The Rebound Phenomenon and Hypertonic Solutions*

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The terms secondary rise in cerebrospinal-fluid pressure or rebound phenomenon after administration of hypertonic solutions should be defined as a significant increase in tension of cerebrospinal fluid following the period of maximum reduction of cerebrospinal-fluid pressure and caused by mechanisms related directly to the use of the hypertonic solution.

In 1920, 1 year after Weed and McKibben introduce hypertonic solutions for reduction of cerebrospinal-fluid pressure, Ebaugh and Stevenson reported a "terminal rise" in intracranial pressure after oral administration of 200 cc. of 19 per cent Ringer's solution to a patient.

Prior to the clinical introduction of hypertonic solution of urea, a number of papers had appeared in the literature reporting a secondary rise in cerebrospinal-fluid pressure or rebound phenomenon following administration of hypertonic solutions of sodium chloride and glucose. Factors reported to cause increased cerebrospinal-fluid pressure include irritation of the meninges as the result of the presence of the needle, meningitis, pleocytosis ascribable to a solution in the manometer made from compressed tablets of sodium chloride dissolved in distilled water, and administration of barbiturate anesthetics.

Since 1954 we have carried out studies on cerebrospinal-fluid pressure with prolonged periods of control prior to the injection of hypertonic solutions. Our experience with hypertonic urea includes 1500 patients and several hundred experiments in rhesus monkeys and dogs. After administration of urea a rebound of pressure to levels above maximum levels of cerebrospinal-fluid pressure, during an adequate duration of the period of control, was not observed. This finding was confirmed by many investigators including Stubbs and Pennybacker, and Keegan and Evans. Wise and Chater reported absence of rebound after administration of hypertonic solution of mannitol. Bullock et al. found no secondary rise in pressure with 50 per cent solution of sucrose.

During the past 3 years reports have appeared in the literature describing secondary rise in cerebrospinal-fluid pressure in dogs and in human subjects after administration of urea. Wise and Chater reported no secondary rise with either urea or mannitol in dogs, but after ligation of all renal vessels, increases were noted which were greater with urea than mannitol. McQueen and Jeanes reported rebound after administration of mannitol to dogs. In a paper by Shenkin et al. 4 of 5 curves of cerebrospinal-fluid pressure following administration of mannitol to patients showed pressures above pre-injection levels.

After a review of the literature, we find that the majority of authors reported only short periods of observation of pressure before or after the injection of hypertonic solutions. In most of these papers the terms rebound phenomenon or secondary rise in pressure have been used to describe any increase in the cerebrospinal-fluid tension above maximum pressure before injection of the hypertonic solution. The authors of most papers dealing with human subjects reported short duration of periods of control.

Since studies which reported secondary rise in cerebrospinal-fluid pressure were done in dogs with short or no periods of control, studies on cerebrospinal-fluid pressure were carried out in dogs for a prolonged period before and after administration of hypertonic solutions in order to evaluate the earlier studies.

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Materials and Methods

In this investigation 110 mongrel dogs weighing 12–15 kg. were used. All animals were fasted for 12 hrs. prior to the start of the experiment. The initial anesthetic in all dogs was 25 mg./kg. sodium pentobarbital administered intravenously with subsequent supplementary doses of 30 mg. given as necessary through a cut-down in the femoral vein. Some dogs received 4 mg./kg. morphine sulfate and 0.6 mg. atropine 45 min. before administration of 15–20 mg./kg. sodium pentobarbital. The animals were placed in a prone position and allowed to breathe room air through an endotracheal tube with an inflatable cuff. An indwelling urinary catheter was placed for measurement of urinary output. A 20-gauge needle was inserted under sterile conditions into the cisterna magna. The needle was connected either to a water manometer, a strain gauge or a Gilson recording manometer. The manometers were provided with pyrex tubing, the inside diameter of which was 1.5 mm. The strain gauge and manometers were filled with sterile nonpyrogenic isotonic saline with the zero base line at the level of the cisterna magna.

The dogs were divided into 6 groups: Group I—50 control dogs whose cerebrospinal-fluid pressure was recorded for periods ranging from 12–36 hrs. Group II—35 dogs received 1 gm./kg. body weight of 30 per cent urea in 10 per cent invert sugar. Group III—8 dogs received 20 per cent mannitol. Group IV—6 dogs received 48 per cent glycerol. Group V—5 dogs received 15 per cent glycine. All agents in Groups III-V were given on an equimolar basis with 1 gm. urea per kg. body weight. Group VI-6 dogs received 0.5–1.0 gm. of sodium chloride in a 30 per cent solution. All solutions were given over a period of 30 min. With the exception of 6 animals in Group II in which 5 per cent dextrose in 0.2 per cent saline was administered intravenously in an amount equal to the urinary output of the previous 5 min., none of the dogs received any fluid other than the hypertonic solution and the anesthetic during the experiment. Cerebrospinal-fluid pressure was recorded continuously from 5 to 15 hrs. prior to and 15 to 34 hrs. following the administration of hypertonic solutions.

Results

Continuous measurements of cerebrospinal-fluid pressure over extended periods have shown that the pressure varies considerably. The mean cerebrospinal-fluid pressure and standard error are plotted every 30 min. for the 50 control dogs in Fig. 1. No fluids other than anesthetic were administered during the 12-hr. period. There is an obvious increase in the mean cerebrospinal-fluid pressure during the first 5 hrs. The mean pressure remains elevated with a slight tendency to decrease during the remainder of the 12-hr. period. The mean increase in pressure of all dogs in this study during the first 5-hr. period of control was 12 mm. of water per hr. The control animals had a mean variation of 174 mm. of water (SE ±18.0) between maximum and minimum cerebrospinal-fluid pressure. Fig. 2 shows two representative curves of control pressure with the gradual increase in pressure continued...
monly observed during the first 5–10 hrs. of each study in this report. Fig. 3 is a plot of the ratio of maximum pressure after injection to maximum pressure before injection of urea against length of period of control. If the solution is administered without a period of control of at least 8 hrs. before the hypertonic solution, the tendency is for the pressure after the injection of urea to exceed the pressure before injection. This fact is illustrated by the preponderance of ratios exceeding 1.0 before 8 hrs. Fig. 4 is a similar plot of ratios obtained with the other agents used in this study. The trend is the same as that obtained with urea in dogs except for an inclination to exceed unity occasionally with periods of control more than 8 hrs. in duration. Fig. 5 superimposes two curves, one with a 6-hr. period of control and one with a 9-hr. period of control prior to administration of urea. The pressure was rising in Dog 21 prior to administration of urea. Within 3 hrs. after administration the pressure had exceeded the pre-injection level by 70 mm. of water. It would appear that urea had halted only temporarily an inevitable rise in pressure.

It is necessary to use a general anesthetic when measuring cerebrospinal-fluid pressure over an extended period in dogs. While sodium pentobarbital is the most convenient agent to employ, it has the disadvantage of causing cerebrospinal-fluid pressure to increase. The depth of anesthesia is difficult to control in dogs and plays an important role in the elevation of cerebrospinal-fluid pressure because of the decrease in respiratory rate of the more deeply anesthetized animal. A single dose of morphine was given to a number of animals in an attempt to decrease the amount of sodium pentobarbital necessary to achieve satisfactory anesthesia. Morphine made the animal more docile and facilitated induction of anesthesia, but there was no apparent difference in the elevation of cerebrospinal-fluid pressure of animals receiving sodium pentobarbital or sodium pentobarbital and morphine. The large fluctuation in spinal-fluid pressure often observed immediately after administration of barbiturate anesthetics in some dogs is illustrated in Fig. 6.

Fig. 7 is representative of data on cerebro-
spinal-fluid pressure after administration of 1 gm./kg. body weight of 30 per cent urea. The mean reduction in cerebrospinal-fluid pressure in 35 dogs was 150 mm. of water (SE ± 11.6). The reduction lasted for a mean period of 178 min. (SE ± 12.0).

Fig. 8 is representative of data on cerebrospinal-fluid pressure after administration of 3 gm./kg. body weight of 20 per cent mannitol. The mean reduction in cerebrospinal-fluid pressure in 8 dogs was 124.5 mm. of H₂O (SE ± 23.5). The reduction lasted for a mean period of 187 min. (SE ± 40.5).

Fig. 9 is representative of data on cerebrospinal-fluid pressure after administration of 1.5 gm./kg. body weight of 48 per cent glycerol. The mean reduction in cerebrospinal-fluid pressure in 6 dogs was 147 mm. of water (SE ± 12.5). Respiratory obstruction will result in elevation of cerebrospinal-fluid pressure. In these studies auffed endotracheal tube was used routinely, but increases in cerebrospinal-fluid pressure secondary to partial obstruction were observed occasionally. The pressure returned to pre-obstruction levels after endotracheal suction. This is well demonstrated in Fig. 9.

Fig. 10 is representative of data on cerebrospinal-fluid pressure after administration of 1.25 gm./kg. body weight of 15 per cent glycine. The mean reduction in cerebrospinal-fluid pressure in 5 dogs was 95 mm. of water (SE ± 10.8). The reduction lasted for a mean period of 124 min. (SE ± 19.8).

Fig. 11 is representative of data on cerebrospinal-fluid pressure after administration of 0.5 gm./kg. body weight of 30 per cent sodium chloride. However, only in 2 of the 4 dogs did the cerebrospinal-fluid pressure exceed the pressure of the control. The mean reduction in cerebrospinal-fluid pressure in 4 dogs was 176.4 mm. of water (SE ± 29.8).
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The reduction lasted for a mean period of 259.2 min. (SE ± 25.0). Two additional dogs received 1 gm./kg. body weight of sodium chloride and are not included in these figures because they were the osmotic equivalent of 2 gm. urea per kg. body weight.

On an equimolar basis there appears to be little difference in the effectiveness of urea, mannitol and glycerol in dogs. Glycine gives a less profound reduction in pressure which lasts for a shorter time. The length and degree of reduction of pressure were greatest with 30 per cent sodium chloride.

**Discussion**

The term rebound, which has never been clearly defined, should be reserved for a significant increase in cerebrospinal-fluid pressure following the period of maximum reduction in cerebrospinal-fluid pressure and caused by mechanisms related directly to the use of the hypertonic solution. It must exceed maximum cerebrospinal-fluid tension established during an adequate period of control prior to administration of the agent. Since the rebound phenomenon was described as occurring after the administration of sodium chloride, it appears that most authors have considered rebound to be any rise in cerebrospinal-fluid pressure, however slight, that occurs after the administration of a hypertonic solution, but they rarely mention the clinical significance of the elevations in pressure.

The mechanism by which hypertonic solutions dehydrate tissues is well known. Rebound is thought to occur when there is more solute in the brain than is present in the plasma. Undoubtedly, all osmotic agents enter the brain substance, but since many of them are known to penetrate cerebral tissue with difficulty, the relevance of this aspect as the cause of rebound can be questioned.

Davson demonstrated that both sodium and chloride enter even the "extracellular" fluid of the brain slowly. The degree and length of reduction in cerebrospinal-fluid pressure achieved with sodium chloride in dogs lend further support to a slow entry of sodium chloride into the brain substance. Two dogs receiving 1 gm./kg. body weight of sodium chloride died with extremely low cerebrospinal-fluid pressure, suggesting the possibility of toxicity. Since intracellular homeostasis requires a fairly definite ratio of concentration of potassium to sodium, the question is raised as to whether entry of small quantities of sodium into the cells of the brain might disturb this balance sufficiently to cause changes in the water content proportionately greater than could be attributed to the osmotic effect alone.

Elkinton, and Schwartz et al. concluded that mannitol, while limited mostly to the compartment of "extracellular fluid," does in fact enter the cellular spaces. McQueen and Jeanes stated that the penetration of mannitol into brain water was scanty and could not attribute the tendency for rebound with mannitol to gradients of concentration of mannitol between brain and plasma.

Schoolar et al. reported that equilibration
of low concentrations of C\textsuperscript{14} urea between blood and white matter required more than 12 hrs. Bradbury and Coxon,\textsuperscript{3} with the use of hypertonic urea followed by constant infusion of urea to maintain elevated levels of urea in blood, did not observe equilibration between plasma and brain water up to 9 hrs. after the start of the experiment. These authors stated that the water of the central nervous system is entered relatively slowly compared to most of the body water and this "should confer upon urea some degree of selectivity as compared with other agents used to promote osmotic shrinkage of tissues." We have administered a single dose of hypertonic C\textsuperscript{14} urea to dogs and found that the level of urea in brain water does not reach equilibrium with the level of urea in plasma during the first 6 hrs. following injection. Fifty per cent of the urea administered in a hypertonic solution is excreted within 5–6 hrs.\textsuperscript{12,17} The rate of excretion of urea is greatly diminished after 6 hrs. and while it is possible that at some later time the level of urea in brain water exceeds the level of urea in plasma, the rate of decrease of urea in plasma is slow enough that a significant gradient of concentration between brain water and plasma is unlikely. To build up a substantial difference in concentration of urea in brain water over concentration of urea in plasma, the two must reach equilibrium while the level of urea in the blood is being rapidly reduced, that is before 5–6 hrs. It is unlikely that any agent that does not rapidly penetrate the brain substance can cause rebound by the mechanism proposed. If there is a rebound it should occur following the period of cerebrospinal-fluid hypotension resulting from hypertonic solutions. Increases in cerebrospinal-fluid pressure occurring 12–24 hrs. after administration of a hypertonic solution cannot logically be attributed to the osmotic agent. In some cases postoperative cerebral edema may occur whether or not hypertonic solutions are administered during operation.

Rosomoff\textsuperscript{26} reported increased brain water 12–18 hrs. after administration of urea and attempted to relate this finding to the rebound phenomenon. Our data indicate that a dog anesthetized for 12–18 hrs. and not receiving urea would also have increased cerebrospinal-fluid pressure and brain bulk. Moreover, we have been unsuccessful in stabilizing the intracranial contents by the freezing technic as described by Rosomoff and attribute this to slow reduction of brain temperature (1°C. at a depth of 4 cm. in 10 min.).

Several experimental artifacts can produce a pseudorebound phenomenon. Among them are: (1) Inadequate periods of control prior to administration of the hypertonic solution.\textsuperscript{1,7,21,26,53} (2) Too rapid administration or administration of clinically prohibitive amounts of the agent, a factor which would encourage excessive uptake by the brain.\textsuperscript{7,26} (3) Lack of control animals subjected to the same experimental conditions without receiving a hypertonic solution.\textsuperscript{21,26} (4) The reporting of changes in cerebrospinal-fluid pressure as per cent of initial pressure which tends to magnify the significance of small changes when the initial pressure is low.\textsuperscript{1} (5) The reporting of a single pressure before and after administration of a hypertonic solution.\textsuperscript{10} (6) Respiratory obstruction. (7) Failure to account for the effect of barbiturate anesthetics on cerebrospinal-fluid pressure.\textsuperscript{1,7,21,26,53} The results of studies on cerebrospinal-fluid pressure in dogs anesthetized with barbiturates should be interpreted with caution.\textsuperscript{14} In this regard McQueen and Jeanes\textsuperscript{22} used sodium pentobarbital in animals receiving urea and not in animals receiving mannitol. It would appear that this could account for the difference in rebound that they have reported in the two groups. Our experiments have shown that under adequate experimental conditions the rebound phenomenon could not be detected with agents used clinically.

The patient with elevated cerebrospinal-fluid tension is likely to exhibit variations in pressure of 200–300 mm. of water over a 24-hr. period (Fig. 12). Stubbs and Pennybacker\textsuperscript{39} have been cited\textsuperscript{20,21,26} as having observed secondary elevation of cerebrospinal-fluid pressure, when in fact they stated, "We have not seen such a secondary rise in pressure after giving hypertonic urea to our pa-
The cerebrospinal-fluid pressure of a patient with glioblastoma multiforme was continuously recorded for 31 hrs. The minimum cerebrospinal-fluid pressure during the 6-hr. period of control was 315 mm. of water and the maximum was 610 mm. of water. The maximum cerebrospinal-fluid pressure during the 25 hrs. after administration of urea (1 gm./kg. body weight) never exceeded the maximum achieved during the pre-injection period of control.

Patients, nor have we seen this in the few cases in which we have made extended manometric studies." Utilizing a period of control for 30 min., Langfitt reported a secondary rise in cerebrospinal-fluid pressure in 4 patients following administration of urea (100 mm. of water in 3 patients and 250 mm. of water in 1 comatose patient with a head injury). Since diuresis is most marked during the first 2 hrs. after injection of urea, Langfitt's administration of fluid "to approximate the urine output" during this period may be another factor responsible for the reported increase in cerebrospinal-fluid pressure. Rapid administration of fluids to patients with space-occupying intracranial lesions is not indicated. Even though they may tend to excrete more water than most patients, the patient receiving hypertonic solutions should not be made an exception to this rule. Replacement of fluid should be spread over a 24-hr. period. We have observed increases in cerebrospinal-fluid pressure of approximately 100 mm. of water after administration of 1 liter of 5 per cent dextrose in water. Similar increases have been reported recently. Einspruch and Clark reported rebound phenomenon in 2 cases without continuous measurement of cerebrospinal-fluid pressure. In their first case, interpretations based on a single measurement of pressure are subject to the criticism that spontaneous fluctuations of greater magnitude might well have occurred during an adequate period of control. Continuous measurement of cerebrospinal-fluid pressure in patients who have not received urea during and after craniotomy may show similar levels of cerebrospinal-fluid pressure to those reported in their second case. Mild to moderate increases in cerebrospinal-fluid pressure (maximum 100 mm. of H₂O) following injection of mannitol are seen in the data of Shenkin et al. No valid conclusions can be drawn without recording cerebrospinal-fluid tension continuously for prolonged periods. Periods of control of short duration do not necessarily represent both high and low inflections of cerebrospinal-fluid pressure.

It is of significance that the over-all conclusion that there is no rebound in dogs coincides with our clinical experience in 1500 patients receiving urea. It is doubtful if any osmotic agent presently in use causes rebound phenomenon when used in dosages recommended clinically. If all factors that affect cerebrospinal-fluid pressure are not taken into consideration, it becomes clear that any agent may give false indications of rebound.

Summary and Conclusion

Experiments on dogs studied with long periods of control before the administration of hypertonic solutions currently in use have shown no evidence of rebound phenomenon. The terms secondary rise in pressure or rebound phenomenon have been used loosely in the past often based on clinical impressions without supporting data and have now unfortunately taken on the form of a truism when referring to hypertonic solutions or other agents that reduce intracranial pressure. It is concluded that findings of rebound after urea and mannitol reported in the literature can be considered as the result of experimental artifacts interpreted as rebound. Experiments are also described with hypertonic solutions of glycerol, glycine and sodium chloride.
References


