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"Heparin-free" Cardiopulmonary Bypass: First Reported Use of Heparinoid (Org 10172) to Provide Anticoagulation For Cardiopulmonary Bypass

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Heparin-induced thrombocytopenia (HIT) occurs in up to 10% of patients receiving heparin.[1] While immune mechanisms have been implicated, an actual anti-heparin antibody has never been identified.[2] Most often, thrombocytopenia is moderate, transient, and well tolerated. Nevertheless, a fair number (10–20%) of patients with HIT may experience limb- and life-threatening thrombosis. A variety of laboratory tests measure the ability of patient's serum or plasma to aggregate platelets in the presence of heparin.[1] Alternatively, a component of platelet release (*e.g.*, serotonin) may be measured to document enhanced activation in the presence of heparin.[3] Treatment of HIT consists of discontinuation of heparin, substitution with another anticoagulant as needed (*e.g.*, coumadin, low-molecular-weight [LMW] heparins or heparinoids), and specific treatment of thrombosis if it has occurred.[1,2] Patients with a history of HIT requiring anticoagulation for cardiopulmonary bypass (CPB) present a particularly vexing challenge. One option is to delay surgery until *in vitro* platelet aggregation no longer occurs and then briefly reexpose the patient to heparin during CPB.[4] Alternatively, anti-platelet drugs (*e.g.*, aspirin, dipyridamole) and prostacyclin analogues may be administered concomitantly with heparin to prevent platelet aggregation while allowing anticoagulation.[5,6]

Since the readministration of heparin to patients with HIT may have catastrophic consequences, a reliable substitute that does not enhance platelet aggregation is needed. Heparinoids—nonheparin glycosaminoglycans retrieved as a by-product of heparin production—may prove useful in this setting. One such experimental heparinoid, derived from porcine intestinal mucosa, is Org 10172 (Organon International, The Netherlands), composed of a heterogenous mixture of dermatan, heparan, and chondroitin sulfates, and LMW heparins.[7] Org 10172 has been proven effective for anticoagulation during CPB in dogs.[8] However, there are no published reports describing the use of heparinoid as the sole anticoagulant for CPB in humans. The following is the first reported case of effective anticoagulation for CPB with heparinoid (Org 10172).

CASE REPORT

A 61-yr-old Caucasian man was admitted to the Duke Heart Center with new-onset chest pain. Pertinent medical history included hypertension, abdominal aortic aneurysm, and peptic ulcer disease. During initial evaluation, the patient experienced an anterior wall myocardial infarction. Emergency cardiac catheterization revealed severe three-vessel coronary artery disease and a left ventricular ejection fraction of 30%. The left anterior descending coronary artery was opened with the use of intravenous urokinase and intravenous and intracoronary tissue plasminogen activator. Therapy postcatheterization in the coronary care unit included oral nifedipine, intravenous nitroglycerin, and intravenous heparin.

Five days after initiation of heparin therapy, the patient developed thrombocytopenia (platelet count 50,000/μl). Heparin was withdrawn and aspirin therapy begun. Although initial *in vitro* platelet aggregation in the presence of heparin was negative, two subsequent studies were positive (despite aspirin therapy and the discontinuation of heparin). Evaluation of a painful left foot by the surgical consultant revealed a cool, pulseless foot, consistent with arterial thrombosis. Reevaluation by the same consultant several hours later revealed a spontaneous return of arterial flow to the left foot.

Because of persistent *in vitro* platelet aggregation in the presence of heparin but not in the presence of Org 10172, the Duke University Medical Center Institutional Review Board (IRB) approved the compassionate use of Org 10172 for thromboprophylaxis and prevention of coronary artery reocclusion. The patient was given an initial bolus of 2,500 anti-factor Xa units intravenously and then received a maintenance dose of 1,250 anti-factor Xa units subcutaneously every 12 h. Anti-factor Xa activity, measured by the method of Teien and Lie,[9] with the use of the chromogenic substrate S-2222 (Bz-Ile-Glu (-OR)-Gly-Arg-p-nitroaniline-HCl; Kabi Vitrum AB, Diagnostica, Sweden), was maintained between 0.2 and 0.4 units/ml plasma. Thrombocytopenia promptly resolved.

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Despite intensive medical therapy, however, the anterior wall myocardial infarction extended, and surgery was recommended. Because of the successful use of Org 10172 as a component of this patient's therapy, we decided, after informed patient consent, to use this agent as the sole anticoagulant for CPB. Upon arrival in the operating room 2,000 anti-factor Xa units of Org 10172 were given intravenously; with incision, 5,000 more were given. The extracorporeal circuit was primed with 7,500 anti-factor Xa units. Fibrin deposition noted in the cardiotomy suction tubing upon initiation of CPB prompted an additional dose of 2,500 units. During CPB, 2,000 anti-factor Xa units were administered hourly. Anti-factor Xa activities were measured every 30 min during CPB and as needed postoperatively on the Automated Clinical Analyzer (Dupont Co., Wilmington, DE), and automated activated clotting time (ACT) was measured concomitantly on the Hemochron® (International Technidyne Co., Edison, NJ). Coronary artery bypass grafting was successfully performed and no further fibrin deposition or clot was noted until immediately prior to separation from CPB.

The platelet count, which was 325,000/μl 2 days prior to surgery, had decreased to 117,000/mcl at the completion of CPB. Because of bleeding postoperatively, protamine (250 mg), 4 units fresh frozen plasma (FFP), and one "adult-pack" of platelets (10 units) was administered. Although a subsequent platelet count documented an increase to 185,000/μl, there was no effect on the increased anti-factor Xa activity. In addition, bleeding continued at an average of 300 ml/h for several hours postoperatively, requiring a total transfusion of 16 units of packed red blood cells for greater than 2,000 ml total chest tube drainage.

Discussion

Standard heparin is a polydisperse collection of sulfated glycosaminoglycans ranging in size from 4,000 to 30,000 d, and is isolated from porcine or bovine intestinal mucosa. LMW heparins (4,000–6,000 d) may be extracted from bovine or porcine intestinal mucosa by a variety of methods, including gel filtration and ultrafiltration, or can be produced in higher yield by techniques that degrade standard heparin (*e.g.*, nitrous acid depolymerization, acidic hydrolysis, and enzymatic depolymerization).[10] Consequently, although LMW heparins have lower mean molecular weights than standard heparin, their biochemical structures are remarkably similar. Compared to standard heparin (3000–30,000 d), LMW heparins and heparinoids (1200–15,000 d) have greater inhibitory effects on factor Xa than on factor IIa, and interactions with platelets are less likely.[11]

Although LMW heparins may affect platelets less readily than does standard heparin, platelet aggregation is still possible. One recent study of *in vitro* platelet effects of various glycosaminoglycans demonstrated that LMW heparins were capable of binding to platelets.[12] Furthermore, Makhoul *et al.*[13] evaluated 25 patients with documented HIT, all of whom clearly demonstrated *in vitro* platelet aggregation in the presence of standard heparin. Further evaluation of two LMW heparin products revealed *in vitro* platelet aggregation in up to 12 of 14 patients studied, whereas Org 10172 exerted no detectable *in vitro* effect on platelets from any of the patients studied. The ability of certain LMW heparins to induce *in vitro* platelet aggregation has also been demonstrated by Blockmans *et al.*,[14] with the use of platelet-rich plasma from a patient with HIT. Although LMW heparins have been used successfully to anticoagulate patients with HIT requiring CPB,[15,16] there have been reports progressive thrombocytopenia in patients with HIT receiving LMW heparins.[17,18]

There are no reports of the use of heparinoid to provide anticoagulation for CPB. Because Org 10172 appears to have no proaggregatory effects on platelets, it may prove useful in patients with HIT. Mikhailidis and associates[19] showed that Org 10172 did not induce *in vitro* platelet aggregation in a population of patients with known hyperaggregable platelets (due to anorexia nervosa and peripheral vascular disease), whereas standard heparin did. Mikhailidis[20] also demonstrated enhanced platelet aggregation and increased thromboxane A_2 release after bolus injection of conventional heparin despite acetylsalicylic-acid-mediated inhibition of platelet function. No such changes occurred after the injection of Org 10172. Bradbrook *et al.* showed a moderate decrease in *ex vivo* platelet adhesiveness 10 min after the injection of Org 10172 to healthy volunteers.[21] The decision to proceed with Org 10172 for parenteral anticoagulation during CPB was based on this available literature and on the following findings encountered during the preoperative care of our patient: 1) clear *in vitro* standard-heparin-induced platelet aggregation, even in the presence of acetylsalicylic-acid-mediated inhibition of platelet function; 2) lack of *in vitro* heparinoid-induced platelet aggregation; and 3) clinical tolerance of heparinoid therapy in low dose as a component of his antianginal regimen.

As is the case with LMW heparins, measured anti-factor Xa activity is most frequently used as an index of the antithrombotic effect of Org 10172.[22] On the other hand, the usefulness of the activated partial thromboplastin time (aPTT) as a measure of the anticoagulant effect of Org 10172 is unclear, as indicated by conflicting reports.[8,22,23] In this patient, the dose of Org 10172 administered subcutaneously twice per day generated anti-factor Xa activities in the 0.2–0.4 units/ml range without prolonging the aPTT. During CPB, however, the aPTT was prolonged to 1.6 times control when the anti-factor Xa activity was measured to be 1.3 units/ml. Furthermore, one study of a LMW heparin demonstrated a good correlation between aPTTs and factor Xa inhibition with doses used for anticoagulation in extracorporeal systems.[24] Although future investigation may demonstrate the application of the aPTT as an index of LMW heparin- or heparinoid-induced anticoagulation during CPB, aPTT is too sensitive to the doses of standard heparin required during routine CPB.

No reports exist demonstrating a dose-dependent ACT response with the use of LMW heparins or heparinoids. Consequently, we decided to evaluate the usefulness of ACT as an index of the anticoagulant effect of Org 10172 in this patient. Figure 1 depicts a high correlation ($r = 0.86$, $P < 0.01$) between anti-factor Xa activity and ACT over the range measured (ACT, 127–218 s; anti-factor Xa activity, 0.25–2.9 units/ml). Should this relationship be substantiated, it may be possible to use the ACT as an inexpensive, practical, and rapid index of this heparinoid's anticoagulant effect when used to provide anticoagulation for bypass, instead of routinely measuring anti-factor Xa activity. It is noteworthy that we did not observe a prolongation of the ACT in the dose range used for thromboprophylaxis (anti-factor Xa levels of 0.2–0.4 units/ml).

Whereas the relationship between the ACT and anti-factor Xa activity clearly is linear, this does not necessarily mean that the relationship is causal. Even though anti-factor Xa inhibition is routinely measured when LMW heparin or heparinoid is used, its significance is far from clear. Antithrombin activity, although not measured in this case, may have contributed to both the prolongation of the ACT and the actual anticoagulant effects noted. Pieters and Lindhout[25] demonstrated that anti-factor Xa activity was less important than antithrombin activity in the prevention of thrombin generation. Indeed, the ability of LMW heparin to inhibit thrombin generation correlated better with antithrombin activity than with anti-factor Xa activity. Furthermore, the coexistence of antithrombin and anti-factor Xa activity is necessary to exert antithrombotic effects, since compounds with either antithrombin or anti-factor Xa activity alone are less effective antithrombotic agents than standard heparins.[26]

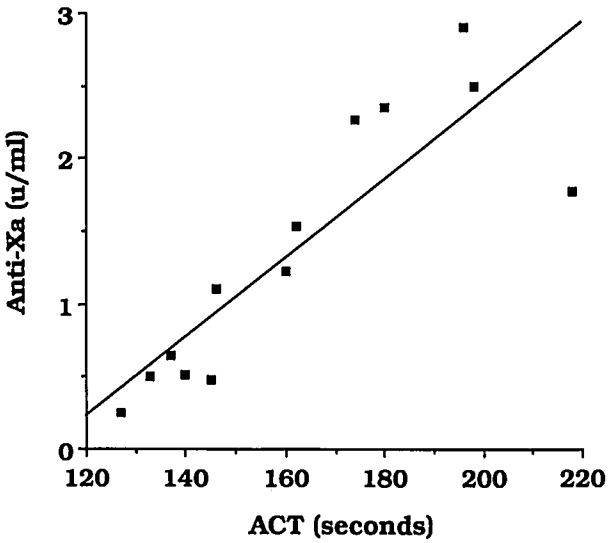

FIG. 1. ACT *versus* anti-factor Xa activity ($r = 0.86$, $P < 0.01$).

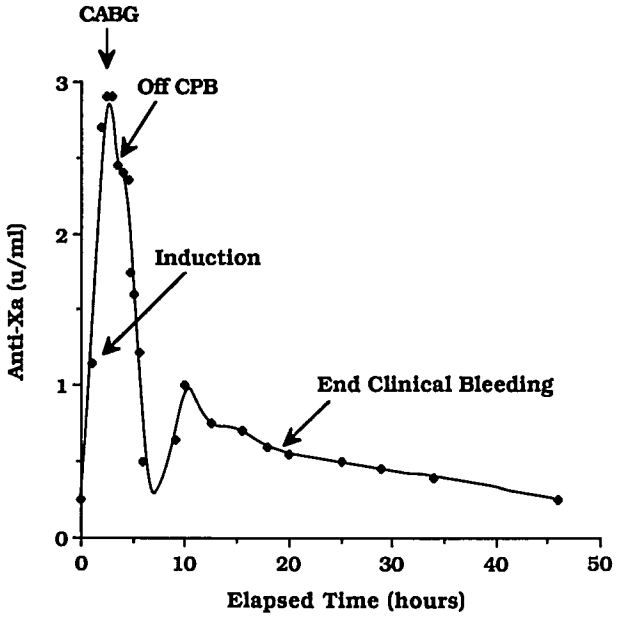

FIG. 2. Anti-factor Xa activity *versus* elapsed time (hours).

Although Org 10172 may prove useful in patients with HIT, its use probably will be limited by a long elimination half-life and the lack of a means of pharmacologic reversal. This is demonstrated, for example, by the data for anti-factor Xa activity *versus* time for the above case (fig. 2). The persistence of anti-factor Xa inhibition for many hours after CPB is consistent with previously reported Org 10172 kinetics.[8] Furthermore, protamine (250 mg) administered intravenously did not produce any detectable reduction in anti-factor Xa activity or clinical bleeding. Nor did the administration of up to 10 units fresh frozen plasma (FFP) demonstrably antagonize the anticoagulant property of this heparinoid. Although such kinetic properties may favor longer dosing intervals when used for thromboprophylaxis, the high doses probably required for anticoagulation for CPB result in a persistence of anti-factor Xa activity capable of potentially inducing unacceptable amounts of bleeding for several hours postoperatively. Nevertheless, in the setting of HIT when parenteral anticoagulation is required, we feel Org 10172 can be effectively used without exacerbating the syndrome of HIT. Careful monitoring of the patient's clinical status, as well as frequent laboratory analysis with replacement therapy as needed, should help to minimize hemorrhagic complications.

Summary

Org 10172 provided adequate anticoagulation for this patient. An excellent correlation between anti-factor Xa activity and ACT was observed at the doses used for CPB.

If high-dose Org 10172 is used, these data suggest that it may be possible to circumvent the measurement of anti-factor Xa activity by using the ACT as an index of this heparinoid's anticoagulant effect. Because postoperative bleeding may be excessive, however, development of a method of reversal of Org 10172 is desirable. Although the optimal ACT, dose, plasma concentration, and means of reversal (*e.g.*, protamine *vs.* heparinase) remains to be determined, heparinoids provide an alternate means of anticoagulation for CPB in patients unable to receive standard heparin.

References

1. Bell WR: Heparin-associated thrombocytopenia and thrombosis. J Lab Clin Med 111:600–605, 1988
2. Warkentin TE, Kelton JG: Heparin-induced thrombocytopenia. Annu Rev Med 40:31–44, 1989
3. Sheridan D, Carter C, Kelton JG: A diagnostic test for heparin-induced thrombocytopenia. Blood 67:27–30, 1986
4. Olinger GN, Hussey CV, Olive JA, Malik MI: Cardiopulmonary bypass for patients with previously documented heparin-induced platelet aggregation. J Thorac Cardiovasc Surg 87:673–677, 1984
5. Makhoul RG, McCann RL, Austin EH, Greenberg CS, Lowe JE: Management of patients with heparin-associated thrombocytopenia and thrombosis requiring cardiac surgery. Ann Thorac Surg 43:617–621, 1987
6. Kappa JR, Ellison N, Fisher CA, Addonizio VP: The use of Iloprost (ZK 36374) to permit cardiopulmonary bypass in two patients with heparin-induced thrombocytopenia. ANESTHESIOLOGY 63: A32, 1985
7. Meuleman DG, Hobbelen PM, van-Dedem G, Moelker HC: A novel anti-thrombotic heparinoid (Org 10172) devoid of bleeding inducing capacity: A survey of its pharmacologic properties in experimental animal models. Thromb Res 27:353–363, 1982
8. Henny CP, Ten-Cate H, Ten-Cate JW, Moulijn AC, Sie TH, Warren P, Büller HR: A randomized blind study comparing standard heparin and a new low-molecular-weight heparinoid in cardiopulmonary bypass in dogs. J Lab Clin Med 196:187–196, 1985
9. Teien AN, Lie M: Evaluation of an amidolytic heparin assay method: Increased sensitivity by adding purified antithrombin III. Thromb Res 10:399–410, 1977
10. Nielsen JI, Ostergaard P: Chemistry of heparin and low-molecular-weight heparin. Acta Chir Scand Suppl 543:52–56, 1988
11. Harenberg J, Heene DL: Pharmacology and special clinical applications of low-molecular-weight heparins. Am J Hematol 29: 233–240, 1988
12. Sobel M, Adelman B: Characterization of platelet binding of heparins and glycosaminoglycans. Thromb Res 50:815–826, 1988
13. Makhoul RG, Greenberg CS, McCann RL: Heparin-associated thrombocytopenia and thrombosis: A serious clinical problem and potential situation. J Vasc Surg 4:522–528, 1986
14. Blockmans D, Bounameaux H, Vermylen J, Verstraete M: Heparin-induced thrombocytopenia platelet aggregation studies in the presence of heparin fractions or semi-synthetic analogues of various molecular weights and anticoagulant activities. Thromb Haemost 55:90–93, 1986
15. Gouault-Heilmann M, Huet Y, Contant G, Payden D, Bloch G, Rapin M: Cardiopulmonary bypass with a low molecular weight heparin fraction (letter). Lancet 2(8363)1374, 1983
16. Massonnet-Castel S, Pelissier E, Dreyfus G, Deloche A, Abry B, Guibourt P, Terrier E, Passelecq J, Jaulmes B, Carpentier A: Low-molecular-weight heparin in extracorporeal circulation (letter). Lancet 8387:1182–1183, 1984
17. Horellou MH, Conard J, Lecrubier C, Samama M, Roque-D'Orbcastel O, de Fenoyl O, Di Maria G, Bernadou A: Persistent heparin induced thrombocytopenia despite therapy with low-molecular-weight heparin. Thromb Haemost 51:134, 1984
18. Messmore HL, Fareed J, Corey J, Griffin B, Miller A, Zuckerman L, Parvez Z, Seghatchian J, Choay J: In-vitro assessment of low-molecular-weight heparin in patients with thrombocytopenia induced by standard heparin. Blood 64(suppl):238a, 1984
19. Mikhailidis DP, Barradas MA, Jeremy JY, Gracey L, Wakeling A, Dandona P: Heparin-induced platelet aggregation in anorexia nervosa and in peripheral vascular disease. Eur J Clin Invest 15:313–319, 1985
20. Mikhailidis DP, Fonesca VA, Barradas MA, Jeremy JY, Dandona P: Platelet activation following the injection of a conventional heparin: Absence of effect with a low molecular weight heparinoid (Org 10172). Br J Pharmacol 24:415–424, 1987
21. Bradbrook ID, Magnani HN, Moelker HC, Morrison PJ, Robinson J, Rogers HJ, Spector RG, Van Dinther T, Wijnand H: Org 10172: A low-molecular-weight heparinoid anticoagulant with a long half-life in man. Br J Pharmacol 23:667–675, 1987
22. Hobbelen PM, Vogel GM, Meuleman DG: Time courses of the antithrombotic effects, bleeding enhancing effects and interactions with factors Xa and thrombin after administration of low-molecular-weight heparinoid Org 10172 or heparin to rats. Thromb Res 48:549–558, 1987
23. Ockelford PA, Carter CJ, Hirsch J: In vivo activity of a new heparinoid. Pathology 17:78–81, 1985
24. Andrassy K, Mörike K, Koderisch J: Human pharmacologic studies of a defined low-molecular-weight heparin fraction (Fragmin®): Evidence for a simultaneous inhibition of factor Xa and IIa (thrombin). Thromb Res 49:601–611, 1988
25. Pieters J, Lindhout T: The limited importance of factor Xa inhibition to the anticoagulant property of heparin in thromboplastin-activated plasma. Blood 72:2048–2052
26. Barrowcliffe TW, Thomas DP: Low-molecular-weight heparins: Antithrombotic and haemorrhagic effects and standardization. Acta Chir Scand Suppl 543:57–64, 1988