

## CASE REPORTS

Table 1. Indices of Coagulation

|                                    | Baseline | ORG + 10 min | CPB + 10 min | CPB + 30 min | 30 min post CPB |
|------------------------------------|----------|--------------|--------------|--------------|-----------------|
| Platelets (1,000/mm <sup>3</sup> ) | 64,000   | 66,000       | 22,000       | 24,000       | 43,000          |
| AF Xa (units/ml)                   | <0.2     | 1.70         | 1.25         | 1.75         | 1.60            |
| ACT (s)                            | 132      | 212          | 220          | 175          | 163             |
| Fibrinogen (mg/dl)                 | —        | —            | 155          | 167          | 237             |

ORG = Organon 1072; CPB = cardiopulmonary bypass; AFXa = antifactor Xa; ACT = activated coagulation time.

administered during CPB to maintain an antifactor Xa activity of 1.25 U/ml, which was similar to that used by Doherty *et al.*<sup>2</sup>

Forty minutes after initiation of CPB, clots were noted in the surgical field and arterial filter of the CPB circuit. The antifactor Xa activity at this time was 1.75 U/ml. The last proximal coronary graft anastomosis was quickly completed and the patient was promptly separated from CPB. Protamine was not given, because it does not reverse the effects of ORG 10172.<sup>8</sup>

Thirty minutes after chest closure, diffuse bleeding was noted, and three units of packed red blood cells were given to treat a hematocrit of 23%, and 12 units of platelets were given for a platelet count of 43,000/ul. The patient was subsequently transported to the intensive care unit, but required reexploration for continued bleeding 3 h later for chest tube drainage in excess of 300 ml/h. The antifactor Xa activity at this time was 1.60 U/ml, and the blood temperature was 37.3° Celsius. No surgical bleeding sites were identified intraoperatively. After reexploration, the patient continued to bleed and was given an additional 18 units of platelets and 4 units of packed red blood cells. Bleeding resolved completely 16 h after initial exposure to the anticoagulant. The patient remained hemodynamically stable, allowing his intraaortic balloon pump to be removed and his sedation discontinued on the second postoperative day. On the third postoperative day, he was arousable to noxious stimuli, but he would not follow commands and he continued to require controlled ventilation. A computed tomography scan and electroencephalogram were consistent with a diffuse metabolic encephalopathy. There was no evidence of an intracerebral bleed or infarction. His neurologic status gradually improved, and the trachea was extubated on postoperative day 12, when he was able to follow commands. After discharge to the regular nursing floor, sepsis developed, which led to a protracted recovery. His neurologic status eventually returned to baseline, and he was discharged to an assisted care facility 7 weeks after initial surgery.

## Discussion

Low molecular weight heparin and heparinoids have molecular weights from 4,000 to 6,000 d and may be extracted from bovine or porcine intestinal mucosa by a variety of methods, including gel filtration and ultrafiltration, followed by degradation techniques such as enzymatic or chemical depolymerization. Although LMWH and heparinoids have a lower molecular weight compared with unfractionated heparin, their biochemical structures are similar. They have a greater inhibitory

effect on factor Xa than on thrombin and have less platelet interaction when compared with unfractionated heparin. These agents demonstrated promise as antithrombotic agents with minimal hemorrhagic properties.

ORG 10172 is a mixture of sulphated glycosaminoglycans derived from porcine intestinal mucosa. It has minimal antithrombin activity and primarily has anti-Xa activity. Consequently, Organon 10172 only moderately prolongs the activated partial thromboplastin time and ACT. Meulman *et al.*<sup>10</sup> showed no significant induction of bleeding and a lack of deposition of thrombi with large doses of ORG 10172, suggesting that this drug has no effect on platelet adhesion. This lack of effect on platelets is supported by the finding that ORG 10172 does not affect collagen-induced serotonin release. Ofosu *et al.*<sup>11</sup> recently demonstrated that ORG 10172 could effectively delay the onset of activation of factors IX and X nearly as effectively as heparin, contributing to its antithrombotic activity.

One of the major complications of heparin administration is thrombocytopenia. Heparin-induced thrombocytopenia is suspected when the platelet count decreases to less than 100,000/ul or the patient experiences new thrombo-hemorrhagic events or increasing heparin requirements while receiving heparin. The mechanism is thought to be immunologically mediated, because platelet-associated immunoglobulin G antibodies that bind to complexes of heparin and platelet factor 4 have been identified in most of these patients.<sup>12</sup> One method of diagnosing HIT is by *in vitro* platelet aggregation studies, which usually become positive from 6 to 21 days after initial heparin exposure. This test may become positive more rapidly if the patient has had previous exposure to heparin. The etiology of the rapid response is thought to be an anamnestic antibody response after reexposure to heparin.<sup>13</sup>

The profound anticoagulation required during CPB presents a challenging problem for the clinician when

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a patient presents with HIT. Low molecular weight heparin and heparinoid compounds are two of the suggested alternatives to standard heparin for anticoagulation during CPB, although they are not currently approved by the Food and Drug Administration for this application, and only a few case reports are published. Although LMWH may affect platelet function less readily than unfractionated heparin, development of progressive thrombocytopenia and positive heparin-associated platelet antibodies have been reported in recent studies.<sup>14,15</sup> In addition, in patients with heparin antibodies to unfractionated heparin, the cross-reactivity with LMWH has been reported to be as high as 80–90%.<sup>16</sup> Crossreactivity of heparin-platelet antibodies with the heparinoid compound ORG 10172 is less (10–18%), such that it may prove useful in patients with HIT.<sup>16–18</sup> Doherty *et al.*<sup>8</sup> reported the successful use of ORG 10172 as the sole anticoagulant in humans during CPB while maintaining an anti-factor Xa level greater than 1.3 U/ml. Similarly, reports by Mikhailidis *et al.*<sup>19</sup> and Ortel *et al.*<sup>20</sup> demonstrated safe use of ORG 10172 in patients with hyperaggregable platelets and a decrease in platelet adhesiveness with documented HIT requiring anticoagulation. Henny *et al.*<sup>6</sup> also demonstrated the safe use of Organon 10172 in a series of dogs undergoing CPB. Based on the available literature and after a lack of *in vitro* aggregation of donor platelets with our patient's plasma in the presence of ORG 10172, the drug was used as the anticoagulant for CPB.

Despite maintaining antifactor Xa activity greater than 1.7 U/ml, thrombosis was observed during placement of the proximal grafts toward the end of CPB. This contrasts with the experience of Doherty *et al.*,<sup>8</sup> who reported a satisfactory outcome with antifactor Xa activity of approximately 1.6 units/ml. It is not stated whether Doherty *et al.*<sup>8</sup> used hypothermic CPB, and the question arises about the anticoagulant activity of ORG 10172 with cooling. There was some correlation between ACT and antifactor Xa activity, but the significance of this is unknown and will probably need further study before establishing a safe ACT for CPB when ORG 10172 is used for anticoagulation. When using unfractionated heparin, full anticoagulation is confirmed by obtaining an ACT > 480 s. This level of anticoagulation is associated with anti-Xa activity of 3.0 U/ml or greater and may warrant careful consideration when using ORG 10172 for CPB.

Currently, there is no reversal agent for Organon 10172, which is a disadvantage that can result in continuous postoperatively bleeding. The administration of

protamine has not been associated with decreased anti-Xa activity, and its use cannot currently be recommended. Until a specific reversal agent is available, support of hemostasis by the judicious use of blood products seems warranted, because ORG 10172's half life is approximately 19 h.

In conclusion, even though ORG 10172 has been used successfully in the treatment of HIT, deep venous thrombosis, stroke, and as the sole anticoagulant for patients who require CPB, this case suggests that dosing regimens are not uniform, and that thrombosis is still a potential complication. If ORG 10172 is to be considered a suitable alternative for anticoagulation for patients with HIT, further studies are required to establish proper protocols to facilitate CPB and to establish anti-factor Xa activity above which thrombosis should not occur.

## References

1. Kraenzler EJ, Starr NJ: Heparin associated thrombocytopenia: Management of patients for open heart surgery. Case reports describing the use of iloprost. *ANESTHESIOLOGY* 1988; 69:964–7
2. Matso T, Kario K, Chikahira Y, Nakao K, Yamada T: Treatment of heparin induced thrombocytopenia by use of argatroban, a synthetic thrombin inhibitor. *Brit J Haematol* 1992; 82:627–9
3. Walenga JM, Fareed J, Bick RL, Pifarre R: New anticoagulants for the cardiovascular patient. *Clin Appl Thromb Haemost* 1995; 1:24–30
4. Riess FC, Lower C, Seeling C, Bleese N, Korman J, Muller-Berghaus G, Potzsch B: Recombinant hirudin as a new anticoagulant during cardiac operations instead of heparin: Successful for aortic valve replacement in man. *J Thorac Cardiovasc Surg* 1995; 110:265–7
5. Addonizio VP, Fisher CA, Kappa JR, Ellison N: Prevention of heparin-induced thrombocytopenia during open heart surgery with iloprost (ZK36347). *Surgery* 1987; 102:796–807
6. Henny CP, Ten Cate H, Ten Cate JW, Mouljijn AC, Sie TH, Warren P, Buller HR: A randomized blind study comparing standard heparin and a new low molecular weight heparinoid in cardiopulmonary bypass surgery in dogs. *J Lab Clin Med* 1985; 106:187–96
7. Magnani HN: Heparin-induced thrombocytopenia: An overview of 230 patients treated with Organon (Org 10172). *Thromb Haemost* 1993; 70:554–61
8. Doherty D, Ortel T, DeBruijn N, Greenberg C, Van Trigt P: "Heparin free" cardiopulmonary bypass: First reported use of heparinoid (Org 10172) to provide anticoagulation for cardiopulmonary bypass. *ANESTHESIOLOGY* 1990; 73:562–5
9. Rowlings PA, Mansberg R, Rozenberg MC, Evans S, Murray B: The use of a low molecular weight heparinoid (ORG 10172) for extracorporeal procedures in patients with heparin dependent thrombocytopenia and thrombosis. *Aust N Z J Med* 1991; 21:52–4
10. Meulman DG: Organon (ORG 10172): Its pharmacological profile in experimental models. *Haemostasis* 1992; 22:58–65
11. Ofusu FA: Anticoagulant mechanisms of Organon (ORG 10172) and its fraction with high affinity to antithrombin III (ORG 10849). *Haemostasis* 1992; 22:66–72

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12. Kelton JG, Smith JW, Warkentin TE, Hayward CPM, Denomme GA, Horsewood P: Immunoglobulin G from patients with heparin-induced thrombocytopenia binds to a complex of heparin and platelet factor 4. *Blood* 1994; 83:3232-9

13. Laster J, Elfrink R, Silver D: Reexposure to heparin of patients with heparin-associated antibodies. *J Vasc Surg* 1989; 9:677-82

14. Gordon DL, Linhardt R, Adams HP Jr: Low-molecular-weight heparins and heparinoids and their use in acute or progressing ischemic stroke. *Clin Neuropharmacol* 1990; 13:522-43

15. Makhoul RG, Greenberg CS, McCann RL: Heparin-associated thrombocytopenia and thrombosis: A serious clinical problem and potential solution. *J Vasc Surg* 1986; 4:522-8

16. Kikta MJ, Keller MP, Humphrey PW, Silver D: Can low molecular heparins and heparinoids be safely given to patients with heparin-induced thrombocytopenia syndrome? *Surgery* 1993; 114:705-10

17. Chong BH, Ismail F, Cade J, Gallus AS, Gordon S, Chesterman CN: Heparin-induced thrombocytopenia: Studies with a new low molecular weight heparinoid, Org 10172. *Blood* 1989; 73:1592-6

18. Magnani NH: Heparin-induced thrombocytopenia (HIT): An overview of 230 patients treated with Organon (Org 10172). *Thromb Haemost* 1993; 70:554-61

19. Mikhailidis DP, Barradas MA, Jeremy JY, Gracey L, Wakeling A, Dandona P: Heparin-induced platelet aggregation in anorexia nervosa and in severe peripheral vascular disease. *Eur J Clin Invest* 1985; 15:313-9

20. Ortel TL, Gockerman JP, Califf RM, McCann RL, O'Connor CM, Metzler DM, Greenberg CS: Parenteral anticoagulation with the heparinoid lomoparan (ORG 10172) in patients with heparin induced thrombocytopenia and thrombosis. *Thromb Haemost* 1992; 67:292-6

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## Severe Dysphonia after Use of a Laryngeal Mask Airway

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COMPLICATIONS that occur after laryngeal mask airway (LMA) use are usually minor and include an incidence of sore throat occurring in 7-16% of patients.<sup>1,2</sup> More severe complications are anecdotal (*i.e.*, lingual artery compression,<sup>3</sup> transient hypoglossal nerve paralysis<sup>4</sup> and transient bilateral vocal cord paralysis).<sup>5-8</sup> We report three cases of severe dysphonia after anesthesia during which an LMA was used.

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### Case Reports

#### Case 1

A 19-yr-old man, weighing 67 kg, underwent surgery for unilateral inguinal hernia. Preoperative assessment disclosed no significant medical problems. After induction with 150  $\mu$ g fentanyl and 2.5  $\text{mg} \cdot \text{kg}^{-1}$  propofol, a fully deflated, size 4 LMA was easily inserted. The cuff was inflated with 20 ml air. Anesthesia was maintained with isoflurane and 50%  $\text{N}_2\text{O}$  in oxygen, and his lungs were ventilated using positive pressure ventilation. The procedure lasted 90 min. The inflated LMA was gently rejected by the awake patient during recovery. A few hours after surgery, the patient complained of pharyngeal paresthesia, sore throat, and dysphonia. On the following days, the dysphonia progressively worsened until the patient was aphonic, and a laryngeal incompetence with fluid aspiration occurred. A direct laryngoscopy showed an immobilized right vocal cord. A stroboscopic examination confirmed a right recurrent nerve palsy. Two months later, the patient recovered vocal cord mobility.

#### Case 2

A 54-yr-old woman, weighing 52 kg, underwent a dilatation and curettage and a breast biopsy. Preoperative assessment did not disclose any relevant medical history. After induction with 100  $\mu$ g fentanyl and 3  $\text{mg} \cdot \text{kg}^{-1}$  propofol, a fully deflated, size 3 LMA, lubricated with silicone spray, was easily inserted. The cuff was inflated with 30 ml air. Anesthesia was maintained with propofol, and the patient spontaneously breathed 60%  $\text{N}_2\text{O}$  in oxygen. The procedure lasted 60 min. During recovery, the LMA was gently expelled by the patient. A few hours later, the patient complained of sore throat and dysphagia. The next day, hoarseness occurred. On the third day, the patient