Efficacy and Safety of Danaparoid Sodium (ORG 10172) in Critically Ill Patients With Heparin-Associated Thrombocytopenia*

Brigitte Tardy-Poncet, MD; Bernard Tardy, MD; Jacqueline Reynaud, MD; Philippe Mahul, MD; Patrick Mismetti, MD; Eliane Mazet; and Denis Guyotat, MD

**Objective:** To evaluate the effectiveness and the safety of danaparoid sodium in the treatment of critically ill patients with standard unfractionated heparin-induced thrombocytopenia (HIT) or low-molecular-weight HIT.

**Setting:** University hospital.

**Patients and methods:** Retrospective analysis of 42 consecutive critically ill patients who were admitted for HIT between October 1992 and February 1997 and were treated either with therapeutic or prophylactic doses of danaparoid sodium.

**Results:** Among the 26 patients treated with therapeutic doses, neither new thrombotic complications nor thrombosis extension was clinically suspected. Two deaths were directly related to lower limb acute arterial thrombosis associated with HIT. Two major hemorrhagic complications were observed when aspirin in addition to danaparoid sodium was administered. When danaparoid sodium was used in prophylactic doses (20 courses of treatment) to prevent either postsurgical or medical thrombotic complications, no thrombotic event was observed. No death related to HIT or danaparoid sodium treatment was observed. One aggravation of a postsurgical cerebral lesion was observed. During danaparoid sodium treatment, a persistence or a recurrence of thrombocytopenia was observed in 6.5% of patients without thrombotic complications.

**Conclusion:** Danaparoid sodium appears to be an efficient and safe treatment in critically ill patients with HIT. The concomitant use of aspirin in addition to danaparoid sodium seems to represent an important additional hemorrhagic risk that should be avoided in patient management.

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**Key words:** heparin; thrombocytopenia; treatment

**Abbreviations:** DVT = deep venous thrombosis; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; OAC = oral anticoagulant; SAPS = simplified acute physiology score

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Type II heparin-induced thrombocytopenia (HIT) is not a rare complication of heparin therapy even if its frequency seems to be lower with low-molecular-weight heparin (LMWH).1 Patients with type II HIT are at risk for serious thromboembolic complications causing deep venous thrombosis (DVT) and pulmonary embolism; lower and upper limb arterial ischemia; cardiac, cerebral, adrenal, or mesenteric infarction; renal failure; or skin necrosis.2

After heparin therapy withdrawal, an immediately available alternative anticoagulant treatment is often mandatory. LMWH is 90% cross-reactive in vitro with HIT-IgG using sensitive assays3,4 and may potentiate the HIT. Treatment with a vitamin K antagonist takes some days before reaching full therapeutic effect. This treatment should be started only when the hemostatic problem of thrombin generation has been brought under control. Indeed, in some HIT patients with DVT, the use of vitamin K antagonist producing acquired protein C deficiency can lead to venous limb gangrene if adequate inhibition of thrombin generation has not been previously reached.5 Reported herein is our experience with the use of danaparoid sodium in 42 critically ill patients with HIT in the treatment or
prevention of a thromboembolic event. Danaparoid sodium is a low-molecular-weight mixture of glycosaminoglycans that shows low cross-reactivity with HIT-IgG (<10%). This low cross-reactivity can be explained by its lack of heparin fragments, its low degree of sulfation, and its low affinity with the platelet factor 4 molecule. Danaparoid sodium can also block platelet aggregation and thromboxane B₂ production that is induced by heparin-dependent antibodies, but it does not affect physiologic platelet function. Efficacy and safety of danaparoid sodium for the prevention and the treatment of DVT have been previously demonstrated.

**Materials and Methods**

Forty-two patients with either acute HIT or past HIT were consecutively treated with danaparoid sodium between October 1992 and February 1997. The clinical and biological findings were retrospectively reviewed. A 1-month follow-up concerning the thrombotic events after danaparoid sodium therapy withdrawal was made for all recovering patients.

**Diagnosis of HIT**

To be included in this study, the diagnosis of HIT had to be considered as very likely or possible using a scoring system proposed by Greinacher et al.9 Briefly, a positive score of 2 points is attributed for each of the following criteria: decrease in platelet count by 50% of pretreatment value; interval of HIT onset >5 days in case of first exposure or interval of HIT onset <4 days in case of reexposure; normalization of platelet count within 10 days after cessation of heparin therapy; and thromboembolic complications during heparin treatment. A positive score of 1 point is attributed for each of the following criteria: decrease in platelet count by 30 to 50% and inflammatory skin reaction at the heparin injection site. A negative score of 1 point is attributed for each of the following criteria: septic events at time of diagnosis; recent treatment with cytostatic or cytotoxic drugs; and preexisting thromboembolic complications. A total score between 6 and 8 corresponds to a very likely HIT; a score between 4 and 5, a possible HIT; and a score between 0 and 3, an unlikely HIT.

A laboratory confirmation of HIT diagnosis using the platelet aggregation test or heparin-induced platelet antibodies assay (Diagnostica Stago; Asnières, France)10 was systematically performed. However, taking into account that the sensitivity of these assays is not 100%, a negative test result was not considered to be an exclusion criteria.

**Cross-reactivity Testing**

Whenever possible before danaparoid sodium administration, danaparoid sodium cross-reactivity with heparin-dependent antibodies was tested in vitro, using a platelet aggregation test with a final concentration of danaparoid sodium of 1 U/mL.

**Supplies of Danaparoid Sodium**

Danaparoid sodium (Organon; Oss, Holland) was provided, as 1.0- and 0.6-mL ampules containing 1,250 and 750 U danaparoid sodium, respectively, for IV or subcutaneous injections.

**Results**

**Characteristics of Patients**

By the scoring schedule of Greinacher et al, HIT was considered very likely for 32 patients and possible for 10 patients. HIT diagnosis was confirmed by the platelet aggregation test or by heparin-induced platelet antibodies assay for 28 of the 32 very likely patients and for 8 of the 10 possible patients. Among these 42 patients, there were 18 men and 24 women with ages ranging from 23 to 92 years (mean, 69 years). On the first day of danaparoid sodium therapy, the mean of the simplified acute physiology score (SAPS) II11 of these patients was 30.6 with a range between 13 and 68. The mean delay of HIT occurrence was dramatically longer when LMWH was prescribed (Table 1). Thrombotic complications related to HIT were observed with the same frequency no matter whether standard unfractionated heparin or LMWH was used (Table 1).

Among the 42 patients, 37 received danaparoid sodium at the acute phase of HIT, whereas 5 had HIT 2 to 6 years before the use of danaparoid sodium. All 37 patients treated during the acute phase of HIT were thrombocytopenic before receiving danaparoid sodium with a mean platelet count of 100,000 to 150,000/mm³, with a range from 40,000 to 100,000/mm³. On average, the platelet count declined further to 75,000/mm³ (range, 50,000 to 100,000/mm³). The serum creatinine level was normal before the acute HIT episode, except in 2 patients (107 and 117 μmol/L). The mean serum creatinine level on the first day of danaparoid sodium therapy was 169 μmol/L (range, 107 to 204 μmol/L).

**Treatment Regimens**

To prevent venous thromboembolism complication either after nonvascular surgery or in medical situations, danaparoid sodium was usually administered as a subcutaneous injection of 600 to 800 U every 12 h. Plasma antifactor Xa activity was monitored only in case of renal insufficiency and had to be maintained between 0.2 to 0.4 U antifactor Xa per milliliter. In postcardiac surgery (coronary artery bypass and aortic or mitral valve replacement), 100 to 300 U/h danaparoid sodium was administered IV to obtain antifactor Xa activity at approximately 0.5 U antifactor Xa per milliliter. For hemodialysis, danaparoid sodium was administered before dialysis with an IV bolus of 40 U/kg to maintain plasma antifactor Xa levels <0.3 U antifactor Xa per milliliter. For hemofiltration, danaparoid sodium was administered IV with an infusion rate of 100 to 400 U/mL to maintain plasma antifactor Xa levels between 0.5 and 1 U antifactor Xa per milliliter.

To treat acute arterial or venous thromboembolism complication, a step-down IV infusion rate was advised (400 U/h for 4 h followed by 300 U/h for 4 h), and then the maintenance infusion rate of 100 to 370 U/h was used to maintain plasma antifactor Xa levels between 0.5 and 0.8 U antifactor Xa per milliliter.

**Monitoring Danaparoid Sodium Effects**

Danaparoid sodium treatment was monitored by antifactor Xa activity using a standard curve, established with control plasma containing danaparoid sodium dilutions. Plasma antifactor Xa levels were measured daily, either every morning while receiving infusion therapy or 6 h after the morning dose while receiving subcutaneous therapy. Plasma antifactor Xa levels were also monitored before each dialysis. Monitoring of the platelet count was performed every day until the end of danaparoid sodium treatment.
56,000 platelets per cubic millimeter (range, 9,000 to 101,000 platelets per cubic millimeter). Eight patients had one hemorrhagic risk factor, and 22 patients had one or more thrombosis risk factors. Three of these patients had both risks. The duration of danaparoid sodium treatment varied considerably between both the different clinical situations encountered and even within particular clinical situations: the median duration of consecutive daily treatment was 10.7 days (range, 1 to 48 days). Among the 42 patients, 29 received oral anticoagulants (OAC) after at least 4 days of danaparoid sodium treatment (except for 3 patients). Danaparoid sodium therapy was stopped when the international normalized ratio value was in the therapeutic range for 48 h.

Clinical Outcomes

Four patients received danaparoid sodium treatment twice, making a total of 46 courses of treatment. Among these 46 courses, 26 were instituted to treat an acute thrombotic complication (group 1, 26 patients) (Table 2) and 20 to prevent thromboembolic complications (group 2, 16 patients) (Table 3).

In group 1, neither a new thrombotic complication nor a thrombosis extension was clinically detected during danaparoid sodium treatment. Among these 26 patients, 6 deaths occurred. Three deaths were related to septic shock (SAPS II, 34, 35, and 51), and one was related to a fatal hemothorax after the placement of a central venous catheter. Two other deaths were directly related to lower limb acute arterial thromboses associated with HIT. For these two patients, diagnosis was delayed by 2 and 3 days, and danaparoid sodium therapy was instituted a few hours after thrombectomy while there was a severe disseminated intravascular coagulation. Thus, danaparoid sodium failed to treat a thrombotic complication of HIT in 2 of 26 patients (7.6%). One patient had a minor GI tract hemorrhage with antifactor Xa activity of 0.9 U per milliliter and international normalized ratio at 10 (oral anticoagulation had started 3 days before). Two major hemorrhagic complications were observed: one hemothorax (described above), and one hematoma (needing transfusion) under the scar of a peripheral vascular bypass. These two patients were receiving 250 mg/d aspirin in addition to danaparoid sodium (antifactor Xa activity, 0.58 and 0.60 U antifactor Xa per milliliter). At the 1-month follow-up after danaparoid sodium therapy withdrawal, no thrombosis recurrence was observed.

In group 2 (16 patients, 20 courses of treatment), no thrombotic event occurred during danaparoid sodium prophylaxis. One patient had a minor tracheal tube hemorrhage associated with epistaxis. One patient, who had an aggravation of a postoperative cerebral lesion, had already bled under LMWH. Two patients died of septic shock (SAPS II, 46 and 68). At the 1-month follow-up after danaparoid sodium therapy withdrawal, only one DVT

<table>
<thead>
<tr>
<th>Type of Molecule (No.)</th>
<th>Thrombocytopenia Occurrence, d</th>
<th>Arterial Thrombosis</th>
<th>Venous Thrombosis</th>
<th>Arterial + Venous Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>USH (26)</td>
<td>13.6 ± 2.3</td>
<td>5 (19)</td>
<td>5 (19)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>LMWH (7)</td>
<td>20.6 ± 5.3†</td>
<td>2 (29)</td>
<td>2 (29)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>USH + LMWH (9)</td>
<td>14.1</td>
<td>0 (0)</td>
<td>3 (33)</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SEM or No. (%). USH = unfractionated standard heparin.
†p = 0.19 using Wilcoxon test.

Table 2—Indications of Treatments With Therapeutic Doses of Danaparoid Sodium*

<table>
<thead>
<tr>
<th>Thromboembolic Events</th>
<th>Before LMWH Treatment</th>
<th>Related to LMWH Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT or PE</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>DVT extension</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Limb arterial thrombosis</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Limb arterial thrombosis + DVT</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>3†</td>
<td></td>
</tr>
</tbody>
</table>

*PE = pulmonary embolism.
†For these three patients, ischemic stroke was associated with an arterial thrombosis, a DVT, or a mitral thrombosis.

Table 3—Indications of Danaparoid Sodium Administered at Prophylactic Doses*

<table>
<thead>
<tr>
<th>Prophylactic Indications</th>
<th>No. of Patients</th>
<th>Dosing Schedule</th>
<th>Administration Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urologic surgery</td>
<td>3</td>
<td>600 to 750 U × 2</td>
<td>SC</td>
</tr>
<tr>
<td>Gynecologic surgery</td>
<td>1</td>
<td>750 U × 2</td>
<td>SC</td>
</tr>
<tr>
<td>Visceral surgery</td>
<td>2</td>
<td>750 U × 2</td>
<td>SC</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>1</td>
<td>750 U × 2</td>
<td>SC</td>
</tr>
<tr>
<td>Cerebral surgery</td>
<td>1</td>
<td>750 U × 2</td>
<td>SC</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>7</td>
<td>130 to 300 U/h</td>
<td>IV</td>
</tr>
<tr>
<td>Medical indications</td>
<td>3</td>
<td>600 to 750 U × 2</td>
<td>SC</td>
</tr>
</tbody>
</table>

*SC = subcutaneous.
recurrence was observed. This occurred in a patient with a gynecologic cancer who had a DVT on day 30 of OAC treatment.

**Laboratory Results**

Before the use of danaparoid sodium, test results for danaparoid sodium cross-reactivity with HIT IgG were negative in the 30 patients so tested. The mean time required for platelet count recovery was 6 days. Eight patients had persistent thrombocytopenia. For five of them, it was related to a major disseminated intravascular coagulation (caused by septic shock in three patients and by lower limb arterial thrombosis in two patients). For one patient, the persistence of thrombocytopenia was related to mistaken heparin injections used to maintain catheter fluidity. For two other patients, thrombocytopenia persistence observed on the third day of danaparoid sodium treatment was considered to be possibly related to danaparoid sodium cross-reactivity. In consideration of this hypothesis, danaparoid sodium therapy was stopped, but the resolution of thrombocytopenia was obtained only 8 and 10 days after danaparoid sodium therapy withdrawal for each patient. Thrombocytopenia also occurred on the third day of danaparoid sodium treatment for one patient previously reported. He had an HIT episode 6 years earlier. He received danaparoid sodium in the postoperative period of a coronary artery bypass in which heparin and iloprost (a prostacyclin analog that inhibits platelet function) were administered. Danaparoid sodium cross-reactivity had not been performed at the time of HIT diagnosis (6 years earlier) but has been demonstrated at the time of the actual episode of thrombocytopenia. Thus, in vivo danaparoid sodium cross-reactivity with HIT-IgG can be estimated in this group of 3 of 46 patients (6.5%) without thrombotic complications observed at the time of the thrombocytopenic period.

**Discussion**

Because we did not clinically observe any new thrombotic episodes during danaparoid sodium treatment either with prophylactic or therapeutic doses, we can consider that danaparoid sodium is an efficient antithrombotic treatment for critically ill patients with HIT. The overall death rate in our study remains high (8 of 42 patients [19%] during danaparoid sodium treatment), reflecting the generally severe condition (severe sepsis, disseminated intravascular coagulation, cancer, etc) of these critically ill patients at the time of danaparoid sodium therapy initiation. However, using danaparoid sodium, the mortality caused by thromboembolic complications related to the HIT syndrome was 2 of 42 patients (5%) in this study compared with the reported mortality (30%) in untreated HIT patients. This rate could probably have been even lower if HIT had been more quickly diagnosed for these two patients. Among 46 treatment episodes, only 3 major hemorrhagic complications (6.5%) were observed. In one patient, there was a hemorrhagic risk (hemorrhagic cerebral lesion), and in two patients, danaparoid sodium was given with aspirin. It appears that danaparoid sodium is a safe drug as long as the classic contraindications of anticoagulant treatment are respected. It is also recommended not to give danaparoid sodium with aspirin (or to do so with caution). Regarding the persistence or the recurrence of thrombocytopenia in danaparoid sodium therapy, in vivo cross-reactivity of HIT-IgG for the danaparoid sodium molecule was observed in 3 of 46 patients (6.5%) in this study, which corresponds to the rate already reported. It is important to note that for the two cases of thrombocytopenia persistence, danaparoid sodium cross-reactivity had not been previously shown by the platelet aggregation test. This means that negative in vitro results may not be totally predictive of the absence of cross-reactivity in vivo. Therefore, close monitoring of the platelet count is mandatory during danaparoid sodium treatment. Although in the past it was considered sufficient to merely withdraw LMWH or unfractionated standard heparin therapy from patients with HIT in the absence of thromboembolism, it is probable that HIT itself often requires antithrombotic therapy even when no thrombosis has occurred. Indeed, it has been established that such patients have a prothrombotic state as evidenced by the presence of several prothrombotic markers. With regard to the safety and efficacy of danaparoid sodium in this group of patients, it might be the suitable drug for subsequent anticoagulant treatment in these HIT patients. Moreover, recent studies indicate that caution should be exercised in the initiation of treatment with OACs, which should be started only when the acute thrombin generation associated with the thrombotic complications of HIT has been brought under control. For this reason, treatment with OACs should probably be undertaken a few days after danaparoid sodium treatment.

Last, in our study, HIT appears to develop in patients receiving LMWH after a longer time than those who are receiving standard heparin. This observation has not been previously made to our knowledge. Perhaps patients receiving LMWH should be monitored longer than we typically do now.

In conclusion, with the systematic in vitro evaluation of danaparoid sodium cross-reactivity with
HIT-IgG before its use, and a platelet count follow-up during its administration, danaparoid sodium appears to be an efficient and safe treatment in critically ill patients with HIT. The concomitant use of aspirin in addition to danaparoid sodium represents an important additional hemorrhagic risk that should be avoided in patient management. Moreover, danaparoid sodium itself inhibits platelet activation induced by heparin-dependent antibodies, and this alone seems to represent a sufficient therapy for most HIT patients.

REFERENCES