The Effect of Urea and Invert Sugar (Urevert) on Cerebral Damage Occurring After Cardiac Arrest* ** ***

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The human brain usually suffers irreversible damage if it endures anoxia for a period in excess of five minutes under normothermic conditions. Cardiac resuscitation techniques, properly applied according to present concepts, make it possible to restore the heart beat after long periods of anoxia, but the patient often dies or remains decerebrate as a result of the pathologic changes in the brain. Any method that will reduce the cerebral edema which follows cerebral anoxia will either prevent neurologic injury or decrease its severity. Hypothermia is beneficial in this respect, as shown by reports published by Williams and Spencer in 1959, Zimmerman and Spencer in 1959, Rosomoff et al. in 1960, and Wolfe in 1960. Urea has been shown to be an effective agent for reducing intracranial pressure and should be applicable to this syndrome. Fremont-Smith and Forbes in 1927, on the basis of experiments in which they injected 50 per cent urea intraperitoneally in three cats, suggested that urea might prove useful clinically. However, no clinical tests were reported prior to the study by Javid and Settlage in 1956. Several experimental studies in dogs and rabbits indicated that urea is toxic when injected intravenously. Extensive clinical experience along with experimental work on monkeys resulted in the establishment of a technique for administering urea in combination with 10 per cent invert sugar.† This seems to be the treatment of choice in reducing intracranial tension in man. This appears to be the only combination that consistently does not produce hemoglobinuria. It consists of 70 ml. of 10 per cent invert sugar in water for each 30 grams of lyophilized urea. The usual dosage is 1 gram of urea per kilogram of body weight, but 1.5 gram per kilogram of body weight can be given safely. It was first believed that the diuretic effect of urea was the important factor in the reduction of cerebrospinal fluid pressure. However, Javid observed that diuresis was not essential, especially in the early phase of cerebrospinal fluid pressure reduction, because there was a reduction in brain volume after intravenous injection of this urea solution at the time of operation, before there was any urinary output; also, there was a drop in cerebrospinal fluid pressure after administration of urea by gastric tube, before there was any diuresis. It appears that urea acts primarily on the basis of osmotic pressure differential between blood and cerebrospinal fluid, although the exact mechanism seems more complicated and requires further study. The two factors which limit the maintenance of cerebrospinal fluid pressure reduction are: (1) the rate at which the urea diffuses from the blood stream, and (2) the rate at which urea is ex-
creted. If the rate of elimination of urea can be decreased, the effect of a reduction in cerebrospinal fluid pressure is prolonged.

Only freshly prepared solutions should be used to avoid decomposition of urea when in solution due to aging. The recommended rate of intravenous administration is 60 drops per minute. Maximal effect occurs within one hour after administration. Reduction of intracranial pressure persists for periods of three to ten hours. Because of the marked diuresis, an indwelling catheter is placed before the urea is given and urinary output is measured.

On the basis of Javid's clinical and experimental evidence, we decided to test the effect of this solution on cerebral damage resulting from cardiac arrest (ventricular fibrillation) of five minutes' duration.

**Experimental Method**

Fifteen mongrel dogs, weighing 25 to 35 pounds, were used. Following a preoperative hypodermic injection of 0.8 mg. atropine, the dog was anesthetized with open ether technique, intubated with an intratracheal catheter and maintained during the operation on ether-oxygen anesthesia with the Rand-Wolfe Respirator. The left chest was shaved. A leg vein was cannulated and connected to a 500 ml. bottle of 5 per cent dextrose and water. The solution of urea, invert sugar and water was prepared. An incision was made through the fifth intercostal space. The heart was exposed and the pericardium was opened. Ventricular fibrillation was induced by shocking the heart with a small current from the electrodes of the Rand defibrillator. The corneal reflex disappeared within a few seconds, indicating that cerebral anoxia had developed. After exactly five minutes from the onset of fibrillation, the heart was pumped rhythmically by hand and the lungs were inflated with 100 per cent oxygen provided by the respirator. Hand pumping produced an effective circulation with a systolic pressure of 60 to 80 mm. Hg. When the muscle tone improved and the cyanosis in the heart disappeared, the heart was defibrillated by shocking it with 110 volts alternating current and 1.5-3.0 amperes. Defibrillation was usually difficult and required several shocks. During this period the heart was pumped by hand. As soon as a coordinated beat and a satisfactory blood pressure were obtained, the solution of urea, invert sugar and water was administered intravenously. The dosage used was 1.5 grams of urea per kg. of body weight, or 50 ml. of solution for a dog weighing 18 kg. This was given over a period of 90 to 120 minutes. It was repeated four times at three hour intervals. As soon as the chest was closed the intratracheal tube was disconnected from the respirator. The tube was left in place to provide an open airway. Morphine sulphate in one-half grain doses was given intramuscularly as needed to keep the dog quiet. After the fourth administration of urea and invert sugar in water was completed, the intratracheal tube was removed and the dog was returned to his cage.

A control group of 15 dogs was used. The anesthesia, the period of fibrillation and defibrillation were the same as in the other group. Urea invert sugar in water was not given. Morphine was given as in the other group.
Results

In the group of 15 dogs treated with urea, invert sugar and water the mortality was 11 (73 per cent); recovery without neurologic deficit occurred in four. Death occurred in the interval of 7½ and 40 hours with an average of 23 hours. These dogs were comatose during this period.

In the control series of 15 dogs, the mortality was 8 (53 per cent), recovery without neurologic deficit occurred in seven. Death occurred in the interval of one to 77 hours with an average of 32 hours. These dogs were comatose during this period.

SUMMARY AND CONCLUSIONS

Two groups of 15 dogs each were subjected to five minutes of ventricular fibrillation. Ventricular fibrillation stops all circulation. The brain was, therefore, subjected to a measured period of complete anoxia. The circulation was restored on the second after five minutes of it being done by hand mechanical insufflation of the lungs with oxygen. The coordinated heart beat was restored. One test-group of dogs was given a solution of urea and invert sugar in water intravenously as soon as the period of anoxia was terminated. Otherwise the management of each group of dogs was the same. The conclusion is that intravenous administration of urea, invert sugar and water did not protect the dog after measured periods of cerebral anoxia. The mortality in the treated group was higher than in the untreated group. According to these experiments urea does not have the same beneficial effect as does hypothermia and it is not a replacement for hypothermia after resuscitation of the heart.

The effect of hypothermia was published. It was determined in two groups of ten dogs each. The dogs in each series were given either promethazine or chlorpromazine in addition to morphine or meperidine to prevent shivering. There were no recovery dogs in the control group. There were three recoveries in the group under hypothermia and the survival period before death was longer in this group. The results in these two series of dogs, cooled and not cooled, are not the same as in the control series reported in this paper. The conclusion is that promethazine and chlorpromazine contributed to death in each series of dogs. The increased death rate seems to be significantly greater when these drugs were used.

RESUMEN

Se sujetaron a cinco minutos de fibrilación ventricular dos grupos de 15 perros cada uno. La fibrilación ventricular detiene toda la circulación. Por tanto el cerebro sufrió un período medido de completa anoxia. La circulación se restableció en el primer segundo después de cinco minutos. Esto se obtuvo por el bombeo a mano del corazón y por la insufilación mecánica de los pulmones, con oxígeno. Los latidos coordinados del corazón se recuperaron. Un grupo de la prueba recibió una solución de urea y azúcar invertida en agua por vía intravenosa tan pronto como el período de anoxia terminó. Fuera de esto el manejo de los dos grupos fue el mismo.

La conclusión fue que la administración intravenosa de urea, azúcar invertida y agua, no protegió al perro después de períodos medidos de anoxia cerebral. La mortalidad en el grupo tratado fue mayor que en el no tratado. De acuerdo con estos experimentos la urea no tiene los mismos efectos benéficos que tiene la hipotermia y no es un substituto de la hipotermia para la resucitación del corazón.

El efecto de la hipotermia fue publicado. Se determinó en dos grupos de 10 perros cada uno. Los perros de ambas series recibieron ya sea prometazina o cloropromazina además de morfina o meperidina para evitar el temblor. No se recuperó ninguno de los perros del grupo de control. Hubo tres recuperaciones en el grupo bajo hipotermia y el período de sobrevivencia antes de la muerte fue mayor en este grupo. Los resultados de estos dos grupos de perros, enfriados y no enfriados, no son los mismos como en las series de control relatadas en este trabajo. La conclusión es que la prometazina y la cloropromazina contribuyeron a la muerte de ambas series de perros.

El aumento en la proporción de las muertes parece significativamente mayor cuando estas drogas se usaron.

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REFERENCES

INFLUENCE OF TUBERCULOSTATIC DRUGS AND ADRENOCORTICAL HORMONES ON ALLERGIC REACTION OF SKIN AND BLOOD IN TUBERCULOUS PATIENTS

The investigations were carried out on 81 tuberculostatic patients and 55 healthy persons who served as controls. In all, 481 tuberculin reaction tests were performed; the average period of followup was ten months.

The findings showed that in tuberculosis of adults, in cases with an acute course, allergic response is in conformity with the general allergy of the body. In 82 per cent of the cases of exacerbation of chronic tuberculosis, unfavorable changes in skin allergy preceded by several months the clinical relapse. Routine chemotherapy does not have any determined and constant influence on the character of the tuberculin skin reactions. Adrenocortical hormones seem to influence allergic response: there appears a trend to shift the body responsiveness towards prevalence of immunity over hypersensitivity; this can be simultaneous with clinical improvement in two-thirds of the cases.

Results of skin tests did not show characteristic differences between healthy persons and tuberculostatic patients.