In 1927 Fremont-Smith and Forbes proposed the use of urea for reducing intraocular and intracranial pressure. Since the administration of concentrated solutions of urea dissolved in isotonic solutions of sodium chloride or dextrose were poorly tolerated in the human, their method did not gain clinical acceptance. Almost 30 years later Javid and Anderson found that 10 per cent invert sugar was a suitable agent for preventing hemolysis and since then urea has received wide clinical application. However, urea is not an innocuous drug.

The purpose of the present communication is to present two cases of hemolysis occurring during urea administration in anesthetized, hypothermic patients undergoing neurosurgical procedures.

Case 1. A 35 year old Panamanian Negro woman was admitted to the neurosurgical service with an 8 month history of progressive right optic nerve degeneration. The past medical and family history and review of systems were noncontributory. There was no history of jaundice or bleeding episodes. Physical examination of the eyes revealed a right temporal field cut, decreased visual acuity, a pale right disc with increased prominence of the lamina cribrosa, sluggish reaction to light and diminished corneal reflex on the right. The blood pressure was 130/88, the pulse was 76 and regular, the respiratory rate was 12 per minute, and her weight was 82 kg. The remainder of the physical examination was noncontributory.

The hemoglobin was 12.4 g./100 ml., the hematocrit was 38 per cent, the white blood count was 4,350 with a normal differential count, the erythrocyte sedimentation rate was 23 mm. in one hour and the fasting blood sugar was 88 mg./100 ml. The blood urea nitrogen, serum electrolytes, endocrine evaluation, cerebrospinal fluid examination, urinalysis, and electrocardiogram were within normal limits. Skull roentgenogram, carotid arteriogram and a pneumoencephalogram demonstrated an intrasellar mass with lateral and suprasellar extension. The preoperative diagnosis was chromophobe pituitary adenoma.

Preoperative management included cortisone acetate 100 mg. intramuscularly 12 hours and 2 hours prior to operation. The patient was given premedication of secobarbital 100 mg. and scopolamine 0.4 mg. intramuscularly one hour prior to operation.

Anesthesia was induced with thiopental 250 mg. in divided doses. Intubation of the trachea was facilitated by the administration of 100 mg. of succinylcholine. Anesthesia was maintained with a mixture of nitrous oxide three liters, and oxygen two liters with halothane 0.5 per cent in a semiclosed system. After the return of spontaneous respiration, the patient was given 30 mg. of d-tubocurarine to maintain apnea. Hyperventilation was accomplished with a Jefferson respirator. Hypothermia was induced with a Thermorite mattress and ice bags applied to the axillary, popliteal, and inguinal regions.

Three hours and 45 minutes after the induction of anesthesia, an infusion of 80 g. of urea (30 per cent lyophilized urea reconstituted in 210 ml. of 10 per cent solution of invert sugar) was administered over a period of 88 minutes. The patient's temperature at this time was 33°C. One hour after the start of urea infusion, the urine drainage was pink in color. A microhematocrit at this time was 30 per cent, with gross evidence of
hemolysis. Two hours after the completion of the area infusion, a microhematocrit was 23 per cent. A venous blood sample revealed increased red cell fragility. One unit of fresh whole blood was then administered. Forty-five minutes later the microhematocrit was 33 per cent, and an arterial blood sample revealed a pH of 7.258, Pco2 of 38 mm. and a base deficit of 12.5 mEq/liter.

Throughout the procedure, the vital signs remained stable. Continuous electrocardiographic monitoring revealed no abnormalities. The lowest temperature recorded from the esophageal thermistor was 30° C. The patient received 200 mg. cortisone acetate in 2,000 ml. 5 per cent dextrose in water during the procedure.

The urine output during the eight hour procedure was 400 ml. Three hours after the completion of the area administration, the patient was oliguria. Twenty-five grams of mannitol with indigo carmine dye were administered intravenously, which resulted in a prompt diuresis.

Except for the hemolysis, the procedure consisting of intracapsular removal of a cystic vascular chromophobe adenoma was uneventful.

During the immediate postoperative period, the patient’s urine output was 1,250 ml. for the first 12 hour period, and 3,425 ml. for the next 24 hours with no evidence of hemoglobinuria. Urine and serum electrolytes were within normal limits. The blood urea nitrogen at the completion of the operation was 60 mg./100 ml. at eight hours 25 mg./100 ml., and at 18 hours 11 mg./100 ml.

Four weeks after the craniotomy, the patient was given a nitrous oxide-thiopental-meperidine anesthesia uneventfully for a breast biopsy.

One month after the operation a venous blood sample revealed no evidence of increased red cell fragility and filter paper electrophoresis was normal.

Case 2. A 50 year old hypertensive Negro woman was admitted to the neurosurgical service with an eight month history of occipital headache, progressive diplopia, almost total blindness and anosmia for two months.

Physical examination revealed a large female weighing 63 kg. who was stuporous with a pulse of 60 per minute and regular. Her blood pressure ranged from 124/90 to 180/120.

The hemoglobin was 12 g. and the hematocrit 41 per cent. A white blood cell count was 3,200 with 54 per cent neutrophils, 40 per cent lymphocytes, 3 per cent eosinophils and 3 per cent monocytes. The red cell count was 3,580,000. A serologic test for syphilis (VDRL) was negative. Urinary specific gravity was 1.010. One plus albuminuria was present. The preoperative diagnosis was intracranial midline meningioma. From the time of admission until the induction of anesthesia, eleven hours later, the patient received 18 mg. of dexamethasone in divided doses.

The patient was given premedication of 0.4 mg. atropine. Anesthesia was induced with small intermittent doses of thiopental totaling 225 mg. Orotracheal intubation was accomplished following one intravenous dose of 80 mg. succinylcholine chloride. Anesthesia was maintained with nitrous oxide-oxygen (6 liters:2 liters)-intravenous meperidine and d-tubocurarine. Hypothermia was induced by means of a Thermorite system and 2 mg. of chlorpromazine, given intravenously in two divided doses.

Hyperventilation was accomplished by means of a Frumin respirator.

At the time of the scalp incision an infusion of Ureaphil (40 g. in 150 ml. of 10 per cent invert sugar) was given over a period of 20 minutes.

Tumor evacuation was begun when the esophageal temperature reached 29.7° C. This was the lowest temperature recorded.

One thousand milliliters of whole blood were given slowly during the procedure and during the immediate postoperative period to replace the estimated loss.

Approximately nine and one-half hours following the induction of anesthesia the urinary drainage bottle, which was attached to an indwelling Foley catheter, contained approximately 1,000 ml. of urine in two layers. The bottom layer was yellow and turbid. The upper layer was pink and clear.

Free hemoglobin was reported in the plasma and urine during the immediate postoperative period. Blood hemoglobin at that time was 8 g./100 ml. with a hematocrit of 25 per cent. The red cell count was
2,930,000. The white blood cell count was 13,500 with 86 neutrophils, 8 monocytes and 6 lymphocytes. Urinary specific gravity was 1.008, acid with three plus albuminuria and a trace of glucose.

A repeat hemogram done later the same day following 2 units of blood revealed 15 g. of hemoglobin with a hematocrit of 42 per cent. The white blood count was 14,600 with 93 per cent neutrophils, 6 per cent lymphocytes and 1 per cent monocytes. Platelets were low normal.

On the second postoperative day the hemoglobin was reported as 11.6 g. with a 36 per cent hematocrit. The red cell count was 3,440,000. The white blood count was 6,650 with 66 per cent neutrophils, 3 per cent eosinophils, 24 per cent lymphocytes and 7 per cent monocytes. Platelets were high normal. The reticulocyte count was 6.6 per cent.

During the following four weeks of convalescence the following studies with these results were obtained: Glucose-6-diphosphatase determination was normal at 20 minutes, filter paper electrophoresis revealed a normal pattern, the Coombs’ test was negative and osmotic fragility of erythrocytes was within normal limits.

The patient was discharged from the neurosurgical service on the twenty-first postoperative day. At that time hemoglobin was 10 g. The hematocrit was 31 per cent. Reticulocytes were 4.2 per cent.

No hematological defect could be demonstrated.

**DISCUSSION**

The rationale behind the use of urea for reduction of intracranial pressure is the production of serum hyperosmolarity with a subsequent reduction in brain volume. The high concentration of urea in the blood creates an osmotic gradient which is unopposed initially in the brain and cerebrospinal fluid due to a slower rate of penetration of the urea into these areas. This results in a shift of fluid from the nervous system towards the vascular stream. This is substantiated by the work of Javid and Anderson who found that urea infused into bilaterally nephrectomized monkeys provided a more pronounced and sustained cerebrospinal fluid pressure drop than in the normal controls. Therefore, while it may appear that the diuretic effect of urea is the most important factor in the reduction of cerebrospinal fluid pressure, it is not essential, particularly during the early phase of cerebrospinal fluid pressure reduction.

Urea is a fairly diffusible molecule which is filtered rapidly through the glomerulus. Since less than 50 per cent tubular reabsorption occurs it is excreted rapidly and there is an obligatory loss of large volumes of water caused by the osmotic effect of the unabsorbed urea. On an average normal diet approximately 30 g. of urea is excreted daily. The normal blood urea nitrogen level is 10 to 20 mg./100 ml. The indications are that 75 to 300 mg./100 ml. may be toxic. Consequently, it should not be used if there is a marked impairment of renal function.

While urea is one of the most useful non-metabolized, nonelectrolyte diuretics, its use is not free from undesirable side effects. There are reports of skin slough following extravascular extravasation, changes in skin turgor, formation of cutaneous blebs, hypotension, tachycardia and thrombosis of veins. In the conscious patient the intravenous administration of urea frequently causes headache, vomiting, diarrhea, weakness and dry tongue. Occasionally there is a secondary rise or rebound of cerebrospinal fluid pressure following urea administration. In dogs, rapid injection of urea caused severe changes in electrolytes characterized by a sharp increase in the serum potassium and a fall in serum sodium sufficient to cause marked changes in the electrocardiogram. However, in man no clinically significant changes in serum electrolytes occurred following a single dose of urea, provided water and electrolyte intake was adequate.

The complication of hemolysis is rare in man when urea is administered as a freshly prepared solution of 30 per cent lyophilized urea reconstituted in 10 per cent inverted sugar. Javid and Anderson mentioned only one case of transient hemoglobinuria in his large series of surgical patients. Others have never reported this complication in man undergoing neurosurgical procedures. In dogs, hemoglobinuria following urea administration is a common finding. However, there are several reported cases of massive, severe intracranial
hemorrhage following the intravenous infusion of freshly prepared urea.20

Information on the mechanism of urea induced hemolysis is provided by the work of Wurster and Shapiro.21 Using beef red cells in vitro, they demonstrated that high concentrations of urea caused hemolysis in the presence of isotonic concentrations of other compounds because a sufficient volume of urea molecules diffused into the cell to cause it to rupture. Therefore, a sufficiently large concentration of any nonpenetrating compound in the medium (such as invert sugar) will inhibit urea induced hemolysis. Experimental evidence was also obtained which indicates that it was necessary for electrolytes to be present in the medium in order to maintain a normal suspension of erythrocytes and the anion may be the important ion in maintaining the integrity of the cell.

Studies on the osmotic fragility of normal human erythrocytes have shown that there is a 20 per cent increment in hemolysis when the temperature falls from 40° to 30° C.22 The amount of free hemoglobin liberated rises from 5-7 mg./100 ml. at 37° to 18 mg./100 ml. of free hemoglobin at 30° C. There is greater red cell fragility at lower pH.

Surgery plus anesthesia alone resulted in abnormal prothrombin times in 20 per cent of the patients studied by Mason and Raaf.9 With the addition of urea the number of patients with abnormal prothrombin times rose to 67 per cent. Bering and Avman14 have demonstrated that the amount of urea required to obtain an adequate reduction of intracranial pressure is considerably reduced at low body temperature. The dose at 28° C. can probably be reduced to one third of that used at normal therma.

Nigerians have increased susceptibility to red cell fragility at low body temperatures.23

SUMMARY

Two cases of hemoglobinuria occurring during the use of intravenous urea concomitantly with hypothermia have been reported. Possible mechanisms have been discussed. It is suggested that when intravenous urea is used for the reduction of intracranial pressures during neurosurgical procedures under hypothermia, the dose be administered slowly and reduced to less than that expected at normothermia.

REFERENCES

Respiratory Gas Studies with Ether Convulsion

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The patient, a four year old Negro girl, weighing 38 pounds, was admitted for repair of a congenital cleft palate. Review of history, physical examination and routine laboratory studies were unremarkable. Premedication consisted of meperidine 30 mg. and scopolamine 0.2 mg., intramuscularly.

Anesthesia was induced using nitrous oxide, cyclopropane and oxygen at a total flow of approximately 10 liters/minute in an adult circle absorption system with unidirectional valves at the mask. Agents were gradually changed to ether, nitrous oxide and oxygen for maintenance with total flow over 5 liters/minute. Dead space of the anesthetic apparatus after intubation was 12 ml.

After an unsuccessful attempt at blind nasotracheal intubation, succinylcholine 50 mg. was given intramuscularly to achieve more adequate relaxation. A No. 3 Davol tube was passed through the nose into the trachea under direct vision. After approximately five minutes of what was believed to be adequate controlled ventilation, the patient was hypventilated in an attempt to re-establish spontaneous respiration. During this period gas flows were nitrous oxide and oxygen at 3.5-1.5 liters/minute, respectively. Ether was administered via a copper Kettle with the oxygen flow gradually reduced from 1,400 ml./minute at time of intubation to zero a few minutes before the subsequent seizures.

Fasciculations of the tongue and face were noted approximately thirty minutes after the succinylcholine had been given. These soon progressed to generalized clonic seizures. Thiopental, 25 mg. was given intravenously to stop the seizures.

Rectal temperature at this time was 37.5° C., and remained so for the duration of the operation. Heart rate was 140 beats/minute. It had been noted prior to the seizures that it slowed to 100 beats/minute between respiration and returned to 140 beats/minute following even a single respiration. Nitrous oxide was discontinued for a few minutes at the time of the seizures and then flow rates were readjusted to nitrous oxide and oxygen at 3.5 liters/minute each. Within a short time the patient was too lightly anesthetized to proceed with surgery so that ether was restarted and was continued throughout the remainder of the case.

Nearly 25 minutes after the seizures, during which time purposeful hyperventilation was performed, arterial blood gases and pH were determined. \(P_{aO_2}\) was 67 mm. of mercury, \(P_{aCO_2}\) was 75 mm. of mercury and pH 7.0. At the end of the procedure the blood gas values were \(P_{aO_2}\) = 80 mm. of mercury, \(P_{aCO_2}\) = 37 mm. of mercury, pH 7.15. The following day the values were \(P_{aO_2}\) = 88 mm. of mercury, \(P_{aCO_2}\) = 37 mm. of mercury, pH 7.38 with the patient breathing room air.

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