Ototoxicity and Nephrotoxicity With Elevated Serum Concentrations Following Vancomycin Overdose: A Retrospective Case Series

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Although a high vancomycin serum concentration is known to be associated with nephrotoxicity, its association with ototoxicity is not well known. The purpose of our study was to examine the latter association in pediatric patients, especially in cases of accidental overdose. Pediatric patients who received vancomycin at our facility between March 2010 and December 2015 with a serum trough concentration > 30 mg/L were enrolled. Age, sex, neonatal hearing screening results, estimated peak vancomycin serum concentration, duration of drug exposure, renal function, and hearing test results were collected. The estimated duration of concentrations above 30 or 80 mg/L were simulated with the Sawchuk-Zaske method. We defined a "high concentration" and "toxic concentration" of vancomycin as 30 to 80 mg/L and > 80 mg/L, respectively. Ototoxicity was assessed based on the auditory brain stem response. We identified 4 females and 2 males with normal hearing at birth. Four of the 6 patients were ≤ 3 months old. All the patients reached an estimated peak serum concentration of > 80 mg/L, and 5 exceeded 150 mg/L. The estimated duration of exposure to a high concentration and toxic concentration of vancomycin was 15 to 62 hours and 8 to 43 hours, respectively. All the patients experienced transient renal dysfunction. Although transient ototoxicity was found in 1 patient, prolonged ototoxicity was not observed in any of the patients. All the patients had received an accidental overdose of vancomycin. Prolonged hearing loss due to a high vancomycin serum concentration was not found in any of the subjects in the present report.

ABBREVIATION KDIGO, kidney disease improving global outcomes

KEYWORDS child; deafness; neonate; nephrotoxicity; ototoxicity; overdose; vancomycin

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Introduction

Vancomycin is widely used for empiric therapy against severe bacterial infections and hospital-acquired infections. The adverse effects of vancomycin are reported as red man syndrome, nephrotoxicity, and rarely, ototoxicity.[1] The incidence of vancomycin-induced nephrotoxicity is reportedly 13.7% to 27.2 % in pediatric patients.[2,3] The risk of developing nephrotoxicity is associated with a high vancomycin trough concentration and concurrent administration of nephrotoxic agents, including loop diuretics, vasopressors, angiotensin-converting enzyme inhibitors, and non-steroidal anti-inflammatory drugs.[4,5] Nephrotoxicity resulting from vancomycin is usually reversible after discontinuation of the drug or modification of the treatment regimen using therapeutic drug monitoring.[5]

Ototoxicity due to vancomycin is generally rare and irreversible, and the risk factors have not been fully elucidated. Previous reports suggested that possible risk factors are age >53 years, a high peak serum vancomycin concentration (>30–80 mg/L), prolonged exposure to a high serum concentration of the drug (>2 weeks), and concurrent administration of other ototoxic drugs.[6–8] In adult cases, vancomycin-related ototoxicity was found to be associated with a peak serum concentration exceeding 80 mg/L in patients with renal failure.[7] Transient ototoxicity was reported at peak serum concentrations of 30.2 to 49.2 mg/L in an adult patient without renal failure.[8]

Cases of accidental vancomycin overdose resulting in a high serum vancomycin concentration have been reported in pediatrics, but the effects of overdosing, specifically ototoxicity, are still unclear.[9,10] The purpose of our study was to examine the incidence and severity of ototoxicity in pediatric patients with a high serum vancomycin concentration.

Methods

We retrospectively reviewed patients' electronic medical records from the period between March 2010 and December 2015 at Tokyo Metropolitan Children's Medical Center in Japan. Our hospital is a tertiary children's hospital with 561 pediatric beds, a PICU, and a NICU. The institutional protocol for vancomycin use in patients without renal impairment is as follows: 1) children older than neonates: 10 to 15 mg/kg every 6

Table 1. Criteria for Kidney Disease Improving Global Outcomes: Stage, Serum Creatinine, Urine Output[13,14]

Stage	Serum Creatinine (Non-Neonates)	Serum Creatinine (Neonates)	Urine Output
1	Increase to 1.5 to 1.9 times baseline	Increase to 1.5 to 1.9 times baseline	<0.5 mL/kg/hr for 6 to 12 hr
	Increase of ≥ –0.3 mg/dL	Increase of ≥ 0.3 mg/dL	
2	Increase to 2 to 2.9 times baseline	Increase to 2 to 2.9 times baseline	<0.5 mL/kg/hr for ≥ 12 hr
3	Increase to more than 3 times baseline	Increase greater than 3 times baseline	<0.3 mL/kg/hr for ≥ 24 hr
	Serum creatinine ≥ 4 mg/dL	Serum creatinine ≥ 2.5 mg/dL	Anuria for ≥ 12 hr
	Initiation of renal replacement therapy	Initiation of renal replacement therapy	
	eGFR < 35 mL/min per 1.73 m^2		

eGFR, estimated glomerular filtration rate

hours; 2) neonates (>28 weeks' gestational age): 10 to 15 mg/kg every 12 hours; and 3) preterm neonates (<28 weeks' gestational age) with creatinine < 0.5 mg/dL: 10 to 15 mg/kg every 12 hours. The vancomycin dosage for preterm neonates with creatinine > 0.5 mg/dL starts at 10 to 15 mg/kg and is adjusted at intervals according to the serum trough concentration.

For all these groups, the serum drug concentrations are measured routinely prior to administration of the fourth or fifth dose. The time of concentration collection was individualized to the specific cases. Serum concentration were performed in the clinical laboratory using an antigen-antibody reaction according to manufacturer specification without modification. If vancomycin serum concentration were above the upper limits of the standard curve, the sample was diluted and the serum concentration was calculated based on the number of dilutions.

In this study, an overdose was defined as an accidental administration of a dose higher than the indicated dose. All patients with a serum vancomycin concentration > 30 mg/L were included. A high and a toxic concentration of vancomycin was defined as 30 to 80 mg/L and > 80 mg/L, respectively.[7,8] Overdoses were detected by pharmacists during their review of patient prescriptions or in routine measurements of the serum drug concentration. If overdosing was detected, the serum concentration was immediately measured, and the trough concentration was ascertained and adjusted.

We collected data on age, sex, underlying diseases, neonatal hearing screening results, other ototoxic medications, indications for vancomycin use, the serum concentration, estimated peak serum concentration, exposure time by simulation, creatinine, and hearing test results. The duration of a serum concentration above 30 or 80 mg/L was simulated with the Sawchuk-Zaske method using actual (measured) and estimated (back-extrapolated) concentration.[11]

Ototoxicity was evaluated using the auditory brain stem response. In Japan, most neonates receive neonatal hearing screening with a simplified method using automated auditory brain stem response assessment. The severity of hearing loss was categorized as moderate (40–60 decibels), severe (61–90 decibels), or profound (>90 decibels).[12] In this study, transient and prolonged hearing loss was defined as impairment lasting < 4 weeks and ≥ 4 weeks, respectively. The presence of a vestibular disorder was determined by clinically assessing for vertigo and dizziness through a medical interview and physical examination. Nephrotoxicity was assessed using the criteria for kidney disease improving global outcomes (KDIGO) and neonatal KDIGO as shown in Table 1.[13,14] Ototoxic medications included aminoglycosides, platinum-containing drugs, loop diuretics, and aspirin.[15] We determined if other ototoxic drugs were administered by reviewing the medical records of patients whose vancomycin serum concentration was >30 mg/L. The hospital's institutional review board approved this study.

Results

We identified 6 patients with a vancomycin serum concentration > 30 mg/L (Table 2). Four of the 6 patients were younger than 3 months old and included 1 preterm patient (patient 2). All 6 patients were Japanese. All the patients reached an estimated peak serum concentration of > 80 mg/L, with the actual serum concentration exceeding 150 mg/L in 5 patients. The estimated duration of exposure to high and toxic concentrations of vancomycin was 15 to 62 hours and 8 to 43 hours, respectively.

All the patients had undergone an automated auditory brain stem response assessment at birth and had passed neonatal hearing screening, indicating that their baseline hearing was normal. Transient, moderate hearing loss (40 decibels) was observed in patient 1, while the other patients were within the normal range. The timing of the first auditory brain stem response varied from day 7 to 81. Prolonged hearing loss was not observed in our cohort (Table 3). In practice, evaluating for vestibular disorders by physical examination was difficult in neonates and infants < 3 months old. In patients 5 and 6, no vestibular disorder was found. Patient 5 concurrently received cisplatin, a platinum-containing drug, in chemotherapy. The other patients did not receive any potentially ototoxic agents. Transient acute

Table 2. Characteristics of Patients With Elevated or Toxic Concentration

Patient	Age (Sex)	Underlying Disease	Indication for Vancomycin	Dose (mg/kg/dose)	Number of Doses	Total Dose (mg/kg/course)	Estimated Peak Concentration* (mg/L)	Actual Maximum Concentration† (mg/L)	Time > 30 mg/L (hr)	Time > 80 mg/L (hr)
1	8 days (Male)	None	Staphylococcal scalded skin syndrome	‡	‡	‡	280	172	35	20
2	17 days (Male)	Low birth weight infant	Methicillin-resistant *Staphylococcus aureus* bacteremia	‡	‡	‡	256	168	36	21
3	2 mo (Female)	Protein-losing gastroenteropathy	Catheter-related blood stream infection	100	7	700	659	357	62	43
4	3 mo (Female)	None	Apnea (suspected severe bacterial infection)	143	2	286	203	152	57	28
5	11 mo (Female)	Retinoblastoma	*Bacillus cereus* bacteremia	150	1	150	161	67	20	9
6	24 mo (Female)	Craniosynostosis, epilepsy	Perioperative antibiotic prophylaxis (Methicillin-resistant *S aureus* colonization)	152	1	152	204	247	15	8

* Estimated represents back-extrapolated serum concentration using Sawchuk-Zaske method.
† Actual represents measured serum concentration.
‡ Unknown.

Table 3. Assessment of Ototoxicity and Nephrotoxicity

Patient	Ototoxicity				Nephrotoxicity	
	Severity of Hearing Loss	Left ABR (dB)	Right ABR (dB)	ABR After Administration of Vancomycin (days)	Acute Kidney Injury Stage	Duration Until Restoration of Kidney Function (days)
1	Moderate*	40	20	15	3	5
	N/A	20	20	73	—	—
2	N/A	30	30	7	2	9
3	N/A	20	20	81	3	5
4	N/A	30	30	7	3	7
5	N/A	20	20	47	1	2
6	N/A	30	30	7	1	2
	N/A	25	20	904	—	—

ABR, auditory brain-stem response; N/A, not applicable

* Severity of hearing loss was categorized as moderate (40–60 dB), severe (61–90 dB), or profound (>90 dB).

kidney injury developed in all the patients but resolved within 9 days (Table 3). None of the patients required renal replacement therapy. All the patients experienced an accidental overdose due to human error.

In patients 1 and 2, the physicians' prescriptions in the electronic medical records were correct, but the vancomycin overdose was discovered when an extremely high trough concentration of the drug was detected, suggesting that the error probably occurred in the preparation or administration of the drug by the nurses. Our medical safety team was unable to ascertain the actual dosage used and the specific causes of the error. In patient 3, a pediatric physician ordered a 7-fold overdose of vancomycin for the treatment of catheter-related blood stream infection. In patient 4, a pediatric physician suspected a severe bacterial infection and administered a 2-fold overdose of vancomycin. Patient 5 received vancomycin for 5 days and a 10-fold higher dose once on the sixth day of treatment. In patient 6, an anesthetist administered a 10-fold higher dose of vancomycin as perioperative antibiotic prophylaxis. All overdoses were accidental. A pharmacist did not review the prescription for patients 3, 4, 5, and 6 because fewer pharmacists were available during the nightshifts and on holidays.

Discussion

The present report is a unique case series examining ototoxicity due to toxic serum vancomycin concentrations in pediatric patients with normal hearing at birth. Although the patients were exposed to extremely high serum concentrations of vancomycin with the estimated peak serum concentration ranging from 161 to 659 mg/L, they did not experience prolonged auditory impairment. In previous studies of preterm infants, no patient developed either transient or prolonged auditory impairment despite achieving a vancomycin serum concentration of 305 to 427 mg/L[9,10,16] (Table 4) even though preterm neonates generally tend to develop hearing problems more often than term neonates.[17] In an animal study, guinea pigs were challenged for 11 to 17 days with vancomycin 200 mg/kg/day without showing any changes in the cochlear hair cell count or auditory brainstem response.[18] A vancomycin serum concentration > 30 and > 80 mg/L in our subjects was observed for up to 3 and 2 days, respectively. A previous report documented 4.5 days of exposure at > 30 mg/L (Table 4). None of these cases developed auditory impairment. In all 6 patients in the present case series, the duration of exposure to a high vancomycin serum concentration was 15 to 62 hours. Although one case of transient ototoxicity was found, a strong association between ototoxicity and longer duration of exposure was not observed.

Evidence has yet to be found of a causal relationship between a high vancomycin serum concentration and prolonged auditory impairment. There are relatively few instances of pediatric vancomycin overdose; hence, the effects of extremely high concentrations of the drug are rarely available for analysis. Our case series and previous reports of infants indicated that the incidence of hearing loss due to high vancomycin serum concentrations was uncommon although more data are needed to corroborate this finding.

Vancomycin-related ototoxicity was also associated with the use of other ototoxic drugs in a previous study.[19] In the present study, patient 5, who received a platinum-containing drug in chemotherapy, did not experience any auditory impairment. Brummett et al,[19] in their review of studies of vancomycin-associated ototoxicity from 1958 to 1985, reported that the drug became ototoxic only when used with other ototoxic agents. Animal studies showed no evidence of ototoxicity when vancomycin alone (200 mg/kg/day for 2 weeks) was administered; however, the addition of

Table 4. Literature Discussing Ototoxicity in Pediatric Patients With High or Toxic Serum Concentrations of Vancomycin

Reference	Patient Background (days old)	Vancomycin Dosage (no. of doses)	Actual Maximum Vancomycin Concentration (mg/L)	Time > 30 mg/L (hr)	Time > 80 mg/L (hr)	Auditory Brain-Stem Response
Miner and Faix[9]	Preterm infant 1 (53)	20 mg/kg/dose (3) and 200 mg/kg/dose (3)	305 (trough)	48*	—	Normal
	Preterm infant 2 (9)	20 mg/kg/dose (2) and 200 mg/kg/day (1)	368 (peak)	72*	—	Normal
Muller et al[10]	Preterm infant 1 (6)	38 mg/kg/dose (1)	32 (trough)	—	—	Normal
	Preterm infant 2 (6)	35 mg/kg/dose (1)	34.5 (trough)	—	—	Normal
Burkhart[16]	Preterm infant (47)	10 mg/kg/dose (3) and 200 mg/kg/dose (6)	427 (trough)	110†	96†	Normal

* Duration of concentration > 40 mg/L.
† Calculated from shown data.

gentamicin (50 mg/kg/day for 2 weeks) resulted in ototoxicity.[20] Bailie et al[21] also reported that the risk of vancomycin-associated auditory impairment in adults increased due to the concurrent use of ototoxic drugs, including aminoglycosides, platinum-containing drugs, loop diuretics, and aspirin. However, a previous study of the association of ototoxicity with vancomycin and gentamicin use in treatments for neonatal infections reported that the combination of these 2 drugs did not increase the ototoxicity risk.[22] It is therefore still unclear whether using vancomycin with other ototoxic drugs is associated with ototoxicity.

Transient ototoxicity was observed in patient 1 in our study. His estimated peak serum concentration was 280 mg/L, and hearing impairment was detected at day 15 and resolved by day 73 after vancomycin administration. In a previous report of a 21-year-old male, transient ototoxicity was found at day 7 after starting vancomycin treatment; the peak vancomycin serum concentration in this patient was 49.2 mg/L. Moderate ototoxicity (40 decibels) in this case improved after 15 days following vancomycin administration.[8] Thus, vancomycin-associated ototoxicity may result from a high serum vancomycin concentration even without concurrent use of other ototoxic agents, but the effects are likely to be transient.

A high serum vancomycin concentration is associated with transient nephrotoxicity.[9,10,16,23] Indeed, nephrotoxicity was observed in all of our patients. However, even in pediatric patients requiring hemodialysis due to a vancomycin overdose, the renal function recovered completely.[16,23] None of our patients needed renal replacement therapy, and all of them recovered completely within 9 days. The results might differ for elderly patients or patients with an underlying disease including chronic renal disease.

Our study has several limitations. First, the small number of cases was not sufficient to allow us to generalize the relatively rare finding of ototoxicity resulting from exposure to a high serum vancomycin concentration over specific periods. However, examining pediatric overdose cases was useful for assessing ototoxicity following exposure to extremely high serum vancomycin concentrations. Second, evaluating vestibular disorders was difficult in neonates and infants and was therefore omitted from our observations. Third, the appropriate timing for the assessment of ototoxicity is unknown; hence, transient ototoxicity might have gone undetected before the auditory testing was done.

Conclusions

The present report is a unique case series examining ototoxicity due to administration of high doses of vancomycin in pediatric patients. Prolonged hearing loss was not found in any of the patients despite exposure to high vancomycin serum concentrations.

ARTICLE INFORMATION

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