

# Mannitol: a review of its clinical uses



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## Key points

Mannitol is a naturally occurring sugar alcohol used clinically primarily for its osmotic diuretic properties.

Mannitol is widely used in the management of cerebral oedema and raised intracranial pressure (ICP) from multiple causes.

Mannitol is used for renal protection in cardiac and vascular surgery and during renal transplantation and in the management of rhabdomyolysis.

There is minimal evidence to support the use of mannitol other than in the management of raised ICP.

Mannitol is widely used in the management of raised intracranial pressure (ICP), for renal protection in cardiac, vascular, and renal transplantation surgery, and in the management of rhabdomyolysis. It has also previously been used for bowel preparation before colorectal surgery. In this article, we discuss the current evidence for the use of mannitol in a variety of clinical situations.

## Pharmacology

Mannitol, chemically 1,2,3,4,5,6-hexanehexol ( $C_6H_8(OH)_6$ ), is a polyol (sugar alcohol) which is widely used in the food and pharmaceutical industries because of its unique functional properties (Fig. 1). In particular, it is about half as sweet as sucrose and, when taken orally, has a cooling effect which is considered desirable in masking bitter tastes. It is a naturally occurring substance found in marine algae, fresh mushrooms, and in the exudates from trees. It is an isomer of sorbitol, which is usually synthesized by the hydrogenation of specialty glucose syrups. Mannitol is available commercially in a variety of white crystalline powder and granular forms, all of which are soluble in water.

In addition to its use in the food and pharmaceutical industries, mannitol is also widely used in medical practice for a variety of indications (Table 1), primarily because of its osmotic properties (see below). For clinical use, it is supplied as sterile solutions of 10% and 20% in a 500 ml bag of water containing 50 and 100 g of mannitol, respectively. Mannitol solutions are acidic (pH 6.3) but proprietary preparations have sodium bicarbonate added for pH adjustment. Mannitol may crystallize if stored at room temperature but can be made soluble again by warming the solution.

Because of its low molecular weight (182), mannitol is freely filtered through the renal tubules. However, as it is not reabsorbed, it continues to be osmotically active in the

tubules and this accounts for its action as an osmotic diuretic. Mannitol also causes release of renal prostaglandins that lead to renal vasodilation and an increase in tubular urine flow that is believed to protect against renal injury by reducing tubular obstruction. It also acts as a free-radical scavenger and reduces the harmful effects of free radicals during ischaemia–reperfusion injury. The relevant actions of mannitol in specific clinical scenarios are discussed in more detail below.

Mannitol has many side-effects including initial volume expansion (increasing the risk of heart failure), subsequent hypovolaemia and hypotension, metabolic acidosis, and electrolyte imbalance, including hypernatraemia and hypokalaemia. In large doses, it can also cause renal failure because of intra-renal vasoconstriction and intravascular volume depletion. Repeated administration may result in unacceptably high serum osmolality ( $>320$  mOsm litre<sup>-1</sup>) and subsequent neurological complications. A comprehensive list of side-effects is given in Table 2.

## Raised ICP

Osmotherapy has been the cornerstone of the medical management of cerebral oedema, irrespective of its aetiology, for decades, and mannitol is the most widely used agent.<sup>1</sup> Although there has never been a randomized comparison of mannitol with placebo, both the Brain Trauma Foundation and the European Brain Injury Consortium identify level II and III evidence to support its use for the treatment of intracranial hypertension after traumatic brain injury (TBI). In a survey conducted in 1996, 100% of neurosurgical units in the UK used mannitol during the treatment of intracranial hypertension.

Mannitol exerts its ICP-lowering effects via two mechanisms—an immediate effect because of plasma expansion and a slightly delayed effect related to its osmotic action. The early

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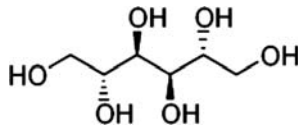
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**Fig 1** Structural formula of mannitol.

**Table 1** Medical uses of mannitol

|                                                                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------|
| Reduction in raised intracranial pressure                                                                                         |
| Preservation of perioperative renal function in patients undergoing major vascular and cardiac surgery and in those with jaundice |
| To promote diuresis and minimize the risk of acute renal failure in patients after renal transplantation                          |
| Preservation of renal function in rhabdomyolysis secondary to crush injuries and compartment syndrome                             |
| Bowel preparation before colorectal surgery, colonoscopy, and barium enemas                                                       |
| Promotion of urinary excretion of toxic materials                                                                                 |

**Table 2** Side-effects of mannitol

|                                                            |
|------------------------------------------------------------|
| Fluid and electrolyte imbalance—particularly hyponatraemia |
| Metabolic acidosis                                         |
| Heart failure                                              |
| Pulmonary congestion                                       |
| Hypovolaemia                                               |
| Hypotension                                                |
| Thrombophlebitis                                           |
| Skin necrosis if extravasation occurs                      |
| Allergic reactions, including anaphylaxis                  |
| Rebound increases in ICP                                   |

plasma expansion reduces blood viscosity and this in turn improves regional cerebral microvascular flow and oxygenation. It also increases intravascular volume and therefore cardiac output. Together, these effects result in an increase in regional cerebral blood flow and compensatory cerebral vasoconstriction in brain regions where autoregulation is intact, resulting in a reduction in ICP. Cardiac output may subsequently decrease to lower than baseline levels because of the peripheral vasodilatation induced by mannitol and care must be taken to ensure that cerebral perfusion pressure is maintained at this time. Mannitol also establishes an osmotic gradient between plasma and brain cells, drawing water from the cerebral extracellular space into the vasculature, thereby reducing cerebral oedema. An intact blood–brain barrier (BBB) is a prerequisite for mannitol's osmotic action and cerebral oedema may be worsened by mannitol administration if the BBB is disrupted.

Despite mannitol being the most commonly used osmotic diuretic in the emergency and intensive care management of intracranial hypertension, there is no evidence to guide the optimal dose and duration of treatment.<sup>2</sup> Management protocols therefore vary from unit to unit. The ICP effect of mannitol is dose-dependent and higher doses also provide a more durable reduction in ICP.<sup>2</sup> The current guidance recommends that 0.25–1.0 g kg<sup>-1</sup> mannitol should be given by i.v. infusion over 20–30 min.<sup>1</sup> Although doses up to 2 g kg<sup>-1</sup> were previously used, these have doubtful (if any) benefits compared with more conventional doses and are associated with a very high incidence of side-effects. The peak ICP effect of

mannitol occurs within 30–45 min and lasts around 6 h. Mannitol becomes less effective with repeated doses and, in any case, multiple administrations can result in an unacceptably high serum sodium and osmolarity that is associated with neurological complications, including osmotic demyelination syndromes. 'Rebound' increases in ICP can also occur after the initial reduction because of eventual passage of mannitol into the brain. This phenomenon can occur with any osmotic agent but appears to be particularly associated with mannitol administration.

Although the effectiveness of mannitol in controlling acutely raised ICP after TBI is well established, there is little evidence to support its prophylactic administration. Mannitol is most effective as a 'bridge' to definitive treatment, for example, to stabilize a patient before removal of an intracranial haematoma. In 2007, the Cochrane collaboration reviewed the use of mannitol after acute TBI and concluded that although it is effective in reversing acute brain swelling, its role in the ongoing management of severe TBI remains unclear.<sup>3</sup> There is no evidence to support a beneficial effect of mannitol beyond the acute phase of TBI. Mannitol administration on the ICU should therefore be guided by ICP monitoring and should be continued only as long as it effectively lowers ICP for a reasonable period of time and while the serum osmolarity remains <320 mOsm litre<sup>-1</sup>.

The application of alternative osmotic agents to mannitol, such as hypertonic saline (HS), has been explored. The effects of HS were first described by Weed and McKibbin in 1919, but it is only recently that evidence for their potential benefit in the management of intracranial hypertension has emerged. In addition to an osmotic action, HS has haemodynamic, vasoregulatory, immunological, and neurochemical effects.<sup>4</sup> In particular, HS relaxes arteriolar vascular smooth muscle and, in association with a reduction in cerebral endothelial cell oedema, improves cerebral microcirculatory flow. It also expands intravascular volume, thereby potentially augmenting cerebral perfusion pressure. Through these multiple actions, HS reduces cerebral oedema and ICP and improves cerebral blood flow and perfusion pressure.

There is some evidence that HS is effective at reducing raised ICP resistant to mannitol and that it has a more favourable effect than mannitol on mortality after TBI.<sup>3</sup> However, there are no large, randomized comparisons of HS against mannitol, or long-term functional outcome studies, proving its superiority.<sup>4</sup>

Continuous infusion and bolus administration of HS have been investigated as alternatives to mannitol to reduce brain swelling and ICP, particularly in the context of TBI.<sup>1–4</sup> However, HS is available in concentrations varying from 1.7% to 29.2% and different protocols for its administration have been described and tested in clinical studies. Three per cent saline is usually used for continuous infusion and 23.4% for bolus administration. There is no definitive evidence defining the optimal osmolar load or duration or timing of treatment for raised ICP.<sup>4</sup> It is important to monitor plasma sodium concentration during administration of HS, aiming for a value between 145 and 155 mmol litre<sup>-1</sup>. HS must be administered via a central venous catheter because of its potential

to cause thrombophlebitis. Side-effects include rebound increases in ICP, volume overload, coagulopathy, and electrolyte abnormalities, particularly hypernatraemia and hyperchloraemic metabolic acidosis.

## Renal protection

Mannitol has been promoted as a renal protective agent in patients at high risk of developing renal failure, such as those undergoing cardiac and vascular surgery, renal transplantation, and in patients with jaundice and rhabdomyolysis. However, the evidence overall suggests that although mannitol increases urine output, it does not reduce the risk of acute renal failure (ARF).

It is important to understand some basic aspects of renal physiology to appreciate the multifactorial pathophysiology of perioperative renal failure. The kidney receives about 20% of cardiac output but renal blood flow (RBF) is not distributed equally throughout the kidney. The renal cortex receives 90–95% of total RBF (equivalent to 500 ml 100 g<sup>-1</sup> min<sup>-1</sup>) and the medulla only 5–10%. Inner medullary blood flow is around five times lower than that in the outer medulla, making the inner medulla the most sensitive to hypoxic insults. Since 80–90% of renal oxygen consumption is utilized to drive active mechanisms (Na/K-ATPase) for solute and water reabsorption and the medulla is metabolically most active, it extracts around 80% of delivered oxygen. Additionally glomerular filtration rate (GFR) parallels RBF over a wide range and renal oxygen consumption is therefore directly proportional to RBF, rendering the kidney exquisitely sensitive to hypoperfusion.<sup>5</sup> Perioperative renal dysfunction therefore most commonly occurs because of acute tubular necrosis (ATN) secondary to hypoxic damage of medullary nephrons, usually because of hypotension, hypovolaemia, or dehydration. In addition, oxygen delivery to the renal medulla may be reduced during hypoxaemia, endothelial cell swelling, and sludging of cell debris and casts in the renal tubules.

There are several reasons why mannitol might be effective in preventing ATN and subsequent ARF. Since it is filtered by the kidneys but not reabsorbed, it remains in the renal tubules and causes an increase in the delivery of sodium to the distal tubules and a continued osmotic diuresis. This results in a 'flushing' effect within the tubules that may reduce the accumulation of necrotic cell debris and casts. Osmotic diuresis is not effective once complete tubular occlusion occurs so mannitol must be administered before the ischaemic insult to be effective. Animal studies have demonstrated that mannitol also improves RBF by changing the pressure–flow relationship within the kidneys, resulting in increased flow at similar levels of perfusion pressure. These changes occur through a variety of mechanisms including local production of vasodilating prostaglandins and a reduction in renin production. While intuitively it seems that a mannitol-induced improvement in RBF should be beneficial, the overall effect is not so straightforward because of the increased oxygen consumption that occurs secondary to higher rates of energy demanding tubular solute reabsorption related to the parallel increase in GFR.

Mannitol also reduces post-ischaemic endothelial cell swelling and decreases ischaemic–reperfusion injuries through scavenging of hydroxyl and other free radicals.

## Cardiac surgery

The incidence of ARF after cardiac surgery is around 5% and its development is associated with a mortality of 10–20%. It is particularly common when cardiopulmonary bypass times exceed 3 h. ARF requiring dialysis occurs in 1–2% of the patients after cardiac surgery and is associated with a higher mortality (up to 50–60%), prolonged intensive care and hospital lengths of stay, and higher overall costs of care. The mechanisms of renal dysfunction after cardiac surgery are multifactorial and include low cardiac output, hypovolaemia, embolic phenomena, pharmacological insults, and reperfusion injury. In addition, exposure to the cardiopulmonary bypass circuit initiates multiple processes, including complement activation and generation of free radicals and inflammatory mediators.

Mannitol is widely used as prophylaxis against ARF after cardiac surgery. Thirty-seven per cent of cardiac surgical centres in the UK include mannitol as part of the prime of the cardiopulmonary bypass circuits. However, recent studies suggest that although mannitol increases urine output, it has no effect on the incidence of ARF.<sup>6</sup> Mannitol cannot therefore be recommended as a prophylactic agent to protect against ARF in patients undergoing cardiac surgery.

## Major vascular surgery

Mannitol is also used for renal protection in major vascular surgery, especially during aortic surgery. Its potential beneficial effects are likely to occur because of the mechanisms discussed above and also from the temporary mannitol-related increase in intravascular volume and the resultant increase in cardiac output, RBF, and GFR.

For greatest efficacy, mannitol must be given before the ischaemic insult. A commonly used regime is the i.v. administration of 0.25–0.5 g kg<sup>-1</sup> of mannitol 10–20 min before aortic clamping, although there is no consensus guidance to support this recommendation. In addition, despite mannitol having been used during aortic surgery for over 30 yr, there is no clear evidence that it reduces the incidence of ARF.<sup>7</sup>

## Rhabdomyolysis

Rhabdomyolysis increases the risk of ARF, which is most likely to occur when creatine kinase levels increase to >5000 U litre<sup>-1</sup>. This risk can be reduced by early volume repletion and possibly also by forced diuresis with mannitol within 6 h of rhabdomyolysis. The benefits of mannitol are related to its effect in flushing out intratubular myoglobin casts, with free-radical scavenging, reduction in blood viscosity, and reno-vasodilation likely to be contributory.

There are several mannitol regimes described for the treatment of rhabdomyolysis. One recommends the i.v. administration of

12.5–25 g of mannitol every 6 h until the myoglobinuria resolves or until the serum osmolarity exceeds 320 mOsm litre<sup>-1</sup>. However, there are no well-designed studies that demonstrate an advantage of mannitol, either alone or in combination with other diuretics, over adequate hydration in improving urinary flow and prevention of myoglobin casts after rhabdomyolysis.<sup>8</sup>

### Renal transplantation

The major immediate postoperative complication after cadaveric renal transplantation is ARF secondary to ATN. It was previously believed that mannitol could reduce the incidence of post-transplantation ARF and thereby improve graft survival.<sup>9</sup> However, recent studies have confirmed that although mannitol given immediately before removal of the vessel clamps reduces the requirement for post-transplant dialysis, it does not improve long-term graft function in the absence of adequate hydration.<sup>10</sup> This might be explained by the fact that although mannitol temporarily increases intravascular volume, this beneficial effect is outweighed by the systemic and renal vasodilatation induced by mannitol. Although the routine use of mannitol over adequate hydration in renal transplantation is not supported by controlled clinical trials, it is the authors' practice, in common with that in other institutions, to administer mannitol 20 g 5 min before reperfusion of the transplanted kidney.

### Jaundiced patients

Clairmont and Von Haberer first linked renal dysfunction and obstructive jaundice in 1910, and many studies have been subsequently attempted to identify the causative factors. These are believed to include hyperbilirubinaemia, increased serum level of bile salts, endotoxaemia, renovascular fibrin deposition, and abnormal systemic and renal haemodynamics, including hypovolaemia. Although renal failure may be associated with any type of jaundice, it is particularly common after obstructive jaundice. The overall incidence of postoperative renal dysfunction in patients with obstructive jaundice is around 60% and it is associated with a high mortality rate. The risk of ARF increases as the serum bilirubin increases.

Several protocols involving fluid and mannitol administration, whether alone or in combination with other diuretics, have been described to prevent postoperative renal dysfunction in obstructive jaundice, but there is no additional benefit of mannitol over adequate hydration.<sup>11</sup>

### Preparation for bowel surgery

Mannitol is poorly absorbed from the gut and has been used as bowel preparation for elective colorectal surgery, colonoscopy, and double contrast barium enema and to facilitate intestinal removal of toxic substances. For bowel preparation, it is administered orally, usually the day before the procedure and must be accompanied by generous hydration.

The Cochrane group analysed 18 randomized controlled trials comparing bowel preparation with no preparation before elective colorectal surgery and identified no difference in the incidence of anastomotic leakage or wound infection.<sup>12</sup> Routine bowel preparation, including the use of oral mannitol, should therefore be eliminated from clinical practice.

### Summary

Mannitol is a standard of care for the management of intracranial hypertension and is recommended by consensus guidelines. There is little evidence to support its continued use for other indications, such as renal protection during cardiac and vascular surgery, or for prophylaxis against ARF in rhabdomyolysis and after renal transplantation, where adequate hydration appears to be effective.

### Declaration of interest

None declared.

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Please see multiple choice questions 29–32.