Heparin Anticoagulation during Cardiopulmonary Bypass in an Antithrombin-III Deficient Patient

Implications Relative to the Etiology of Heparin Rebound

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Solo way, Henry B., and Christiansen, T. W.: Heparin anticoagulation during cardiopulmonary bypass in an antithrombin-III deficient patient. Implications relative to the etiology of heparin rebound. Am J Clin Pathol 73: 723-725, 1980. A case of antithrombin-III (AT-III) deficiency was diagnosed on the basis of a diminished anticoagulant effect following the administration of heparin for cardiopulmonary bypass. The clinical evaluation and interpretation of a diminished response to heparin is discussed, as are considerations relative to the treatment of AT-III deficient persons whose disorder is not manifest until they are already anesthetized for cardiovascular bypass. The implications of AT-III deficiency relative to the mechanism of heparin rebound are also discussed. (Key words: Antithrombin-III deficiency; Heparin rebound; Monitoring heparin during cardiopulmonary bypass.)

THE METHOD for achieving anticoagulation in patients undergoing cardiopulmonary bypass has been standardized and simplified by the protocol developed by Bull and associates. With this method, the celite-activated whole blood clotting time (ACT) is performed prior to the administration of heparin. Then a test dose of 2 mg/kg heparin is administered intravenously, and a second ACT determined. These two values are plotted on a graph in which the ACT in seconds is represented on the y-axis and the administered heparin in mg/kg is represented on the x-axis. The line drawn through the two plotted points is extrapolated to an ACT of 480 sec, and the additional heparin required to achieve this level of anticoagulation is calculated and administered.

Although for most patients anticoagulation can be adequately achieved with heparin doses of less than 6 mg/kg, occasional patients require considerably more heparin to reach an ACT of 480 sec. One such patient was recently encountered. His diminished response to heparin was suspected, and subsequently demonstrated, to represent antithrombin-III (AT-III) deficiency. His response to the infusion of fresh frozen plasma was dramatic, and instructive relative to other patients whose AT-III deficiency first becomes manifest as heparinization is undertaken preparatory to cardiopulmonary bypass.

Report of a Case

A 68-year-old man was admitted to Valley Hospital for coronary artery bypass surgery because of progressive angina. There was no past history and no family history of recurrent venous thrombosis or of embolic phenomena. On the evening before surgery a hematologic panel was performed. This included a bleeding time, platelet count, tourniquet test, prothrombin time, partial thromboplastin time, and ACT. All values were within normal limits. The ACT was 97 sec (normal 90–120 sec).

Just before heparin was administered in the operating room on the following morning, the ACT was 89 sec. Using a modification of the Bull protocol, a test bolus of 3.7 mg/kg sodium heparin was administered intravenously at 8:15 A.M., and a repeat ACT was performed in duplicate. The average determination was 212 sec. Then an additional 2.3 mg/kg of heparin was given at 8:40 A.M. (total 6.0 mg/kg). The next ACT was 367 sec. Heparin from a different manufacturer was obtained and administered intravenously in a dose of 1.7 mg/kg at 9:00 A.M. (total 7.7 mg/kg). The ACT dropped slightly to 340 sec. At 9:20 A.M. and additional 2.3 mg/kg of the new heparin was given (total 10.0 mg/kg). An ACT was begun and the pathologist was called in for consultation.

After a total of 10.0 mg/kg of heparin was given over one hour, the ACT had risen to 420 sec (duplicate analyses). The consultation suggested that (1) the patient might have AT-III deficiency, (2) a bypass begun with an ACT of less than 450 sec was hazardous, and (3) adequate heparin anticoagulation could be achieved with either more heparin, or heparin cofactor in the form of fresh frozen plasma (FFP), or both.

Since half an hour was required to thaw FFP, and increased anesthesia time would unnecessarily contribute to morbidity, it was elected to administer additional heparin immediately so that bypass could commence, while simultaneously thawing three units of FFP for subsequent infusion. At 9:50 A.M. 3.8 mg/kg of the new heparin
was given (total 13.8 mg/kg). The ACT obtained 5 min later was 545 sec. The bypass was commenced, and a triple graft procedure was performed without incident. At approximately 10:20 A.M., an infusion of three units of FFP was begun. Upon its completion another ACT was performed. It was 830 sec, indicating that heparin rebound had been induced by FFP. This tentatively confirmed the diagnosis of antithrombin-III deficiency.

At the conclusion of the bypass at 12:45 P.M. (pump time 120 min) the heparin effect was neutralized with 9.7 mg/kg of protamine sulfate. Ten units of platelets were also given. The ACT corrected to 98 sec. Postoperatively there was continued blood loss, which necessitated the administration of whole blood, FFP, and eventually re-exploration and ligation of bleeders. Just before the re-operation, but after four units of whole blood and two units of FFP had been given, the ACT was determined as 161 sec. Protamine sulfate, 100 mg, corrected the ACT to 118 sec, suggesting that heparin rebound had again been induced by blood products.

A sample of preoperative serum obtained the morning of surgery was tested for AT-III content by radial immunodiffusion. It was determined that the patient was indeed AT-III deficient. His AT-III was 18 mg/dl, which is significantly below the lower limit of the normal range (normal 22–39 mg/dl).

Discussion

The case presented raises a number of issues. First is the differentiation of conditions that may account for the failure to obtain expected responses to intravenous heparin. The initial step should be the review of the calculations used to determine the administered dose. Next, the concentration of the heparin solution should be checked. Heparin for intravenous administration is packaged at concentrations of 1,000 u/ml and 10,000 u/ml. Errors due to the use of incorrect heparin concentrations have been reported, and can result in under- or overheparinization. The laboratory monitoring of heparin therapy is subject to a number of variables. The results of the ACT can be affected by the temperature of the reaction, the volume of blood introduced into the reaction vessel, the skill of the technologist in reading the endpoint, the instrumentation and manufacturing technic of the celite-containing tubes, and the quality of the bottles or lot numbers of heparin.

After excluding the possibility of such interfering effects, it is necessary to consider that the patient has failed to respond adequately to heparin. Failures to respond to heparin fall into two categories. When heparin is administered in the treatment of thrombophlebitis or pulmonary embolism, a diminished response will obtain as long as platelet aggregation and release continue to liberate platelet factor 4. During this initial period of active coagulation, extraordinary amounts of heparin will be required to maintain the desired level of anticoagulation. When active clotting is not in progress, and when the patient has not recently received protamine sulfate, a diminished response to heparin suggests AT-III deficiency. Although preoperative screening for hemostatic defects is routine in most institutions, such screens do not ordinarily include AT-III determinations. And when AT-III deficiency is suspected during a cardiopulmonary bypass, time will not permit the luxury of definitive testing before the institution of appropriate therapy. So, when other causes of a diminished response to heparin have been excluded, a series of decisions must be made. Should the procedure be cancelled? If not, is it safe to perform the cardiopulmonary bypass with a level of anticoagulation less than that recommended by Bull and associates? Finally, if it is elected to effect a greater degree of anticoagulation before the bypass, what is the most effective way to achieve this? As the case of our patient illustrates, a diminished response to heparin in and of itself is not cause to abort a bypass procedure. Whether bypass can be undertaken with minimal risk of inducing disseminated intravascular coagulation at lower ACTs has not been determined. But Doty and associates have shown experimentally that when bypass is undertaken at ACTs of less than 400 sec, there is a rapid appearance of fibrin monomer in the plasma.

To obtain an ACT that poses a minimal risk of inducing disseminated intravascular coagulation, two courses of action are feasible. One can give additional heparin. Even though AT-III deficient persons have diminished responses to heparin, their ACTs can be brought up to the desired range by giving unusually large doses of heparin. Since the major risk of heparin overdose is bleeding, large doses of heparin can safely be given to persons deficient in AT-III. On the other hand, the majority of patients undergoing bypass receive blood products during or shortly after surgery. Since fresh frozen plasma and banked plasma both contain adequate levels of AT-III, infusion of blood products will result in an augmented response to heparin. This is exactly what happened in the case presented here. For this reason, we suggest that when a markedly diminished response to heparin has occurred after a test bolus of intravenous heparin has been given, plasma should be infused and the ACT repeated. A dramatic increase in the ACT will establish a tentative diagnosis of antithrombin-III deficiency and may avoid an overshoot of the heparin effect following the administration of blood products.

A final implication of this report concerns the phenomenon of heparin rebound. It has been reported that rebound may occur for unknown reasons after heparin therapy. Some authors suggest that heparin is sequestered extravascularly and becomes mobilized from these extravascular sites to re-enter the blood. A more plausible explanation is that rebound occurs when blood components containing AT-III are infused into a patient whose own AT-III level is diminished—owing to either a congenital deficiency or, more likely, an acquired...
one—or whose AT-III is already complexed by a heparin excess. In the latter case, the heparin excess cannot exert an anticoagulant effect until additional AT-III is made available. The administration of blood products containing AT-III thus induces the so-called rebound.

References

5. Soloway HB: Unpublished data

Null Cell (Non-T, Non-B) Acute Lymphoblastic Leukemia Terminating as Malignant Histiocytosis

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A case of null cell acute lymphoblastic leukemia (ALL) terminating in malignant histiocytosis (HMR) is discussed. The patient was a 22-year-old man who presented in January 1976 with ALL. Cell surface markers on the bone-marrow blasts showed that 1% formed rosettes with sheep erythrocytes (T cells) and 4% showed immunofluorescent staining for immunoglobulin; terminal transferase levels were elevated, confirming the diagnosis of null cell ALL. The patient was treated intensively with a combination of chemotherapy and cranial irradiation. One year after diagnosis, he was maintained in partial remission (10–15% blasts). His terminal episode was characterized by pancytopenia. The bone marrow was replaced by malignant histiocytes. Cell surface membrane staining for cytophilic antibody was positive, whereas terminal transferase levels were in the range of nonlymphoid malignancies. (Key words: Acute lymphoblastic leukemia; Null cell leukemia; Malignant histiocytosis.)

IN 1908 Rowley reported a case of fatal anemia associated with enormous numbers of circulating phagocytes described as “large lymphocytes,” which had devoured not only large numbers of erythrocytes, but leukocytes as well. In all probability this report dealt with an early example of the disease entity subsequently defined in 1939 by Scott and Robb-Smith as histiocytic medullary reticulosis (malignant histiocytosis). Malignant histiocytosis (HMR) is an uncommon illness, yet since 1969 six cases of HMR have been reported to occur as a terminal event of acute lymphocytic leukemia. In the most recently reported two instances of this association, lymphocyte surface markers were investigated, and in both cases the lymphoblast possessed T-cell characteristics. The present report describes another patient who had acute lymphoblastic leukemia (ALL); but of null cell origin, which terminated as HMR.

Report of a Case

A 22-year-old white man was admitted to the hospital in January 1976 for evaluation of anemia. He had been in good health until three months before admission, when he experienced night sweats and fatigue.

On admission, physical examination revealed splenomegaly. The remainder of the examination was unremarkable. Glucose, electrolytes, BUN, SMA-12, Coomb’s tests, haptoglobin, VDRL, urinalysis, and chest x-ray were negative or showed no abnormality. The hematocrit was 34%, hemoglobin 11.0 g/dl and leukocyte count 11,000/cu cm with a differential showing 25% lymphocytes, 13% immature lymphocytes, 36% lymphocytes, 23% neutrophils, 2% myelocytes, and 1% metamyelocytes. A bone-marrow examination revealed increased cellularity with 80% lymphoblasts; there was no evidence of histiocytic proliferation (Fig. 1). The diagnosis of acute lymphoblastic leukemia was made.

The patient was given induction chemotherapy with vincristine