

THE USE OF MANNITOL IN NEUROSURGERY AND NEURO-OPHTHALMOLOGY

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Hyperosmolar agents for intracranial hypertension started to be used in the early 20th century and they still are an important component of the management of the treatment of patients with cerebral edema. Among these, mannitol is the most commonly used intraoperative hypertonic solution in patients undergoing brain surgery. In this paper, we discuss the current evidence for the use of mannitol in neurosurgery and neuro-ophthalmology, with focuses on its pharmacokinetics and its main physiologic effects.

Keywords: mannitol, cerebral edema, osmotic, intracranial hypertension, glaucoma, ocular pressure, brain surgery

INTRODUCTION

There is a huge interest in discovering new natural compounds that have promising neuroprotective and anti-inflammatory activity.¹⁻⁵

Since it was first used in 1940 for exploring the glomerular filtration rate in humans,⁶ mannitol has been increasingly used in medicine, as hypertonic solution in the treatment of intracranial and intraocular hypertension or as diuretic in crush injury, compartment syndrome or salicylate, bromide or barbiturate poisoning.⁷

Included in the World Health Organization model list of essential medicines,⁸ mannitol is considered a safe and important medication for elevated intracranial pressure (ICP). Due to its osmotic properties, it is currently used in medicine, as well as in the pharmaceutical and food industries.

PHARMACOLOGY

Mannitol (C₆H₁₄O₆) (Fig. 1) is a naturally occurring 6-carbon sugar alcohol, an isomer of

sorbitol, produced by a few microorganisms and plants.⁹ Mannitol naturally occurs in fresh mushrooms, figs, larches, yeasts, olives, marine algae and in the exudates from trees, especially from manna ash (*Fraxinus ornus*).⁹⁻¹⁵ It is synthesized by the hydrogenation of specialty glucose syrups and it is available in a variety of white crystalline powder and granular forms, which are water soluble.⁹ It is a non-hygroscopic substance, poorly soluble in water and stable at temperatures above 160 °C.¹⁶

MANNITOL PRODUCTION

Mannitol may be produced by catalytic hydrogenation of sucrose, fructose or a glucose-fructose mixture or by fermentation and extraction from seaweed.^{10,12,17} Both mannitol and sorbitol are produced during hydrogenation, which are then separated based on their solubility. The efficiency of the hydrogenation process is

low, since the result is a mixture with only 25%

mannitol, which requires purification.¹⁶

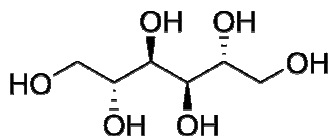


Figure 1: Chemical structure of mannitol

In 2005, whereas over 70% of the mannitol produced in China was extracted as a by-product of alginate and iodine production from seaweed,¹⁸ the rest of the world produced mannitol (50,000 tons/year) by industrial means, namely by hydrogenation of 50% fructose/50% glucose syrups at high 70-140 atmosphere pressure and high 120-160 °C temperatures, by using Raney nickel catalyst and hydrogen gas.^{19,20} In this reaction, glucose is hydrogenated into D-sorbitol, while fructose is hydrogenated into a mixture of D-sorbitol and D-mannitol, yielding a 30% mannitol - 70% sorbitol mixture. Mannitol is then purified by chromatography to remove the metal catalyst, followed by a low-temperature crystallization to separate it from sorbitol.^{12,20} Unfortunately, this chemical hydrogenation process has several drawbacks, such as the costly chromatographic purification step, the need for highly purified substrates and the high reaction temperatures and pressures.²¹ Also, the final result is a poor mannitol yield, with only approximately 15% crystalline mannitol, and in this process, mannitol is the only by-product in a reaction that produces mostly sorbitol; this makes mannitol production dependent on the sorbitol market and price.¹²

Various authors have lately proven that heterofermentative lactic acid bacteria are able to convert D-fructose into D-mannitol under mild conditions,²¹⁻²⁵ whereas cyanobacteria have been considered a mannitol producer.²⁶

PHYSICAL AND CHEMICAL PROPERTIES

Mannitol is about half as sweet as sucrose and it is therefore preferred in the food industry to mask bitter tastes.⁹ Mannitol is also considered a sweetening food additive and has been approved by the European Union and labeled as E421 according to the European legislation.¹⁶ When mannitol is added, this should be mentioned on

the package, since when eaten in excessive amounts, it may have laxative effects, due to slower and incomplete digestion.²⁷⁻²⁹

Low mannitol hygroscopicity makes it useful for products that require stability at high humidity, and since it has no reaction with active components in drugs, it is used as a pharmaceutical formulating agent.^{20,23,30}

Mannitol solutions are acidic (pH 6.3) and therefore sodium bicarbonate is added in solutions used in medicine for pH adjustment.⁹ Mannitol may crystallize at room temperature, but it can be made soluble again by warming the solution.⁹ The osmolarity of hypertonic mannitol (20%) is approximately equivalent to that shown by 3.2% hypertonic saline.³¹ The physical and pharmacokinetic properties of mannitol are shown in Table 1.

Mannitol is used in a wide variety of solutions ranging from 5% g/100 mL to 25% g/100 mL with an osmolality between 274 and 1.372 mOsm/L,³² (Table 2), whereas for clinical use, mannitol may be found in sterile 10% and 20% solutions in a 500 mL bag of water containing 50 and 100 g of mannitol, respectively.⁹

BIOLOGICAL PROPERTIES

Due to its low molecular weight (182 Da), mannitol is filtered in the glomeruli and reabsorbed in the nephron as an osmotic diuretic.³³ However, since it is not absorbed, mannitol continues to be osmotically active in the tubules, and this explains its action as diuretic osmotic. It does not undergo biotransformation.³⁴

After oral administration, mannitol is partially absorbed. About 25% is absorbed in the small intestine, whereas the unabsorbed fraction of 75% undergoes fermentation by the intestinal flora,^{10,12,21,29} and the main products of bacterial fermentation are organic acids.³⁵

Table 1
Physical and pharmacokinetic properties of mannitol^{16,36,58,115-117}

Characteristic	Description
Molecular weight	182 Daltons
Osmolarity (20%)	1098mOsm/L
Volume of distribution	0.471 L/kg
Onset	about 15 min
Maximal effect	about 45 min
Duration	about 6 h
Half-life	70-100 min
Biotransformation	None
Excretion	Renal
Reabsorption	7%
Sweetness ^a	0.5-0.7
Caloric value [kcal/g] (EU)	2.4
Heat of solution	-29
Viscosity at 25 °C	low
Hygroscopicity	low

^asucrose sweetness = 1

Table 2
Comparison of mannitol and different concentrations of hypertonic saline³⁴

Solution	Sodium concentration (mmol L ⁻¹)	Osmolarity (mOsm L ⁻¹)	Equiosmolar dose mL (275 mOsm)	Dose (mL kg ⁻¹) for 80 kg person
NaCl 0.9%	154	308	892	11
Ringer's lactate	130	275	1000	12.5
Saline 1.7%	291	582	472	5.9
Saline 3%	513	1027	268	3.4
Saline 5%	856	1711	161	2
Saline 7.5%	1283	2566	107	1.3
Saline 10%	1712	3424	80	1
Saline 30%	5000	10.000	27.5	0.34
Mannitol 10% (1 g mL ⁻¹)		549	502	6.3
Mannitol 20% (2 g mL ⁻¹)		1098	251	3.1

When administered intravenously, mannitol distributes primarily in the extracellular compartment and is excreted unchanged in urine.^{36,37} Therefore, 90% of the injected dose is recoverable in urine within the first 24 hours.^{37,38}

Intraoperative pharmacokinetic studies have shown that plasma half-life of mannitol is 2.2-2.4 h.^{39,40} Its action begins 15-20 min after its administration and its peak effect on the brain occurs 30 min after its administration and lasts 90 min to 6 h, depending on etiology.³³

USE OF MANNITOL IN NEUROSURGERY

In 1960, mannitol was first used by Scharfetter to decrease ICP,^{36,41,42} and it has since become the most commonly used intraoperative hypertonic solution.^{43,44}

Mannitol is an efficient means to lower ICP elevation (Class II)⁴⁵ and it is recommended in

acute intracranial hypertension when there are symptoms of transtentorial herniation (Class III).^{45,46} Thus, mannitol is the primary treatment for the control of cerebral edema and intracranial hypertension in patients with brain tumors, head trauma, stroke, subarachnoid hemorrhage or other lesions.⁴⁷⁻⁵³ For the comfort of both patients and doctors, its administration facilitates the resection of brain tumors and vascular malformations, thus reducing the need of brain retraction.^{41,54-56} Nevertheless, there is no evidence to guide the optimal dose or duration of treatment⁵⁷ and no ICP threshold has been set above which mannitol is recommended.³³

Although a 20% solution administered intravenously at a dose of 0.15-0.20 g/kg over 30-60 minutes used to be considered safe, doses up to 2 g/kg in a single administration may be currently used.^{37,42,58} The peak ICP effect of mannitol

occurs within 30-45 min and lasts about 6 hours.⁹ In case of multiple administrations, mannitol becomes less effective and may lead to unacceptably high serum sodium and osmolality, which may, in turn, result in an osmotic demyelination syndrome or other neurological complications.

USE OF MANNITOL IN OPHTHALMOLOGY

Osmotic agents were used in ophthalmology to soften the eye prior to surgery as early as 1904 by Contonnet.^{59,60} He used hypertonic sodium chloride for the same procedure, while magnesium sulfate, sorbitol, glycerol, urea and mannitol were used as ocular hypotensive substances.⁵⁹ Since then, mannitol has been used as hypertonic intravenous solution to reduce intraocular pressure.⁶¹ The ocular hypotensive effects of mannitol are useful in different ophthalmological diseases, such as acute angle-closure glaucoma, chronic open angle glaucoma and different forms of secondary glaucoma or before intraocular surgery to reduce eye pressure.⁶¹

Mannitol is a solute in the intravascular space, which increases the tonicity of the blood plasma. The increased tonicity of the blood plasma draws water out of the vitreous humor of the eye and into the intravascular space and decreases the intraocular pressure.^{62,63}

For ocular hypertension, the dosing of mannitol usually ranges from 0.25 g/kg to 2 g/kg administered intravenously over 30 to 60 minutes, the effect appearing within 5 to 10 minutes and lasting up to approximately 6 hours.^{62,63} 100 mL of mannitol administered 30-60 minutes before surgery decreases eye pressure and increases the depth of the anterior chamber of the eyeball. Rebound rise in intraocular pressure does not occur within the first two hours.⁶⁴

Smith *et al.*⁶⁵ studied the reduction of intraocular pressure in normotensive and glaucomatous eyes along with blood osmolality using mannitol solution and the results were the following: in normotensive eyes, the reduction of ocular tension was achieved in a percentage of 48% (average fall about 8 mm of Hg) and 52% in glaucomatous eyes with the return of intraocular pressure to its initial value between 2½ and 4½ hours from the time of the initial reading.^{59,65} In the same way, Weber *et al.* published a retrospective study on 28 subjects and found that the volume of the eyeball decreases after

intravenous administration of mannitol, while orbit volume increases when intraocular pressure normalizes.⁶⁶

In 2019, Ramachandra *et al.* published a prospective comparative study on two patient groups (30 eyes in each group), in which IOP \geq 40 mmHg. Mannitol (20%, 1 g/kg) was administered intravenously after 30 minutes and IOP was recorded at 30-minute intervals up to 2 hours and after three or four hours since the mannitol was administered to the two groups of patients (group 1 – vitrectomized and silicon-oil filled eyes; group 2 – non-vitrectomized open-angle eyes). The study concluded that mannitol significantly reduces IOP in both vitrectomized and non-vitrectomized eyes.⁶⁷

The cardiac function must be monitored when mannitol is administered, as the fluid shifts can precipitate heart failure. Additional electrolytes, including sodium, potassium, and osmolality should be monitored and it should be stopped if significant electrolyte abnormalities develop and osmolality reaches 320 mOsm or higher.⁶⁸

PHARMACOKINETICS

Unfortunately, the pharmacokinetics of mannitol is largely descriptive,⁶⁹ since the traditional biexponential 2-compartment model has been described in several studies on animals and humans,^{40,70-72} which predisposes to Type II errors, and moreover, the influence of covariates on kinetics has not been accurately assessed.⁶⁹ From the pharmacokinetic viewpoint, osmotic perturbation is the single most important determinant of mannitol pharmacologic behavior.⁶⁹ Consequently, it has been proven that the mannitol administration method (short and long-term infusion) and its concentrations (10%, 20% and 30%) influence the pharmacokinetic parameters.⁶⁹ Moreover, the relation between plasma mannitol concentrations and ICP is multifactorial, since serum osmolality is determined not only by plasma mannitol concentrations, but also by other serum electrolytes, osmolytes and the concomitant volume shifts.^{73,74}

MECHANISMS OF ACTION

Mannitol acts in a biphasic fashion in reducing ICP. Initially, in the first stage, mannitol improves blood dynamics (rheology), especially by reducing blood viscosity. This occurs by reducing red cell rigidity, which improves red cells passage through small blood vessels independent of

hematocrit.⁷⁵ However, this effect disappears 4 hours after its administration.⁷⁶

Mannitol also increases intravascular volume due to increased plasma osmolality, as well as increasing cardiac output.⁷⁷ Compensatory cerebral vasoconstriction occurs in response to reducing viscosity and intravascular volume expansion, but only when the autoregulatory pathways are intact.⁷⁷ When autoregulation is impaired, the reduction in ICP may be modest or even absent. Thus, for instance, one may notice increased cerebral blood flow in areas of injured brain with impaired autoregulation, due to decreased blood viscosity.⁷⁶

In the second stage, ICP reduction occurs due to the fact that mannitol extracts water from the cerebral extracellular space into the intravascular compartment through the osmotic gradient between blood and brain, and this requires an intact blood-brain barrier to form an osmotic membrane.⁷⁶ Despite the controversial debates about where the volume is removed, prior studies have shown that both injured and uninjured tissues from traumatic brain injury contribute to the volume of water lost.^{76,78-80}

As concerns the mannitol action mechanisms on ICP lowering, Ravussin also emphasized the existence of three action mechanisms, as follows.⁸¹ (1) Mannitol directly improves cerebral perfusion pressure, as a result of the transient increase of the cardiac output that occurs during the first minutes of administration.⁸² When cerebral autoregulation is preserved, cerebral perfusion pressure increase leads to cerebral vasoconstriction, and therefore to cerebral blood volume diminution and also to reducing ICP. (2) Mannitol increases cerebrovascular resistance caused by reflex vasoconstriction of cerebral arterioles, after an initial improvement in cerebral blood flow. The effects of mannitol on cerebrovascular resistance are visible within minutes of administration, as a result of hypervolemia. This occurs as a consequence of cardiac output improvement, haemodilution and decrease of blood viscosity.^{45,81,83} These changes are followed by a fall in the cerebral blood volume, which eventually decreases ICP.⁸⁴ (3) Mannitol impacts cerebral blood volume directly, as it promotes a shift of water from the intracellular to the extracellular compartment, thus establishing an osmotic gradient between plasma and brain cells and thus improving cerebral edema.

In other words, mannitol decreases ICP by decreasing the overall water content of the brain and the cerebrospinal fluid volume, as well as by blood volume vasoconstriction.⁸⁴⁻⁸⁶ It also improves cerebral perfusion by decreasing viscosity and by modifying red blood cell rheology.⁸⁷ Due to these effects, mannitol has been reported to decrease cerebral edema, to decrease the extent of cerebral infarction and neurologic deficit, in several experimental models of ischemic stroke, especially when it is administered within six hours after stroke onset.⁸⁸⁻⁹²

Mannitol also acts as a free-radical scavenger, which may limit the damage to neuronal mitochondria⁷ and decrease the risks associated with free radicals during ischemia-reperfusion injury.^{9,10,12,13,93-95}

ADVERSE EFFECTS

Repeated mannitol administration may cause a 'rebound phenomenon', an ICP increase, which precipitously rises back to an elevated level after initial response.⁷⁶ At first, some authors believed that this rebound phenomenon is a consequence of the fact that the osmotic agent leaks into injured brain parenchyma across a damaged blood-brain barrier, with the accumulation of mannitol in extracellular fluid and pulling water with it.^{9,85,96} In order to confirm this theory, Sankar *et al.* have proven *in vivo* mannitol accumulation within a meningioma and its peritumoral region, by means of magnetic resonance spectroscopy.⁹⁷

Nevertheless, it seems that the rebound phenomenon is more often related to osmotic compensation within the central nervous system, allowing for increased intracellular concentrations of electrolytes.⁷⁶ It seems that repeated administration of osmotic agents, especially in the setting of poor CNS compliance, promotes the rebound phenomenon.⁹⁸ This worsening of cerebral edema by multiple doses of mannitol has been also proven by experiments on cats.⁹⁹ Research on dogs has shown that after mannitol overdosing, CSF concentration increases 2 h after infusion.¹⁰⁰ Another research on rabbits has proven cerebral water content reduction, and also CSF osmolality increase 2 h after infusion.⁸⁶

Mannitol was associated with potentially serious electrolyte abnormalities, most notably hyperkalemia,^{43,55} especially when high doses of mannitol were administered (2.0 g/kg body weight),¹⁰¹ and several cases of post mannitol

hyperkalemia were also reported in literature.^{42,101-105} Other most common complications of mannitol therapy are cardiopulmonary edema,^{85,96} hypersensitivity reactions,¹⁰⁶ severe dehydration, progressive hyperosmolarity or hemolysis.⁶⁹ It is of particular interest to prohibit the use of mannitol in case of renal failure, a fact proven by several studies (Table 3). The effects of mannitol

on the renal profile are the following: profound natriuresis and diuresis, impairment of urinary concentration and dilution capacity, isometric tubular vacuolization, raised renal interstitial and intratubular pressures, increased extracellular fluid volume and changes in cortical and medullary blood flow.^{58,107-110}

Table 3
Main studies reported in literature on mannitol-induced acute renal failure (after Nomani *et al.*³⁷)

Author	Year	Patients with acute renal failure (n=)	Primary diagnosis	CNS insult
Kim ¹¹⁸	2014	153	Intracerebral hemorrhages	Yes
Fang ¹¹⁹	2010	53	Brain trauma	Yes
Chen ¹²⁰	2007	94	Subarachnoid hemorrhage	Yes
Gondim ¹²¹	2005	11	Intracerebral hemorrhages	Yes
Dziedzic ¹⁰⁹	2003	0	Intracerebral hemorrhages	Yes

Mannitol may be nephrotoxic due to several mechanisms, including dose-dependent vasoconstriction of the renal artery and intravascular volume depletion from osmotic diuresis.^{111,112} It may also cause kidney failure,^{38,113,114} since mannitol promotes urinary excretion of magnesium, potassium, bicarbonate and phosphate ions.^{7,34} (Table 3).

CONCLUSION

Since mannitol was noted to reduce brain edema almost a century ago, osmotic agents including mannitol have represented standard care in the management of intracranial hypertension, recommended by consensus guidelines. Nevertheless, further studies are necessary to achieve the ideal mannitol pharmacokinetic model.

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