Thrombolytic Drugs as a New Treatment for Acute Respiratory Distress Syndrome: A Brief Report

Robert M. Hardaway, MD

Texas Tech University School of Medicine, El Paso, Texas

ABSTRACT

Hemolysis of red cells has been shown to precede the development of shock-like states. All cell walls, both animal and bacterial, are composed of a phospholipid bilayer. The inner layer includes an amino component and is thrombogenic when exposed to the circulation, as occurs when the cell is fragmented. This in turn may initiate disseminated intravascular coagulation (DIC), in which the microclots may temporarily occlude the microcirculation, causing tissue necrosis and multiple organ failure. Several animal experiments are briefly described which demonstrate the lethality of this mechanism. A clinical trial involving patients with acute respiratory distress syndrome (ARDS) refractory to traditional treatment modalities also demonstrates the effectiveness of thrombolytic drugs.

INTRODUCTION

It has been recognized for over a century that a mismatched blood transfusion often causes a severe, sometimes fatal, reaction, a reaction consisting of the immediate onset of shock, usually with associated clotting abnormalities and renal failure. Significantly, there is usually hemoglobinuria, denoting hemolysis. In fact, the destruction of red cells under any circumstances is often accompanied by severe, sometimes fatal, results. It was noted in 1954, that a transfusion reaction frequently resulted in disseminated intravascular coagulation (DIC), and it was postulated that the microclots of DIC occluded the microcirculation, resulting in renal failure.[1]

All cell membranes, bacterial as well as mammal, are made up of an inner and an outer layer of phospholipids, the hydrophobic tails projecting into the space between the layers. It was found that compounds containing choline were distributed through the outer leaflet of the membrane, while aminophospholipids were found exclusively on the cytoplasmic side of the inner leaflet.[2] When red blood cells "sickle", or lyse as in paroxysmal nocturnal hemoglobinuria, these aminophospholipids are translocated from the inner to the outer leaflet and are thus exposed to the surrounding medium.[3] This exposure also occurs whenever red cells or tissue cells are broken by means such as trauma, heat, cold, anoxia, viruses or plasmodia. Bacterial cell walls demonstrate the same translocation phenomenon when broken by antibodies, antibiotics or

heat. Feola et al[4] found that even extremely small amounts of these aminophospholipids "not only activate intravascular coagulation, (evidenced by a drop in the serum fibrinogen and deposition of fibrin in the microcirculation of most organs), but also produces thrombycytopenia, leukopenia, fibrinolysis (appearance of 'fibrin split products' in the plasma), activation of the alternate pathway of complement (elevation of factors C3a des Arg and C5a des Arg) and, possibly activation of the kinin-system (suggested by the development of circulatory instability and bronchospasm). When present in greater amounts, these compounds can be lethal." To demonstrate this, aminophospholipids were infused into rabbits over a 30-minute period. They all developed DIC with thrombocytopenia, low fibrinogen, and appearance of fibrin split products. The lungs were congested and edematous, livers were enlarged and congested, and spleens contained hemorrhagic infarcts. Rabbits are particularly sensitive to DIC, perhaps in part because their reticulo-endothelial system (RES) is unable to remove fibrin efficiently from the circulation. This is illustrated by the Shwartzman reaction, in which two injections of endotoxin are required to produce a fatality. The first fills the RES with fibrin; the second proves fatal, because the RES is already full of fibrin and cannot remove it fast enough. Pigs and humans have a more efficient RES and are able to cope with the excess fibrin.[5]

Further evidence that the cell walls themselves are toxic, not just the intact organisms, is given by the observation of Elaine Tuomanen,[6] who tells how her friend, Alexander Tomay, "accidentally challenged animals with killed pneumococci, and yet the animals got sick. Dead bacteria seemed as harmful as living ones. How could this be?"

There are several examples of the toxicity of inner cell walls. The Herxheimer reaction may be due to the broken cell walls of the spirochete. Ascitic fluid contains many broken cells, which when reinjected into the circulation by the Leveen shunt results in DIC. If one injects human amniotic fluid (which contains many broken cells) intravenously into a dog, DIC results.[7] The pulmonary artery pressure rises, blood may become incoagulable, and multiple organ failure may result. If one filters the amniotic fluid before injecting it, the fluid is harmless. The dead fetus syndrome and the reperfusion syndrome may be due to absorption of damaged cellular debris.

EXPERIMENTS

Several experiments done over the last 40 years elucidate the problem.[8-10]

Experiment I

Sixteen healthy pigs were divided into two groups, control and treated.[8] All 16 pigs were injected with an identical dose of heat-killed culture of E. coli organisms. Eight of the pigs were also given 250,000 units of urokinase (Abbokinase, a plasminogen activator) diluted in 20 mL saline and injected over a 20-minute period starting 20 minutes after the E. coli injection. The 8 untreated pigs were given 20 mL of saline. These untreated pigs all developed extremely low arterial PO2 and severe acidosis and died within 24 hours. At autopsy, they showed congested, edematous lungs and congested liver and bowel mucosa. The 8 pigs treated with plasminogen activator all survived 24 hours. They were sacrificed and at autopsy showed minimal lesions.

Experiment II

Four healthy pigs were injected with a heat-killed culture of pneumococcus organisms in the same dose as the E. coli. Four other pigs were injected with a killed culture of pneumococcus except

that the culture was diluted to 0.1 of the above. All eight pigs died within 24 hours, most before 6 hours, and autopsy showed congested edematous lungs.

Experiment III

Nine pigs were given 60 standard blows to each thigh with a carpenter's hammer (under anesthesia), being careful not to damage skin, bone or vessels.[9] Blood volume was kept in a normal range with normal saline IV. Nine other pigs similarly traumatized were given 250,000 units of urokinase (Abbokinase) IV, starting 4 hours after the trauma. The 9 untreated pigs all died within 48 hours, and at autopsy showed congested, hemorrhagic lungs. The 9 treated pigs all survived 48 hours and were sacrificed. At autopsy, their lungs showed minimal lesions. The blood of all pigs, treated and untreated, showed hemolysis.

Experiment IV

Twenty-two dogs were bled to a mean arterial pressure of 40 mm Hg, and maintained in a state of hemorrhagic shock for 4 hours. The removed blood was treated carefully, allowed to come in contact only with plastic, never air or glass.[10] Seven dogs were subjected to the same hemorrhagic shock and were given 10 mL of their own blood which had been frozen and thawed (producing hemolysis). The 22 dogs subjected only to hemorrhagic shock had a 9% mortality. The seven dogs subjected to the same hemorrhagic shock and given 10 mL of their own hemolyzed blood all died within 24 hours. The administration of fibrinolysin (an activated plasmin no longer manufactured) in a separate series of this same study, this time utilizing 13 dogs subjected to hemorrhagic shock and hemolyzed blood, significantly lowered mortality from 100% to 38%.[10]

Experiment V

A clinical trial of treatment of severe ARDS with thrombolytics was conducted. Twenty patients suffering from ARDS secondary to trauma or sepsis were treated with thrombolytics after treatment with respiratory support, including positive end expiratory pressure (PEEP), had failed to bring Pao_2 up to 60 mmHg Treatment consisted of 1000 units of Urokinase (Abbokinase. Abbott) per pound of body weight intravenously in saline as a bolus in 10 minutes followed by 1000 units per pound of body weight per hour for 24 hours. Every case responded favorably, the average Pao_2 rising from 47.7 mmHg to 231.5 mmHg, P=0.0001. There was no bleeding or changes in clotting parameters, which were normal both before and after treatment.[11]

Patients were not included in the protocol until 48 hours after injury or surgery, if they had a head injury or if they had a history of a clotting defect or stroke.

DISCUSSION

The fact that death could be prevented by a plasminogen activator is evidence that the problem was due primarily to intravascular coagulation (DIC), occluding the microcirculation of the organs, especially the lungs, liver, and kidneys. The administration of a thrombolytic lysed these microclots, restoring circulation to the organs and saving the animal's or human's life.

It is postulated that the rupture of cell membranes (bacterial or mammal) by any means (cold, heat, trauma, antibiotics, antibodies, viruses, plasmodia, sickling or incompatible blood) may result in intravascular clotting (DIC). Of course most infections are managed successfully by the body's own immune system or by antibiotics without resulting in DIC. Small amounts of broken cell

walls are easily dealt with in individuals with a functioning reticuloendothelial system and adequate circulation. It is only when other factors, such as severe hemorrhage or extensive trauma, are present that the possibility of DIC becomes a problem. This occurs in both traumatic and septic shock. The DIC may in turn cause acute respiratory distress syndrome and multiple organ failure by obstructing the microcirculation in any and all organs, including lung, liver, kidney, and brain.[11] These types of shock have a high mortality rate but can be treated effectively and safely with thrombolytics after normovolemia is achieved. This same process may be involved in some cases of coronary thrombosis, pulmonary embolism, and stroke.

REFERENCES

1. Hardaway RM, McKay DG, Williams JH. Lower nephron nephrosis with special reference to hemorrhagic diathesis following incompatible blood transfusion reaction. *Am J Surg*. 1954;87:41-49.

2. Schwartz RS, Chiu DTY, Lubin B. Studies on the organization of plasma membrane phospholipids in human erythrocytes. In: Krucheber WE, Eaton JW, Aster J, et al, eds. *Erythrocyte Membranes, Vol 3, Recent Clinical and Experimental Advances*. New York, NY: AR Liss; 1984:89-122.

3. Chiu D, Lubin B, Shobet SB. Erythrocyte membrane lipid organization during sickling process. *Br J Hematol*. 1973;41:223-234.

4. Feola M, Simoni J, Conigardo PC, et al. Toxicity of polymerized hemoglobin solution. *Surg Gynecol Obstet*. 1988;166:211-222.

5. Hardaway RM. *Syndromes of Disseminated Intravascular Coagulation with Special Reference to Shock and Hemorrhage*. Springfield, Ill: Charles Thomas Publisher; 1966:148.

6. Tuomanen E. Breaching the blood-brain barrier. *Sci Am*. 1993;268:80-84.

7. Hardaway RM, Johnson O. Clotting mechanisms in endotoxic shock, a manifestation of intravascular coagulation. *Ann Surg*. 1961;154:791-802.

8. Hardaway RM. A review of septic shock. *Am Surg*. 2000;66:22-29.

9. Hardaway RM, Williams CH, Marvasti M, et al. Prevention of adult respiratory distress syndrome with plasminogen activator in pigs. *Crit Care Med*. 1990;18:1413-1318.

10. Hardaway RM, Burns VW. Mechanism of action of fibrinolysin in the prevention of "irreversible" hemorrhagic shock. *Ann Surg*. 1963;157:305-309.

11. Hardaway RM. Traumatic and septic shock alias post-trauma critical illness. *Br J Surg*. 1998;85:1473-1479.