man weighing 76 kg was being treated with unfractionated heparin for unstable angina when HITT developed. The patient was scheduled for surgery when an abrupt fall in platelet count from 115,000 to 67,000 over a 48-hour period was identified while he was receiving heparin therapy. The diagnosis of HITT was confirmed by a heparin-induced platelet activation assay, and the decision was made to use danaparoid anticoagulation for the management of this patient's unstable angina.

Before the beginning of the operation, intravenous aprotinin was administered because this was standard antifibrinolytic therapy at our institution for reoperations to minimize postoperative blood loss. A 7500 IU (100 IU/kg) load of danaparoid was given intravenously and an infusion was started at 533 IU per hour ($7 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Within a half hour of initiating the danaparoid, the presence of small fibrin strands in pericardium prompted the administration of 2 additional 1500 IU boluses and an increase in the background infusion rate to 760 IU per hour. The further accumulation of clot in the operative field prompted the surgeon to perform a left anterior descending coronary artery anastomosis off CPB and to abandon the valve replacement procedure. Unfortunately, at the end of the operation a 4-mm ST-segment elevation occurred in lead V₅, presumably because of blood clot formation in the artery during the anastomosis. The patient was transferred to the surgical intensive care unit, where immediate recovery was complicated by persistent ST-seg-

ment elevation and some central chest discomfort on awakening. A perioperative myocardial infarction was diagnosed. The patient eventually recovered and was discharged to his home. He awaits valve replacement surgery once platelet-bound antibodies to heparin disappear.

Discussion. A number of alternatives to heparin for use during CPB surgery have been suggested for patients with HITT, such as ancrod, iloprost, and danaparoid. Numerous shortcomings, however, have been identified with ancrod and iloprost in this setting. The clinical usefulness of danaparoid during CPB is limited by the lack of a rapid method for monitoring the adequacy of anticoagulation, lack of a reversal agent, and a very long elimination half-life, which makes it extremely difficult to titrate. Significant postoperative bleeding has been identified with the use of danaparoid for cardiac operations. The recommended therapeutic antifactor Xa level for CPB is between 1.5 and 2 U/mL.¹ Interestingly, danaparoid exerts its antifactor Xa activity without noticeable effects on other blood coagulation parameters and thus cannot be monitored by routine testing procedures, such as activated partial thromboplastin times and activated clotting times.¹

We had initially selected the danaparoid regimen of Westphal and coworkers² of 100 IU/kg (7500 IU) with a continuous infusion of $7 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (533 IU/h).² The use of a continuous infusion was believed to be optimal, since bypass time for the procedure was anticipated to be longer than 1 hour, and in the absence of antifactor Xa monitoring, sole anticoagulant therapy with intermittent boluses of the drug would be impractical. In the 2 hours of trying to establish an anticoagulated state for CPB and in the performance of a left anterior descending coronary artery anastomosis off CPB, our patient received a cumulative dose of about 12,000 IU (ie 158 IU/kg) of danaparoid.

The currently recommended protocol is a 125 IU/kg intravenous bolus, with 3 IU/mL in the priming fluid, and an intravenous infusion of $7 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.³ The infusion is to be started at the time of bypass hook-up and stopped about 45 to 60 minutes before the anticipated completion of CPB. This protocol does not presently recommend antifactor Xa monitoring. The failure of danaparoid anticoagulation for this patient may have been due to inadequate loading with this agent from an overestimation of the contribution of its preoperative use. However, the 12,000 IU danaparoid cumulative exposure over 2 hours had no preventive effect on fibrin generation. Note that with the long elimination half-life of danaparoid (ie, anticoagulant activity) of around 24 hours,¹ little activity would have been lost over the 2-hour titration period. It is possible that a crossover reaction from heparin to danaparoid-induced thrombocytopenia and thrombosis may have developed.¹

From the Departments of Pharmacy,^a Cardiac Surgery,^b and Anaesthesia,^c St Boniface General Hospital, Winnipeg, Manitoba, Canada.

Received for publication July 27, 1999; revisions requested Aug 2, 1999; revisions received Sept 28, 1999; accepted for publication Sept 28, 1999.

Address for reprints: Robert E. Ariano, PharmD, Department of Pharmacy, 409 Tache Ave, St Boniface General Hospital, Winnipeg, Manitoba, Canada R2H-2A6 (E-mail: rariano@gwmail.sbg.h.mb.ca).

J Thorac Cardiovasc Surg 2000;119:167-8

Copyright © 2000 by Mosby, Inc.

0022-5223/2000 \$12.00 + 0 12/54/103300

However, the patient's platelet count continued to rise well after the discontinuation of heparin and institution of danaparoid, making this possibility less likely. An interaction with the antifibrinolytic agent aprotinin was also hypothesized; however, Wilhelm and colleagues⁴ reported a successful, albeit single, case of danaparoid use in a patient concurrently receiving aprotinin. It could be that after fibrin clot starts to form, no amount of danaparoid will reverse this in the presence of the antifibrinolytic action of aprotinin. Tachyphylaxis to danaparoid might also have been a possibility, especially since the man had received the drug for 6 days before the operation and heparin by continuous infusion for 5 days before that. Prolonged use of these agents before the procedure could have depleted his antithrombin III stores and thus made him relatively resistant to danaparoid anticoagulation.⁵

Conclusions. Danaparoid may be a useful alternative to heparin in patients with HITT undergoing CPB procedures. However, a number of concerns are raised by this report. The inability to monitor antifactor Xa levels in the operating room makes this form of anticoagulation troublesome. Caution would be advised when using danaparoid for CPB in patients who are concurrently receiving the antagonist to fibrinolysis, aprotinin. Vigilance as well would be advised in patients who

had received prolonged infusions of either heparin or danaparoid before cardiac surgery, since they may be more resistant to surgical anticoagulation.

REFERENCES

1. Wilde MI, Markham A. Danaparoid: a review of its pharmacology and clinical use in the management of heparin-induced thrombocytopenia. *Drugs* 1997;54:903-24.
2. Westphal K, Martens S, Strouhal U, et al. Heparin-induced thrombocytopenia type II: perioperative management using danaparoid in a coronary artery bypass patient with renal failure. *Thorac Cardiovasc Surg* 1997;45:318-20.
3. Laposata M, Green D, Van Cott EM, Barrowcliffe TW, Goodnight SH, Sosolik RC. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy. The clinical use and laboratory monitoring of low-molecular weight heparin, danaparoid, hirudin and related compounds, and argatroban. *Arch Pathol Lab Med* 1998;122:799-807.
4. Wilhelm MJ, Schmid C, Kececioglu D, Mollhoff T, Ostermann H, Scheld HH. Cardiopulmonary bypass in patients with heparin-induced thrombocytopenia using Org 10172. *Ann Thorac Surg* 1996;61:920-4.
5. Hathaway WE. Clinical aspects of antithrombin III deficiency. *Semin Hematol* 1991;28:19-23.