urine osmolality and sodium concentration were consistent with ADH effects despite his apparent volume-expanded state.

An intriguing aspect of this disorder is the time course of symptoms and hyponatremia. The patient was asymptomatic until almost an hour after he stopped running, and his serum sodium level fell from 119 to 111 mmol per liter during the first hour of hospital admission without his receiving any hypotonic fluids. Splanchnic ischemia, which may impair enteral absorption, can occur during endurance exercise.[5] It is possible, therefore, that part of the water ingested by our patient was not absorbed while he was running. With the cessation of exercise and reperfusion of the splanchnic bed, this sequestered water could have been absorbed rapidly, worsening his hyponatremia and expanding his body fluid volume. Although this seems a likely explanation for the abrupt fall in his serum sodium level, continued ADH secretion is required for the absorbed water to be retained.

Hyponatremia after endurance exercise has been attributed to sodium and water losses in sweat and replacement with water.[2,5] According to this view, urinary water retention results from ADH secretion stimulated by a reduction in extracellular fluid (ECF) volume occurring as a consequence of sodium loss. If this construction is correct, the urine sodium concentration should be vanishingly low. In this patient, however, the urine sodium level of 38 mmol per liter was consistent with the evidence on physical examination of a normal or increased ECF volume. It is possible that the physical stress of endurance exercise results in continued ADH secretion after the cessation of exercise, even when the ECF volume is expanded and hyponatremia is present. Various stresses including pain, hypoxia, hypercapnia, and hypoglycemia have been associated with ADH secretion and hyponatremia.[4] Clearly more work needs to be done to characterize the factors responsible for this syndrome. Our patient had been taking ibuprofen, a prostaglandin inhibitor. Severe hyponatremia has been reported with the use of this class of drugs,[6,7] presumably because prostaglandin is a normal antagonist to the hydroosmotic effect of ADH. Whether this drug was a contributing factor in the development of hyponatremia in our patient is unknown.

The treatment of hyponatremia with an isotonic or hypertonic saline solution is critically important when notable encephalopathy is present.[4,8,9] If there is evidence of ECF volume expansion, furosemide is a useful therapeutic adjunct through its effect of reducing the ECF volume and allowing the subsequent retention of administered sodium.[10] Its use can be hazardous, however, if the ECF volume is reduced. An improved understanding of the role of sodium chloride loss, fluid replacement, and ADH secretion in this life-threatening complication of ultramarathon competition is needed to develop a rational approach to treatment and, more important, to prevent its development. Given the findings in one patient, we recommend that athletes be cautioned regarding the overzealous ingestion of water during endurance exercise. They should also be cautioned about the possible effects of nonsteroidal anti-inflammatory drugs on renal function and urinary dilution.

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Use of Aprotinin to Reduce Intraoperative Bleeding

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BLEEDING DURING a surgical procedure is a common problem associated with both morbidity and death of surgical patients in the United States; it increases the risk of multisystem organ failure and death. Transfusion therapy is associated with the additional risks of allergic reaction and the transmission of infectious diseases such as hepatitis and the acquired immunodeficiency syndrome. Despite tremendous advances in blood banking, public concern about the safety of America's blood supply has substantially increased the fear of transfusion for many patients having surgical treatment.

The use of aprotinin, a serine protease inhibitor, has been shown recently to reduce dramatically the blood loss in operations that involve cardiopulmonary bypass and in other cardiac operations.[1-7] Several of the studies showing efficacy and safety have been randomized, placebo-controlled trials.[1-4,6] The drug is now used extensively in Europe and the Middle East for cardiac surgery. Although the mechanism of action has not been clearly established, it appears that aprotinin improves platelet function, which is impaired following cardiopulmonary bypass.[7,8] Apro-

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ABBREVIATIONS USED IN TEXT

HIV = human immunodeficiency virus
KIU = kallikrein-inhibiting unit

tinin may also decrease fibrinolysis.[7,9] Clinical trials are currently underway in the United States to obtain approval for the use of the drug during operations that involve cardiopulmonary bypass.

Aprotinin has also been used to decrease blood loss in operations that do not require cardiopulmonary bypass.[10-17] It has been used during orthotopic liver transplantation, substantially reducing the transfusion requirement and intensive care unit stays for treated patients.[10-13] It has also been used in neurosurgery, orthopedic surgery, gynecologic surgery, urologic surgery, and plastic surgery.[7,14-19] Reports evaluating its effectiveness in these types of operations come mostly from Germany where it has been used for many years in various surgical procedures.[14] The use of aprotinin in patients having noncardiac operations outside the United States is not uncommon despite a lack of large, carefully controlled clinical trials.

Noncardiac surgical procedures that place patients at an increased risk of bleeding include major orthopedic reconstructions of the back for scoliosis; frequently intraoperative transfusion is required, and in some cases the amount of bleeding can be life threatening. Patients positive for the human immunodeficiency virus (HIV) who have excessive bleeding during a surgical procedure place operating room staff at an increased risk of exposure to HIV during the procedure. In this report we describe the case of a woman with severe scoliosis who suffered massive hemorrhage during a back reconstruction in 1982. During treatment of that hemorrhage, she acquired HIV. When she presented for a second major back reconstruction in 1992, she was treated with aprotinin, resulting in minimal blood loss.

Report of a Case

The patient, a 31-year-old woman, was born prematurely and was diagnosed as having cerebral palsy at about 6 months of age. At the time of her first admission for back correction, she had a prominent spastic diplegia. She had severe scoliosis with a double major curve and back pain and, at age 21 years, entered Stanford University Medical Center (Palo Alto, California) for fixation. Under general anesthesia with halothane, nitrous oxide, and pancuronium bromide, she underwent a Luque rod fixation of the posterior spine from T-4 to the pelvis. After the first hour of the procedure, she had lost about 17% of her estimated blood volume, and hypotensive anesthesia was begun by adding sodium nitroprusside to keep her mean arterial pressure between 60 and 65 mm of mercury. Despite this measure she continued to bleed excessively, and by the end of her 12-hour surgical procedure her estimated blood loss was more than 9 liters. She was transfused with 18 units of blood, 8 units of fresh frozen plasma, 16 units of platelets, 6 liters of a normal saline solution, and an unstated amount of cell-saver blood. She was transferred to the intensive care unit, intubated, and placed on full mechanical ventilation. Her initial laboratory tests revealed a hematocrit of 0.36, a platelet count of 90×10^9 per liter (90,000 per μl), a prothrombin time of 14.2 seconds (control, 11.8 seconds), and a partial thromboplastin time of 79 seconds (control, 32 seconds). She received 2 additional units of fresh frozen plasma, but her prothrombin time and a partial thromboplastin time remained unchanged. She again received 2 units of fresh frozen plasma, and again her prothrombin time was 14.2 seconds (control, 11.8 seconds); this time the partial thromboplastin time was 32 seconds (control, 31 seconds). She required no further transfusion of blood or blood products. The endotracheal tube was removed on postoperative day 1, and she was discharged from the hospital on postoperative day 18.

The patient did well initially, but within a year the Luque rods had fractured, and in 1983 she underwent removal of the Luque rods under general anesthesia. Multiple pseudoarthroses were found between L-1 and L-5, but they were not repaired. No bone work was done, and blood loss was minimal. She again did well, but she had increasingly severe back pain and became wheelchair-dependent by 1989. She was observed for the next two years on multiple conservative treatments without success. In view of the continued severe pain, she was referred for anterior and posterior fusions of the spine from T-11 to S-1.

At a blood bank where the patient's blood was being collected for autologous transfusion, screening revealed that she was HIV-positive. Because she had no other risk factors, it was presumed that she had acquired HIV during her first operation. In view of her history of massive hemorrhage with her first back operation, and in view of her HIV-positive status, she was offered the use of aprotinin during the procedure on a compassionate-use basis. A protocol for the use of aprotinin was approved by the Stanford University Administrative Panel on Human Subjects in Medical Research, and the patient signed informed consent. Aprotinin (Trasylol) was provided by Miles Pharmaceutical Inc.

The patient was premedicated with midazolam hydrochloride after an intravenous line was placed. Anesthesia was induced with sodium thiopental after which pancuronium was given. Anesthesia was maintained with the use of isoflurane. A radial arterial line was then placed, and a central venous line was placed through the right internal jugular vein. A test dose of 500 kallikrein-inhibiting units (KIU) was given through the central line. There was no hemodynamic effect, and a loading dose of 2 million KIU was given over 30 minutes by the central line. The operation was begun with the patient in the left lateral decubitus position. Aprotinin was given continuously during the 11-hour procedure at a rate of 500,000 KIU per hour by the central venous catheter. The first portion of the operation was the anterior fusion from T-11 to S-1 carried out by thoracotomy, splitting the diaphragm, and using the tenth rib for a bone graft. There

was minimal bleeding during the retroperitoneal dissection and the disc removals, during which about 90% of each disc was removed. Following the anterior fusion, the diaphragm and pleura were closed and the patient was placed in the prone position where posterior fusions were done from T-11 to S-1. Bleeding was again minimal. During the entire procedure, the patient received 3 units of packed red blood cells and no blood products. She was taken to the intensive care unit, intubated, and placed on full mechanical ventilation. Her initial postoperative hematocrit was 0.34 (preoperative hematocrit, 0.32). The platelet count was 150×10^9 per liter (150,000 per μl), and the prothrombin and partial thromboplastin times were within normal limits. The endotracheal tube was removed on postoperative day 2 because of pain and splinting from her thoracotomy incision. Her postoperative course was complicated by small bowel ileus. She was discharged on postoperative day 11.

Nine months after the operation she is healthy, well, and much more comfortable. She has returned to work full time and is taking zidovudine prophylactically.

Discussion

Patients with HIV present a risk to surgical staff, especially if massive bleeding occurs during a surgical procedure. Patients who have had a surgical procedure in which massive bleeding has occurred are generally thought to be at risk for excessive bleeding during subsequent surgical procedures of a similar nature. Patients having major surgical correction of scoliosis are at a high risk of bleeding. This patient presented a difficult problem because she was thought to be at risk for bleeding during anterior and posterior spinal fusion from T-11 to S-1. She was also HIV-positive, and excessive bleeding during the long procedure would place the surgical staff at risk of exposure to HIV-positive blood. The patient was having severe pain, several attempts at medical management of her pain had failed, and she was now wheelchair bound and having difficulty carrying out her daily functions at work. The only option left for her was surgical therapy.

Aprotinin was used in an attempt to reduce blood loss during the procedure to minimize both the obvious risks to her as the result of bleeding and the risks to the surgical staff as they performed the operation. The operation during which aprotinin was administered was associated with minimal blood loss despite the fact that this procedure was more extensive than was the one in which massive bleeding occurred. The first bleeding episode may have been complicated by transfusion-related coagulopathy because both the prothrombin time and the partial thromboplastin time were prolonged, and the platelet count was mildly decreased. Nevertheless, heavy bleeding did not occur during the second procedure even though considerable dissection was carried out over a period of 11 hours. The major question that cannot be answered by this report is whether the use of aprotinin actually caused the minimal blood loss of the second operation. The surgeon reported a much drier field than he expected, especially considering the previous operation and the massive bleeding encountered then. That question can only be answered by a blinded, placebo-controlled trial of this type of operation.

Most studies that have evaluated the use of aprotinin in cardiopulmonary bypass have shown it to be effective in decreasing bleeding without increasing the risk of thrombotic complications.[1-9] There appear to be no adverse effects of aprotinin administration despite concerns about a procoagulant effect.[7] The use of aprotinin in noncardiac operations is not as well established, but there are several reports of its efficacy. Mallet and co-workers have described substantially less blood transfused in aprotinin-treated patients undergoing orthotopic liver transplantation.[12] In orthopedic surgery, Ketterl and associates showed a decrease in platelet aggregation during total hip replacement and a threefold reduction in transfusion requirement.[14,15] In neurosurgical procedures, aprotinin has been used to decrease the incidence of rebleeding in patients with subarachnoid hemorrhage.[16,17] The topical application of aprotinin has also been used to decrease intraoperative and postoperative bleeding in neurosurgical procedures.[18] The antifibrinolytic properties of aprotinin have been used to decrease bleeding in prostatic operations. One study combined the use of aprotinin with ϵ-aminocaproic acid and achieved a 50% reduction in blood loss in prostatectomy.[19]

The second question raised by this report is the mechanism of action whereby aprotinin decreased bleeding in this type of operation. Aprotinin use has been best studied in patients who are undergoing cardiopulmonary bypass wherein it is thought that exposure of the platelets to the bypass pump interferes with their function. The bleeding time is increased after cardiopulmonary bypass, and the use of aprotinin prevents this increase in bleeding time.[9] Aprotinin, a serine protease inhibitor, inhibits a large number of proteases. Serine protease inhibitors can be shown to inhibit a number of platelet functions. Various hypotheses have been used to explain how aprotinin may be improving platelet function and decreasing bleeding, but each has experimental evidence that casts some doubt on them.[7] In addition, aprotinin may be having an effect of inhibiting fibrinolysis. In liver transplantation, the major effect of aprotinin seems to be to decrease bleeding by inhibiting fibrinolysis.[10-12] This inhibition of fibrinolysis appears to be due to an inhibition of tissue plasminogen activator.[13] Although kallikrein inhibition, a known effect of aprotinin, may be responsible for this phenomenon, it has not been studied in liver transplantation.

Aprotinin may be improving platelet function and decreasing fibrinolysis in noncardiac operations by a similar mechanism to that seen during bypass procedures and liver transplantation. The degree of abnormality may not be as great as that seen in cardiac operations because the contact with the oxygenator may exaggerate the abnormalities in platelet function seen in those cases. Similarly, the effects on fibrinolysis may not be as great as the abnormalities seen in liver transplantation where the source of many coagulation factors is temporarily removed. The

beneficial effects of aprotinin use probably occur even before the carrying out of cardiopulmonary bypass, but its dramatic effect in these patients has meant that most investigators have focused their research efforts on that procedure. In noncardiac surgical procedures such as described in this report, trauma to scar tissue may release tissue plasminogen activator and activate fibrinolysis that, in turn, is attenuated by aprotinin. Unfortunately, no markers of hemostasis such as fibrin-degradation products were evaluated in this patient. Future controlled trials will offer the opportunity to evaluate the mechanism of action of aprotinin in noncardiac surgical procedures.

The case reported here may represent two possible uses of aprotinin that deserve further investigation: minimizing blood loss during an orthopedic operation and minimizing blood loss in HIV-positive patients requiring surgical therapy. The results also suggest that aprotinin may have beneficial effects in many surgical procedures not yet studied. The well-known dangers of bleeding during surgical procedures and of transfusion therapy make this an important subject worthy of further evaluation. The apparent safety of aprotinin administration means that the drug, if used in a wide variety of procedures, could have wide surgical application.

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Successful Enteral Refeeding After Massive Small Bowel Resection

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EXTENSIVE SMALL BOWEL RESECTION (>70%) is associated with severe nutritional consequences. The short-gut syndrome usually develops in patients with less than 150 cm of intact small bowel.[1] Malabsorption, dehydration, metabolic abnormalities, and nutrient deficiencies are possible problems if nutrition support is not implemented immediately after bowel resection.

Total parenteral nutrition (TPN), the most aggressive form of nutrition support, is usually necessary in the initial stages of recovery. The enteral route is preferred for long-term support, but tolerance is dependent on the extent of the small bowel resection, the site of remaining bowel (especially the ileum and ileocecal valve), the functional capacity of the remaining gut, and the presence or absence of concomitant gastrointestinal disease.[2] The amount of small bowel necessary for adequate nutrient delivery by the enteral route has been reported at variable lengths.

Report of a Case

The patient, a 62-year-old man, was admitted to the Level I Trauma Center at the University of New Mexico Medical Center (Albuquerque) with multiple stab wounds to his back and neck following a family altercation. Although enteral nutrition support (tube feeding) was started on the first day of hospital admission, TPN was instituted on day 5 because of tube feeding intolerance (diarrhea, abdominal distention). An exploratory laparotomy was done on hospital day 16 to rule out an intra-abdominal source for the patient's sepsis and abdominal distention, following which infarcted small bowel was resected from the proximal jejunum to the ileum. The distal ileum (57 cm in length), the ileocecal valve, and the colon were left intact.

After this operation, TPN was continued in amounts to meet the patient's estimated calorie and protein needs

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