Rapid Anticoagulation Using Ancrod for Heparin-Induced Thrombocytopenia

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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 x 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 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 x 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 x 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 previous history of heparin-induced thrombocytopenia. Ancrod is a valuable alternative to heparin because it does not induce thrombocytopenia and is not affected by warfarin. Ancrod is effective in rapidly lowering fibrinogen levels to less than 0.5 g/L. The dose of ancrod can be adjusted to maintain the fibrinogen level between 0.5 and 1.0 g/L. Ancrod therapy is safe and effective, with no thromboembolic recurrences or significant bleeding episodes. Ancrod therapy is well tolerated, with no major side effects noted. Ancrod is an effective alternative to heparin in patients with a history of heparin-induced thrombocytopenia.
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.16-18

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.19,20 Resistance to the drug, presumably caused by anti-ancrod antibodies, has been reported to occur in patients 4 to 6 weeks after initiating ancrod.21 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 heparin22,23 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.27 Our results are consistent with other reports describing the successful use of ancrod in two patients with venous thrombosis who developed heparin-induced thrombocytopenia19 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]

C Demers, JS Ginsberg, P Brill-Edwards, A Panju, TE Warkentin, DR Anderson, C Turner and JG Kelton