MONOGRAPH

Tobramycin (intravenous) Monograph - Paediatric

Scope (Staff):	Medical, Pharmacy, Nursing
Scope (Area):	All Clinical Areas

Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this DISCLAIMER

QUICKLINKS

DRUG CLASS

Aminoglycoside antibiotic.[1-3]

Tobramycin is a High Risk Medicine.

INDICATIONS AND RESTRICTIONS

Tobramycin is active against a broad range of gram-negative bacteria, including *Pseudomonas aeruginosa.* Tobramycin should be used in combination with other agents for serious gram-negative bacterial infections outside of the urinary tract as clinical outcome data for aminoglycoside use as monotherapy for systemic bacterial infections have indicated worse outcomes in some circumstances .[4, 5]

IV: Monitored (orange) antibiotic

As per indications stipulated in Formulary One. For any other use, phone approval must be obtained from ChAMP before prescribing as per the Children's Antimicrobial Management Program (ChAMP) Policy

CONTRAINDICATIONS

- Hypersensitivity to tobramycin, any aminoglycoside (e.g. gentamicin or amikacin) or any component of the formulation.[2, 3, 6]
- Previous vestibular or auditory toxicity due to an aminoglycoside.[2, 3]

PRECAUTIONS

- Use tobramycin with caution in patients with renal impairment .[3, 6]
- Use tobramycin with caution in patients with neuromuscular disease e.g. myasthenia gravis as the risk of muscle weakness and respiratory depression is increased.[2, 3, 7]
- Some brands contains sodium metabisulfite which may cause allergic reactions in susceptible people.[8]
- Clinically evident vestibular ototoxicity (nausea, vomiting, vertigo, nystagmus, difficulties with gait) and cochlear ototoxicity (noticeable hearing loss, tinnitus, a feeling of fullness in ear) occur in 2–4% of patients. Rates of both are higher if pure tone audiometry and electronystagmography are used to detect impairment (high frequency hearing loss in up to 26% of patients). Ototoxicity may be delayed in onset and is irreversible in about 50% of people; permanent deafness may occur.[3, 9]
- Ototoxicity can occur as an idiosyncratic reaction after single-dose aminoglycoside exposure in individuals who are genetically predisposed. Ototoxicity is more commonly the result of cumulative aminoglycoside exposure. Under certain circumstances, genetic testing *prior* to treatment with long course aminoglycosides or in children requiring repeated course may be considered following consultation with the infectious diseases team.[3, 7]

FORMULATIONS

Listed below are products available at PCH, other formulations may be available, check with pharmacy if required:

- 80 mg/2 mL Vial
- 500 mg/5 mL Vial (kept in Pharmacy Compounding Service (PCS) unit and used only for Hospital in the Home (HiTH) tobramycin IV doses - preservative free.)

Imprest location: Formulary One

DOSAGE & DOSAGE ADJUSTMENTS

Neonates: Refer to Neonatal Medication Protocols

Dosing in Overweight and Obese Children: Dosing should be based on adjusted body weight for overweight or obese children.[1, 5, 6, 9]

IV/IM:

General once daily dosing:

- **Children ≥ 4 weeks to < 10 years old:** 7.5 mg/kg/dose (to a maximum of 320 mg) ONCE daily.[1]
- **Children ≥ 10 years to < 18 years:** 6-7 mg/kg/dose (to a maximum of 560mg) ONCE daily.[1] The higher dose is only recommended for patients with septic shock and/or those requiring intensive care support.
- No further dose increases should be made without consulting Infectious Diseases or ChAMP.

Cystic fibrosis (CF) patients:

- **4 weeks to 18 years initial dose:** 10 mg/kg/dose (to a maximum of 660 mg) ONCE daily. The dose can be increased based on AUC calculations to a maximum of 15 mg/kg/dose or 750 mg ONCE daily (whichever is less).[1, 7, 9]
- For all CF patients with planned admission for treatment with tobramycin, the first dose should be charted for morning administration to allow for assessment of therapeutic drug monitoring on the first dose of tobramycin during business hours. If patients are admitted in the afternoon, the tobramycin should be commenced on the first morning of the admission – unless clinically unwell in which case refer to the Sepsis pathway.
- Consideration of the need for additional hydration should be given to ensure there is no dehydration following fasting for theatre prior to commencing tobramycin to reduce the risk of nephrotoxicity.

Inhalation:

Please refer to the separate Inhaled Tobramycin monograph.

Renal impairment:

- eGFR calculator
- Where possible, consider using a less nephrotoxic agent.
- Dosage adjustment may be required in cases of impaired renal function (with creatinine clearance of less than 60 mL/minute/1.73 m^2).[6]
- In patients with creatine clearance less than 60 mL/minute/1.73 m^2 a single dose may be administered with subsequent dosing based on therapeutic drug monitoring.[5, 7]

Hepatic impairment:

- No dosage adjustment is required.[6, 7]

ADMINISTRATION

NOTE: Inhalation formulations (e.g. Tobramycin 300 mg/5 mL solution for inhalation or Tobi Podhaler®) **MUST NOT** be administered via the intravenous or oral route.

IV Injection:

- The required dose may be diluted to a suitable final volume (up to 20 mL) with compatible fluid and administered over 3 to 5 minutes.[6, 8]

IV infusion:

- Dilute to a suitable volume (up to 100 mL) with compatible fluid to allow infusion over 20 to 60 minutes.[8, 10]

IM injection:

- If IV access is not available this medication may be given by IM injection undiluted into a large muscle mass. The IV route is preferred for patients with suspected shock or sepsis.[8, 10]
- IM injection is NOT suitable for premature neonates due to smaller muscle mass.[7]
- Refer to Intramuscular (IM) injections for further information.

COMPATIBILITY *(LIST IS NOT EXHAUSTIVE)*

Compatible fluids:

- Sodium chloride 0.9%
- Glucose 5%
- Glucose 10% (if final concentration of tobramycin is ≤ 6 mg/mL)
- Glucose/sodium chloride solutions (if final concentration of tobramycin is ≤ 6 mg/mL)
- Hartmann's[8, 10]

Compatible at Y-site:

Compatibilities of IV drugs must be checked when two or more drugs are given concurrently.

MONITORING

Therapeutic drug monitoring:

Monitoring for patients with normal pharmacokinetics:

- Trough level, with a paired creatinine level should be taken immediately prior to the 4th dose. The trough level should be below the limit of detection (<0.2 mg/L).
- If the trough level is greater than or equal to 0.2 mg/L, contact Pharmacy for advice as this indicates reduced clearance of tobramycin and cessation or dose adjustment may be required.
- Follow-up levels should be performed twice weekly unless the clinical situation dictates otherwise (e.g. impaired renal function and/or concurrent use of nephrotoxic drugs where levels should be collected more frequently).

Patients with altered pharmacokinetics:

- Includes patients with Cystic fibrosis, oncology patients, patients with significant trauma, patients in intensive care, patients with severe burns or patients with impaired renal function.[3]
- These patients should have therapeutic drug monitoring (TDM) completed with the **FIRST or SECOND** dose of tobramycin on initiation of therapy. For patients requiring dose adjustment, TDM should be collected with the **FIRST** dose of tobramycin following any dose adjustment.
- Monitoring should be based on calculating the drug concentration in the body relative to time, monitoring area under the curve (AUC).
- AUC measurement involves a mathematical calculation that requires the recording of the drug concentration at two specific times.
- Refer to the form MR860.91 Gentamicin and Tobramycin AUC reporting form for the specific times required.
    - This form should be kept in the patients notes on the ward and it will be collected and interpreted by the ward pharmacist who will then calculate the AUC.
    - The target AUC level for Cystic fibrosis patients is 70-100 mg/L.hr. If the calculated AUC is not within the recommended range, a dose adjustment will be required.
    - In cases of a high AUC (>125 mg/L.hr) a dose should be withheld, the dose reduced and recommenced when a trough level is undetectable.[6]

- In cases of a low AUC, the dose can be increased based on AUC calculations to a maximum of 15 mg/kg/dose or 750 mg ONCE daily (whichever is less).[1, 7, 9]

- **ALL** patients with altered pharmacokinetics require ongoing monitoring of their tobramycin AUC levels at a minimum of once weekly AND/OR following any dose adjustment.

HiTH patients

- Patients with altered pharmacokinetics (e.g. CF patients) must have their tobramycin AUC determined and within the target range before admission to HiTH. These levels can be taken with the FIRST dose of tobramycin.
- Require weekly monitoring of their trough levels with paired renal function monitoring.[6]
- Trough levels should remain below the limit of detection (<0.2 mg/L).
- If the trough level is greater than or equal to 0.2 mg/L, contact Pharmacy for advice as this indicates reduced clearance of tobramycin and cessation or dose adjustment may be required.

Process of therapeutic drug monitoring:

- Blood samples for therapeutic drug monitoring (TDM) for tobramycin may be collected via a capillary blood sample OR via accessing a central venous access device (CVAD) line.
- A capillary blood sample (i.e. finger prick or heel prick for infants <6 months) should be used if there is no CVAD in-situ.
- For patients with a CVAD in-situ (especially Cystic Fibrosis patients) the following process should be used:[12]
    - Stop all fluids running through the CVAD line.
    - Flush the line with sodium chloride 0.9%. The volume used is three times the internal line-filling volume of the CVAD device (as per table below).
    - Collect an initial blood sample to be **discarded.** The volume taken is three times the internal line-filling volume of the CVAD device PLUS the additional volume of the IV tubing, injection caps and connectors (as per table below). This is to ensure there is no residue tobramycin in the line which may falsely elevate levels.
    - Collect a therapeutic drug level monitoring sample of blood to send to PathWest for determination of the AUC.
    - Administer another flush of sodium chloride 0.9% (volume as per table below) to ensure line does not clot after blood sample is taken.
    - Recommence fluids if required:

Line type	Approximate internal fill volume of CVAD and line	Flush and discard volume
PICC and Non-tunnelled CVC	1 mL	3 mL
Tunnelled line (broviac) and Implanted (port)	2 mL	6 mL

Collection tube:

- **Paediatric -** Lithium Heparin-PST (GREEN), Lithium heparin, No Gel (DKGN LITH) or Serum, no gel (RED) [13]
- **Minimum volume required:** 300 microlitres[13]

For further information, refer to the PathWest test directory.

Monitoring in Neonates:

- Please refer to Neonatal Medication Protocols

Additional monitoring:

- Renal function and electrolytes should be performed at baseline and weekly whilst on treatment. More frequent monitoring (2-3 times a week) is required if renal function is unstable.[5, 6]
- Patients receiving treatment > 2 weeks (e.g. for Cystic Fibrosis exacerbation) with tobramycin must be monitored for hearing loss and vestibular toxicity every 1 to 2 weeks.[3, 7]

ADVERSE EFFECTS

Common: Nephrotoxicity (usually reversible, but can be anticipated if treatment extends beyond 7-10 days, or if pre-existing renal impairment), vestibular and cochlear toxicity, vomiting, tinnitus, dysphonia.[3, 9]

Infrequent: nausea, skin reactions, cough[9]

Rare: Anaphylaxis, bronchospasm, oliguria, peripheral neuropathy and neuromuscular blockade, electrolyte disturbances, diarrhoea, dizziness, anaemia, chest discomfort, eosinophilia, fever, headache.[3, 9]

STORAGE

- 80 mg/2 mL ampoule should be protected from light and stored below 25˚C.[8]
- 500 mg/5 mL vial and preservative free ampoules should be protected from light and refrigerated between 2 and 8˚C.[2, 8]

INTERACTIONS

This medication may interact with other medications; consult PCH approved references (e.g. Clinical Pharmacology), a clinical pharmacist or PCH Medicines Information Service on extension 63546 for more information.

Please note: The information contained in this guideline is to assist with the preparation and administration of **tobramycin (intravenous)**. Any variations to the doses recommended should be clarified with the prescriber prior to administration

Related CAHS internal policies, procedures and guidelines

Children's Antimicrobial Management Program (ChAMP) Policy

ChAMP Empiric Guidelines and Monographs
KEMH Neonatal Medication Protocols

References

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