ARTICLE

Heparin-Induced Thrombocytopenia

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ABSTRACT

Heparin-induced thrombocytopenia is the most common immune-mediated adverse drug reaction, occurring in 1% to 3% of postoperative patients receiving unfractionated heparin prophylaxis for 7 to 14 days. Approximately 1 in 100 patients receiving a therapeutic dose of unfractionated heparin for a week or more will experience thrombosis related to heparin-induced thrombocytopenia.

Heparin-induced thrombocytopenia is characterized by activation of coagulation and platelets. Diagnosis of the condition should take into account the timing of the thrombocytopenia (which typically occurs on day 5 to 10 after initiation of heparin), the degree of the thrombocytopenia, and the presence of new thrombosis.

Use of warfarin alone to treat acute heparin-induced thrombocytopenia complicated by deep venous thrombosis sometimes results in loss of a limb because of venous limb gangrene, probably because warfarin can cause severe reduction in protein C without a simultaneous reduction in the generation of thrombin in these patients. New treatments now available in Canada to reduce thrombin generation in heparin-induced thrombocytopenia (such as danaparoid and lepirudin) are useful in managing the thrombotic consequences of heparin-induced thrombocytopenia.

Key words: heparin-induced thrombocytopenia, treatment, pathogenesis, drugs

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RÉSUMÉ

La thrombocitopénie d'origine héparinique représente la réaction indésirable d'origine immunologique la plus courante. En effet, elle survient chez 1 % à 3 % des patients qui reçoivent un traitement prophylactique post-opératoire à l'héparine non fractionnée durant 7 à 14 jours. Environ 1 patient sur 100 qui reçoivent une dose thérapeutique d'héparine non fractionnée pendant une semaine ou plus souffrira de thrombose associée à une thrombocytopénie d'origine héparinique.

La thrombocytopénie d'origine héparinique est caractérisée par l'activation de la coagulation et des plaquettes. Le diagnostic de cette affection devrait tenir compte du moment auquel survient la thrombocytopénie (cette dernière survenant habituellement entre le cinquième et le dixième jour après le début de l'héparinothérapie), du degré de la thrombocytopénie et de la présence de nouveaux thrombi.

Le recours à la warfarine seule pour traiter une thrombocytopénie aiguë d'origine héparinique compliquée par une thrombose veineuse profonde peut entraîner quelques fois la perte d'un membre à cause d'une gangrène veineuse du membre, probablement parce que la warfarine cause une diminution prononcée du taux de protéine C sans réduction simultanée du taux de thrombine chez ces patients. Les nouveaux traitements maintenant offerts au Canada pour réduire la production de thrombine dans les cas de thrombocytopénie d'origine héparinique (comme le danaparoide et la lépirudine) sont utiles dans le traitement des conséquences thrombotiques de la thrombocytopénie d'origine héparinique.

Mots clés : thrombocytopénie d'origine héparinique, traitement, pathogenèse, médicaments

INTRODUCTION

Heparin-induced thrombocytopenia is an extraordinary blood reaction. It is seen by internists, hematologists, surgeons, laboratory physicians, even dermatologists. This range of practitioners reflects the common use of heparin, the wide spectrum of complications caused by heparin-induced thrombocytopenia, and the importance of laboratory confirmation of the diagnosis.[1] This article discusses the pathogenesis and clinical features of this disorder, and summarizes current treatment approaches, with emphasis on newly recognized treatment pitfalls (such as warfarin-induced venous limb gangrene) for the uninformed clinician.

FREQUENCY

Heparin-induced thrombocytopenia is the most common immune-mediated adverse drug reaction affecting platelets, occurring in as many as 1% to 3% of postoperative patients who have received unfractionated heparin prophylaxis for 7 to 14 days, respectively.[2] The condition is strongly associated with new venous and arterial thrombotic events, such as deep vein thrombosis or pulmonary embolism in a postoperative patient receiving subcutaneous heparin prophylaxis (which is intended to prevent that very complication!).[2,3] Prospective studies suggest that about 1 in 100 patients who receive therapeutic-dose unfractionated heparin for a week or more will experience thrombosis related to heparin-induced thrombocytopenia.[4]

Heparins vary in their immunogenicity and associated risk for causing heparin-induced thrombocytopenia.[2] In a study of 665 postoperative patients who received either unfractionated heparin (n = 332) or low-molecular-weight heparin (n = 333), heparin-induced thrombocytopenia occurred significantly more often in the patients who received the unfractionated heparin preparation (2.7% and 0%, respectively; p = 0.002). A higher frequency of formation of the antibodies associated with heparin-induced thrombocytopenia was also observed in the patients who received unfractionated heparin (7.8% and 2.2%, respectively; p = 0.020). The greater immunogenicity of unfractionated heparin is probably related to the greater capacity of longer heparin chains to bind to platelet factor 4 in the formation of the antigen.

PATHOGENESIS

Heparin-induced thrombocytopenia is caused by IgG antibodies that recognize a complex of heparin and platelet factor 4, an endogenous protein found in platelets.[5-8] These pathogenic antibodies, after combining with the heparin – platelet factor 4 complexes, interact with platelet Fc receptors, triggering potent platelet activation.[9-11] The platelet activation is characterized by the generation of procoagulant, platelet-derived microparticles.[11] There is also evidence that the antibodies can trigger tissue-factor generation by activating endothelial cells; this activation occurs through recognition of platelet factor 4 bound to endothelial heparin-like substances.[7,12] Thus, heparin-induced thrombocytopenia is characterized by activation of coagulation in addition to activation of platelets, and this combination of activities provides the rationale for treatment with a drug that reduces thrombin generation in heparin-induced thrombocytopenia, specifically, danaparoid sodium or recombinant hirudin.[1]

Clinical Diagnosis

Heparin-induced thrombocytopenia should be suspected when one or more of the following are observed:[4]

1. characteristic timing of the thrombocytopenia (the platelet count begins to fall on day 5 to 10 [inclusive] of heparin therapy, with the first day of heparin use being day 0);
2. mild to moderately severe thrombocytopenia;
3. occurrence of thrombosis or other characteristic sequelae of heparin-induced thrombocytopenia.

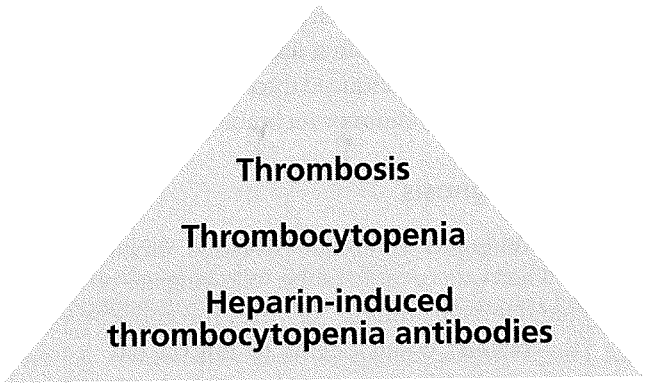
Each of these clinical features is discussed in more detail later.

Laboratory Confirmation

In our laboratory, platelet-activating heparin-induced thrombocytopenia antibodies are detected by the platelet ^{14}C-serotonin-release assay,[13,14] the only laboratory assay for this condition that has been validated in a blinded assessment. A positive assay is strongly associated with thrombocytopenia (odds ratio 78; 95% confidence interval 12.0 to 819; $p < 0.001$).[2] Unfortunately, the requirement for radiolabelled serotonin restricts the use of this assay. Although platelet aggregation assays are widely used in North America to diagnose heparin-induced thrombocytopenia, their sensitivity and specificity are poor.[15,16] An enzyme-linked immunoassay based on detecting antibodies that recognize the heparin – platelet factor 4 complex has also been developed.[7,15] We sometimes use this assay, especially for the occasional serum samples that give indeterminate results in the serotonin-release assay (such samples show strong but heparin-independent platelet activation).

Iceberg Model

Not all patients who have heparin-induced thrombocytopenia antibodies go on to experience the condition.[2,17] However, the risk for thrombosis appears to be highest among patients whose thrombocytopenia occurs in association with heparin-induced thrombocytopenia antibodies, and lower among patients in whom the antibodies form but thrombocytopenia does not occur;[2] This observation led us to propose the "iceberg model" of heparin-induced thrombocytopenia:[4]



Among orthopedic surgical patients receiving unfractionated heparin in whom heparin-induced thrombocytopenia antibodies form, thrombocytopenia occurs in about one-third, and at least half of these patients experience venous thrombosis.[2]

Current research efforts are aimed at elucidating the clinical and biologic factors determining which patients develop heparin-induced thrombocytopenia antibodies, thrombocytopenia, and thrombosis.

Early and Late Thrombocytopenia

Thrombocytopenia associated with a fall in platelet count that began between days 5 and 10 of heparin therapy is highly likely to have been induced by the heparin.[2] In contrast, a fall in platelet count that begins in the first 4 days of heparin therapy is unlikely to be related to heparin-induced thrombocytopenia antibodies; accordingly, we call this phenomenon non-immune heparin-associated thrombocytopenia.[1] This benign syndrome is usually related to other clinical factors (such as perioperative hemodilution) and does not necessitate discontinuation of heparin.

There is an important exception to the rule that early thrombocytopenia does not represent heparin-induced thrombocytopenia: if an immediate, unexpected post-heparin drop in platelet count occurs in a patient who received heparin within the previous 100 days, acute heparin-induced thrombocytopenia should be suspected. In our view, this phenomenon is caused by pre-existing heparin-induced thrombocytopenia antibodies related to the recent exposure to heparin, rather than an anamnestic immune response.[18]

Degree of Thrombocytopenia

The median platelet count in a large series of patients with heparin-induced thrombocytopenia was approximately 50 to 70 x 10^9/L.[2-4] For about 80% of the patients, the nadir in platelet count was between 20 and 150 x 10^9/L. In only 10% of the patients was the nadir less than 20 x 10^9/L; this profile is distinctly different from that in other drug-induced immune thrombocytopenic syndromes (such as those caused by quinine or sulpha antibiotics), in which the platelet count of almost all patients is less than 20 x 10^9/L.[11] For about 10% of patients with clinically significant heparin-induced thrombocytopenia, the platelet count never falls below 150 x 10^9/L. Nevertheless, a fall in platelet count of more than 30% beginning after 5 days of heparin therapy is usually seen in these patients.[19] In general, an unexplained fall in platelet count of more than 30% after 5 days of heparin should prompt investigations for heparin-induced thrombocytopenia and, possibly, discontinuation of heparin, depending upon the clinical situation.

Thrombosis and Other Clinical Sequelae

Venous thromboembolism, especially proximal deep venous thrombosis and pulmonary embolism, are the most frequent complications of heparin-induced thrombocytopenia.[2,3] These two conditions occur in as many as 50% and 25%, respectively, of patients with heparin-induced thrombocytopenia.[2,3] An unusual syndrome of limb loss known as venous limb gangrene has recently been associated with warfarin treatment of heparin-induced thrombocytopenia.[20,21] Clinicians should be aware that adrenal vein thrombosis in heparin-induced thrombocytopenia can lead to bilateral adrenal hemorrhagic infarction, an important cause of acute adrenal failure in hospitalized patients.[4,22] Administration of corticosteroids can be a life-saving measure, and physicians should consider this diagnosis in a thrombo-

cytopenic patient receiving heparin who experiences abdominal pain or hypotension (or both).

Arterial thrombosis is also relatively common, accounting for approximately 20% of cases of thrombosis associated with heparin-induced thrombocytopenia.[2,3] Large vessels are most susceptible to developing platelet-rich thrombi ("white clots"), and the relative frequency of thrombosis is as follows: aortoiliofemoral thrombosis (acute limb ischemia) > thrombotic stroke > myocardial infarction.[3] Intriguingly, this distribution ranking is the reverse of that seen in general medical practice.

Heparin-induced skin lesions occur in about 10% to 20% of patients who develop heparin-induced thrombocytopenia antibodies during subcutaneous injection of heparin. These lesions range from painful erythematous plaques to frank necrosis.[23] About three-quarters of the patients with skin lesions do not have thrombocytopenia; however, all have readily detectable heparin-induced thrombocytopenia antibodies.[23] We advise continued monitoring of platelet count for several days after heparin is discontinued because of skin lesions, given that delayed-onset thrombocytopenia and associated risk for arterial thrombosis have been described in some of these patients.[24]

Acute systemic reactions are characterized by unexpected symptoms and signs that begin 5 to 30 min after a heparin bolus is administered to a patient sensitized to heparin.[25-27] The clinical features include fever or chills, tachycardia or hypertension, dyspnea, chest pain or tightness, flushing, and diarrhea. A few patients have transient global amnesia.[27] The pathogenesis of these reactions is obscure, but it may be related to acute in vivo platelet activation. Clinicians should immediately suspect acute heparin-induced thrombocytopenia, discontinue the heparin, and obtain a platelet count; an unexpected fall in platelet count confirms the diagnosis.

Decompensated disseminated intravascular coagulation, manifesting as low fibrinogen levels, occurs in 5% or fewer of patients with heparin-induced thrombocytopenia.[4] Nevertheless, an element of disseminated intravascular coagulation occurs in most patients with heparin-induced thrombocytopenia; in one study, laboratory evidence for increased thrombin generation (elevated thrombin-antithrombin complexes) occurred in 24 of 25 patients with heparin-induced thrombocytopenia.[20] It is possible that acquired deficiency of natural anticoagulant factors such as antithrombin III contributes to the disseminated thrombi that are seen in some patients (white clot syndrome).

TREATMENT

Caveats

Recent evidence suggests important caveats in the treatment of heparin-induced thrombocytopenia. For example, it is now recognized that oral anticoagulants such as warfarin can worsen thrombosis in many patients with this condition. Further, important disadvantages of other treatments, such as ancrod and low-molecular-weight heparin, have now been recognized.

Warfarin-induced venous limb gangrene is defined as peripheral limb necrosis complicating deep venous thrombosis despite the presence of palpable or Doppler-identifiable arterial pulses; this disorder is characterized pathologically by subcutaneous vein and venule thrombosis.[20,21] We observed this complication in about 10% of patients who received warfarin for acute deep venous thrombosis complicating heparin-induced thrombocytopenia.[20] The hallmark of this syndrome is a supratherapeutic international normalized ratio: the median value was significantly higher in patients with venous limb gangrene than in control patients with heparin-induced thrombocytopenia who also received warfarin for deep venous thrombosis (5.8 and 3.1, respectively; $p < 0.001$). Laboratory investigations suggest that the pathogenesis of this devastating syndrome is an acquired, transient disturbance in procoagulant–anticoagulant balance: a warfarin-induced reduction in the natural anticoagulant, protein C, together with persisting thrombin generation despite the use of warfarin.[20] Progression from phlegmasia cerulea dolens to venous limb gangrene can probably be prevented by reversal of warfarin's paradoxical prothrombotic effect (through administration of vitamin K and fresh frozen plasma).[20]

Ancrod, a defibrinogenating snake venom, was approved in 1992 in Canada for the treatment of heparin-induced thrombocytopenia, on the basis of a small uncontrolled experience.[27] The drug has not been approved for this indication in any other country and has several disadvantages. First, it must be given slowly over 24 to 48 h to avoid acute intravascular microthrombosis, and thus it cannot effect rapid anticoagulation. Second, ancrod does not decrease, and may even increase, thrombin generation in heparin-induced thrombocytopenia.[28] This may explain why several Canadian patients have experienced venous limb gangrene during combined treatment with ancrod and warfarin.[20] Third, the defibrinogenating effect is difficult to predict, and severe hypofibrinogenemia and bleeding can result. Fourth, ancrod appeared less effective in a retrospective comparison with danaparoid.[28] Thus,

ancrod therapy is not pharmacologically rational in a syndrome of increased thrombin generation.[1] Because more promising agents are now available for the treatment of heparin-induced thrombocytopenia, we no longer use ancrod for this condition.[1,29]

Low-molecular-weight heparin presents a therapeutic conundrum: although this type of heparin is less likely to cause heparin-induced thrombocytopenia,[2] it is associated with a substantial risk of worsening thrombocytopenia or thrombosis (or both) in a patient with acute heparin-induced thrombocytopenia.[29] The reason is that heparin-induced thrombocytopenia antibodies activate platelets to the same degree in the presence of low-molecular-weight heparin as in the presence of unfractionated heparin, according to sensitive assays of washed platelets.[2,28,30] Thus, low-molecular-weight heparin is not recommended as a treatment for heparin-induced thrombocytopenia.[1,29]

Danaparoid (Orgaran)

Danaparoid sodium (Orgaran) has been available in Canada since 1994. It is a mixture of anticoagulant glycosaminoglycans (heparan sulphate, dermatan sulphate, and chondroitin sulphate) with predominant anti-factor Xa activity.[31] Indeed, the anti-Xa:anti-IIa (thrombin) ratio is about 22:1, which is far greater than that of either low-molecular-weight heparin (3:1 or 4:1) or unfractionated heparin (1:1). The half-life of its anti-factor Xa activity is approximately 25 h. Danaparoid has a relatively low frequency (approximately 10% to 20%) of detectable, but generally weak, in vitro cross-reactivity with heparin-induced thrombocytopenia antibodies.[28,30-32] Further, our experience with danaparoid for acute heparin-induced thrombocytopenia has not shown any correlation between in vitro cross-reactivity and clinical outcomes.[28] In a randomized clinical trial in Australia, treatment with danaparoid was successful in about 90% of patients with heparin-induced thrombocytopenia, which was significantly greater than the success rate for the dextran-treated control patients.[33] We have observed a similar frequency of successful treatment.[28] Worldwide, danaparoid has been used in over 700 patients with heparin-induced thrombocytopenia.[34,35] The drug has been approved for the treatment of heparin-induced thrombocytopenia in several countries (including the Netherlands, New Zealand, and Germany); in other countries, such as Canada and the United States, danaparoid has been approved for prophylaxis of deep venous thrombosis, but it is frequently used off label for the treatment of heparin-induced thrombocytopenia. Danaparoid is associated with a low frequency of bleeding complications, even when anticoagulant activity is not monitored, because there is a high likelihood of achieving a therapeutic dose with standard dose regimens. There is one exception: in patients with renal failure, the drug can accumulate, and we recommend reduced dosing and monitoring of anticoagulant activity (using anti-factor Xa levels) in these patients. Dosing recommendations and methods of drug administration are outlined in Appendix 1.

Isolated Heparin-Induced Thrombocytopenia

At our medical centre, approximately half of all patients with heparin-induced thrombocytopenia are recognized only after a new thrombotic event has occurred. The remaining patients, either with or without an initial venous or arterial thrombotic event prompting the use of heparin, are said to have isolated heparin-induced thrombocytopenia. We recently reported the results of a large retrospective cohort study (n = 62),[3] in which there was a surprisingly high frequency of thrombosis, even when the patients' heparin-induced thrombocytopenia was managed by discontinuing the heparin or by substituting warfarin for heparin. Two patients died suddenly within a few days after discontinuation of the heparin; in one case, the death was caused by massive pulmonary embolism (no post-mortem study was performed in the other patient). We found that the 30-day thrombotic event rate was approximately 50% in patients with isolated heparin-induced thrombocytopenia.[3] Most of these events occurred in the first 10 days after diagnosis of heparin-induced thrombocytopenia. Similar findings were seen in our prospective study:[2] 3 of 4 patients with recognized isolated heparin-induced thrombocytopenia developed venous thrombosis shortly after heparin was discontinued because of the thrombocytopenia.

Because of the life-threatening nature of isolated heparin-induced thrombocytopenia, we recommend that all patients with clinically suspected heparin-induced thrombocytopenia undergo anticoagulation with a suitable, rapid-acting anticoagulant, such as danaparoid. We usually administer therapeutic doses, although we use prophylactic doses in patients with renal failure and those at high risk for bleeding. If heparin-induced thrombocytopenia is confirmed by laboratory testing we continue the danaparoid until the platelet count has recovered and reached a steady plateau. We routinely perform predischarge duplex ultrasonography in these patients to confirm that partially treated, subclinical deep venous thrombosis is not present. If heparin-induced thrombocytopenia is not

confirmed by sensitive laboratory testing (for example, by the platelet serotonin-release assay), we discontinue the danaparoid and readminister unfractionated or low-molecular-weight heparin, if anticoagulation is still indicated. The rationale for this recommendation is that therapeutic-dose danaparoid is likely to be effective for patients with heparin-induced thrombocytopenia who have subclinical thrombosis, given its high success rate (about 90%) in patients with thrombosis associated with heparin-induced thrombocytopenia. However, our practice has not been formally evaluated in a clinical trial.

Adjunctive and Other Treatments

Surgical removal of limb-threatening arterial clots, or medical thrombolysis, should be considered in carefully selected patients. We have used plasmapheresis with success to reverse warfarin anticoagulation in a patient with severe phlegmasia cerulea dolens that threatened limb viability (incipient venous limb gangrene). Antiplatelet drugs such as acetylsalicylic acid might be helpful in patients at high risk for arterial thrombosis, but we recommend their use as adjunctive, rather than as primary, treatments for heparin-induced thrombocytopenia in appropriate patients.

Hirudin, produced by the medicinal leech, specifically inhibits thrombin. Lepirudin (Refludan) is a variant hirudin manufactured by recombinant technology. On the basis of results of a prospective cohort study using historic controls that was performed in Germany,[36] lepirudin was recently approved in both the European Union and the United States for treatment of heparin-induced thrombocytopenia complicated by thrombosis. Although currently available in Canada only by emergency drug release, its pharmacodynamic and pharmacokinetic properties, which differ from those of danaparoid, and the evidence for its efficacy in heparin-induced thrombocytopenia, suggest that it should be a welcome addition to the therapeutic armamentarium available to Canadian clinicians.

The new understanding of the importance of thrombin generation in the pathogenesis of heparin-induced thrombocytopenia, and the availability of agents effective in controlling this process, mean that Canadian physicians and pharmacists have a better prospect of avoiding disastrous outcomes in patients with heparin-induced thrombocytopenia.

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Appendix 1. Guidelines for IV or SC Administration of Danaparoid Sodium (Orgaran®)

Indications	Treatment of acute heparin-induced thrombocytopenia with or without associated thrombosis (generally use in therapeutic doses, see below)
	Anticoagulation for patients with a history of heparin-induced thrombocytopenia (use in prophylactic or therapeutic doses, depending upon the clinical indication)
Classification	Antithrombotic agent with predominant anti-factor Xa activity and also some anti-thrombin (factor IIa) activity
Dosage*	
Therapeutic	
IV loading dose	< 60 kg: 1500 units (2 ampoules) 60 to 75 kg: 2250 units (3 ampoules) 75 to 90 kg: 3000 units (4 ampoules) > 90 kg: 3750 units (5 ampoules) Followed by 400 U/h for 4 h, then 300 U/h for 4 h, then maintenance dosing
IV maintenance	150 to 200 U/h†

Appendix 1. Guidelines for IV or SC Administration of Danaparoid Sodium (Orgaran®) ... continued

SC maintenance	1500 units q12h to 1500 units q8h† (after initial IV loading dose, without step-down)
Prophylactic	750 anti-Xa units q8h or q12h† (SC)
Administration‡	
Loading dose	Undiluted or diluted in small volume of IV fluid and administered over 5 min
Continuous infusion	Add 3 ampoules (2250 U) to 250 mL or add 6 ampoules (4500 U) to 500 mL; therefore, 400 U/h = 44 mL/h, 300 U/h = 33 mL/h, 200 U/h = 22 mL/h, 150 U/h = 17 mL/h, and so on
Compatibility and stability	Dextrose and saline solutions only; do not mix with any other solution or any other medication; stable for 24 h once mixed in solution; protect from light
Warfarin overlap	An advantage of danaparoid is that its anticoagulant effects do not interfere with measurements of the international normalized ratio (INR). We recommend starting warfarin when the platelet count has largely recovered (approximately 100 x 10^9/L or greater). The danaparoid should be tapered when the INR begins to rise and should be stopped when the INR approaches 2.0.
Adverse effects	Bleeding, rash, or pain or skin reactions at injection sites. Clinically significant cross-reactivity with heparin-induced thrombocytopenia antibodies manifesting as worsening thrombocytopenia or new or progressive thrombosis has been reported, but appears to be uncommon (occurring in less than 5% of patients).
Cautions	Renal failure (reduce dose by 25% to 50% and monitor by means of anti-factor Xa levels). Use with caution in patients with epidural anesthesia, history of gastrointestinal ulceration, or severe untreated hypertension. Do not use in patients with hemorrhagic stroke. May be used with caution in combination with acetylsalicylic acid and nonsteroidal antiinflammatory agents.

Sources: Warkentin and colleagues,[1] Chong,[37] and unpublished data, Organon Canada.

* Assumes availability of ampoules with 750 units of anti-factor Xa.

† In general, the lower dose range is for smaller patients or those with venous thromboembolic disease; the higher dose range is for larger patients or those with arterial thromboembolism. For patients receiving therapeutic-dose danaparoid, dose adjustments can be made on the basis of anti-factor Xa levels, if available (therapeutic target range, 0.5 to 0.8 anti-Xa units), although routine anti-Xa monitoring is not necessary in most clinical situations. However, monitoring is strongly recommended in patients with renal failure, as danaparoid will accumulate in these patients, as well as in patients with life-threatening or limb-threatening thrombotic complications. Note: For anti-factor Xa measurements, the laboratory must determine a standard curve using danaparoid, rather than low-molecular-weight heparin; otherwise, the anti-Xa level will be overestimated.

‡ Higher concentrations can be used in fluid-restricted patients.