The Effects of Isosorbide on Serum and Cerebrospinal Fluid Osmolality and on the Spinal Fluid Pressure in Man*

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**I**sosorbide is a dihydric alcohol with a molecular weight of 146, formed by the removal of 2 molecules of water from 1 molecule of sorbitol. We recently reported that orally administered isosorbide lowered cerebrospinal fluid (CSF) pressure in dogs. This paper reports our findings when this osmotic diuretic was administered orally to humans.

**Methods**

A dose of 2 gm/kg body weight was chosen as being probably both safe and effective. The 50% isosorbide solution† was administered via nasogastric tube to comatose patients; conscious cooperative patients drank the iced solution. The CSF pressure was measured with a water manometer attached to a needle in the lumbar subarachnoid space. Osmolality of samples of serum and CSF were determined by the method of freezing point depression.‡

**Results**

**Case 1.** A 32-year-old woman with a presumptive diagnosis of "pseudotumor cerebri" possibly related to Griseofulvin®. She was given 2 gm/kg of 50% isosorbide every other day for three doses. The effect of the first treatment is shown in Fig. 1. The serum electrolyte concentrations were normal several hours after this study, and her headache and visual obscurations subsided progressively. On examination 6 months later, she was free of symptoms, and the papilledema had disappeared completely.

**Case 2.** A 21-year-old man with a head injury and parietal skull fracture. On the fifth day post-injury, a right-sided subdural hematoma was evacuated. There was also evidence of temporal-lobe contusion. The study illustrated in Fig. 2 was done 2 days later.

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‡ Advanced Osmometer, Model 31-L.
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**Case 3.** A 55-year-old man with a head injury and occipital skull fracture. His conscious state was impaired for 5 days, followed by gradual recovery. The study illustrated in Fig. 3 was done on the seventh day following injury.

![Chart of CSF pressure and serum osmolality after isosorbide in patient in Case 3.](image)

**Case 4.** A 45-year-old man who had had a partial temporal lobectomy for glioblastoma multiforme several weeks before this study (Fig. 4). The osmotic gradient between serum and CSF reached a maximum of 28 milliosmols (mOsm) at 90 min.

**Case 5.** A 53-year-old man who had had several cerebral infarcts in the several months preceding this study (Fig. 5). Maximum osmotic gradient of 21 mOsm was reached at 120 min.

**Case 6.** A 77-year-old man who had had partial resection of a parietal glioblastoma multiforme 2 months before this study (Fig. 6). Maximum osmotic gradient of 35 mOsm was reached at 90 min.

**Case 7.** A 30-year-old man who had extensive brain trauma with an acute subdural hematoma. This study (Fig. 7) was done 3 days postoperatively while the patient was hypothermic and had been receiving dexamethasone in large doses for 2 days.

**Case 8.** A 27-year-old man who had had a severe head injury with drainage of an acute subdural hematoma 2 days previously (Fig. 8).

The following three patients received isosorbide without CSF pressure measurements:

**Case 9.** A 25-year-old woman with "pseudo-tumor cerebri" who received two doses of isosorbide, 3 gm/kg, in 3 days. Symptoms improved at the time. When seen 1 year later, the papilledema had subsided completely.

**Case 10.** A 65-year-old man who had had persistent CSF otorrhea for 8 days after a basal skull fracture. On the ninth day, he received 2 gm/kg of isosorbide; the otorrhea ceased within 2 hours and did not recur.

**Case 11.** A 50-year-old woman who was receiving radiation therapy for an unverified malignant glioma deep in the motor area. She was given 1.5 gm/kg of isosorbide, which did not produce any obvious alteration of findings.

**Discussion**

The onset of action of isosorbide in lowering CSF pressure appears to be very prompt after oral administration although this may vary with the speed of absorption from the intestine. Studies in animals have shown that,
Fig. 5. Chart of CSF pressure (solid line) and serum and CSF osmolality after isosorbide in patient in Case 5.

Fig. 6. Chart of CSF pressure (solid line) and serum and CSF osmolality after isosorbide in patient in Case 6.

Fig. 7. Chart of CSF pressure and serum osmolality after isosorbide in patient in Case 7.

Fig. 8. Chart of CSF pressure after isosorbide in patient in Case 8.
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![Chart of changes in osmolality](image)

**Fig. 9.** Chart of changes of serum osmolality (upper section) and osmotic gradient in patients given oral isosorbide. In upper section, solid line joins means of determination indicated by round dots. Note how serum osmolality alone may be misleading in late determinations, for after 210 min, serum osmolality in Case 6 (square dots) remains elevated, but the osmotic gradient between serum and CSF has returned close to baseline.

after oral administration, 95 to 97% of the dose is absorbed and subsequently excreted in the urine mainly unchanged. Isosorbide equilibrates in about 45 min in a volume of fluid equivalent to 0.9 of total body water. Our studies suggest that it is either largely excluded from or equilibrates slowly with the CSF and brain water, thus accounting for the osmotic gradient between serum and CSF and its effect of lowering CSF pressure. In patients undergoing cataract extraction, concentration of isosorbide in the aqueous humor averaged 55% of plasma levels 1 to 3 hours after oral administration.

Both acute and chronic studies in animals and humans suggest that isosorbide has an extremely low toxicity and is mainly inert. It causes an osmotic diuresis with onset within 30 to 60 min of ingestion and a duration of 3 to 7 hours. In patients with cirrhosis, the half time for excretion of an oral dose is 12 hours compared to 3 hours for a comparable dose of intravenous mannitol. There is an increase in sodium excretion during the isosorbide diuresis without significant changes of glomerular filtration rate or renal plasma flow. Isosorbide appears to be completely filtered by the glomerulus and partially re-absorbed in the proximal tubule.

In our own studies, oral isosorbide, 2 gm/kg, raised serum osmolality by 17 to 30 mOsm/liter in six cases and 50 mOsm/liter in one case, with the peak of serum osmolality being reached at 40 to 90 min after administration (Fig. 9). This is very similar to the results reported by Becker in his glaucoma studies, namely, an increase in serum osmolality of 19 to 30 mOsm/liter at 1 to 2 hours after administration. The maximum osmotic gradient between CSF and serum in the three cases that we studied was 21, 28, and 35 mOsm/liter at 90 to 120 min after oral administration (Fig. 9).

It can be seen from Fig. 9 that determination of serum osmolality without CSF osmolality may be misleading, that is, probably the osmotic gradient between serum and CSF (and brain) is what determines movements of water and electrolytes rather than serum osmolality alone. (We have determined the osmotic gradient by subtracting CSF osmolality from serum osmolality, so that a positive gradient indicates a serum osmolality greater than CSF.) In Case 6 (Fig. 6 and
square dots in Fig. 9), serum osmolality remains high up to 480 min after isosorbide intake, but osmotic gradient returns close to baseline at 360 min or before.

As in studies with other osmotic agents, the decrease in CSF pressure correlates quite well with the onset of elevated serum osmolality and the increase in osmotic gradient between CSF and serum. However, the return of CSF pressure to the baseline does not correlate well with changes in osmolality, although the beginning of rising pressure appears to occur at about the same time as the osmotic gradient stops increasing or starts decreasing. This lack of correlation is particularly apparent in patients with space-occupying lesions and is probably related to the compensatory changes that are assumed to have taken place in the other intracranial compartments. When intracranial fluid is decreased by the osmotic agent, these compensatory changes may be reversed, and when fluid subsequently re-enters the CSF and the brain, it probably takes some time for these compensations of the other compartments to readjust. This may account for some instances of "rebound overshoot" of CSF pressure.

Oral isosorbide was well tolerated by these patients. When the entire dose was given rapidly by nasogastric tube, the vomiting of small amounts of fluid occurred in two patients. Conscious cooperative patients were able to drink the iced solution in 10 to 15 min without difficulty.

Oral isosorbide does not appear to have any obvious advantage over mannitol for acute administration in comatose patients or during surgical procedures when the alimentary route should be avoided. However, for repeated usage over a period of days or weeks, oral isosorbide may prove very useful. Further studies will be necessary to determine its long-term effectiveness in the treatment of such conditions as "pseudotumor cerebri" and hydrocephalus. The rate of formation of CSF has been shown to be related to the osmotic gradient between serum and CSF.2 Thus, it is conceivable that repeated treatments with an osmotic agent, such as isosorbide, may actually alter the course of such conditions as hydrocephalus.

Summary

Isosorbide, a dihydric alcohol formed by the removal of two molecules of water from sorbitol, is an effective osmotic diuretic which is absorbed from the gastrointestinal tract. It has previously been shown to be effective in lowering CSF pressure in dogs after oral administration. In this study, oral administration to 8 patients with increased CSF pressure was effective in lowering the CSF pressure without creating any serious side effects.

Serum osmolality was raised 17 to 30 milliosmols after oral administration of 2 gm/kg isosorbide, and a maximum osmotic gradient between CSF and serum of 21, 28, and 35 milliosmols was attained at 90 to 120 minutes.

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References