Further Studies on the Effectiveness of Agents Used to Lower Intracranial Pressure

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The reduction of cerebrospinal-fluid pressure has been accomplished by a number of agents. New compounds are introduced with great enthusiasm, only to lose their vogue as various manifestations of toxicity become apparent. Currently, hypertonic solutions are popular, although there is question as to individual effectiveness as well as mode of action. If the mode of action of these agents is the simple causation of an osmolar diuresis, evaluation of compounds on an equiosmolar basis should reveal identical effects. Furthermore, if osmolar diuresis is the principal action, additional benefit might be gained by the addition of other types of diuretic agents. Several experiments were designed in order to test these hypotheses.

Experimental Technique

Mongrel dogs were anesthetized with intravenous pentobarbital. Tracheal intubation was used in all animals in order to insure adequate airways. All dogs were placed in a right lateral decubitus position, and a polyvinyl catheter was inserted into the left femoral vein. The bladder was catheterized, and the volume of urine was measured every 20 minutes. A cisternal puncture was done with an 18-gauge needle, which was attached by a 3-way stopcock to a standard water manometer, filled with 0.9 per cent normal saline. Satisfactory puncture was indicated only if the cerebrospinal fluid was found to be crystal-clear, and the meniscus oscillated with respiration and heartbeat. The entire system was allowed to stabilize for 30 minutes before the experiment began. Readings of the pressure were made every 5 minutes. The animals received no supplemental fluids during the experiment.

In experiments where intra-arterial administration was done, the vertebral artery was cannulated in the neck. This artery was chosen as it is the major arterial supply to the brain in this species. Care was taken to avoid opening the pleura, and the animal was discarded if this occurred. The experimental agent was injected by hand slowly over a period of 15 minutes.

There were several groups of animals, each of which was tested with a parenteral injection of equiosmolar solution over a 15 to 20-min. period. The solutions used were hypertonic urea, hypertonic Sorbitol and hypertonic mannitol. In instances as noted in the protocol, certain groups of animals also received chlorothiazide (Diuril), a nonmercurial diuretic. Cerebrospinal-fluid pressure was then monitored for 4 to 6 hours.

1. The 1st group received urea 1.5 gm./kg. body weight administered intravenously.
2. A 2nd group received urea 1.5 gm./kg. body weight via the vertebral artery.
3. A 3rd group received mannitol 4.5 mg./kg. intravenously.
4. A 4th group received sorbitol 4.5 mg./kg. intravenously.
5. A 5th group received mannitol 4.5 mg./kg. as well as intravenous chlorothiazide 0.25 gm./total weight.
6. A 6th group received sorbitol 4.5 mg./kg. as well as intravenous chlorothiazide 0.25 gm./total weight.
7. A small control group of dogs received intravenous chlorothiazide 0.25 gm. only.
8. Two small groups of animals received mannitol 4.5 mg./kg. and sorbitol 4.5 mg./kg., respectively, via the vertebral artery.

Results

Cerebrospinal-fluid pressure. As illustrated in Figs. 1–5, all agents used were capable of lowering intracisternal pressure. In all cases the fall in pressure was prompt, usually leading to a rapid phase of reduction within 15 min. after administration. Figs. 2–5 reveal that pressures were frequently reduced to atmospheric or subatmospheric levels, but not when urea was used (Fig. 1). Since a simple open-ended water manometer was used, subatmospheric pressure could not be recorded properly. In diagrams which show pressure to be between 0–1, it may have been
Four to 6 hours after urea is administered, the resultant pressure value exceeds the initial opening pressure. Urea caused rebound in 100 per cent of animals (Fig. 1), whereas mannitol plus Diuril demonstrated this phenomenon in only 13 per cent of the cases (Fig. 2). Sorbitol plus Diuril showed 25 per cent rebounds (Fig. 3), sorbitol alone showed 44 per cent rebounds (Fig. 4), and mannitol alone, 66 per cent (Fig. 5). No effect on cerebrospinal fluid was noted with chlorothiazide alone. A very precipitous and rapid fall occurred in animals given the hypertonic agent intra-arterially.

All agents induced copious diuresis. Rarely did insignificant diuresis occur, but this was associated with rebounds, and was not statistically significant.

Tolerance of Experimental Technique. All dogs tolerated the experiment and seemed perfectly normal in later observations, with the exception of the group receiving intra-arterial injections. In this group, virtually every animal died during the experimental period, regardless of the agent used.

Discussion

Any agent which induces an osmotic diuresis can reduce cerebrospinal-fluid pressure. Mannitol and sorbitol differ from urea by being confined to the extracellular fluid spaces. As they do not enter the brain cells readily, the osmotic equilibrium is delayed but does occur with these agents. The equilibrium, which is common to all such agents, is characterized by a rebound of the cerebrospinal-fluid pressure to levels potentially above the initial one. Obviously, before the pressure can reach the initial pressure, it rises at some rate toward this level. The slope of this rise may be flattened if an agent does not readily cross the cellular membrane, is metabolized, or excreted rapidly. Furthermore, if additional diuresis is created, as when chlorothiazide was given, the period of decreased cerebrospinal-fluid pressure is lengthened. This is again related to the diuresis induced.
Agents to Lower Intracranial Pressure

Fig. 4. Four to 6 hours after sorbitol is administered, the resultant pressures exceeded the initial opening pressures 44 per cent of the cases.

Fig. 5. Four to 6 hours after mannitol is administered, the resultant pressure exceeds the initial opening pressure 66 per cent of the cases.

More precipitous lowering of the cerebrospinal-fluid pressure occurs with intra-arterial injections of these agents. A large number of the dogs failed to survive this route of administration regardless of the agent employed. The exact explanation of this result is not yet clear although it may be related to the level of dose.

Since mannitol has been shown to be less toxic than urea and as effective as urea, it appears at present to be the agent of choice for lowering cerebrospinal-fluid pressure. Combined mannitol and Diuril produced in experimental animals the most effective action of hypertonic solutions that we have observed. The seeming lack of toxicity in animals does not preclude changes in electrolytes and volume which bear further evaluation before the method can be recommended. Further studies using sorbitol will have to be done before its clinical use can be recommended.

It is likely the intra-arterial administration of these agents in these doses cause extreme dehydration of the brain. This was fatal to all animals within a few minutes after administration. While it is possible that lower doses may be tolerated, the agents should not be given intra-arterially in man until further experimental work is done.

Summary

Results from the administration of several hypertonic solutions on the cerebrospinal-fluid pressure have been compared. Equimolar doses of urea, sorbitol, and mannitol have been given, singly and combined, with a diuretic agent, chlorothiazide. Prompt reduction of pressure occurred with all agents. Rebound of the cerebrospinal-fluid pressure to higher than original levels also occurred with all agents. A reduction of the number of rebound phenomena seen and a prolongation of the time of reduced cerebrospinal-fluid pressure was found with the addition of chlorothiazide. Mannitol and chlorothiazide produced the most prolonged reduction with the least incidence of rebound.

Administration of any of these compounds into the vertebral artery produced death of the animal in a high percentage of trials.

Lyovac Diuril chlorothiazide was supplied by Merck, Sharp & Dohme (as standard solution which contained 500 mg. chlorothiazide, 250 mg. mannitol, and 0.4 mg. thimerosal per vial).

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References


