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Clinical impact of laboratory error on therapeutic drug monitoring of once-daily tobramycin in cystic fibrosis: Case series

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Abstract

Once-daily dosing intravenous tobramycin is commonly used to treat cystic fibrosis pulmonary exacerbations. Clinicians often utilize historical therapeutic drug monitoring data to individualize the dose among patients who have been treated with tobramycin previously. This case series involves three patients with cystic fibrosis who had supra-therapeutic tobramycin levels despite use of a once-daily dosing that produced therapeutic drug levels during a previous hospital admission, raising questions about the validity of these levels. Investigation into several potential sources of error led to the discovery of an analyzer error in the laboratory. Once the laboratory's tobramycin analyzer was recalibrated, the reported levels were comparable to historical levels. This case series emphasizes the clinical importance of critically analyzing reported levels, and specifically, the importance of utilizing past therapeutic drug monitoring data, if available, for all patients treated with intravenous tobramycin. If a patient was therapeutic on a similar dose of tobramycin during a previous admission, a dose adjustment may not be necessary, and clinicians should consider repeating levels while pursuing alternative explanations for the discrepant serum levels.

Keywords

Cystic fibrosis, aminoglycoside, tobramycin, therapeutic drug monitoring, laboratory error

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Introduction

Intravenous (IV) tobramycin is utilized in the treatment of cystic fibrosis (CF) pulmonary exacerbations in the setting of *Pseudomonas aeruginosa* colonization.[1] Tobramycin is often administered as a once-daily dosing (ODD), with an empiric dose of 10 mg/kg/day being most common.[2] Many clinicians utilize historical therapeutic drug monitoring data to individualize the dose among patients who have been treated with tobramycin previously.[2] To ensure safe and effective treatment with ODD, the dose is adjusted upward or downward to maintain serum concentrations within a specified target range if indicated. We present a case series involving three patients with CF who were each found to have supra-therapeutic tobramycin levels despite use of an ODD dose that produced therapeutic drug levels during a previous hospitalization. Upon investigation, it was determined that an unnoticed and unreported laboratory error involving the tobramycin analyzer occurred. The purpose of this case series is to illustrate the clinical importance of considering multiple factors when assessing drug levels during ODD of tobramycin in CF.

Case series

Each patient was admitted for treatment of a CF pulmonary exacerbation and received ODD tobramycin at a weight-based dose that produced therapeutic concentrations during the most recent hospitalization (Table 1). The actual body weight for each patient changed less than 3% between the time of the most recent and current hospitalizations. Throughout the current hospitalization, each patient had normal renal function and hydration status as based on blood urea nitrogen (BUN) and serum creatinine (SCr) values and urine output. Home treatment with inhaled tobramycin was discontinued upon admission in each patient. Serum samples for tobramycin analysis were drawn approximately 2 and 10 h post start of

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Table 1. Tobramycin therapeutic drug monitoring for previous and current hospitalization.

Case/hospitalization	Date	Dose (mg)	Dose (mg/kg)	First collected level (mg/L)[a]	Second collected level (mg/L)[b]	Calculated peak (mg/L)[c,d]	Calculated 18-h level (mg/L)[d]	Calculated trough (mg/L)[d,e]	AUC (mg·h/L)[d]
Case 1									
Previous admission[f]	05/16/XX	670	9.9	21.4	1.5	24.8	0.16	0.027	103.3
Current, day 2	10/18/XX	660	10	27.8	2.7	38.4	0.24	0.04	158.8
Current, day 3	10/19/XX	660	10	41.7	2.4[g]	57.9[h]	0.15[h]	0.018[h]	209.2[h]
Current, day 4	10/20/XX	660	10	20.6[g]	2.4[g]	27.0	0.28	0.055	121.8
Case 2									
Previous admission[f]	04/06/XX	560	10	21.3	1.3	25.8	0.1	0.013	98.3
Current, day 1	10/18/XX	560	9.9	26.4	n/a	n/a	n/a	n/a	n/a
Current, day 2	10/19/XX	560	9.9	33.1	1.8[g]	47.6[h]	0.1[h]	0.011[h]	167.2[h]
Current, day 3	10/20/XX	560	9.9	23.2[g]	1.3[g]	33.3	0.07	0.008	117.7
Current, day 4	10/21/XX	480	8.5	18.9[g]	1.2[g]	26.6	0.08	0.01	98.3
Case 3									
Previous admission[f]	04/11/XX	450	10.2	16.0	0.8	24.3	0.04	0.004	83.2
Previous admission[f]	04/12/XX	550	12.5	15.7	1.5	26.9	0.15	0.024	109.3
Current, day 1	10/19/XX	450	10	28.1	1.0[g]	43.5[h]	0.04[h]	0.003[h]	137.0[h]
Current, day 2	10/20/XX	450	10	14.3[g]	1.3[g]	19.3	0.12	0.02	79.6
Current, day 3	10/21/XX	550	12.2	29.4[g]	1.4[g]	42.0	0.06	0.006	141.5
Current, day 4	10/22/XX	500	11.1	19.4[g]	1.4[g]	26.3	0.1	0.014	101.0

AUC: area under the concentration time curve; n/a: not available.
[a]Drawn 2 h post start of infusion (precise dose and sampling times were documented in the chart per hospital policy and were all within 10 min of scheduled time).
[b]Drawn 10 h post start of infusion (precise dose and sampling times were documented in the chart per hospital policy and were all within 10 min of scheduled time).
[c]Calculated peak corresponds to the level 0.5 h post 0.5-h infusion.
[d]Peak goal: 25–30 mg/L; 18-h goal: <1 mg/L; trough goal: <0.1 mg/L; AUC goal: 90–110 mg·h/L.
[e]Calculated trough corresponds to the level 24 h post-dose.
[f]Previous and current hospitalizations occurred during the same calendar year.
[g]Level drawn following re-calibration of tobramycin analyzer.
[h]Estimate, because the calculated levels were based on one level drawn before re-calibration of tobramycin analyzer, and one level drawn after re-calibration of tobramycin analyzer.

infusion per our CF center's policy. The target tobramycin serum concentrations were as follows: calculated peak (0.5 h post 0.5-h infusion) 25–30 mg/L, calculated 18-h level <1 mg/L, calculated trough <0.1 mg/L, and area under the concentration time curve (AUC) 90–110 mg·h/L.[2,3] These goals were based on those targets used in randomized controlled trials, usual practice within CF centers across the United States, and the institution's experience with dosing tobramycin as an ODD in CF. The peak serum concentration was used to determine whether the dose was therapeutic, while the trough and AUC were used to determine whether the dose was safe. Because ODD may be monitored through collection of a single aminoglycoside serum concentration (e.g. an 18-h post-dose level),[4] our CF center's policy is to utilize patient-specific pharmacokinetic parameters to calculate the 18-h level, which is then used as a baseline marker for follow-up. Per this protocol, an 18-h post-dose level is drawn 7 and 14 days after attainment of a therapeutic dose in order to rule out accumulation. Target concentrations were calculated based on patient-specific pharmacokinetic parameters using a validated online dosing calculator designed specifically for the institution's CF center (http://www.pharmacistassist.com/). All samples were collected via peripheral venipuncture and were analyzed in the hospital's laboratory using a Beckman Coulter UniCel DxC 800 Chemistry Analyzer (Beckman Coulter, Brea, CA, USA).

Case 1

Patient 1 was a 17-year-old 66-kg female admitted on 10/17. She presented with increased productive cough, green sputum, some hemoptysis, decreased pulmonary function tests (PFTs), and a recent weight loss of approximately 3 kg. A chest X-ray was obtained on admission which revealed patchy perihilar infiltrates and bronchial wall thickening with moderate bilateral bronchiectasis. The admission BUN and SCr values were 9 and 0.84 mg/dL, respectively. The sputum culture obtained on 10/17 grew few mucoid *P. aeruginosa* and rare methicillin-resistant *Staphylococcus aureus*. She was treated with vancomycin 532 mg IV every 6 h, rifampin 600 mg *per os* (PO) once daily, piperacillin/tazobactam 3.375 g IV every 6 h, and tobramycin 660 mg IV every 24 h (10 mg/kg/dose), all of which were started on day

2 of admission (10/18). Tobramycin serum levels that were collected after the first dose on 10/18 indicated that the 2- and 10-h levels were 27.8 and 2.7 mg/L, respectively, translating to an elevated peak and AUC (Table 1). Because the levels were significantly different compared with the patient's historical serum concentrations, the dose was continued and the levels were repeated the following day under the assumption that an error had occurred. The repeat 2-h level on 10/19 was again noted to be elevated at 41.7 mg/L. However, prior to collection of the 10-h post-dose level, the analyzer error was discovered and corrected. Therefore, the dose was not adjusted, and the levels were repeated following the 10/20 dose, which revealed the 2- and 10-h levels of 20.6 and 2.4 mg/L, respectively, yielding an extrapolated peak and AUC that were within the target range (Table 1). The patient was continued on this dose for the remainder of her hospital stay. She demonstrated improvement in pulmonary function and no signs/symptoms of aminoglycoside toxicity and was discharged to home after completing her antibiotic course.

Case 2

Patient 2 was a 19-year-old 56.5-kg male admitted on 10/18. He presented with increased cough and sputum production and decreased PFTs for the past month. A chest X-ray was obtained on admission which revealed increased mucus plugging and coarse lung markings that were most prominent in the right upper lobe. The admission BUN and SCr values were 9 and 0.81 mg/dL, respectively. The most recent sputum culture from 10/10 grew three strains of few *P. aeruginosa*. He was treated with ceftazidime 2 g IV every 8 h and tobramycin 560 mg IV every 24 h (9.9 mg/kg/dose). Following the first dose on 10/18, a 2-h level was reported as 26.4 mg/L, but because it was suspected to be erroneous, the 10-h level was not obtained. The levels were therefore reordered with the next dose. Tobramycin serum levels that were collected after the second dose on 10/19 indicated that the 2-h level was 33.1 mg/L (Table 1). However, prior to collection of the 10-h post-dose level, the analyzer error was discovered and corrected. Therefore, because of the analyzer error and because the levels were extremely dissimilar to the patient's historical serum concentrations, the dose was not adjusted and the levels were again repeated. Following the 10/20 dose, the 2- and 10-h levels were 23.2 and 1.3 mg/L, respectively, yielding an extrapolated peak and AUC that were slightly elevated (Table 1). The dose was decreased 15%, resulting in the 2- and 10-h levels of 18.9 and 1.2 mg/L, respectively, yielding serum tobramycin concentrations that were within the target range (Table 1). The patient was continued on this dose for the remainder of his hospital stay. He demonstrated improvement in pulmonary function and no signs/symptoms of aminoglycoside toxicity and was discharged to home after completing his antibiotic course.

Case 3

Patient 3 was a 26-year-old 45-kg male admitted on 10/19. He presented with shortness of breath upon minimal exertion, increased cough and sputum production, and decreased PFTs. A chest X-ray was obtained on admission which revealed moderate hyperexpansion with prominent bronchovascular markings and bronchiectasis that was most severe in the upper lung fields. The admission BUN and SCr values were 11 and 0.49 mg/dL, respectively. Hemoglobin A1C was 6.3% and urine was negative for microalbumin. The sputum culture obtained on 10/23 grew moderate *P. aeruginosa* and moderate *Stenotrophomonas maltophilia*. He was treated with cefepime 2 g IV every 8 h and tobramycin 450 mg (10 mg/kg/dose) IV every 24 h. Tobramycin serum concentrations that were collected after the first dose on 10/19 indicated that the 2-h level was 28.1 mg/L (Table 1). However, the analyzer error was discovered and corrected prior to collection of the 10-h post-dose level. Therefore, because of the analyzer error and because the levels were extremely dissimilar to the patient's historical serum concentrations, despite use of a potentially sub-therapeutic dose (based on historical dose/level data), the dose was not adjusted and the levels were repeated. The repeat levels following the 10/20 dose revealed the 2- and 10-h levels of 14.3 and 1.3 mg/L, respectively, yielding an extrapolated peak and AUC that were sub-therapeutic. After one additional dose adjustment, the dose was ultimately increased 10%, resulting in the 2- and 10-h level of 19.4 and 1.4 mg/L, respectively, levels that were deemed to be therapeutic. The patient was continued on this dose for the remainder of his hospital stay. He demonstrated improvement in pulmonary function and no signs/symptoms of aminoglycoside toxicity and was discharged to home after completing his antibiotic course.

Discussion

Each patient described in this case series had supra-therapeutic tobramycin serum concentrations reported by the laboratory, despite receiving a tobramycin dose that was individualized using historical therapeutic drug monitoring data. Based on a superficial assessment of these levels, a dose reduction appeared to be indicated. However, historical therapeutic drug monitoring data from the previous hospitalization, which occurred during the same calendar year, indicated that the tobramycin levels during this hospitalization were drastically different for each patient. This raised questions about the validity of these levels. The health-care team, led by the consulting clinical pharmacist, hypothesized that these levels were inaccurate, and that an outside factor was to be blamed. Scenarios explored included the following: (1) an error made by the pharmacist while preparing the medication, (2) an incorrect dose dispensed by the pharmacist, (3) a medication administration error by the nurse, (4) inaccurate collection and/or incorrect documentation of the timing of

blood samples for tobramycin analysis by the nurse, (5) drug–drug interactions and/or drug–laboratory interactions, and (6) an error in the analysis of tobramycin levels in the laboratory.

We reviewed pharmacy documentation detailing the preparation and distribution of tobramycin that was administered to each patient on the dates of 10/18 and/or 10/19. Upon inspection, it was determined that the tobramycin was accurately prepared and that the correct dose was delivered to the floor. We then reviewed the medication administration record (MAR) and the "therapeutic drug monitoring stickers," which are used by nursing to document the precise time of the medication dose and collection of levels. Based on review of these documents, it was determined that the nurse administered the correct dose to each patient at the correct time, and that the timing of all blood samples was appropriate. The MAR was further scrutinized to ensure there were no drug–drug or drug–laboratory interactions that may have affected the reported levels. Pharmacokinetic studies conducted in patients with CF have demonstrated that aerosolized tobramycin is systemically absorbed, and as a result can produce measurable serum concentrations.[5] In line with these data, a clinically significant change in the tobramycin trough has been reported when inhaled and intravenous tobramycin is administered concurrently.[6] And previous case reports have documented the occurrence of falsely elevated serum tobramycin levels in patients receiving both inhaled and intravenous tobramycin due to contamination of finger-prick blood samples by the nebulized drug.[7–9] However, because the inhaled antibiotics were discontinued upon admission to the hospital, this can be ruled out as a potential cause. We reviewed the method by which nursing obtained the blood samples because falsely elevated tobramycin levels have been reported when blood is collected from a central venous access device rather than from peripheral venipuncture.[10,11] This was ruled out as a potential cause because the blood samples were drawn via peripheral venipuncture which aligns with our CF center's policy. The final potential cause for the discrepant levels on our differential was that an error occurred during the analysis of blood samples in the laboratory. We contacted the laboratory to discuss the cases, and after completion of research by laboratory personnel, it was determined that despite established quality control policies and procedures to ensure accurate data reporting within the laboratory, an analyzer error had occurred that resulted in the reporting of the erroneously high serum levels. It remains unclear whether the erroneous concentrations obtained from the malfunctioning analyzer occurred as a consequence of instrument calibration drift or a gross instrument error. Nevertheless, once the laboratory's tobramycin analyzer was recalibrated, the reported levels were comparable to historical levels.

Failing to adjust tobramycin dosing based on an elevated 18-h level, trough, or AUC increases the risk for toxicity.[12] Therefore, upon encountering high serum levels, the dose is typically reduced. However, reducing a dose when it is actually therapeutic may place the patient at risk for treatment failure in the short term and increase the risk for developing resistant bacterial species in the lung over time. Based on the initial set of levels, to achieve a target AUC of approximately 100 mg·h/L, patients 1, 2, and 3 would have required a 52% reduction to 316 mg (4.8 mg/kg/dose), 40% reduction to 335 mg (5.9 mg/kg/dose), and a 27% reduction to 329 mg (7.3 mg/kg/dose), respectively. If the dose would have been reduced to this extent, both the peak serum concentration and the AUC would have been significantly below targets. To ensure safe and effective treatment, it is therefore essential to consider the entire clinical picture while engaging in therapeutic drug monitoring and to not simply react to numbers reported by the laboratory.

Clinicians rely on accurate laboratory results to provide optimal patient care. They therefore typically trust what is reported by the laboratory to be accurate. However, the accuracy of these levels can be dependent on the laboratory's quality control policies and procedures, the analyzer used within the laboratory, and the experience of the laboratory personnel. Even with experienced personnel, reliable equipment, and established quality control, reporting errors may still occur and go unnoticed until after patient care decisions based on these laboratory data are made. In this case, the laboratory performed a root-cause analysis, determined that the equipment used to analyze tobramycin levels was outdated, and subsequently purchased a new analyzer.

In summary, this case series emphasizes the clinical importance of critically analyzing reported levels, and specifically the importance of utilizing past therapeutic drug monitoring data, if available, for all patients treated with intravenous tobramycin. If a patient was therapeutic on a similar dose of tobramycin during a previous admission, a dose adjustment may not be necessary, and clinicians should consider repeating levels while pursuing alternative explanations for the discrepant serum levels.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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