MANNITOL

(*man*-i-tole)

OSMOTIC DIURETIC

Prescriber Highlights

- Osmotic diuretic used for acute oliguric renal failure, to reduce intraocular & intracerebral pressures, to enhance urinary excretion of some toxins &, with other diuretics, to rapidly reduce edema or ascites (caution)
- Contraindications: Anuria secondary to renal disease, severe dehydration, intracranial bleeding (unless during craniotomy), severe pulmonary congestion, or pulmonary edema
- Halt treatment if progressive heart failure, pulmonary congestion, or progressive renal failure/damage develop
- Adverse Effects: Fluid & electrolyte imbalances, GI (nausea, vomiting), cardiovascular (pulmonary edema, CHF, tachycardia), & CNS effects (dizziness, headache, etc.)
- Adequate urine output, fluid, & electrolyte monitoring & treatment mandatory
- Be certain crystals are dissolved in solution before administering

Uses/Indications

Mannitol is used to promote diuresis in acute oliguric renal failure, reduce intraocular and intracerebral pressures, enhance urinary excretion of some toxins, (*e.g.*, aspirin, some barbiturates, bromides, ethylene glycol) and, in conjunction with other diuretics, to rapidly reduce edema or ascites when appropriate (see Contraindications-Precautions below). In humans, it is also used as an irrigating solution during transurethral prostatic resections.

Pharmacology/Actions

After intravenous administration, mannitol is freely filtered at the glomerulus and poorly reabsorbed in the tubule. The increased osmotic pressure prevents water from being reabsorbed at the tubule. To be effective, there must be sufficient renal blood flow and filtration for mannitol to reach the tubules. Although water is proportionately excreted at a higher rate, sodium, other electrolytes, uric acid, and urea excretions are also enhanced.

Mannitol may have a nephro-protective effect by preventing the concentration of nephrotoxins from accumulating in the tubular fluid. Additionally, it may minimize renal tubular swelling via its osmotic properties, increase renal blood flow and glomerular filtration by causing renal arteriole dilatation, decreased vascular resistance, and decreased blood viscosity.

Mannitol does not appreciably enter the eye or the CNS, but can decrease intraocular and CSF pressure through its osmotic effects. Rebound increases in CSF pressures may occur after the drug is discontinued.

Pharmacokinetics

Although long believed to be unabsorbed from the GI, up to 17% of an oral dose is excreted unchanged in the urine after oral dosing in humans. After intravenous dosing, mannitol is distributed to the extracellular compartment and does not penetrate the eye. Unless the patient has received very high doses, is acidotic, or there is loss of integrity of the blood-brain barrier, it does not cross into the CNS.

Only 7–10% of mannitol is metabolized, the remainder is excreted unchanged in the urine. The elimination half-life of mannitol is approximately 100 minutes in adult humans. Half-lives in cattle and sheep are reported to be between 40–60 minutes.

Contraindications/Precautions/Warnings

Mannitol is contraindicated in patients with anuria secondary to renal disease, severe dehydration, intracranial bleeding (unless during craniotomy), severe pulmonary congestion or pulmonary edema.

When using for increased CSF pressure, an intact capillary membrane is required for efficacy. If this membrane is disrupted, mannitol can leak into the brain interstitium and increase cerebral edema.

Mannitol therapy should be stopped if progressive heart failure, pulmonary congestion, progressive renal failure or damage (including increasing oliguria and azotemia) develops after mannitol therapy is instituted.

Mannitol is relatively contraindicated for treating secondary glaucomas, as it may cross the damaged "blood-aqueous barrier" and increase intraocular pressure (IOP).

Do not administer more than a test dose of mannitol until determining whether the patient has some renal function and urine output. Adequate fluid replacement must be administered to dehydrated animals before mannitol therapy is begun. Do not give mannitol with whole blood products, unless at least 20 mEq/L of sodium chloride is added to the solution or pseudo-agglutination may result.

Be certain any crystals in solution are redissolved before administering; an in-line IV filter is also recommended.

Adverse Effects

Fluid and electrolyte imbalances are the most severe adverse effects generally encountered during mannitol therapy. Adequate monitoring and support are imperative.

When used for oliguric renal failure, the potential exists for volume overload should oliguria persist.

Other adverse effects that may be encountered include GI (nausea, vomiting), cardiovascular (pulmonary edema, CHF, tachycardia), and CNS effects (dizziness, headache, etc.).

Reproductive/Nursing Safety

In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

It is not known whether this drug is excreted in milk, but it is unlikely that it would pose significant risk to nursing offspring.

Overdosage/Acute Toxicity

Inadvertent overdosage can cause excessive excretion of sodium, potassium, and chloride. If urine output is inadequate, water intoxication or pulmonary edema may occur. Treat by halting mannitol administration and monitoring and correcting electrolyte and fluid imbalances. Hemodialysis is effective in clearing mannitol.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving mannitol and may be of significance in veterinary patients:

- **LITHIUM**: Mannitol can increase the renal elimination of lithium
- **SOTALOL**: Mannitol's effects on potassium and magnesium may increase the risk for QT prolongation

Laboratory Considerations

- Mannitol can interfere with **blood inorganic phosphorus** concentrations and **blood ethylene glycol** determinations.

Doses

- **DOGS & CATS:**

For treatment of oliguric renal failure:

a) After correcting fluid, electrolyte, acid/base balance and determining that the patient is not anuric: Mannitol (20–25% solution) 0.25–0.5 gm/kg IV over 5–10 minutes. If diuresis occurs, may repeat q4–6 hours or administered as a constant infusion (8–10% solution) for first 12–24 hours of therapy. (Polzin 2005a)

b) After rehydration, but not fluid overloaded give mannitol at 0.25–0.5 gm/kg IV slowly over 5–10 minutes; repeat dose at 30–40 minute intervals up to 1.5 gm/kg total. Author prefers using furosemide for ARF. (Bersenas 2007)

c) In fluid replete animals: 0.5 gram/kg IV over 20–30 minutes; if significant diuresis is accomplished within 30 minutes, may administer as a CRI of 60–120 mg/kg/hr IV or as intermittent boluses repeated every 4–6 hours. Mannitol is contraindicated in patients who are still dehydrated, hypervolemic, or anuric. (Waddell 2007a)

d) After rehydration, give mannitol 0.5 gm/kg IV slowly; repeat dose at 15-minute intervals up to 1.5 gm/kg total. Urine production should begin within 15 minutes; monitor carefully for dehydration and give fluids as necessary to maintain balance. (Breitschwerdt 1988)

For adjunctive treatment of acute glaucoma:

a) Drug of first choice in the acute patient; 0.5–1 g/kg IV given over 15–20 minutes; withhold water for 3–4 hours. IOP reduction begins in 20–30 minutes and has a 4–6 hour duration of effect. Efficacy reduced in patients with anterior uveitis. (Wilkie 2002)

b) If latanaprost (*Xalatan®*) has not affected pupil size and started to reduce IOP after one hour, give mannitol (20%) at 1–2 g/kg IV over a period of 20 minutes and withhold water for 1–2 hours. Peak effect is about 90 minutes after administration. (Millichamp 2006)

For adjunctive treatment of increased CSF pressure/cerebral edema:

a) 0.5–1.5 g/kg IV over 10–20 minutes. Maximum effect occurs 10–20 minutes after administration and the effects last for 2–5 hours. May repeat every 6–8 hours based on clinical response and intracranial pressure monitoring. Do not use if patient hypovolemic. Monitor serum osmolality and electrolytes. (McDonnell 2004)

b) 0.25–1 gram/kg IV q4–6h as needed (Barton 2002b)

c) Secondary to trauma: 100–500 mg/kg slow IV, if a positive effect is seen, may repeat every 2 hours for 3 doses. Crystalloid infusion may need to be adjusted to prevent dehydration or hypovolemia. Furosemide at 0.75 mg/kg may be administered prior to mannitol to reduce CSF formation. (Rudloff 2006a)

d) Secondary to trauma: 0.5–1 gram/kg IV followed 20 minutes later by furosemide (1 mg/kg IV). Potential risk for worsening intracranial hemorrhage, but patients that are dying before your eyes can benefit from this aggressive therapy. (Mazzaferro 2007)

To measure glomerular filtration rate in dogs:

a) 1.1–2.2 grams/kg IV slowly over 15–30 minutes (McConnell and Hughey 1987)

- **CATTLE, SWINE, SHEEP, GOATS:**

For adjunctive treatment of cerebral edema:

a) 1–3 gm/kg IV (usually with steroids and/or DMSO) (Dill 1986)

As a diuretic for oliguric renal failure:

a) 1–2 gm/kg (5–10mL of 20% solution) IV after rehydration; monitor urine flow and fluid balance (Osweiler 1986)

- **HORSES:**

a) 0.25–2 gm/kg as a 20% solution by slow IV infusion (Schultz 1986)

Monitoring

- Serum electrolytes, osmolality
- BUN, serum creatinine
- Urine output
- Central venous pressure, if possible
- Lung auscultation

Client Information

- Mannitol should be administered by professional staff in a setting where adequate monitoring can occur.

Chemistry/Synonyms

An osmotic diuretic, mannitol occurs as an odorless, sweet-tasting, white, crystalline powder with a melting range of 165°–168° and a pK_a of 3.4. One gram is soluble in about 5.5 mL of water (at 25°C); it is very slightly soluble in alcohol. The commercially available injectable products have approximate pH's of 4.5–7.

Mannitol may also be known as: cordycepic acid, E421, manita, manitol, manna sugar, mannite, mannitolum, Eufusol M 20, *Am-Vet® Mannitol Injection 20%*, *Isotol®*, *Manicol®*, *Manniject®*, *Maniton®*, *Mannistol®*, *Mannit-Losung®*, *Mannite®*, *Mede-Prep®*, *Osmofundin 15% N®*, *Osmofundin 20%*, *Osmofundina®*, *Osmofundina® Concentrada*, *Osmorol®*, *Osmosteril® 20%*, *Resectisol®* and *Thomaemannit®*.

Storage/Stability/Compatibility

Mannitol solutions are recommended to be stored at room temperature; avoid freezing.

Crystallization may occur at low temperatures in concentrations greater than 15%. Resolubolization of the crystals can be accomplished by heating the bottle in hot (up to 80°C) water. Cool to body temperature before administering. An in-line IV filter is recommended when administering concentrated mannitol solutions. Alternatively, heated storage chambers (35°–50°C) have been suggested to assure that soluble product is available at all times. Microwaving glass ampules/vials has been suggested, but explosions have been documented and this procedure cannot be recommended. Supersaturated solutions of mannitol in PVC bags may show a white flocculent precipitate that will tend to reoccur even after heating.

Drugs reported to be physically **compatible** with mannitol include: amikacin sulfate, bretylium tosylate, cefamandole naftate, cefoxitin sodium, cimetidine HCl, dopamine HCl, gentamicin sulfate, metoclopramide HCl, netilmicin sulfate, tobramycin sulfate, and verapamil HCl.

Mannitol should not be added to whole blood products to be used for transfusion. Sodium or potassium chloride can cause mannitol to precipitate out of solution when mannitol concentrations are 20% or greater. Mannitol may be physically **incompatible** when mixed with strongly acidic or alkaline solutions.

Mannitol is reportedly stable when mixed with cisplatin for a short period of time, but advanced premixing of the drugs should be avoided because a complex may form between them.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Mannitol for injection 20%: 20 g/100 mL in 100 mL single-dose vials. *Am-Vet® Mannitol Injection 20%* (IVX); generic (Phoenix Pharm, Neogen); (Rx). Labeled for use in canine species.

Mannitol for Injection 18%: 180 mg/mL in 100 mL vials; *Mannitject®* (Butler); generic (Vedco); (Rx). Labeled for use in dogs

HUMAN-LABELED PRODUCTS:

Mannitol for Injection

Mannitol Injection: 5% (50 mg/mL; 275 mOsm/l) in 1000 mL;

10% (100 mg/mL; 550 mOsm/l) in 500 mL and 1000 mL;

15% (150 mg/mL; 825 mOsm/l) in 150 mL & 500 mL;

20% (200 mg/mL; 1100 mOsm/l) in 250 mL and 500 mL;

25% (250 mg/mL; 1375 mOsm/l) in 50 mL vials and syringes (12.5 grams/vial); generic; (Rx)

Mannitol Solution: Genitourinary Irrigants: 5 g/100 mL in distilled water (275 mOsm/L) in 2000 mL; *Resectisol®* (Kendall McGaw); (Rx)

MARBOFLOXACIN

(mar-boe-***flox***-a-sin) Zeniquin®

FLUOROQUINOLONE ANTIBIOTIC

Prescriber Highlights

- Veterinary oral fluoroquinolone antibiotic effective against a variety of pathogens
- Not effective against anaerobes
- Contraindications: Hypersensitivity to fluoroquinolones; Relatively contraindicated for young, growing animals due to cartilage abnormalities
- Caution: Hepatic or renal insufficiency, seizure patients, or dehydration
- Adverse Effects: GI distress; does not appear to cause ocular toxicity in cats
- Drug interactions

Uses/Indications

Marbofloxacin is labeled for the treatment of susceptible bacterial infections in dogs and cats.

Pharmacology/Actions

Marbofloxacin is a bactericidal agent. The bactericidal activity of marbofloxacin is concentration dependent, with susceptible bacteria cell death occurring within 20–30 minutes of exposure. Like other fluoroquinolones, marbofloxacin has demonstrated a significant post-antibiotic effect for both gram - and + bacteria and is active in both stationary and growth phases of bacterial replication.

Its mechanism of action is not thoroughly understood, but it is believed to act by inhibiting bacterial DNA-gyrase (a type-II topoisomerase), preventing DNA supercoiling and DNA synthesis.

Marbofloxacin has a similar spectrum of activity as the other veterinary commercially available agents. These agents have good activity against many gram-negative bacilli and cocci, including most species and strains of *Pseudomonas aeruginosa*, *Klebsiella* spp., *E. coli*, Enterobacter, Campylobacter, Shigella, Salmonella, Aeromonas, Haemophilus, Proteus, Yersinia, Serratia, and Vibrio species. Other organisms that are generally susceptible include *Brucella* spp., *Chlamydia trachomatis*, Staphylococci (including penicillinase-producing and methicillin-resistant strains), Mycoplasma, and *Mycobacterium* spp. (not the etiologic agent for Johne's Disease).

The fluoroquinolones have variable activity against most streptococci and are not usually recommended to use for these infections. These drugs have weak activity against most anaerobes and are ineffective in treating anaerobic infections.

Resistance does occur by mutation, particularly with *Pseudomonas aeruginosa, Klebsiella pneumonia,* Acinetobacter, and Enterococci, but plasmid-mediated resistance is thought to occur only rarely.

Pharmacokinetics

In dogs, marbofloxacin is characterized as being rapidly absorbed after oral administration with a bioavailability of 94%. Peak plasma levels occur in about 1.5 hours. Protein binding is low and the apparent volume of distribution is 1.2–1.9 L/kg. Elimination half-life averages 9–12 hours. The drug is eliminated unchanged in the urine (40%) and bile/feces. Only about 15% of a dose is metabolized in the liver.

In cats, absorption after oral dosing is nearly complete and peak serum levels occur about 1–2 hours post-dose. Terminal elimination half-life is about 13 hours.

Renal impairment does not significantly alter dosing requirements.

Contraindications/Precautions/Warnings

Like other quinolones, marbofloxacin is labeled as contraindicated in small and medium breed dogs up to 8 months of age, large breeds to 12 months old, and giant breeds to 18 months old. It is also labeled as contraindicated in cats under 12 months of age. Quinolones are also contraindicated in patients hypersensitive to them.

Marbofloxacin can (rarely) cause CNS stimulation and should be used with caution in patients with seizure disorders.

The FDA has prohibited the use of this drug in food-producing animals.

Adverse Effects

With the exception of potential cartilage abnormalities in young animals (see Contraindications above), the adverse effect profile of marbofloxacin is usually limited to GI distress (vomiting, anorexia, soft stools, diarrhea) and decreased activity.

Other fluoroquinolones have, in rare incidences, caused elevated hepatic enzymes, ataxia, seizures, depression, lethargy, and nervousness in dogs. Hypersensitivity reactions or crystalluria could potentially occur.

It is not known if marbofloxacin can also cause the ocular toxicity that has been reported with high dose enrofloxacin in cats. While unlikely, FDA's Adverse Drug Reaction database has received 14 reports (as of July 3, 2007) of blindness associated with marbofloxacin. Causal effect cannot be proven, but use higher dosages carefully.

Reproductive/Nursing Safety

Safety of marbofloxacin during pregnancy has not been established.

Overdosage/Acute Toxicity

It is unlikely an acute overdose of marbofloxacin would result in signs more serious than either anorexia or vomiting, but the adverse effects noted above could occur. Dogs receiving 55 mg/kg per day for 12 days developed anorexia, vomiting, dehydration, tremors, red skin, facial swelling, lethargy, and weight loss.