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THE EFFECT OF INTRAVENOUS HYPERTONIC SOLUTIONS ON THE KIDNEY

By

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This study was initiated by information that a paper had been read at the November 1938 annual meeting of the Central Society for Clinical Research reporting kidney damage in dogs who had been given intravenous injections of hypertonic sucrose. (Lindberg,Wald and Barker, of Chicago)

Since 50% sucrose solution is frequently given intravenously in the Wisconsin General Hospital to reduce intracranial pressure, we considered that it might be of interest to study the postmortem kidney sections of those patients who had been given intravenous hypertonic sucrose at some time before exitus, to see if we could discover any changes that might be attributed to the use of sucrose.

Weed and McKibben in 1919 were probably the first to advocate the use of intravenous hypertonic solutions. Following this work such measures came into fairly common use in hospitals thruout the country.

The saline mixtures first used (20-30% Ringer's solution and 19-20% Sodium Chloride) were found to be somewhat toxic and to cause crenation of the red blood cells. Since 1922 dextrose solutions, usually 50% (in some hospitals 30%) have been widely used. Their use has been criticized because dextrose, being a metabolite, diffuses out of the arterio-venous circulation into the cerebrospinal fluid, producing a secondary rise in cerebrospinal fluid pressure, and hence in the intracranial pressure, offsetting the good effect of the drop in pressure primarily attained.

The further objection to the use of dextrose, less well substantiated by experimental and clinical evidence, is that it probably diffuses from the cerebrospinal fluid and from the blood stream into the brain substance as well as into the other tissues of the body, to an extent that may increase cerebral edema. Sachs and others who still advocate the use of dextrose believe that repeating the injection of dextrose before the secondary rise, and so continuing until the need for such therapy has passed, will keep the balance in favor of diuresis and dehydration of the brain substance.

It was thought that some agent which would lower intracranial pressure effectively without a subsequent rise, and which could safely be given intravenously would be an ideal substitute for dextrose.

Masserman in 1934, working with 85 human subjects whose brains were untraumatized, offered evidence of the production of spinal fluid pressures far higher than the initial ones following the intravenous injection of 50% dextrose. Bullock, Kinney and Gregerson confirmed this finding in dogs in 1934; and in the same paper reported the use of sucrose under the same conditions producing a marked reduction of cerebrospinal fluid pressure without any subsequent rise in levels higher than the initial level.

Bullock, Gregerson and Kinney in 1935 made a study of four hypertonic solutions and reported further animal experimentation indicating the superior efficiency of sucrose in reducing cerebrospinal fluid pressure without subsequent rise.

Gregerson and Wright found that sucrose does not pass the hemato-encephalic barrier as does dextrose. The latter substance when injected into a vein passes readily into the cerebrospinal fluid producing a glycorrachia proportional to the glycemia.

The same year Masserman working with 35 human subjects with intact brains, found that doses of 300 to 500 cc of sucrose produced falls in pressure of the spinal fluid from 21 to 140 mm of water, below the basic level, and remained below the base line from 2 to 8 hours. From 78 to 92% of the sucrose could be recovered from the urine in 24 hours. No toxic effects were noted.

Since the time of the above experiments in 1934 and 1935 sucrose has been widely used to reduce intracranial pressure in patients with cerebral injury, in patients with cerebral neoplasm, and in other conditions accompanied by increased intracranial pressure. Its use has also been advocated as a diuretic and many of its physical effects have been studied. Little attention has been paid to its effect on the kidneys.

Helmholz in 1933 reported the case of a boy who had been given repeated injections of 20% sucrose before he died, and at autopsy showed severe hydropic degeneration of the kidney tubules. Helmholz also experimented with rabbits and observed that after even one injection of sucrose there was a swelling of the convoluted tubules, which persisted from one to three weeks depending on the amount of sucrose used. As a result of experiments on which sucrose was given at varying intervals he suggested a 5 to 7 day interval between injections.

In a very recent paper in the Proceedings of the Staff meetings of the Mayo Clinic (May 17,1939) Cutler reported a small series of patients who had been given hypertonic solutions of dextrose or sucrose during the week before death. These were contrasted with a much larger group who had not received such injections. Eleven kidneys from an autopsy series of 320 subjects showed hydropic degeneration of the tubules. Of the 11 hydropic kidneys 4.5% were from patients who had had hypertonic dextrose. Of the non hydropic group only 26.2% of the patients had had dextrose. The contrast was more evident with the sucrose. 36.4% of the hydropic kidneys were from patients who had had sucrose, whole only 1.3% of the non-hydropic kidneys were from patients who had had no sucrose. The patients who had had sucrose numbered 8 in all. The 50% of these who showed the hydropic changes had received sucrose in the amount of 6 grams per kilo of body weight; while those who did not show the hydropic change had received only one gram per kilo of body weight, in the same one week period.

Dr.Helmholz who discussed the paper reported that the kidneys of his experimental rabbits return to normal function and to nearly normal architecture within 39 days even after a severe degeneration of the tubules caused by 20% sucrose injections.

Besides these two papers from Rochester, and the one from Chicago, first cited, there have been few criticisms of the use of intravenous sucrose. Other criticisms have been based on opinion rather than specific evidence. The problem merits further clinical, pathological and laboratory study.

The present paper sets forth an attempt to evaluate the autopsy material for the years 1935, 1936, 1937 and 1938 pertinent to the problem of the effect of intravenous hypertonic solutions on the microscopic structure of the kidney.

The case finding method has been to select from the protocols those cases where a postmortem examination of the brain was obtained in addition to the usual examination. The clinical records of these cases were studied to determine which had been given hypertonic solutions by vein during the hospital treatment. The amounts of such fluids were noted and the time which had elapsed between the series of injections and the demise of the patient.

The cases were classified in five series, numbered from 1 to 5, according to the amount of intravenous hypertonic solution given and the time between treatment and exitus. Several cases were not used because the dosage records were equivocal. Two cases were considered separately because they fell outside the range of the characteristic time interval between the treatment and the postmortem fixation of the kidney sample. When the microscopic slides of the kidneys were examined two specimens were eliminated because of postmortem necrosis.

A small controlled series was obtained of patients with brainpathology at postmortem similar to the pathology experimental group who had not been given any intravenous hypertonic solutions.

Table 1 indicates the number of cases in each group and the basis of their selection:

Group no.	No of Cases	I.V. Fluid given	Amt. in cc	Interval since last dose
1	16	50% sucrose	200-1200	1-4 das.
(a)	1	" "	500	9 mos.
(b)	1	" "	250	1 mo.
2	12	" "	50-150	1-10 das.
3	10	50% dextrose	50-300	4-14 das.
4	19	none		

It will be seen from this table that the first group was arbitrarily chosen on the basis of dosage of 200 or more cc of intravenous sucrose. There was an almost equal number of cases which had been given 150 cc, or less. In all cases in Groups 1 and 2 the last injection was given on the day of the patient's death or not more than four days before. The previous portions of the total amount given had been administered in most cases throughout the two weeks previous to the final dose. Since intravenous sucrose is usually excreted 75 to 90% during the 24 hours after administration, it was considered that all of this group had had the sucrose at an interval suitable to have demonstrated the immediate effects on the kidney.

The two cases "a" and "b" had had their sucrose treatment terminated at intervals so much longer than the rest of the series that they were considered separately.

Series 2 differs from series 1 only in the smaller amounts of sucrose. The dextrose series #3 was not subdivided because the number was small, and the largest amount of dextrose given did not exceed 300 cc. The control series is not ideal. The cases were chosen from the "brain autopsy" protocols of patients who had cerebral pathology similar to the cases in series 1, 2 and 3, but who had not been given any intravenous hypertonic solutions. Those who had had magnesium sulfate solution by rectum were too small in number to make a separate series, so they were eliminated, as possibly complicating the control group.

Table 2 shows the result of the study of the kidney sections of the various groups of patients:

Group no.	No. Cases	No. showing lipoid: fatty or hydropic damage	Expressed in %
1(Sucrose)	16	9	52.5
(a) "	1	0	
(b) "	1	0	
2(Sucrose)	12	2	16.6
3(dextrose)	10	2	20.0
4(control)	19	5	26.2

This series is too small to be treated statistically, and yet it appears that there is a sufficiently larger number of the cases which had 200 or more cc of intravenous sucrose which show kidney damage than of the cases which had been given smaller amounts of sucrose, or had been given dextrose, or no

hypertonic solution. It may also be of some interest that neither of the patients who had received the sucrose the year before or the month before showed any kidney damage.

The kidney pathology which was most frequently noted throughout the series (in all cases designated as showing "kidney damage" in Table 2) was lipoid degeneration of the cells of some of the tubules. In no case was the damage sufficient to be called necrosis. The tubules in some of the sections showed "fatty degeneration" and in a few cases "hydropic degeneration".

We distinguish between hydropic and fatty or lipoid degeneration on the basis of the regularity in size and contour of the vacuoles. Lipoid droplets are of even size, round, clean cut and smaller than the similar fatty droplets. The hydropic vacuoles are more irregular in size and contour. Our slides were not fixed and stained with the intention of demonstrating beyond argument the lipoid or fatty nature of the droplets. The tissue was fixed in Zenker's solution and stained with haematoxylin and eosin. It remains for some future student of the subject who may be interested in this series of cases to find out whether any of the kidney slices were fixed so as to preserve the fatty materials, and if such can be found to determine beyond doubt whether we are here dealing with a lipoid degeneration.

Summary

We have presented a small series of cases treated with intravenous hypertonic solutions of two sugars. The dextrose treated cases showed less kidney damage than the sucrose treated cases. Dosages of less than 200 cc. of 50% sucrose had less effect than larger doses given at a similar time interval before death.

Microscopic examination of the kidneys of affected cases showed lipoid, fatty or hydropic degenerations.

The control series consisted of cases with similar brain lesions, but not treated with hypertonic solutions. The kidneys of the control group showed only half as many cases of degenerative change as the kidneys of the group which had received the larger dosages of sucrose, and about the same number of instances of lesions as were shown by the dextrose and the low sucrose group.

The small number of cases studied makes it impossible to draw definite conclusions regarding the effect of the therapeutic use of intravenous hypertonic sugar solutions on the kidney; but the findings are suggestive of some toxic effect on the kidney and further study seems justified.

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