The Effect of Glycerol on Cerebral Edema Induced by Tri-ethyltin Sulphate in Rabbits*

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It is hardly necessary to enumerate the various symptoms and signs of cerebral edema in a neurosurgical journal, but its management in many clinical conditions still remains a problem. Since the rediscovery of the efficacy of intravenous hypertonic urea solutions, there has been a search for other less toxic substances. These have included hypertonic sodium chloride, hypertonic sucrose, magnesium sulphate, mannitol and sorbitol.

Glycerol has been tried, as it has an osmotic action, and also has the advantage of low toxicity and versatility of administration. There is ample clinical evidence of its effectiveness in reducing both cerebral edema and increased intra-ocular pressure. There appear to be no studies of its mechanism of action at tissue level. The current theory is that it withdraws water by means of osmotic force.

Rabbits intoxicated with tri-ethyltin sulphate (TET) provide excellent laboratory models for studying cerebral edema. The biochemical criteria of cerebral edema are well established, consisting of a 100 per cent increase in water concentration above normal, and 190 per cent increase in sodium content. Knowledge of these criteria allows a quantitative assessment of changes due to any pharmacological agent. We have already shown that intravenous hypertonic urea solutions reduce the sodium and water concentrations in TET intoxicated rabbits by significant amounts. Such reductions constitute an objective improvement in the cerebral edema.

TET intoxication affects only the cerebral white matter, leaving peripheral white matter and gray matter almost unaffected. It has been postulated that the selective poisoning is a result of enzyme inhibition, but this has not been verified.

Materials and Methods

New Zealand white rabbits weighing between 2.5 and 3.5 kg were selected. Thirteen rabbits received TET 0.5 per cent intraperitoneally in a daily dose of 1 mg./kg. body weight. On the 7th day, the animals were given glycerol intravenously. The total dose of glycerol was determined by calculating the osmotic equivalent of a dose of urea. Four grams of urea are equivalent to 6 grams of glycerol. The glycerol was administered as a 60 per cent solution, 4 gm./kg. body weight. Ten normal rabbits were given IV glycerol and used as controls.

Control data on normal rabbits have been previously established, as have those for animals intoxicated with TET.

At hourly intervals up to 6 hours, rabbits were killed by means of exsanguination. The brain was immediately removed and placed in a high humidity chamber, relative humidity greater than 95 per cent. Using a dissecting microscope, samples of white matter weighing approximately 10–20 mg. were removed. They were weighed on a Cahn microbalance, using previously weighed aluminum foil planchettes. These samples were dried overnight in a constant temperature oven at 100°C. They were reweighed the following day. The percentage dry weight was calculated.

The dessicated material was dissolved in concentrated nitric acid, and the solutions used for flame photometry, to determine sodium and potassium concentrations. A flame photometer with a lithium internal standard was used. The Na/K ratio was calculated.

Results

Table 1 indicates the sodium, potassium and water concentrations in control and intoxicated animals given IV glycerol. The values have been recalculated in terms of 100 gm. dry weight to eliminate changes due to dilution. These recalculated values permit comparison between animals at different stages following glycerol treatment. These values have been shown in Fig. 1 for water and sodium respectively.
Glycerol and Cerebral Edema in Rabbits

There was a sharp fall 1 hour after the dose of glycerol, similar to that seen in the urea experiments. Water falls by 9.5 per cent, and sodium by 15 per cent. These values are significant (t test on the raw data, p < 0.05). Two to 4 hours after glycerol, there was practically no further change in water or sodium. After 5 hours, there was an additional drop, with water falling by 20 per cent and sodium by 27.7 per cent (significant values). After 6 hours, the onset of “rebound” was observed, the water and sodium values returning to the original values. It seems that the sodium does not climb as high as the water content.

Variations in the potassium were very small, and were not significant.

**Discussion**

Glycerol has been known to have marked hygroscopic properties for a very long time but, compared to urea, mannitol and sucrose, it is somewhat inconspicuous in the attack on cerebral edema. Ophthalmologists have used it topically to clear corneal edema in the various corneal dystrophies such as bullous keratopathy. The detailed kinetic studies of urea uptake and turnover by brain tissue have not been performed on glycerol, neither with radioactive labelling nor in physiological experiments.

Like urea and mannitol, glycerol has the ability to reduce both cerebral edema and the ocular pressure when the latter is pathologically raised in acute glaucoma. While the secretion of aqueous humour and cerebrospinal fluid may be similarly affected, there are marked differences between the swollen brain, and the mechanical block of the anterior chamber angle of the eye. The common factor in the two situations is presumably the osmotic action of these solutions.

Urea has a molecular weight of 60, is non-polar and enters all body compartments. Nevertheless it is differentially retained by brain tissue, attracting water from white matter into fluid compartments. This has been shown to occur in TET-induced edema in rabbits.

Glycerol has a molecular weight of 92, is non-polar, presumably can enter all body compartments, and similarly seems to cause water to leave swollen white matter in TET-intoxicated rabbits. Both these substances are metabolically active and able to enter the body’s chemical circuits. Glycerol is a nutrient yielding 4.2 K cal per gram. It also forms an ingredient of neutral fat (di- and triglycerides), and some phosphatides.

When it is given in excess, glycerol has a diuretic action, being excreted via the kidneys. That its anti-edema action is not due to diuresis is illustrated by its effectiveness in nephrectomized animals.

The effectiveness of glycerol dehydration, plotted against time, seems to be fairly similar to that for urea. The initial fall at 1 hour is the greatest single drop in water content, and may possibly be correlated with the sharp change in cerebrospinal fluid pressure in Reed and Woodbury’s experiments.
subsequent smaller changes, with the maximal loss at 5 hours, may reflect the gradual uptake of glycerol by brain substance, similar to that which they found for urea. They showed a biphasic behavior for urea dehydration, considering that the second or "slow" phase could be due to urea entering glial cells. After 6 hours, the effect of glycerol begins to wane, again similar to urea.

As each new hyperosmotic agent begins to be exploited clinically, optimistic claims are made for its ideal properties, in particular the absence of "rebound." This claim has been made for glycerol too, but the present experiments refute it, just as it was refuted for urea and mannitol. Inevitably, the forcible withdrawal of water, whether or not followed by sodium, causes a disruption of the normal or pathologically disturbed fluid compartments. In accordance with Claude Bernard's dictum, the milieu interieur must be maintained.

When very powerful osmotic agents are used, these swings occur violently, with damage to the organism. This was seen in the urea experiments, when the rabbits developed seizures 1 or 2 hours after the administration of urea.

Perhaps the most important property of glycerol in this context is its milder action, enabling it to be given several times without apparent risk of serious side effects. "Gentler action" means less effective withdrawal of water and sodium, 20% compared to 28% for urea. Osmolality levels have not been measured, but presumably the glycerol raises serum osmolality less than a comparable amount of urea. As the water and sodium withdrawn must ultimately be excreted by the kidneys, glycerol is still a dangerous substance to employ in patients with renal impairment.

In other respects glycerol is a safe drug. Even in extremely large doses, it has not been found to be toxic. Its versatility in administration is another point in its favor. It may be given parenterally as well as by gastric tube. The taste is nauseating when given in any quantity, so it must go directly into the stomach. If the glycerol is mixed with lemon juice, alert patients can drink the glycerol mixture without too much distaste.

As in the previous studies on urea, there is now laboratory confirmation of empirical clinical observations, that glycerol reduces cerebral edema caused by tri-ethyltin sulphate intoxication.

Summary

Rabbits, intoxicated with tri-ethyltin sulphate, were given intravenous glycerol prior to being sacrificed. Analyses of cerebral white matter revealed a significant reduction in water and sodium content. Glycerol has been shown to be an effective osmotic agent for reduction of diffuse cerebral edema due to TET intoxication.

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References