High tobramycin serum concentrations after tobramycin inhalation in a child with renal failure

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Sir,

Inhaled tobramycin is used to treat chronic lung infections caused by Pseudomonas aeruginosa in cystic fibrosis. The advantages of inhalation over parenteral administration are direct endobronchial delivery and minimal systemic toxicity. Tobramycin inhalation is considered safe and effective.1,2 Serum levels in cystic fibrosis patients after inhalation are generally low (<1 mg/L).2,3 Without evidence for drug accumulation in serum,2 Therefore, routine monitoring of systemic tobramycin levels after inhalation is not indicated.

We report elevated serum tobramycin concentrations in a child with renal failure receiving inhaled tobramycin.

An 11-year-old child was admitted to a paediatric intensive care unit for an out-of-hospital cardiac arrest. Resuscitation was complicated by bilateral pneumothorax. Extracorporeal membrane oxygenation was started on admission and continued for 4 days. Rhabdomyolysis on day 2 caused acute renal failure with oliguria. Continuous veno-venous haemofiltration (CVVH) was started on day 6. On day 8, atelectasis of the right superior lobe was detected. The patient received antimicrobials to successfully treat Staphylococcus aureus ventilator-associated pneumonia and systemic Candida albicans infection. In the fourth week intravenous ciprofloxacin was commenced to treat P. aeruginosa pneumonia. Because of increased diuresis and severe cloting of the line, CVVH was discontinued in the fifth week. The subsequent rise in creatinine decreased spontaneously after 5 days. One day after CVVH discontinuation, tobramycin for inhalation (TOBI®, Novartis Pharma, Basel, Switzerland) at 300 mg twice daily was started, delivered by a vibrating mesh nebulizer (Aerone® Pro, Aerogen, Galway, Ireland), because of increased respiratory distress with oxygen requirement, fever and elevated C-reactive protein levels. Inhalation was preferred to intravenous infusion because of renal impairment. Ciprofloxacin was switched to meropenem because of resistance of P. aeruginosa. In the sixth week of admission a CT scan showed emphysema, for which thoracoscopic surgery and drainage was performed.

Seven days after starting tobramycin for inhalation the tobramycin serum level (13.8 mg/L 6 h after administration) was interpreted as a sampling error. The test was repeated after the weekend on day 10. The concentrations were 17.9 mg/L (trough) and 17.1 mg/L (1 h after administration). Tobramycin was discontinued on the 11th day. Concentrations after the last dose were 14.1 mg/L (after 1 h) and 13.4 mg/L (after 6 h). Five days after discontinuation the levels were <0.5 mg/L and renal function improved accordingly (figure 1). The patient’s respiratory condition gradually improved and subsequent cultures were negative. The patient recovered and was discharged to a rehabilitation centre 3 months after hospital admission. We obtained informed consent from both patient and parents to publish this report.

Several possible causes for the high tobramycin levels were considered. Erroneous substitution of inhalation for intravenous therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were excluded. Skin contamination of therapy and medication with probable cross-reactivity of the tobramycin immunoassay were exclude.
hypothesize that the high tobramycin levels in our case were caused by systemic accumulation resulting from renal dysfunction, but these levels are high compared with the previously reported cases.5 – 10 Possibly an inflammatory response after prolonged resuscitation, pneumothorax, atelectasis, empyema and mechanical ventilation contributed to increased absorption.

We used the pharmacokinetic software tool MW\Pharm 3.5 (Mediware bv, Groningen, The Netherlands) to estimate the bioavailability of the inhaled tobramycin. The measured tobramycin concentrations in this case matched a dosage regimen of 120 mg of tobramycin intravenously twice daily (corresponding to 4 mg/kg twice daily), suggesting a bioavailability of 40%, 3-fold higher than usual (12%).2 The elimination half-life was prolonged to ≏1 day (normally 1.3–13 h).2

High serum tobramycin concentrations are related to nephrotoxicity and ototoxicity.2 The creatinine increase in our case was most probably attributable to CVVH discontinuation 1 day before starting tobramycin. Hearing loss was pre-existent in this patient due to bilateral tympanic membrane perforation. Audiological testing after tobramycin exposure showed hearing loss in both ears. It is not clear whether the hearing loss was worsened by tobramycin.

Case reports show elevated tobramycin levels following inhalation in patients with renal insufficiency due to systemic accumulation. Respiratory-related disorders like mechanical ventilation or pneumothorax possibly contribute to increased systemic absorption of tobramycin in these patients. It is therefore recommended that tobramycin levels should be monitored in patients with renal dysfunction receiving tobramycin by inhalation.

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This study was carried out as part of our routine work.

**Transparency declarations**
None to declare.

**References**