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## *Hyperosmotic agents in glaucoma*

*Allan E. Kolker*

*Hyperosmotic agents lower intraocular pressure by creating an osmotic gradient between the blood and the ocular fluids. Factors affecting the osmotic gradient are described. The currently used hyperosmotic agents are discussed, and the advantages and disadvantages of each are mentioned. Oral glycerol is the agent of choice in most cases of glaucoma, but it may produce nausea and vomiting in many patients. Isosorbide, a new hyperosmotic drug, tends to have fewer side effects than glycerol. Mannitol remains the most effective intravenously administered hyperosmotic agent. These drugs are of greatest value in the acute glaucomas and make the management of these diseases much safer and more effective.*

**T**he widespread use of hyperosmotic agents during the past decade represents a significant therapeutic contribution to

the management of acute glaucoma. Acute angle-closure glaucoma, in particular, while still a serious ocular emergency, has become far safer to manage as a result of these drugs. The necessity to operate on an eye with markedly elevated intraocular pressure has all but been eliminated. Effective hyperosmotic agents are available for both oral and intravenous use. Unfortunately, all of these drugs may have side

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From the Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine, St. Louis, Mo.

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effects which can be serious and even potentially fatal. Intelligent use of these drugs demands a thorough understanding of the factors affecting their actions.

Hyperosmotic agents lower intraocular pressure by creating an osmotic gradient between the blood and the ocular fluids. Rapidly increasing the blood osmolality by some 20 to 30 mOsm. per liter results in loss of water from the eye to the hyperosmotic plasma. This transfer of water from the eye to the circulation is manifested by a decrease in the intraocular pressure. The amount of this fall in pressure is dependent upon the degree of its elevation and the osmotic gradient induced. Transfer of a given volume of water will have a much greater effect on an eye with high pressure than on an eye with normal intraocular pressure. If previously occluded trabecular outflow channels are also opened, such as may occur in angle-closure glaucoma, the fall is further markedly enhanced and prolonged.

#### Factors that determine the osmotic gradient

Factors affecting the osmotic gradient are summarized in Table I.<sup>1</sup>

**Molecular weight and concentration.** Since the change in blood osmolality depends upon the number of milliosmoles of substance administered, agents with low molecular weight have a potentially greater effect than large molecular weight compounds at the same dosage. For example, 1 Gm. per kilogram of urea (molecular weight 60) to a 70 kilogram patient represents almost 1,200 mOsm. The same

dose of mannitol (molecular weight 182) represents less than 400 mOsm. As pointed out below, however, other factors also contribute to the osmotic gradient, such that the dose of these 2 agents is about the same.

Most osmotic agents are administered as solutions, the osmolality of which is directly proportional to the concentration. Drugs with low solubility require larger volumes of solution, with subsequently less effect on blood osmolality.

**Distribution in body water.** Agents confined to the extracellular fluid space (e.g., mannitol) produce a greater effect on blood osmolality at the same dosage than do agents distributed in total body water (e.g., urea). Thus, urea requires 2 to 3 times the dosage (in milliosmoles) of mannitol to produce the same osmotic gradient.

**Ocular penetration.** Agents which enter the eye rapidly produce less of an osmotic gradient than those which penetrate slowly or not at all. It should also be noted that ocular permeability to some agents is greatly increased when the eye is inflamed and congested. This is particularly true of urea.<sup>2</sup>

**Dose of agent and weight of recipient.** The ultimate change in blood osmolality depends upon the total dose given, as well as the weight of the patient. Because of a "balancing out" of many factors, such as those previously noted, most hyperosmotic agents currently used are effective at a dose in the range of 1 to 2 Gm. per kilogram.

**Method of administration.** Agents administered intravenously bypass absorption from the gastrointestinal tract and, therefore, tend to produce a more rapid and greater osmotic gradient than orally administered agents. When intravenous administration is used, a rate of 60 to 100 drops per minute is recommended.

**Rate of excretion.** Most hyperosmotic agents are excreted rapidly in the urine. Some, such as glycerol and alcohol, are also metabolized. The more rapidly an agent is cleared from the circulation, the

**Table I.** Factors in determining osmotic gradient

Molecular weight and concentration
Dose used
Rate and method of administration
Rate of excretion
Distribution in body water
Ocular penetration
Nature of diuresis

less effect it will have on osmolality and intraocular pressure.

**Nature of diuresis.** Most osmotic agents induce a considerable diuresis. When the excreted urine is hypoosmotic, as in the case of alcohol, the diuresis can considerably increase the blood osmolality in excess of the serum alcohol concentration.

Two additional factors regarding hyperosmotic agents should be emphasized—blood-vitreous gradient and pressure rebound.

**Blood-vitreous gradient.** As noted above, some agents enter the eye more readily

than others, especially the inflamed eye. Ethyl alcohol, for example, enters the aqueous rapidly, and yet effectively lowers intraocular pressure. The major reason for the effectiveness of alcohol, as well as other hyperosmotic agents which enter the eye, lies in the fact that penetration into the avascular vitreous is relatively slow. Thus, a blood-vitreous gradient is created and water moves from the vitreous into the circulation, with resultant decrease in intraocular pressure. The gradient may be greater and more prolonged with those agents that do not enter the eye (e.g.,

**Table II.** Intravenous hyperosmotic agents in common use

Agent	Molecular weight	Usual dose (Gm./Kg.)	Distribution	Ocular penetration	Advantages	Disadvantages
Urea	60	1-2†	Total water	Good	Rapid action, non-metabolized, less cellular dehydration, low molecular weight	Unstable, penetrates eye, slough and phlebitis, more rebound diuresis
Mannitol	182	1-2‡	Extracellular	Very poor	Rapid action, stable, nonmetabolized, less irritating, penetrates eye poorly	Larger volume, cellular dehydration, diuresis
Ascorbate	198*	0.5-1‡	Total water	Good	Rapid action, less diuresis	Penetrates eye, unstable

\*1 mOsm. = 99 mg.  
†30 per cent solution.  
‡20 per cent solution.

**Table III.** Oral hyperosmotic agents in common use

Agent	Molecular weight	Usual* dose (Gm./Kg.)	Distribution	Ocular penetration	Advantages	Disadvantages
Glycerol	92	1-1.5	Extracellular	Poor	Less diuresis, penetrates eye poorly, stable	Nausea and vomiting, calories, diabetes, slower pressure fall than intravenous
Isosorbide	146	1-2	Total water	Good	Well tolerated, no caloric value, rapid absorption, stable, nonmetabolized	Penetrates eye (slowly), slower pressure fall than intravenous
Alcohol	46	0.8-1.5	Total water	Good	Rapid absorption, readily available, stable, palatable, hypotonic diuresis	Nausea and vomiting, calories, diuresis, penetrates eye rapidly, CNS effects, slower pressure fall than intravenous

\*Usually given in 50 per cent solution.

mannitol), provided they are retained in the blood.

**Pressure rebound.** The creation of a blood-vitreous gradient explains the movement of water from the eye into the blood. Such transfer of water increases the osmolality of the vitreous, so as to approach that of the blood. As the hyperosmotic agent is cleared from the circulation, the osmolality of the blood may fall below that of the vitreous. The vitreous, now hyperosmotic, draws water *into* the eye with resultant increase in intraocular pressure. In glaucoma, this may result in a pressure rebound unless the cause of the elevated pressure has been relieved during the period of hypotony (e.g., by relief of angle closure).

The hyperosmotic agents presently employed for intravenous administration are described in Table II.<sup>3-5</sup> Sodium ascorbate becomes ionized in solution, and therefore provides 2 mOsm. for each milliosmole given. The advantages and disadvantages of these agents are also listed in Table II. Thus, urea has several properties, such as low molecular weight and greater solubility, which make it a good hyperosmotic agent. Counterbalancing these are the disadvantages of ocular penetration, especially when the eye is inflamed, instability of the solution requiring preparation just before use, and the potential risk of skin slough if the solution extravasates. At the present time, mannitol appears to be the drug of choice for intravenous administration.

The more frequently employed oral drugs are described in Table III,<sup>6-10</sup> along with the advantages and disadvantages of each. All orally administered drugs tend to be somewhat slower in their action than the intravenous drugs. They are also safer. Glycerol is presently most often used and is a very effective hyperosmotic agent. Its main disadvantage is the frequency with which it induces nausea and vomiting. This constitutes a distinct problem in the therapy for acute glaucoma and an even greater disadvantage for preoperative use. In addition, glycerol must be used with caution

in diabetic patients since it often produces hyperglycemia. Isosorbide appears to represent a potentially very useful hyperosmotic drug which is reasonably palatable, rarely induces nausea or vomiting, and comes prepared as a 50 per cent stable solution which can be kept in the office until needed. Its actions are similar to those of glycerol, and its side effects are less.<sup>11</sup> Ethyl alcohol is rarely employed therapeutically, but certainly can be used in an emergency situation in the form of straight scotch or bourbon whiskey. Inhibition of antidiuretic hormone production by alcohol produces a hypotonic diuresis, resulting in a more prolonged and greater blood hyperosmolality. This increases the duration of effect of alcohol compared to other hyperosmotic drugs.

#### Clinical use<sup>12</sup>

**Angle-closure glaucoma.** In the therapy of glaucoma, hyperosmotic agents are of greatest value in acute angle-closure glaucoma. Many ophthalmologists keep oral glycerol in their offices for use in such cases. Glycerol, 1 ml. per kilogram, in an equal volume of either fruit juice or cola drink, along with topical miotics, will terminate most attacks of acute angle-closure glaucoma. Isosorbide can also be used in doses of about 2 Gm. per kilogram. If the patient is vomiting, intravenous mannitol should be administered as soon as he arrives at the hospital. A dose of 1 Gm. per kilogram, given over a period of 30 to 60 minutes, will lower intraocular pressure in almost all patients. Lower doses are frequently sufficient, and the administration should be stopped when the pressure has fallen and the pupil has become miotic. Once the acute attack has terminated, iridectomy becomes a much safer and often a curative procedure. If the eye is markedly congested, it is often best to postpone iridectomy for several days, as long as the intraocular pressure remains normal. Prophylactic iridectomy in the opposite eye can be performed during this interval.

**Secondary glaucoma.** In the secondary glaucomas, hyperosmotic agents are valuable preoperatively or as a means of controlling pressure and preventing damage until the underlying disease process can be controlled. Surgery for lens-induced glaucoma becomes much safer when performed at normal intraocular pressures following osmotic therapy. The glaucoma occurring after blunt trauma will frequently subside spontaneously after several days, but may be uncontrollable until then. Oral hyperosmotic agents have been given daily, or even up to 3 times daily, for periods of several weeks without complications. In these instances, to avoid the large caloric value of glycerol or alcohol, isosorbide has distinct advantages. In markedly inflamed eyes and in hemorrhagic glaucoma, oral glycerol or intravenous mannitol are preferable, since they penetrate the eye poorly. Surgery for traumatic hyphema with secondary glaucoma is often avoided when hyperosmotic agents are given. Clearing of the hyphema and normalization of pressure are frequently seen following oral glycerol or intravenous mannitol. The phenomenon of "pressure rebound," discussed earlier, may be important in these instances. It is seen less often when glycerol or mannitol is used than when the other hyperosmotic agents are employed.

**Malignant glaucoma.** This rare form of secondary glaucoma, which follows glaucoma or cataract surgery, deserves special mention.<sup>13</sup> In addition to lowering intraocular pressure, the action of hyperosmotic agents on the vitreous becomes vital in the therapy of malignant glaucoma. As water is transferred from the vitreous to the circulation, vitreous volume is decreased and the vitreous face moves posteriorly. The use of strong cycloplegics (3 per cent atropine) will usually break posterior synechias and dilate the pupil. This permits communication between the anterior and posterior chambers, and usually terminates the glaucoma. In the phakic eye, atropine tightens the zonules and pulls the

iris-lens diaphragm posteriorly, thereby tending to open the anterior chamber angle. Most cases of malignant glaucoma can be relieved in this fashion.

**Open-angle glaucoma.** Hyperosmotic agents prove most useful in open-angle glaucoma as a means of lowering intraocular pressure prior to surgery. Recently, Virno and associates<sup>14</sup> and Bietti<sup>15</sup> have described the use of oral ascorbic acid, in doses of 0.5 Gm. per kilogram per day, divided into 4 doses, in the treatment of primary open-angle glaucoma. The drug appears to be effective when administered in this fashion, and no serious side effects are reported after daily use up to 6 months. Unfortunately, this requires taking up to 70 to 80 tablets of ascorbic acid per day. In addition, many patients develop gastrointestinal irritation and diarrhea with this amount of medication. Linnér,<sup>16</sup> using oral doses of ascorbic acid of 2 Gm. daily or a 10 per cent solution 3 times daily, found a slight but significant fall of about 1.1 mm. Hg in intraocular pressure in ocular hypertensives. His data suggest a slight reduction in the rate of aqueous formation as the mechanism. We<sup>17</sup> found no significant change in uncontrolled open-angle glaucoma patients when low doses of oral ascorbic acid were used. Gnädinger and Willome<sup>18</sup> also could find no significant effect on intraocular pressure with this dose. It is doubtful that hyperosmotic agents will be useful for long-term therapy of most cases of primary open-angle glaucoma.

#### Side effects

No discussion of hyperosmotic agents would be complete without mention of the side effects, which may be serious.<sup>19, 20</sup> The reported side effects and complications of these drugs are listed in Table IV.

Headaches, nausea, and vomiting are the most frequent side effects and may be hazardous when the drugs are used preoperatively. Compazine, 10 mg. given intramuscularly 30 to 45 minutes before preoperative glycerol, will usually avoid

**Table IV.** Side effects of hyperosmotic agents

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Headaches and back pain
Dehydration
Nausea and vomiting
Vertigo, chills
Agitation and disorientation
Chest pain, congestive failure, pulmonary edema
Diuresis—urinary retention
Vitamin K deficiency
Subdural hematoma

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this complication. Its use, however, adds to the potential side effects inherent when still another drug is administered. The intense diuresis that follows many hyperosmotic agents may lead to urinary retention requiring catheterization. Pulmonary edema and congestive heart failure may be precipitated in elderly patients with borderline cardiac and renal status. This is especially true of mannitol. Being confined to the extracellular fluid space, mannitol greatly increases blood volume and may overload the cardiac reserve. Cellular dehydration, including cerebral dehydration with resultant disorientation, may also occur more often with mannitol than with the other agents.

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