Rapid Anticoagulation Using Ancrod for Heparin-Induced Thrombocytopenia

By Christine Demers, Jeffrey S. Ginsberg, Patrick Brill-Edwards, Akbar Panju, Theodore E. Warkentin, David R. Anderson, Christopher Turner, and John G. Kelton

In order to determine the efficacy and safety of ancrod, a rapid acting defibrinogenating drug, for patients with heparin-induced thrombocytopenia, 11 consecutive patients who required anticoagulant therapy because of venous thromboembolism and who developed acute heparin-induced thrombocytopenia or had a history of heparin-induced thrombocytopenia were treated with ancrod. Heparin therapy was discontinued (in patients receiving heparin) and ancrod started at a dose of 1 to 2 U/kg every 24 hours with subsequent daily doses adjusted to maintain fibrinogen levels between 0.5 and 1.0 g/L. Ancrod was continued until warfarin had become effective. The platelet count increased to more than 150 \times 10^9/L within 2 to 10 days in all thrombocytopenic patients. Two patients with a history of heparin-induced thrombocytopenia maintained normal platelet counts while receiving ancrod. Two patients had recurrent venous thrombosis while receiving warfarin, 10 days after ancrod was discontinued: one of these patients had metastatic pancreatic carcinoma and developed phlegmasia cerulea dolens and the other patient developed a venographically proven extension of her deep venous thrombosis. One patient suffered a bleeding episode into the thigh with a 16-g/L decrease in her hemoglobin level while receiving ancrod therapy. No other side effects were noted. Our experience indicates that ancrod therapy is a reasonable approach for patients with heparin-induced thrombocytopenia who require anticoagulant therapy.

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Heparin is widely used as the initial treatment of patients with deep venous thrombosis and pulmonary embolism and is also used for the prophylaxis of venous thromboembolism. Approximately 1% to 5% of patients who are treated with heparin become thrombocytopenic, and although the thrombocytopenia by itself rarely causes bleeding, it can be complicated by venous or arterial thrombosis. The management of patients with heparin-induced thrombocytopenia has become a dilemma for physicians. If heparin therapy is continued, exacerbation of thrombocytopenia and thrombosis may occur. Although oral anticoagulants are effective in preventing recurrent venous thrombosis, their onset of action is slow due to the long half-lives of the vitamin K-dependent factors. Thus, there is a need to overlap heparin and oral anticoagulant therapy by several days in patients with acute deep venous thrombosis or pulmonary embolism. Therefore, if heparin-induced thrombocytopenia occurs before the initiation of warfarin therapy or before a therapeutic effect is achieved, it may be hazardous to discontinue heparin and wait for an effect from warfarin because thromboembolic recurrence may occur. Furthermore, patients with prior heparin-induced thrombocytopenia who present with recurrent deep venous thrombosis or pulmonary embolism present a management problem because rechallenge with heparin may be associated with recurrence of heparin-induced thrombocytopenia. Thus, there is a need for an alternative anticoagulant to heparin that is safe, effective, and rapid. Ancrod is a rapid-acting defibrinogenating agent derived from the Malayan pit viper that is immunologically distinct from heparin and does not cause immune thrombocytope-nia. Several studies have reported that this agent is effective for the treatment of acute deep venous thrombosis. However, we were able to identify only two case reports in which ancrod therapy was used for patients with heparin-induced thrombocytopenia. Over the last 5 years, it has been our practice to use ancrod for the treatment of patients developing heparin-induced thrombocytopenia. We are reporting our experience with 11 consecutive patients with heparin-induced thrombocytopenia who were managed with ancrod therapy.

MATERIALS AND METHODS

Patient population. Consecutive inpatients at Chedoke-McMaster Hospitals, Henderson General Hospital, and Hamilton General Hospital in Hamilton, Canada, who required parenteral anticoagulant therapy because of venous thromboembolism and who developed acute heparin-induced thrombocytopenia or had a history of heparin-induced thrombocytopenia were potentially eligible for ancrod therapy. In our hospitals, the initial treatment of acute venous thrombosis consists of 5 to 10 days of heparin therapy administered as a continuous intravenous infusion. The heparin dose is adjusted to maintain an activated partial thromboplastin time between 60 and 85 seconds, which corresponds to a heparin level of 0.2 to 0.4 U/mL using the protamine sulfate assay. Warfarin is commenced within 5 days of initiating heparin therapy and warfarin is stopped when the International Normalized Ratio (INR) has been between 2 and 3 (prothrombin time ratio of 1.3 to 1.5) for 24 hours.

Heparin-induced thrombocytopenia was diagnosed clinically if the patient had a decrease in the platelet count of greater than 50% from the preheparin value or if a platelet count of less than 70 \times 10^9/L occurred in patients while receiving heparin therapy in the absence of other causes (drugs, sepsis, or disseminated intravascular coagulation). The presence or absence of antiheparin antibodies was not used to define heparin-induced thrombocytopenia because the results were not always available when the clinical decision to stop heparin was made. However, the serotonin release assay was positive in all patients.

Parenteral anticoagulant therapy was considered necessary if an acute venous thromboembolic event had occurred and warfarin was not appropriate. If anticoagulant therapy was indicated, parenteral anticoagulation was continued until the platelet count returned to more than 150 \times 10^9/L within 2 to 10 days. If the platelet count did not increase, warfarin therapy was continued. If the patient was not thrombocytopenic, the heparin therapy was discontinued (in patients receiving heparin) and ancrod started at a dose of 1 to 2 U/kg every 24 hours with subsequent daily doses adjusted to maintain fibrinogen levels between 0.5 and 1.0 g/L. Ancrod was continued until warfarin had become effective. The platelet count increased to more than 150 \times 10^9/L within 2 to 10 days in all thrombocytopenic patients. Two patients with a history of heparin-induced thrombocytopenia maintained normal platelet counts while receiving ancrod. Two patients had recurrent venous thrombosis while receiving warfarin, 10 days after ancrod was discontinued: one of these patients had metastatic pancreatic carcinoma and developed phlegmasia cerulea dolens and the other patient developed a venographically proven extension of her deep venous thrombosis. One patient suffered a bleeding episode into the thigh with a 16-g/L decrease in her hemoglobin level while receiving ancrod therapy. No other side effects were noted. Our experience indicates that ancrod therapy is a reasonable approach for patients with heparin-induced thrombocytopenia who require anticoagulant therapy.

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ANCROD FOR HEPARIN-INDUCED THROMBOCYTOPENIA

had either not been started or had not caused a prolongation of the INR to 2 to 3 for 24 hours.

**Treatment regimen.** Patients developing heparin-induced thrombocytopenia who required ongoing parenteral anticoagulant therapy had heparin discontinued (if receiving heparin) and ancrod therapy started. Those patients with previous heparin-induced thrombocytopenia who required parenteral anticoagulants had therapy initiated with ancrod as described subsequently. The following protocol was used to provide guidelines for the management of patients with heparin-induced thrombocytopenia. Ancrod was started at a dose of 1 to 2 U/kg administered either as an intravenous infusion over 6 to 24 hours or subcutaneously. This was followed by a maintenance dose of 1 to 2 units per kg every 24 hours, with the dose adjusted to maintain a fibrinogen level (using the Clauss method) between 0.5 and 1.0 g/L. Ancrod therapy was discontinued when concomitant warfarin had produced prolongation of the INR to 2 to 3 for 24 hours. The choice of the subcutaneous or intravenous route of ancrod administration was left to the discretion of the attending physician.

**Follow-up and outcome measures.** Outcome measures included recurrent venous thromboembolic events and bleeding. Daily hemoglobin levels and platelet counts were performed while patients received ancrod therapy.

**RESULTS**

Eleven patients (six women and five men) with a median age of 66 years (range 48 to 80) were evaluated between November 1985 and April 1990. Nine patients were treated with ancrod because their platelet count had decreased while receiving heparin therapy, whereas two patients were treated with ancrod because they presented with acute venous thrombosis and had a previous history of heparin-induced thrombocytopenia. Table 1 summarizes the characteristics of the patients.

Seven patients received ancrod intravenously (administered as an infusion over 6 to 12 hours) and four were treated with combined intravenous and subcutaneous ancrod. All patients required 1 to 2 U/kg of ancrod every 24 hours to maintain the fibrinogen level between 0.5 and 1.0 g/L. Ten of 11 patients had a decrease in their fibrinogen level to less than 1.0 g/L within 24 hours of starting ancrod, and all patients had a nadir fibrinogen level of less than 0.5 g/L. The duration of ancrod therapy varied from 1 day to 30 days (median of 3 days).

**Outcome measures.** All patients treated with ancrod because their platelet count had decreased while receiving heparin therapy had a recovery of their platelet count to more than 150 × 10^9/L within 2 to 10 days (median of 6 days) of discontinuing heparin. The two patients with a history of heparin-induced thrombocytopenia maintained normal platelet counts while receiving ancrod therapy.

There were no thromboembolic recurrences in nine of the patients either while on ancrod or in follow-up (6 weeks to 1 year) after their acute deep venous thrombosis. Two patients had recurrent venous thrombosis while receiving warfarin, both 10 days after ancrod had been discontinued; one patient with metastatic pancreatic carcinoma developed phlegmasia cerulea dolens and one patient had a venographically proven extension of her deep venous thrombosis. No patient developed arterial thrombosis while on ancrod. One patient suffered a bleeding episode into the thigh with a 16 g/L drop in her hemoglobin level while receiving ancrod therapy. The bleeding episode was diagnosed clinically and did not result in serious morbidity. At the time the bleeding episode occurred, the fibrinogen level was 0.5 to 0.7 g/L, the platelet count was 57 × 10^9/L, and the INR was 2.7. One patient treated with ancrod for 30 days developed ancrod resistance after 27 days of treatment. There were no other side effects noted.

**DISCUSSION**

Physicians must frequently manage patients who require immediate antithrombotic therapy but have a current or a

### Table 1. Clinical Summary of the Patients With Heparin-Induced Thrombocytopenia

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Indication for Anticoagulant Therapy</th>
<th>Nadir Platelet Count (10^9/L)</th>
<th>Delay for Platelet Increase &gt; 150 × 10^9/L (d)</th>
<th>Bleeding Episode</th>
<th>Recurrence</th>
</tr>
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<tbody>
<tr>
<td>76</td>
<td>DVT</td>
<td>425</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
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<td>74</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>DVT/PE</td>
<td>68</td>
<td>5</td>
<td>No</td>
<td>Yes†</td>
</tr>
<tr>
<td>54</td>
<td>DVT/PE</td>
<td>74</td>
<td>10</td>
<td>No</td>
<td>Yes‡</td>
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<tr>
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<td>Axillary DVT</td>
<td>47</td>
<td>4</td>
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<td>64</td>
<td>DVT</td>
<td>26</td>
<td>7</td>
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<td>No</td>
</tr>
<tr>
<td>76</td>
<td>PE</td>
<td>59</td>
<td>4</td>
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<td>No</td>
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<tr>
<td>66</td>
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<td>No</td>
</tr>
<tr>
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<td>6</td>
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<td>No</td>
</tr>
<tr>
<td>48</td>
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<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>80</td>
<td>DVT/PE</td>
<td>52</td>
<td>7</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Heparin-induced thrombocytopenia.
†Extension of DVT, 10 days after stopping ancrod while receiving adequate warfarin (INR between 2 and 3).
‡Terminal carcinoma, phlegmasia cerulea dolens 10 days after stopping ancrod therapy.
§Increase in thigh volume and 16 g/L decrease in hemoglobin concentration.
previous history of heparin-induced thrombocytopenia. The optimal method of management for patients with heparin-induced thrombocytopenia remains uncertain. In this report we describe our experience using the anticoagulant drug ancrod in a group of patients with heparin-induced thrombocytopenia who required rapid anticoagulation. We were interested in three issues concerning ancrod therapy; its efficacy, its safety, and the development of guidelines for using this drug.

The first issue of interest was the efficacy of ancrod. The platelet count returned to normal in all of our patients with heparin-induced thrombocytopenia and there was no decrease in the platelet count in patients with previous heparin-induced thrombocytopenia. Two patients developed recurrent venous thromboembolism, but both recurred 10 days after ancrod therapy had been discontinued. Furthermore, one patient had widespread metastatic carcinoma, which is independently associated with a high rate of recurrent venous thromboembolism.10-12

The next issue of concern was the safety of ancrod therapy. We found ancrod to be a relatively safe antithrombotic agent; no patient had a serious complication from this therapy. The bleeding rate in this study is consistent with other studies reporting patients treated with either ancrod or warfarin therapy.13,14 Resistance to the drug, presumably caused by anti-ancrod antibodies, has been reported to occur in patients 4 to 6 weeks after initiating ancrod.15 One of our patients experienced resistance after 27 days of ancrod therapy. No other adverse experiences occurred in our study.

The final intent of our study was to develop guidelines that would allow safe and effective administration of ancrod. We found our protocol to be useful and convenient for the administration of ancrod. The major limitation of this study is the relatively small number of patients evaluated. However, based on our data the following guidelines for ancrod therapy can be suggested. Ancrod should be started at a dose of 1 to 2 U/kg administered intravenously over about 6 hours to achieve defibrinogenation. This dose reduced the concentration of fibrinogen into the therapeutic range (0.5 to 1.0 g/L) in 10 of 11 patients within 24 hours of starting ancrod. Although the optimal therapeutic range in patients receiving ancrod therapy is unknown, the targeted fibrinogen level of 0.5 to 1.0 g/L used in our study seems to be adequate because none of the patients had recurrent venous thrombosis while receiving ancrod. Subsequent doses of ancrod can be administered once daily, subcutaneously or intravenously based on the results of daily fibrinogen level measurements. Most patients required 1 to 2 U/kg per day. Oral anticoagulants should be administered on the same day ancrod is started. The monitoring of oral anticoagulant therapy in patients treated with ancrod can be a potential problem if the fibrinogen decreases to such low levels that the INR becomes prolonged. Therefore, it may be reasonable to monitor the levels of factor II to ensure that a therapeutic oral anticoagulant effect has been achieved.

Due to the relative infrequency of heparin-induced thrombocytopenia, a cohort study rather than a randomized trial was performed. The major limitation of this design is the fact that formal comparison of ancrod with other regimens such as the continuation of heparin, the substitution of low-molecular heparin, or the use of warfarin alone is not possible. However, reports of arterial thrombosis with continuation of standard heparin15,20 and of persistence of thrombocytopenia due to cross-reactivity of low molecular heparin and standard heparin24-25 suggest that these options are suboptimal. In addition, if warfarin alone is used, patients will not be anticoagulated for at least 48 hours and will be prone to thromboembolic recurrence.20 Our results are consistent with other reports describing the successful use of ancrod in two patients with venous thrombosis who developed heparin-induced thrombocytopenia26 and with two randomized trials in which ancrod was successfully used as the initial treatment in patients with venous thromboembolism.11,12 In summary, our experience indicates that ancrod therapy is a reasonable approach for patients with heparin-induced thrombocytopenia who require anticoagulant therapy.

REFERENCES

Rapid anticoagulation using ancrod for heparin-induced thrombocytopenia [see comments]

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