

## CASE REPORT

# Severe Apnea in a Premature Infant after Accidental Vancomycin Overdose Responsive to Treatment with Exchange Transfusion

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### Abstract

**Background:** Mostly seen toxicities following vancomycin are ototoxicity and nephrotoxicity. We here report a very low birth weight preterm neonate who developed severe episodes of apnea after accidental iatrogenic vancomycin overdose, responsive to treatment with double volume exchange transfusion.

**Case report:** A preterm neonate weighing 1380 grams received two doses of 10-fold of the normal dose of vancomycin per kg in this age group. She developed sudden onset of frequent and severe episodes of apnea, which required noninvasive ventilation. Using fluorescence polarization immunoassay, serum vancomycin level was found to be 84 µg/mL 10 hours after the last dose. The patient underwent exchange transfusion. Apnea episodes terminated 12 hours after exchange transfusion. The blood level of vancomycin decreased from 84 µg/mL before exchange to 67 µg/mL immediately post-exchange and eventually to less than 1 µg/mL in 36<sup>th</sup> hour after exchange.

**Discussion:** Target peak concentration of vancomycin in neonates is between 20 and 40 µg/mL and trough concentration ranges from 5 to 10 µg/mL. Peak serum concentration of our patient can be back extrapolated to be about 336 µg/mL which was higher than the target level. This high plasma levels of vancomycin might be the cause of apnea in our patient as evidenced in similar reports.

**Conclusion:** Apnea is a potential sign of vancomycin overdose in neonates and infants treated with this antibiotic. Exchange transfusion is a potential effective treatment to rapidly resolve this unwanted complication.

**Keywords:** Apnea, Drug Overdose, Premature Infant, Vancomycin, Whole Blood Exchange Transfusion

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## INTRODUCTION

Vancomycin is one of the first-choice antibiotics for the treatment of late-onset nosocomial sepsis in neonatal intensive care unit (NICU) (1). Vancomycin pharmacokinetics differs in neonates; because its volume of distribution is higher and renal excretion is lower due to the fact that organ functions are not mature enough in this age-group (2,3). Toxicity of vancomycin might be either due to infusion-related adverse effects or drug-related toxicity. Infusion-related adverse effects occur as a result of rapid infusion, generally in less than 1 hour, causing histamine-mediated rash of the face, neck, upper trunk and back, which has been known as "red man's syndrome". Drug-related toxicities occur as a result of the chemical nature of the drug itself. Mostly seen toxicities following vancomycin are ototoxicity manifesting with hearing loss, nephrotoxicity manifesting with increase in serum creatinine or urine analysis abnormalities, neutropenia, thrombocytopenia, eosinophilia, chills, fever, rash, and metabolic acidosis (4).

There are few reports on vancomycin toxicity in neonates. Nephrotoxicity and ototoxicity are the most well-known toxic effects of vancomycin and the main focus points for

neonatologists (4). In addition, data on association of serum concentration and toxicity of vancomycin are inadequate. Moreover, no standard treatment and antidote exists for vancomycin intoxication. Reported successful treatment options for intoxicated neonates were multi-dose activated charcoal and invasive procedures such as exchange transfusion, and hemodialysis (5-7). On the other hand, some scientists reported good clinical outcomes after supportive treatments without invasive interventions. We here report a very low birth weight preterm neonate who developed severe episodes of apnea after accidental iatrogenic vancomycin overdose responsive to treatment with double volume exchange transfusion.

## CASE PRESENTATION

A preterm baby girl weighing 1290 grams was delivered by cesarean section in the 29<sup>th</sup> week of gestation due to maternal preeclampsia. She was given surfactant at the first hour for respiratory distress syndrome. She needed nasal noninvasive ventilation for two days and oxygen treatment for 10 days. Apnea of prematurity started at 6<sup>th</sup> days of life (DOL) and continued until 12<sup>th</sup> DOL. She received total parenteral nutrition until 12<sup>th</sup> DOL and later she was totally

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fed with her mothers' breast milk via enteral route. She received caffeine citrate, one of the pharmacological managements for apnea (8), at a maintenance dose of 5 mg/kg/dose following the loading dose (20 mg/kg) from the first DOL.

On the 16<sup>th</sup> DOL, sepsis and/or necrotizing enterocolitis (NEC) was suggested for the patient as she developed abdominal distension, bilious gastric residuals, and dilated loops in ileocecal region observed on plain abdominal radiographs. Hence, she was administered piperacillin-tazobactam (50 mg/kg/dose, two times a day) and vancomycin (10 mg/kg/dose, three times a day) intravenously, while her actual weight was 1380 g at that day. Sepsis workup including complete blood count, C-reactive protein (CRP) and blood culture revealed hemoglobin of 9.7 g/dL, white blood cell count of 22,400 cells/ $\mu$ L, CRP of 3.45 mg/dL (laboratory upper limit was 6 mg/dL). After 12 hours of initiation of the antibiotic treatment, she developed sudden onset of frequent and severe episodes of apnea, which required noninvasive ventilation. CRP was repeated and found to be negative. Hypo/hyperthermia, patent ductus arteriosus, hypoglycemia, hypocalcemia, acidosis, atelectasis, and intraventricular hemorrhage were ruled out by relevant tests.

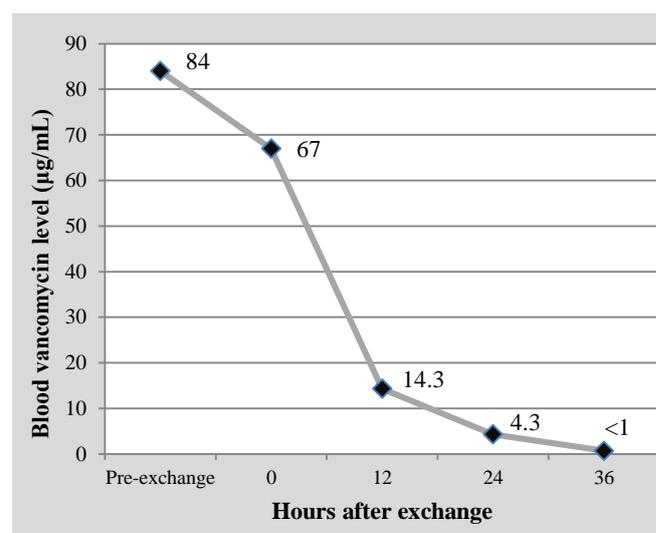
After tests were completed, potential error in vancomycin dosing was recognized. Although she should be given 13.8 mg/dose (10 mg/kg/dose) of vancomycin every 8 hours, she was given 138 mg/dose. The mistake was realized at the beginning of the third dose (when the 3<sup>rd</sup> dose was not started) and the drug was stopped immediately. Using fluorescence polarization immunoassay, serum vancomycin level was found to be 84  $\mu$ g/mL, 10 hours after the second dose. Double-volume exchange transfusion was performed through an umbilical venous catheter. Cessation of apnea episodes was observed 12 hours after exchange transfusion, and so she was gradually weaned off from nasal noninvasive ventilation. Important laboratory values of the patient in pre-exchange, immediately post-exchange and 36<sup>th</sup> hour post-exchange are shown in table 1. Her hemoglobin level and platelet count increased significantly, while the changes in blood urea nitrogen and serum creatinine were unremarkable. In addition, the blood level of vancomycin decreased from 84  $\mu$ g/mL before exchange to 67  $\mu$ g/mL immediately post-exchange and eventually to less than 1  $\mu$ g/mL in 36<sup>th</sup> hour after exchange (Figure 1). Piperacillin-tazobactam was stopped on 5<sup>th</sup> day of treatment as blood culture was sterile. Urine output did not change and urine analysis was normal.

Brainstem auditory evoked responses, retinal examinations, cranial and renal ultrasonographies, renal function tests, and cardiorespiratory functions were normal before she was discharged on 97<sup>th</sup> DOL and appropriate neurodevelopmental milestones were observed at 1<sup>st</sup> year of age. Parental consent was obtained to report this case.

## DISCUSSION

The case presented in this paper emphasizes apnea as a potential sign of vancomycin overdose in neonates and infants treated with this antibiotic. In addition, it provides an evidence for usefulness of exchange transfusion as a potential treatment to resolve this unwanted complication.

Our patient was inadvertently administered two doses of 10-fold of the normal dose of vancomycin per kg in this age group. de Hoog et al reviewed pharmacokinetics of vancomycin in neonates and concluded that the major determinants of dosage are renal function and postconceptional age. They also asserted that target peak concentration of vancomycin is between 20 and 40  $\mu$ g/mL (1 hour after a one-hour infusion) and trough concentration ranges from 5 to 10  $\mu$ g/mL (4). Studies involving neonates with variable gestational and postconceptional ages have proven that elimination half-life of vancomycin is between 3.5 and 10 hours (3,4). Vancomycin half-life of our patient



**Figure 1.** Blood levels of vancomycin before and after exchange transfusion

**Table 1.** Important laboratory investigations of the patient before and after exchange transfusion

Lab parameter	Visit		
	Pre-exchange	Immediately post-exchange	36 <sup>th</sup> hour post-exchange
Hemoglobin (g/dL)	9.2	12.7	11.3
Blood urea nitrogen (mg/dL)	20	14	15
Creatinine (mg/dL)	0.41	0.64	0.43
Platelet count (cells/ $\mu$ L)	690,000	67,000	168,000

was calculated to be about 6 hours which is in line with the literature. Our patient's serum vancomycin level was determined to be 84 µg/mL in 10<sup>th</sup> hour after the last infusion; therefore, peak serum concentration can be back extrapolated to be about 336 µg/mL showing both were higher than the target levels. This high plasma levels of vancomycin might be the cause of apnea in our patient as evidenced in similar reports (7,9). Etiologies of apnea in premature neonates include seizure, intraventricular hemorrhage, pulmonary disorders, patent ductus arteriosus, NEC, anemia, hypo or hyperthermia, hypoglycemia, electrolyte imbalance, and sepsis (8). We excluded them step by step via cranial ultrasound, lung X-ray, the document of formerly performed echocardiogram, skin temperature and serum electrolyte test. Sepsis was also excluded with regards to the cultures being sterile and that she exhibited no deterioration of clinical condition following antibiotic termination. Another potential reason for apnea in neonates is anemia (8). Although hemoglobin level was somehow decreased in our patient, as the levels of hemoglobin were relatively similar during the days prior to apnea and after that, it seemed that anemia cannot be the cause of abrupt apnea. Therefore, vancomycin toxicity was the most reasonable explanation for this acute, unexplained, and unexpected clinical condition.

It is not certain if enhanced drug removal treatment is a necessary therapeutic measure for every neonate with vancomycin toxicity. The main desired benefit of drug removal therapies for vancomycin overdose is to reduce the chance of morbidities of this intoxication, especially in neonates. According to literature, seven neonates with no pre-existing renal disease were reported for vancomycin overdose with serum levels between 32-427 µg/mL, who were either undergone drug removal treatments such as hemodialysis and enteral charcoal administration or followed without any intervention (5-7,9,10). Four neonates of two twin pairs with different symptoms were followed with supportive treatment and all ended up with clinical improvement (9,10). Müller et al reported two late preterm newborns who were given 35 to 38 mg/kg/dose of vancomycin in 1 minute. These patients developed apnea, reversible nephrotoxicity, metabolic acidosis, flushing, and cyanosis. The vancomycin serum concentrations were found to be 32 and 34.5 µg/mL, nine hours after drug administration with no enhanced elimination technique (9). Miner et al reported two premature infants who received 10-fold the standard dose of vancomycin resulting in peak plasma concentrations over 300 µg/mL. In their report, only one infant had a transient increase in serum creatinine. They considered close observation without any intervention and observed normal vancomycin serum levels in less than 72 hours (10).

Among the reported cases that received drug removal therapies, Burkhart et al and Kucukguclu et al demonstrated that multi-dose activated charcoal administration to two neonates whose serum vancomycin levels were 427 and 167 µg/mL were effective in reducing serum concentration of the drug (5,7). Nonetheless, activated charcoal was not feasible for our patients since she was suspicious of having NEC and

followed as nil by mouth. The other option is renal replacement therapy, which is mostly reported to be successful in older children (11-15). In this respect, Lemaire et al shared their successful experience about treatment of a neonate with vancomycin toxicity with serum vancomycin level of 222 µg/mL (6). However, we did not prefer this procedure as it being highly invasive and unavailability of suitable equipment to perform the procedure for a 1380-gram preterm neonate. According to our patient's gestational age, postnatal age, weight, and clinical condition, exchange transfusion was planned to be performed. These results of serum vancomycin values in our patient were in line with a similar report, which presented comparable pre-exchange and post-exchange vancomycin serum levels (5). We decided to perform exchange transfusion because of intractable apneas in our patient and limited therapeutic choice we had, although the procedure is associated with some risks and there is controversy over the effectiveness of the procedure to reduce drug concentrations in young children (5). We were able to eliminate 17 µg/mL of vancomycin during one exchange process. This was not a surprise actually as preterms has larger body water content, which results in greater volume of distribution and decreased total clearance (4). Although effectiveness of the procedure was questioned after computing the eliminated drug level, clinical improvement in the patient was dramatic enough to be satisfied.

Pathogenesis of apnea in vancomycin toxicity is not clearly known. Cerebrospinal fluid (CSF) concentration of the drug can be assumed to be about 7-68% of serum (16). Ventriculitis and intracranial hypotension are known neurotoxic effects due to vancomycin toxicity; while the underlying mechanisms of these complications are ascertained to be CSF inflammatory response, direct toxic lesions on brain stem and axonal damage (17). Respiration control in preterm neonates takes place in ventral surface of medulla. Perhaps high dose vancomycin could affect this region via the mentioned mechanisms leading to abrupt onset of apnea, and this effect disappears as the vancomycin level declines.

In addition to apnea, our patient experienced a decrease in platelet count pre- and post-exchange. Although vancomycin may induce thrombocytopenia itself, thrombocytopenia is a well-known side effect of exchange transfusion (18). Moreover, low platelets are common signs following neonatal infections, especially NEC (19). As thrombocytopenia was present before the procedure of exchange transfusion in our patient, we have no conclusive evidence to attribute the cause of thrombocytopenia neither to vancomycin overdose nor to NEC.

## LIMITATIONS

The absence of CSF analysis and so vancomycin level in this fluid is a major limitation of our study. We could not perform lumbar puncture as the patient developed severe bradycardia and hypoxia when appropriate position was held for the procedure. As the cessation of apnea episodes after normal serum vancomycin levels was achieved, it is hypothetically logical to say that the increase in CSF

vancomycin was the cause of apnea. However, there is no concrete evidence to prove this hypothesis. Hence, it could be useful to evaluate drug level in CSF in similar cases in future studies.

## CONCLUSION

Generally speaking, iatrogenic drug overdose might happen in any medical setting (20). Unexplained or unexpected clinical symptoms should bring in mind drug prescription/administration mistakes similar to what we observed in the presented case. Experienced nurses and NICU staff have important role in early recognition of prescription errors, especially when a clinical pharmacologist is not available. Although we experienced that exchange transfusion is helpful for a neonate with vancomycin overdose, it is not certain whether enhanced drug elimination is necessary to be performed for such cases or not, due to limited number of cases reported in this context.

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