Oral Glycerol for the Reduction of Intracranial Pressure*

GIAMPAOLO CANTORE, M.D.,† BENIAMINO GUIDETTI, M.D., † and MICHELE VIRNO, M.D.‡
Neurosurgical Department, Neurological Institute of Rome University, Rome, Italy

LITERATURE of recent years reports several works on the clinical use of hypertonic solutions administered by slow intravenous infusion for reduction of intracranial pressure. Among the numerous osmotic agents tested to reduce experimentally induced cerebral edema in the animal, glycerol has proved particularly effective both by intravenous and oral route. Considering such experimental results, glycerol has been applied on neurological, ophthalmological and, chiefly, neurosurgical patients.

Glycerol (1,2,3-propanetriol) is a trivalent alcohol. It is oxidized by the organism through intermediate stages, analogous to those of the carbohydrate-oxidation cycle. As an integral part of fats (glycerides) and phosphatides, glycerol usually is present in the animal tissues at a rate of approximately 1 per cent of body weight. Oxidized to carbon dioxide and water, it produces 4.32 kg. calories per gm. Such value is slightly greater than that produced by glucose. When larger amounts of glycerol are given, however, the drug is not metabolized completely by the organism since part of it is excreted in the urine.

Glycerol increases plasmatic concentration. Its mechanism of action, therefore, would be to draw liquids from the tissues, particularly from those more hydrated.

At convenient doses, glycerol promotes diuresis yet diuresis itself does not condition the action of the drug since reduction of intracranial hypertension in the nephrectomized animal did not differ from that obtained in the normal animal.

In 1929, Ferber and Rabinowitsch described the action of oral glycerol administered as food to 60 patients. No toxic effects or gastrointestinal disorders were noted. In 1933, Johnson et al. studied the replacement of carbohydrate by glycerol in the diet of man and animal and pointed out the absolute tolerance of the drug taken orally. In order to examine the eventual toxicity of higher doses of glycerol, these authors administered daily 9 gm. of glycerol per kg. of body weight to the dog over a period of 1 year. The animals thus treated showed no toxic signs both in vivo and at postmortem examination. Subsequently, a group of students was submitted to a daily treatment of 1–3 gm. of glycerol per kg. of body weight over a period of 50 days. Never were toxic effects noted. Johnson et al., therefore, concluded: “... within extensive limits glycerol compares favorably with carbohydrate as a source of energy.”

We are not aware of any work, from a laboratory or clinic, dealing with therapeutic application of glycerol for the reduction of intracranial hypertension, other than those already mentioned, which appeared in 1961.

During this study, oral administration has been applied chiefly, since oral glycerol displays the following qualities (Fig. 1):

1) Promptness and intensity of action in reducing intracranial pressure.
2) Possibility of repeating administration several times over a long period, thus avoiding “rebound overshoot,” common to osmotic substances.
3) Lack of toxicity.

Method

Different kinds of glycerol are supplied. We have always used pure products. Single oral dos-
ages ranged between a minimum of 0.5 gm. and a maximum of 2 gm. per kg. of body weight. In many instances, daily dosages of over 5 gm. per kg. (1.5 gm. per kg. as initial dose, and 0.5–0.7 gm. per kg. every 3 hrs.) have been attained. Such dosages could be repeated even for several days without complaints of troublesome effects.

To attenuate the sweetish taste of glycerol, 50 per cent solutions in 0.9 per cent saline have been prepared. Lemon juice was also added. Cooling of the mixture and concurrent ingestion of small amounts of food facilitated the uptake of glycerol. Parenteral injection of an anti-emetic substance, 15–30 min. prior to ingestion of glycerol, was made in patients predisposed to vomiting. Patients, unable to drink spontaneously because of their critical condition, were given glycerol by means of gastric or duodenal tube (Fig. 2). No additional protein or electrolyte was needed during prolonged treatments with glycerol, ranging from several days to months, when patients were feeding on normal diet. Whereas in torpid or comatose patients, water-saline balance was maintained under strict control and suitable amounts of protein and electrolytes were administered.

In diuresis following administration of glycerol, excretion of electrolytes was not significant. (Data dwelling on this subject, obtained from neurosurgical and cardiopathic patients, will be discussed in a subsequent paper.)

In stuporous and anesthetized patients, an indwelling catheter always was applied to prevent excessive vesical loading.

Glycerol was used both in hyperazotemic and markedly hyperglycemic patients with extremely satisfying results. In the latter case, concurrent administration of hypoglycemic agents was applied.

For intravenous infusion, sterile, 30 per cent glycerol solutions in 10 per cent inverted sugar or in 6 per cent depolymerized dextran diluted in 0.9 per cent saline have been prepared. The solution was injected at a rate of 60 drops per min. Glycerol, 0.8–1 gm. per kg. of body weight, always produced a marked anti-edematous effect, even in the most serious cases. Intravenous infusion, however, has been used only in a limited number of cases because of the frequent occurrence of transient hemoglobinuria. Further studies are being carried out presently in order to prevent hemolysis following intravenous administration.

**Results**

Glycerol, 1–2 gm. per kg. of body weight, was given to 258 patients, chiefly neurosurgical, from April 1961–April 1963. Oral administration was used in most cases. In a limited number of cases, intravenous infusion was applied. Glycerol was administered before, during and after surgery. In a few instances, the drug was given to patients with nonsurgical lesions of the nervous system.

Sixty-two patients suffering from space-occupying intracranial processes were treated with glycerol before surgical intervention. The doses administered varied according to the patient’s condition. In stuporous and torpid patients, oral glycerol, 0.5 gm. per kg. every 3–4 hrs., reduced intracranial hypertension to an extent that within 30–60 min. from the start of the first administration, the patients’ conditions highly improved and complete responsiveness returned. Solids and liquids were administered at the same time with glycerol, so that a convenient water, salt and protein balance could be maintained.

The most dramatic results with glycerol have been obtained in patients admitted to the hospital in comatose conditions. Administration of glycerol, 1.5 gm. per kg., was
Giampaolo Cantore, Beniamino Guidetti and Michele Virno

Fig. 2. G.P., a 45-year-old woman, weighing 66 kg., (Clinic No. 3540) was suffering from glioma of basal ganglia. Brain before (above) and 40 min. after administration (below), by means of gastric tube, of 132 gm. of glycerol in a 50–50 mixture of glycerol and 0.9 per cent saline.

begun immediately by gastric tube. Two hrs. subsequently, if the patient was still lethargic, glycerol, 1 gm. per kg., was given. Once responsiveness and cardiocirculatory conditions returned to normal, a maintaining therapy of 0.5–0.7 gm. of glycerol per kg. every 3–4 hrs. was applied until all diagnostic procedures and, eventually, surgical intervention were carried out.

Oral glycerol has been used in 75 patients in the operating room during intracranial surgery. The purpose was to reduce cephalic bulk, to facilitate exposure during operative procedures without sacrificing or removing cortical areas.

Glycerol was used chiefly during surgical extraction of tumors of the base of the skull (meningiomas, adenomas, craniopharyngiomas, etc.) and of every expanding intracranial process accompanied by marked cerebral edema (brain abscess, metastatic tumors, etc.). In a few cases, the drug has been administered during neurosurgical intervention on patients suffering from saccular and arteriovenous aneurysms and trigeminal neuralgias.

Usually after having introduced a gastric or duodenal tube, glycerol, 1.5–2 gm. per kg., was administered 30 min. prior to opening the dura mater. About 30 min. later, upon incision of the dura mater, evidence of significant reduction of brain volume was found. Within the subsequent 40–60 min., the brain gradually retracted, thus facilitating operative procedures tremendously.

Upon opening the skull, even during prolonged intracranial surgery, no "rebound overshoot" has ever been noted (Fig. 3). Once the desired reduction was attained, liquids accumulated in the stomach were removed to prevent vomiting.

Oral glycerol was given postoperatively to 84 patients who, following intracranial surgery, had signs of cerebral edema or of increased cerebrospinal-fluid pressure. Its use has been extremely valuable in resolving the postoperative course more satisfactorily.

Oral glycerol has proven very helpful, too, during roentgen-ray therapy in patients already operated upon for intracranial neoplasms to combat postradiation cerebral edema.
Daily doses of oral glycerol were administered for several days in the treatment of cerebral edema (25 cases) following head injuries, once diagnostic examination had excluded the presence of an intracranial hematoma.

In a limited number of patients suffering from "pseudotumor cerebri," glycerol, 0.5 gm./kg. was given for a period of 8 weeks. The drug was found to be fairly well tolerated and results were satisfying. Glycerol also was used successfully in nontumoral cephalgia and headache. The number of such patients examined, however, is still too small to draw any useful indication.

Effect of Oral Glycerol on Intraocular Pressure. During previous researches carried out at the Ophthalmological Department of The Rome University,\textsuperscript{16,17} the action of oral glycerol on intraocular hypertension has been studied both in man and animal. Forty-six cases have been analyzed on the whole. Of these patients, 26 had suffered from various types of glaucoma and 20 had completely normal intraocular pressure. The most dramatic effect with glycerol has been obtained in cases of acute angle-closure glaucoma. Oral glycerol, 1.5 gm./kg. was shown to lower progressively intraocular pressure which, within 60–90 min., was brought to about normal levels. Such levels of pressure were maintained in some cases for several days (Fig. 4).

The effect of oral glycerol (1–1.5 gm./kg.) on other nonacute forms of glaucoma was a marked reduction of intraocular pressure, lasting 4–6 hrs. Tension, then, rose again to pretreatment levels. Tension-lowering effect induced by oral glycerol (1 gm./kg.) has

![Graph showing effect of oral glycerol on intraocular pressure](image)

**Fig. 4.** Effect of oral glycerol on intraocular pressure in 6 patients during attack of acute angle-closure glaucoma. (Average values measured by Schiötz' tonometer.) At "G" oral glycerol, 1.5 gm./kg. of body weight, was administered. In all glycerol-treated patients, about 1 hr. after administration, intraocular pressure was brought to about normal levels.
proven particularly useful in patients with normal ocular pressure when intraocular hypotony was needed to proceed with orbital surgery.

From the data obtained in ophthalmology, oral glycerol is found to be highly effective in lowering intraocular hypertension.

Conclusions

Oral glycerol has proven to be a very helpful agent to lower intracranial pressure and decrease the mass of the brain in the following specific situations:

a) In patients suffering from intracranial decompensating increased pressure and herniation of the brain, especially just prior to or during diagnostic studies. Glycerol is found to improve the general conditions to an extent that diagnostic studies, and, subsequently, surgical procedures could be carried out.

b) In patients with any type of hydrocephalus with decompensation.

c) In the treatment of head injuries when symptomatology could be attributed to edema resulting from cerebral contusions.

d) In patients suffering from space-occupying processes of the base of the skull. Glycerol facilitated surgical procedures, permitting easy access to the structures beneath the brain without injuring or amputating the sound parts of the encephalon.

e) To prevent damage to the brain when intracranial tension is high and the dura mater is about to be opened.

f) In patients whose general conditions on postoperative days, following intracranial surgery, suddenly deteriorated and increased unresponsiveness developed because of "brain swelling."

g) During roentgen-ray therapy following operative intracranial procedures.

The effectiveness of glycerol, as well as of urea and mannitol, proves that the osmotic method is the most valuable for the reduction of cerebral edema and intracranial and intraocular pressure.

As compared with the other osmotic agents commonly used for this purpose, glycerol exerts its prompt and intense effect by oral route. Since oral glycerol might be considered a "food-substance," it is possible to administer this drug safely over a long period of time and to repeat its doses every 3 hrs. without dangerous "rebound overshoot," which often follows the administration of the best known osmotic agents.

Oral glycerol, furthermore, lacks those toxic side-effects which are, for the most part, bound to intravenous administration of osmotic methods.

Summary

Referring to preceding experimental and clinical studies, the authors established that oral glycerol is a highly effective agent for the reduction of cerebral edema and cerebrospinal-fluid pressure.

Value, indications and lack of toxicity of oral doses employed are described briefly. The satisfying results obtained in neurosurgical cases before, during, and after surgery are reported.

Glycerol has also been used successfully for the management of problems of increased intracranial and intraocular pressure.

It appears that oral glycerol represents a true step forward in neurosurgery since it affords the following advantages:

1) Promptness and intensity of action in reducing intracranial hypertension.

2) Possibility of repeating administrations, without secondary "rebound overshoot."

3) Lack of toxicity.

References


5. Ferber, J., and Rabinowitsch, S. Cited by Hanke.1

6. Hanke, M. E. The physiological action of gly-
Glycerol for Reduction of Intracranial Pressure


11. Nicloux, M. Cited by Hanke.⁴

12. Plosz, P. Cited by Hanke.⁴


