Hemolytic Transfusion Reaction Occurring in a Patient with Acute Renal Failure

By PHILLIP E. HOFFSTEN AND HUGH CHAPLIN, JR.

ACUTE RENAL FAILURE is a well-known, though by no means inevitable, consequence of acute intravascular hemolytic transfusion reaction. The mechanism responsible for the renal damage is not fully understood, but undoubtedly depends on complex interrelationships of the plasma "free hemoglobin" concentration, the filtered load of hemoglobin, the per cent reabsorption of filtered water, urinary pH, hypotension and the possibility that nephrotoxic substances are released into the circulation in relation to the intravascular antigen-antibody reaction.[1] The distribution of extracorpuscular hemoglobin in the circulating plasma and the relationship of free and protein-bound hemoglobin to the renal excretion of hemoglobin have been well-described by Lathem in studies on normal human volunteers.[2,3] So far as we know, similar studies of the disappearance rates for free and protein bound hemoglobin in the plasma have not been reported for human subjects with markedly reduced renal function.

The present brief report concerns a patient severly traumatized in an automobile accident, who in the fifth week of artificial kidney dialysis for presumed acute tubular necrosis experienced an acute intravascular hemolytic transfusion reaction. Measurements were made of the diappearance of free and protein-bound hemoglobin from the plasma following the reaction and the effect of the reaction upon the course of the renal lesion was documented. The results supplement existing knowledge about the disposal of plasma hemoglobin compounds and the mechanisms of renal damage in acute intravascular hemolytic transfusion reactions.

MATERIALS AND METHODS

Case Report

This was the first Washington University Medical Center admission for R.H., a 50 year old white male executive, who entered the hospital three days after an automobile accident. The patient had been completely well prior to the accident. His acute injuries included a fracture of the left humerus, a fracture of the left radius, and a comminuted fracture of the left pelvis into 5 major fragments. The bladder was severed from the urethra and extensive bleeding into the soft tissues about the pelvis had occurred.

He was admitted to a nearby hospital in shock and underwent exploratory laparotomy.

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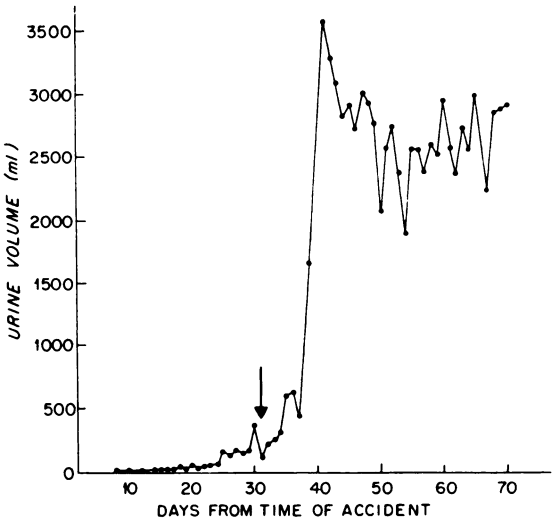

Fig. 1.—24-hour urine volumes from the time of admission to the Washington University Medical Center. The arrow denotes the time of the transfusion reaction.

There was no damage to the gastrointestinal tract. Both ureters were intact. A Foley catheter was put in place to establish a track from the bladder to the urethra. His blood group was O Rh-positive and he was given 23 units of blood to maintain his blood pressure. During the next 48 hours, his urine output slowly diminished and the serum potassium rose acutely to 6.8 mEq/1. For this reason he was transferred to the Washington University Medical Center on August 12 for hemodialysis. After extensive workup, his diagnosis was presumed to be acute tubular necrosis; no evidence of extra-renal urinary obstruction was found.

During the period from August 12 to September 11, the patient underwent twelve hemodialyses on the Kolff twin coil* dialyzer. There were no complications and the patient's urine output increased slowly as shown in Figure 1 to a high of 392 ml. per 24 hrs. on Sept. 10.

On the morning of September 11, 1967 the dialysis coil was primed with one unit of group O, Rh-positive blood saved from the previous dialysis. Inadvertently, a unit of group AB, Rh-positive packed cells was infused into the coil behind the unit of O+ whole blood. At 8:53 a.m. the dialysis was started at a rate of 60 ml./min. After 2 to 4 minutes the patient became quite apprehensive and exclaimed that something was wrong. He then lost consciousness; and pulse and blood pressure were unobtainable. At 8:57 a.m. the arterial and venous lines were clamped and resuscitative procedures begun. Within two minutes the patient regained consciousness and had a tachycardia with a blood pressure of 170/80. The initial suspicion was that the blood used to prime the coil was contaminated and that the patient's clinical state represented endotoxin shock. However, a gram-stained smear of lightly centrifuged plasma from the coil blood revealed no organisms. Subsequently it was discovered that this group O patient had received approximately one third of a unit of group AB blood.

Studies on a sample of the patient's blood obtained 1 hour after the transfusion accident revealed a plasma hemoglobin concentration of 480 mg. per 100 ml., complete absence of group AB donor cells, and 4+ agglutination of group A and group B test cells by the patient's plasma. These findings were consistent with complete intravascular destruction of 60–80 ml. of AB donor cells.

During the next 4 hours he remained hypotensive and in critical condition. Two units of group O blood were transfused and by 1:00 p.m. the blood pressure stabilized at 120/70. Subsequently, the patient underwent a 6 hour dialysis, at the end of which time (10½ hours after the transfusion accident) the plasma hemoglobin concentration had fallen to 22 mg. per 100 ml. The urine output was 8 ml. during the 16 hours following the transfusion

*Travenol Laboratories Inc., Morton Grove, Ill.

Table 1

Time after the transfusion accident	Plasma hemoglobin concentrations in mg. per 100 ml. Total	Free	Bound
1 hour	480	298	182
3½ hours	280	143	137
7 hours	95	55	40
10½ hours	22	14	8

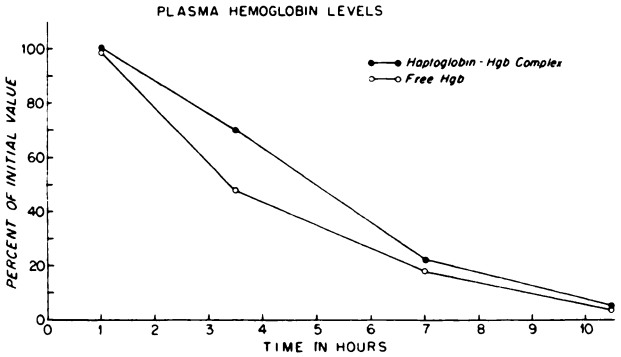

Fig. 2.—Relative disappearance rates for free and protein-bound hemoglobin from the patient's plasma. Infusion of the incompatible red cells occurred at time zero. The curves are qualitatively similar to those reported by Murray et al.[6] for nephrectomized rabbits. Absolute values in mg. per 100 ml. are shown in Table 1.

accident, but rose to 202 ml. during the subsequent 24 hours and increased gradually over the next 4 days, whereupon a characteristic diuretic phase of acute tubular necrosis ensued (Fig. 1). Hemodialysis was not necessary after September 16, and by November 15 the creatinine clearance had stabilized at 53 ml. per minute and the blood urea nitrogen concentration was in the range 12–15 mg. per 100 ml.

His subsequent recovery has been marked by many complications characteristic of a patient so severely injured, but he has continued to improve. At the time of this writing his residua from the accident are an ilial bladder implaced 6 months after the accident and numbness and partial paralysis of the left leg attributed to a left sciatic plexus injury.

Special Studies

Plasma Hemoglobin Pigments

Plasma hemoglobin concentrations were measured by the method of Hanks et al.;[4] the proportions of free and bound plasma hemoglobin were estimated by a modification of the paper electrophoresis method described by Lathem and Worley.[2] Methemalbumin was present in only trace amounts in all samples and was ignored in the calculations presented in Table 1 and Figure 2.

The initial plasma sample, obtained approximately 60 minutes after the reaction occurred, was grossly red and contained 480 mg. of hemoglobin per 100 ml.—the normal value being 0.3–0.6 mg. per 100 ml.[5] Measurement of the free and bound hemoglobin revealed 182 mg. per 100 ml. bound to haptoglobin and 298 mg. per 100 ml. free in the plasma. Subsequent samples (taken into dry EDTA anticoagulant) were obtained after 2½, 6 and 9½ hours. The absolute values for free and bound plasma hemoglobin concentrations are shown in Table 1 and the values calculated as percents of the initial values are plotted in Figure 2. The disappearance of the haptoglobin-hemoglobin complex was approximately linear at a rate of 18 mg./100 ml./hr.—normal range 6–25 mg./100 ml./hr.[2] The disappearance of free hemoglobin was at a single exponential rate (T½ 2.5 hrs.) over the first six hours and probably throughout the 9½ hour period—the slightly low final value probably reflecting the inaccuracy of the paper electrophoresis technic at low hemoglobin levels. Approximately 8 ml. of urine was excreted during the interval covered by these blood samples; its color was yellow with a faintly orange caste (spec. gravity 1.010). Thus, the

disappearance rates described above occurred in the absence of excretion of hemoglobin into the urine.

Discussion

Once it was recognized that an acute intravascular hemolytic transfusion reaction had occurred, the immediate clinical problem concerned the possible damaging effects on the kidneys that might be expected from the high level of free hemoglobin circulating in the plasma. In view of the low prereaction urine output, loss of hemoglobin into the urine could not be expected to contribute appreciably to clearance of hemoglobin from the plasma. While Lathem's studies in hemoglobinuric normal volunteers[3] indicated that metabolism of free hemoglobin was more important than renal excretion in lowering plasma free hemoglobin levels, no reports were available for disappearance rates in the anuric heman subject. Since the hemoglobin molecule was too large to cross the artificial dialysis membrane, there appeared to be only one therapeutic maneuver which could speed the lowering of the plasma free hemoglobin level—namely, "plasma-exchange" transfusion. Multiple phlebotomies, with return of the patient's cells resuspended in normal donor plasma would lower plasma free hemoglobin by two means: a) simple removal of hemoglobin-containing plasma, and b) supplying of donor plasma haptoglobin which could bind free hemoglobin and thereby render it nonfilterable across the glomerulus. Because the rate of free hemoglobin metabolism in the oliguric human was not known, nor did we know the free haptoglobin levels in individual donor units, it was not possible to calculate precisely the volume of donor plasma that would be required to reduce the plasma free hemoglobin concentration to normal. However, it seemed possible that 2 to 3 liters of plasma might be required. The proposed "plasma exchange" procedure was considered to have several important hazards: hepatitis risk, coagulation disorder, potassium load, not to mention the hemodynamic effects and technical difficulties of performance in this critically ill patient. In light of these hazards and in view of the pathophysiologic interpretation that nephrotoxic hemoglobinuria was not likely to occur in this patient (see ahead), it was elected not to attempt plasma-exchange transfusion.

The disappearance of bound and free hemoglobin from the patient's plasma over the succeeding 9½ hours was rapid (Table 1 and Fig. 2) and could hardly have been improved upon by plasma exchange transfusion. Haptoglobin-bound hemoglobin was cleared in an essentially linear manner and at a normal rate. Although there are no published data on plasma free hemoglobin disappearance rates in severely oliguric human subjects, Murray et al.[6] have published disappearance rates in nephrectomized rabbits. They reported single exponential rates, with a T½ of 39 minutes in sham-operated animals and 75 minutes in nephrectomized animals. The T½ of 2½ hours observed in the present patient is within the range reported by Lathem[3] for hemoglobinuric normal human volunteers (average T½, 207 mins.). Thus the lack of opportunity for renal clearance of hemoglobin had a negligible effect on the plasma-free hemoglobin clearance rate. Had the present authors been certain that this

would be the case, the decision not to do plasma-exchange would have been more easily made.

Immediately prior to the time the transfusion reaction occurred, a reasonable estimate of the patient's maximum urine to plasma creatinine ratio would be in the range of 5:1. Under such circumstances, approximately 20 per cent of the patient's filtered water would be excreted, thus preventing concentration of the filtered hemoglobin. In theory, one of the mechanisms by which filtered hemoglobin may lead to the development of acute renal failure is through the formation of relatively insoluble acid hematin at acid pH and its precipitation subsequent to concentration during reabsorption of filtered water. Thus, this patient's functioning nephrons would have been partially protected because of the diminished fraction of filtered water reabsorbed. Under these circumstances, the free hemoglobinemia occurring in this patient with acute renal failure would be expected to be less of a threat to his filtering nephrons than if his kidneys had been functioning normally; and any nonfiltering but regenerating nephrons should have been protected completely.

In Figure 1, it appears that the patient was entering the diuretic phase of acute tubular necrosis at the time the transfusion reaction occurred. For the 16 hours following the reaction, he remained essentially anuric, excreting only 16 ml. of dark yellow urine. The following day he excreted 202 ml. of urine, and the 24 hour urine volume had increased to 3500 ml. within a week. It therefore appears that the diuretic phase of the patient's acute renal failure may have been delayed one week as a result of the transfusion reaction.

Assuming the patient had a normal glomerular filtration rate prior to the automobile accident, his present creatinine clearance of 53 ml. per min. indicates a significant loss of nephrons. As pointed out in the review by Price and Palmer,[7] not all patients with acute tubular necrosis have complete recovery of renal function. Their data indicate that a creatinine clearance of 53 ml./min. after recovery from acute tubular necrosis would not be an unexpected value.

It is evident that the patient described in the present report had two possible causes for nephron loss: 1) the presumed acute tubular necrosis following the automobile accident, and 2) the hemolytic transfusion reaction. It is not possible to determine the relative roles of either cause in determining the final creatinine clearance of 53 ml. per minute. It is gratifying, nevertheless, that the transfusion accident did not long delay the development of the diuretic phase and that the ultimate level of renal function was well within the range necessary to sustain a normally active life.

Summary

An acute hemolytic transfusion reaction due to ABO-incompatibility occurred in a patient during the fifth week of oliguria secondary to post-traumatic acute renal failure. Resort to "plasma-exchange" transfusion to reduce the high level of free hemoglobin in the circulation was considered and rejected. Sequential measurements of free and haptoglobin-bound hemoglobin documented rapid disappearance of both components from the patient's plasma

in the absence of hemoglobinuria. Within one week, the patient entered the diuretic phase, and ultimately stabilized at normal levels of urine volume, with a creatinine clearance of 53 ml per minute. The implications of free hemoglobinemia in the oliguric phase of acute renal failure are discussed.

SUMMARIO IN INTERLINGUA

Un acute reaction de hemolyse post transfusion in consequentia de incompatibilitate a ABO occurreva in un patiente durante le quinte septimana de oliguria secundari a acute insufficientia renal de occurrentia posttraumatic. Esseva considerate—sed rejecite—le possibilitate de effectuar transfusion a "excambio de plasma" pro reducer le alte nivello de hemoglobina libere in le circulation. Mesurationes sequential de hemoglobina libere e ligate a haptoglobina demonstrava le rapide disparition de ambe iste componentes ab le plasma del patiente in le absentia de hemoglobinuria. Intra un septimana, le patiente entrava in le phase diuretic e ultimemente attingeva stabilisation a nivellos normal del volumine urinari, con un clearance de creatinina de 53 ml per minuta. Es commentate le signification de hemoglobinemia libere in le phase oliguric de acute insufficientia renal.

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