2007

Tobramycin-Induced Hepatotoxicity

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OBJECTIVE: To report a case of tobramycin-induced hepatotoxicity.

CASE SUMMARY: A 20-year-old female was hospitalized for treatment of *Pseudomonas aeruginosa* bacteremia and osteomyelitis. Empiric intravenous antibiotic therapy with piperacillin/tazobactam, vancomycin, and ciprofloxacin was started, and based on the results of culture and sensitivity testing, was changed to intravenous ceftazidime and tobramycin 70 mg every 8 hours on hospital day 3. Liver enzyme levels then increased over days 3–6. Tests for hepatitis A, B, and C were all nonreactive, and HIV testing was negative. On day 8, therapy was changed from ceftazidime to piperacillin/tazobactam and the tobramycin dose was increased to 100 mg every 8 hours. Due to a continued increase in total bilirubin, aspartate aminotransferase, and alanine aminotransferase, piperacillin/tazobactam was discontinued and aztreonam was started on day 10. All antibiotics were stopped on day 12 and the elevated liver parameters began to decrease. Aztreonam and ciprofloxacin were restarted on day 16, and most laboratory test results returned to baseline levels by day 19; total bilirubin and alkaline phosphatase decreased to lower than baseline values.

DISCUSSION: This case illustrates a possible occurrence of tobramycin-induced hepatotoxicity. Liver enzymes rose when tobramycin therapy was initiated, markedly increased when the tobramycin dose was increased, then resolved upon discontinuation of therapy. Other medication-related causes were ruled out by temporal relationship or rechallenge (aztreonam). Use of the Naranjo probability scale indicated a possible relationship between hepatotoxicity and tobramycin therapy. Other adverse reaction scales specific for evaluation of drug-induced liver disease were also used. Both the Council for International Organizations of Medical Sciences and Maria and Victorino scales indicated a probable likelihood of tobramycin-induced hepatotoxicity. This patient was not rechallenged with tobramycin due to the highly suggestive timeline present, lack of specific symptoms, and unnecessary risk to the patient.

CONCLUSIONS: Although no other case reports on this interaction have been published through October 9, 2007, historical data from tertiary sources reveal the possibility of aminoglycoside-induced hepatotoxicity; therefore, tobramycin induced hepatotoxicity cannot be ruled out in this patient. Clinicians should be aware of this adverse event.

Drug-related hepatotoxicity is an uncommon occurrence; its true incidence is difficult to determine.[1] Despite this, a significant number of drugs have been shown to cause hepatotoxicity. Because there are few clinical or laboratory manifestations that may specifically link liver injury with medication use, a temporal relationship between the initiation of a drug and liver injury and resolution of symptoms following withdrawal of the drug becomes extremely important.[2] Tobramycin is more commonly associated with neurotoxicity (vestibular and auditory) and nephrotoxicity, although elevation in hepatic enzyme levels is reported as a

possible adverse effect of its use.[3] To date, no case reports of tobramycininduced hepatotoxicity have been published; however, historical data from tertiary sources reveal the possibility of aminoglycoside-induced hepatotoxicity.[4]

We present a case of liver injury following administration of tobramycin.

Case Report

A 20-year-old female was admitted with a chief symptom of pleuritic chest pain accompanied by fever and chills. Medical history included methicillin-resistant *Staphylococcus aureus* endocarditis and anxiety. Surgical history included open reduction and internal fixation of her right femur in 2005 with methicillin-susceptible *S. aureus* osteomyelitis and cellulitis and a tricuspid valve replacement in 2004. The patient reported a history of illicit intravenous drug abuse prior to 2004 and rare alcohol use. Her home medications included paroxetine 40 mg daily, alprazolam 1 mg twice daily, metoclopramide 10 mg as needed, and hydrocodone/acetaminophen 7.5 mg/325 mg every 4–6 hours as needed. She had no known drug allergies.

Two blood cultures performed on samples obtained on the patient's arrival were positive for *Pseudomonas aeruginosa*. Magnetic resonance imaging of the right lower extremity revealed some abnormal intensity in the right distal femur, correlating with osteomyelitis. Hepatitis A, B, and C serologic tests were nonreactive and HIV testing was negative. Other laboratory values are shown in Tables 1 and 2.

The patient's home medications, except for metoclopramide, were continued on admission. Drug therapy during hospitalization included hydromorphone 0.5–1 mg, oxycodone/acetaminophen 5 mg/325 mg, promethazine 12.5 mg, docusate sodium 100 mg, and immediate-release oxycodone 5 mg. Empiric antibiotic therapy was started with intravenous piperacillin/tazobactam 3.375 g every 6 hours, intravenous vancomycin 1g every 12 hours, and intravenous ciprofloxacin 400 mg every 12 hours. Upon the return of the susceptibility patterns, therapy was changed on hospital day 3 to intravenous ceftazidime 2 g every 8 hours and intravenous tobramycin 70 mg every 8 hours. Liver enzyme levels increased daily over the following 3 days (Figure 1). Total bilirubin and albumin decreased slightly during this time. Alkaline phosphatase initially declined, but began to rise on day 4. By day 6, there was a persistent elevation in liver enzymes and drug-induced hepatotoxicity was considered. Ceftazidime was considered the primary suspect for hepatotoxicity; it was discontinued on hospital day 8 and therapy with intravenous piperacillin/tazobactam 4.5 g every 6 hours was

started. That same day, the tobramycin dose was increased to 100mg intravenously every 8 hours. Due to a continued increase in aspartate aminotransferase and alanine aminotransferase levels between days 8 and 10, piperacillin/tazobactam was discontinued and intravenous aztreonam 2g every 8 hours was started. Although total bilirubin initially decreased, it began to rise on day 8 and peaked at day 12, with alkaline phosphatase peaking on day 8.

Despite the discontinuation of piperacillin/tazobactam and ceftazidime, there was a continued dramatic elevation in liver enzymes; all antibiotics were stopped on day 12. On hospital day 14, total bilirubin and alkaline phosphatase began declining; on day 16, antibiotic therapy was restarted with intravenous aztreonam 2g every 8 hours and intravenous ciprofloxacin 400 mg every 8 hours. Liver enzymes continued to trend downward and all laboratory values had returned to baseline prior to the patient's discharge on day 19. Total bilirubin and alkaline phosphatase decreased to lower than baseline values; ALT remained slightly above baseline. Oral ciprofloxacin 750 mg twice daily was continued for an additional 8 weeks.

Table 1. Laboratory Values

	Day				
Parameter	**Admission**	**8**	**12**	**19**	**Reference Range**
Serum creatinine (mg/dL)	0.6	0.7	0.7	0.8	0.6–1.1
BUN (mg/dL)	10	10	13	11	8–25
White blood cell count (x $10^3/\mu L$)	9.2	4.8	5.4	3.7	4.8–10.8
Albumin (g/dL)	2.7	2.4	2.7	2.4	3.5–5
Bilirubin (mg/dL)					
Total	3.2	1.8	4.9	1.5	0.2–1.0
direct	2.6	NR	NR	1.1	0–0.4
indirect	0.6	NR	NR	0.4	0–1.1
Alkaline phosphatase (units/L)	215	432	330	158	53–148
AST (units/L)	52	332	970	42	5-34
Amylase (units/L)	39	NR	NR	NR	25-125
Lipase (units/L)	43	NR	NR	NR	8-78
INR	1.23	NR	1.22	NR	0.8-1.4
aPTT	33.8	NR	41	NR	21.4-31

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; NR = not reported.

Discussion

Nephrotoxicity and neurotoxicity are the adverse events most commonly associated with aminoglycosides. This case illustrates a possible occurrence of tobramycin-induced hepatotoxicity. The patient presented with an active infection, bilirubinuria, and mildly elevated total bilirubin, alkaline phosphatase, and aspartate aminotransferase.

Although this patient's medical history did not include liver dysfunction, laboratory values including total bilirubin, international normalized ratio, alkaline phosphatase, and albumin were abnormal upon admission, indicating underlying liver disease. Urobilinogen was also initially elevated; however, it returned to normal less than 12 hours after admission (a level of 2.0 is considered trace amounts by our institution's laboratory). This decrease may have been due to the initiation of antibiotics. Alkaline phosphatase and aspartate aminotransferase were also mildly elevated upon admission. While this was also suggestive of liver dysfunction, the elevation in alkaline phosphatase may have been due to osteomyelitis. This patient denied a history of alcohol use but reported a distant history of intravenous cocaine abuse, which may have contributed to the underlying liver dysfunction. It would not be expected that this level of liver dysfunction would put her at a greater risk of experiencing drug-induced hepatotoxicity; however, females tend to have increased susceptibility.[1]

Table 2. Urinalysis

Laboratory Value	Day 1 (1045)	Reference Range
Appearance	clear	
Color	dark yellow	
Specific gravity	1.024	1.005–1.030
Urine		
pH	6.0	4.5–7.0
protein	30	negative
glucose	negative	negative
Ketones	negative	negative
Nitrites	negative	negative
Urobilinogen (mg/dL)	4.0	none—trace
Bile	moderate	negative
WBC esterase	negative	negative

WBC = white blood cell.

Upon initiation of empiric antibiotic therapy, liver enzymes remained stable. Figure 1 shows the strong correlation between the initiation of tobramycin and the elevation of liver enzyme levels. This persistent elevation, despite discontinuation of antibiotics more commonly recognized as offenders, such as ceftazidime and piperacillin/tazobactam, reinforces the likelihood of tobramycin-induced hepatotoxicity. Both ceftazidime and piperacillin/tazobactam were discontinued 3–5 days before the spike in liver enzymes, and piperacillin/tazobactam was restarted after persistent elevation of liver enzymes. Given the short halflives of these drugs, there is a low probability of a delayed hepatotoxicity reaction. Other antibiotics used were excluded by the same timeline, or in the instance of aztreonam, by rechallenge.

Nondrug causes of hepatotoxicity were evaluated throughout the patient's hospital stay. An ultrasound of the right upper quadrant, performed on admission, revealed only nonspecific gallbladder thickening. A follow-up computed tomography scan on hospital day 11 showed no specific findings. Viral hepatitis was excluded by negative serologic tests for hepatitis A, B, and C, along with a negative HIV panel. However, given the time lag between time of infection and positive testing, it is possible that the patient may have been infected recently.

Evaluation of the case, using the Naranjo probability scale, indicated a possible relationship between hepatotoxicity and tobramycin therapy in our patient.[5] Liver enzymes increased when tobramycin was initiated and resolved upon discontinuation of therapy. Additionally, when the tobramycin dose was increased, subsequent liver enzyme levels were markedly increased. Tobramycin concentrations attained during admission were never supratherapeutic. Other medication-related causes were ruled out, as the timeline associated with their administration did not correlate with the rise in liver enzymes and the patient reported taking all home medications as prescribed prior to admission.

Although the Naranjo scale is the most commonly used method of calculating adverse event probability, other methods specific for the evaluation of drug-induced liver disease are available. The accuracy of the Naranjo probability scale, when used to evaluate drug-induced liver disease, was questioned by Garcia Cortes et al.[6] They discussed the discrepancy found when evaluating cases of drug-induced liver disease on the Naranjo scale versus the Council for International Organizations of Medical Sciences (CIOMS)[7] or the Maria and Victorino (M&V)[8] scales. Depending on the scale used, the categorized likelihood of drug-induced reaction can change. When evaluated on the CIOMS scale, our case had a score of 8, corresponding with a probable likelihood of tobramycin-induced hepatotoxicity; when assessed on the M&V scale, our case scored 15, also corresponding with a probable likelihood.

Our patient was not rechallenged with tobramycin due to the highly suggestive timeline present, lack of specific symptoms, and unnecessary risk. The patient did not have symptoms common with liver injuries, such as rash or eosinophilia; however, she was febrile at various times throughout admission. These fevers were likely due to osteomyelitis and bacteremia.

The mechanism of hepatic injury with tobramycin is unclear. Currently, no dosage adjustments are necessary for hepatic insufficiency and the primary route of elimination is renal (60–85%). In addition to renal clearance, other routes of elimination include feces (35–79%) and bile (minimal amount).[9]

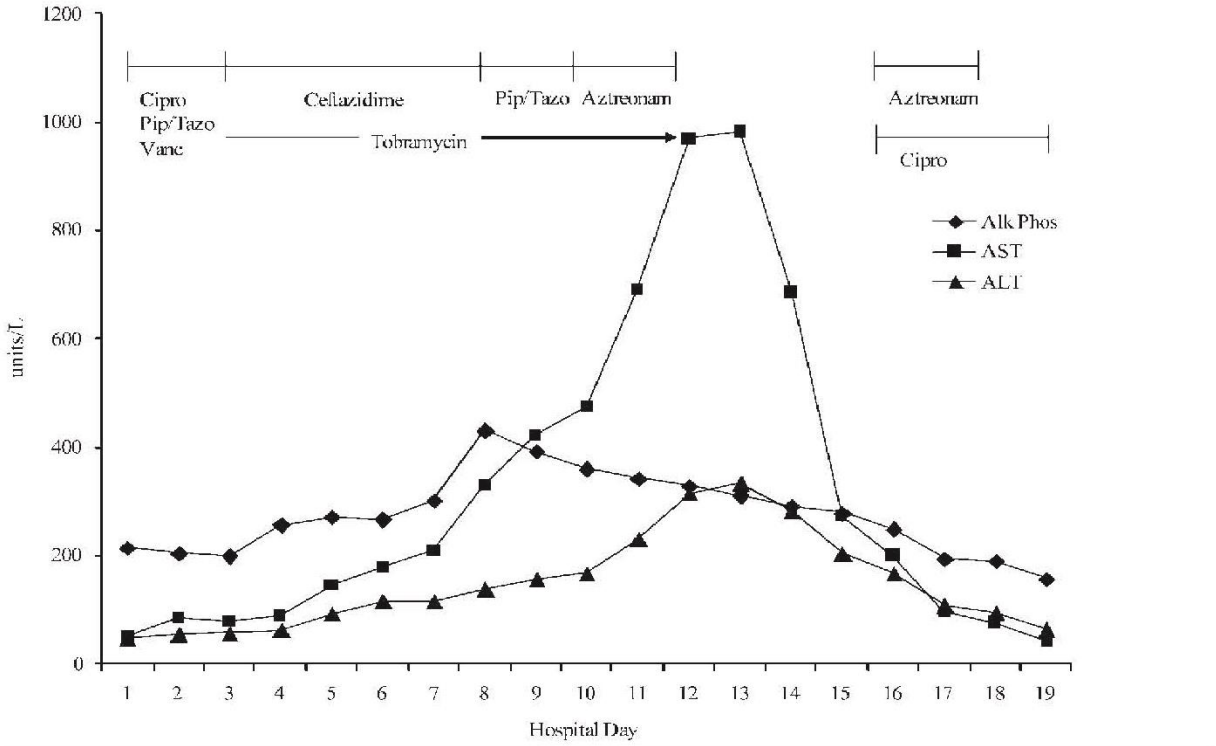

Figure 1 Liver function enzymes in relation to antibiotic administration. Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate

Conclusions

Although no other case reports on this interaction have been published, practitioners cannot rule out the possibility of tobramycin-induced hepatotoxicity. Early recognition and dose changes or drug withdrawal may prevent unnecessary intervention or permanent damage.

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