Experimental Use of Isosorbide: an Oral Osmotic Agent to Lower Cerebrospinal Pressure and Reduce Brain Bulk*

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The effectiveness of hypertonic osmotic solutions in lowering cerebrospinal fluid pressure and reducing cerebral edema or brain bulk has been established. At the Mannitol Symposium held in February, 1962, at the Walter Reed Army Institute of Research, Washington, D.C., the efficacy and application of mannitol as an intravenous osmotic agent were reviewed. Mannitol is of value in decreasing brain bulk and in lowering cerebrospinal fluid pressure when given intravenously, but it produces marked gastrointestinal intolerance when given orally and it is poorly absorbed by the gastrointestinal tract. Thus, there is a need for an effective oral osmotic hypertonic solution.

Smith et al., in studying other hexitols and their anhydrides, observed that the renal clearance of isosorbide (1,4:3,6-dianhydro D-glucitol) in dogs was about one-half that of creatinine, sorbitol, mannitol, dulcitol, and sorbitan. However, they reported renal clearance only after intravenous injection of isosorbide. Other researchers confirmed the diuretic activity of isosorbide when given orally, and showed that, in contrast to hexitols, effective osmotic diuretic doses of isosorbide do not produce diarrhea. The approximate threshold laxative dose for isosorbide given orally to fasted rats is 17.8 gm./kg. body weight, 10 to 20 times greater than the threshold doses for hexitols and hexitans.

Isosorbide is a dihydric alcohol formed by removing 2 molecules of water from sorbitol, a sugar alcohol, under vacuum at elevated temperatures in the presence of strong acids. Its molecular weight is 146.14 and its structural formula is shown in Fig. 1. Studies on isosorbide have revealed a low order of toxicity. The acute oral LD$_{50}$ for the dog is greater than 31 gm./kg.; up to 12 gm./kg. body weight have been given orally for 30 days in dogs without evidence of toxicity or gross pathologic changes. The minimum effective diuretic oral dose in the dog is 1 gm./kg. body weight.

The purpose of this paper is to report studies carried out in dogs to determine the effectiveness of oral as well as intravenous isosorbide in lowering spinal fluid pressure and reducing brain bulk. Serum osmolality was determined as a means of elucidating the mechanism of action of isosorbide and measuring its degree of absorption through the gastrointestinal tract.

Method

Female mongrel dogs weighing between 10 and 14 kg, were anesthetized with intravenous sodium pentobarbital (25 mg./kg. body weight initially with supplemental doses as needed). An endotracheal tube was inserted and attached to a Bird
respirator which controlled respirations throughout all the experiments.\* Cerebrospinal fluid pressure was continuously recorded through a needle placed in the cisterna magna and connected to a Statham strain gauge manometer and Grass polygraph or to a water manometer. Urine volume (via an indwelling catheter), serum osmolality (determined by the method of freezing point depression with an Advanced Instruments Model 31-L Osmometer) and blood pressure (measured in the femoral artery) were recorded at half-hour intervals. No intake of fluid was allowed during the experiments. The dogs were sacrificed at the end of the test period.

Isosorbide 50% solution† (3.0 gm./kg. body weight) was given intravenously in 6 non-fasting dogs at an infusion rate of 1 gm./min. after the cerebrospinal fluid pressure had been stable for at least 30 minutes.

Isosorbide 50% solution (3.0 gm./kg. body weight) was given via a feeding tube in 7 non-fasting dogs and 4 fasting dogs after the cerebrospinal fluid pressure had stabilized.

Isosorbide 50 per cent solution was given in 3 separate doses (each 3.0 gm./kg. body weight) 3 hours apart via a feeding tube after the cerebrospinal fluid pressure had stabilized.

Results

A. Intravenous isosorbide in 6 non-fasting dogs. (Fig. 2) The administration of 3.0 gm./kg. body weight of 50% isosorbide solution intravenously at an infusion rate of 1

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*Because variations in CO₂ can affect cerebrospinal fluid pressure, blood CO₂ was measured in the 1st 6 dogs. Because blood CO₂ did not vary significantly during the test period, it was not determined in the remaining dogs.

† Supplied as Hydronal\* by the Director of Medical Services, The Stuart Company, Division of Atlas Chemical Industries, Inc. Caution: Hydronal\* is produced for oral administration only. The intravenous administration to dogs in this investigation was carried out solely to permit direct comparison with mannitol.