CASE REPORT

Vancomycin Overdose in a 6-Month-Old Girl

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INTRODUCTION

Vancomycin is a commonly used antibiotic for the treatment of serious gram-positive infections. The use of this agent has increased over the past decade, as organisms have become increasingly resistant to penicillinase-resistant penicillins.[1,2] Formal pharmacokinetics-based dosing strategies for infants were first reported in 1980.[1] Since then, various dosing regimens for vancomycin have been studied in neonates and infants to take into account their differing kidney maturation status. Vancomycin dosing strategies typically target a "therapeutic range" (peaks of 20 to 40 mg/L, troughs of 5 to 10 mg/L) in an effort to enhance efficacy and minimize the potential toxic effects of the drug. The primary toxicities of concern to clinicians are ototoxicity and nephrotoxicity. However, definitive data that support concentration-efficacy or concentration-toxicity relationships for vancomycin are lacking.[3] The following case illustrates the clinical course of an infant who was inadvertently given a 10-fold overdose of vancomycin.

CASE REPORT

A 6-month-old Caucasian girl with a history of multiple congenital anomalies was admitted to hospital for repair of a ventricular septal defect and pulmonary artery debanding. The child's heart lesions consisted of 2 ventricular septal defects and coarctation of the aorta. Other congenital anomalies included pelvic right kidney, hip dysplasia, tracheomalacia, and choanal stenosis. Coarctation repair and pulmonary artery banding had been performed on the 10th day of life. At the time of her current surgery, the child weighed 5.34 kg. The following laboratory test results were obtained on the day of surgery: serum sodium 140 mmol/L (normal range 135 to 145 mmol/L), potassium 3.5 mmol/L (normal range 3.7 to 5.6 mmol/L), serum creatinine 25 µmol/L (normal range 10 to 90 µmol/L), blood urea nitrogen 2.8 mmol/L (normal range 1.8 to 8.2 mmol/L), WBC 11.9 x 10^9/L (normal range 6 to 18 x 10^9/L), hemoglobin 144 g/L (normal range 101 to 129 g/L), and platelets 143 x 10^9/L (normal range 180 to 440 x 10^9/L).

Medications before admission included furosemide 4 mg orally once daily and budesonide by nebulizer. The patient's postoperative course was complicated by labile blood pressure, hypovolemia, thrombocytopenia, and intermittent fever. Empiric antibiotic coverage with cefazolin 200 mg IV q8h was instituted and continued for the first 3 postoperative days. Antibiotics were reinstituted on the sixth postoperative day because of a persistent increase in temperature and a newly elevated WBC count (15.5 x 10^9/L). The new antibiotic regimen consisted of cefotaxime 250 mg IV q8h and vancomycin 100 mg IV q8h. At the time of antibiotic initiation, the results of laboratory tests were as follows: sodium 141 mmol/L, potassium 4.2 mmol/L, serum creatinine 24 µmol/L, blood urea nitrogen 1.9 mmol/L, WBC 15.5 x 10^9/L, hemoglobin 92 g/L, and platelets 273 x 10^9/L. Samples for determination of vancomycin concentrations were drawn around the third 100-mg dose; the peak (sample collected 1 h after a 1-h infusion) was 24 mg/L, and the trough (immediately before the dose) was 8 mg/L. The calculated vancomycin half-life and volume of distribution were 3.8 h and 4.13 L (or 0.77 L/kg), respectively. The vancomycin dose was increased to 120 mg IV q8h, for reasons not clearly documented. Forty-eight hours later (on the ninth postoperative day) the patient was transferred out of the intensive care unit. Upon transfer, the vancomycin dose was again reduced to 100 mg, although the rationale for this dosing adjustment by the physician is also unclear. Serum creatinine level was stable throughout this period, ranging from 22 to 24

µmol/L. On the ninth postoperative day (the fourth day of vancomycin therapy) at 5:00 PM, 1000 mg (200 mg/kg) of vancomycin, rather than the prescribed 100-mg (20 mg/kg) dose, was inadvertently administered because of a labelling error. At that time, the patient's weight was 4.99 kg. The error was detected that same evening, before administration of any further doses. Concurrent medications at the time consisted of ranitidine 10 mg po bid, furosemide 4 mg po q8h, acetaminophen 80 mg po q4h prn, and codeine 2.5 to 5.0 mg po q4h prn. The patient was assessed approximately 3 h after the 100-mg dose was given; she was flushed but normotensive, and her heart rate was within normal limits. The flushing resolved without intervention. A sample was drawn 13 h after the overdose, and the vancomycin level was reported as 154 mg/L (as determined by fluorescence polarization immunoassay on the TDx analyzer [Abbott Laboratories, Irvine, Texas] in the Chemistry Laboratory, BC's Children's Hospital) with a serum creatinine value of 63 µmol/L. Serial vancomycin and serum creatinine levels were obtained 32 and 64.5 h after the overdose; vancomycin was 72 and 22 mg/L and serum creatinine was 81 and 74 µmol/L, respectively. The vancomycin level continued to decline, although the half-life calculated by linear regression analysis (r^2 = 0.9996) of the 3 data points was 18.2 h. The patient's serum creatinine level returned to baseline values 7 days after the overdose. The results of urinalysis, performed on the day that the patient's serum creatinine peaked, were within normal limits except for trace amounts of red and white blood cells.

Auditory brainstem response examination, performed 9 days after the overdose, yielded normal results for threshold to click stimuli and response to tonal stimuli at 500, 2000, and 4000 Hz for each ear. However, the possibility of mild hearing loss could not be ruled out, and a follow-up behavioural and audiological assessment at 10 to 12 months of age was recommended. Intermittent fever and leukocytosis complicated the patient's recovery. A 4-week course of cloxacillin 250 mg IV q6h and cefotaxime 250 mg IV q8h was started for possible endocarditis beginning 48 h after the overdose. Serial samples for blood culture drawn at this time and throughout the patient's stay in hospital yielded negative results (except for contaminants), and the patient remained afebrile, with blood counts within normal limits. She continued to improve clinically. On repeat vancomycin testing 19 days after the overdose, the drug was undetectable. Twenty-three days after the overdose, the patient was transferred to a community hospital for completion of the prescribed antibiotic therapy.

DISCUSSION

We have reported a case of accidental vancomycin overdose in a 6-month-old girl, which resulted in flushing and a transient rise in serum creatinine level, both resolving without intervention. A search of both the MEDLINE (January 1966 to September 1999) and EMBASE (January 1988 to August 1999) databases using "vancomycin", "poisoning", "drug overdose", "overdose", and "intoxication" as key words and as text words revealed 5 previous English-language reports involving a vancomycin overdose in neonates or infants.[4-8]

Burkhart and colleagues[4] reported on the course of a 47-day-old premature boy who was inadvertently given a total of 1476 mg of vancomycin over a 4-day period, which resulted in a vancomycin level of 427 mg/L at 9 h after the last dose. Vancomycin therapy was preceded by separate 5- and 18-day courses of antibiotics, including gentamicin, for necrotizing enterocolitis. These authors intervened by instituting exchange transfusion and administering activated charcoal by nasogastric tube. The exchange transfusion had no apparent effect on serum vancomycin levels, and vancomycin concentration in the exchanged blood was not measured. Activated charcoal was reported to have decreased the vancomycin half-life from 35 to 12 h. The patient ultimately experienced a transient increase in serum creatinine, which rose from a baseline of 27 µmol/L to a peak of 123 µmol/L within 3 days after the start of vancomycin treatment and then decreased to 53 µmol/L 10 days after the vancomycin was discontinued. The results of hearing tests were normal. Because the patient's serum creatinine improved continuously during the vancomycin elimination phase, it is difficult to assess the contribution of activated charcoal to the elimination of vancomycin.[4] Previous literature for adult humans[9] and for rabbits[10] has suggested that activated charcoal has little effect on vancomycin clearance. Some authors attribute the lack of charcoal effect to the large molecular weight of this antibiotic.[10] However, these findings were in the setting of standard dosing regimens of vancomycin and the results may not apply to a case of overdose in an infant. Further study of activated charcoal administered enterally is needed in this setting.

In 1996, Kucukguclu and colleagues[5] reported their experience with a 17-day-old girl who received 500 mg of vancomycin during a surgical procedure. The peak vancomycin level, 1 h after dose administration, was

165.7 mg/L. Intervention with activated charcoal (1 g/kg by nasogastric tube q4h, 12 doses) was instituted and the vancomycin half-life was reported to be 9.4 h. The patient's blood urea nitrogen and serum creatinine were reported to have remained within normal limits, and no hearing deficits were detected by auditory-evoked response measurements.[5] A vancomycin half-life of 9.4 h is within normal limits for this age group.[11] Again, it is difficult to assess any contribution that activated charcoal may have had on vancomycin clearance in this patient.

Panzarino and colleagues[6] used charcoal hemoperfusion to treat a 14-month-old child who had received 200 mg/kg of vancomycin cumulatively over 3 doses. The patient had preexisting renal dysfunction with a baseline serum creatinine level of 309 µmol/L. The vancomycin level 5 h after the final dose was 338 mg/L. Intervention was initiated because of progressive deterioration of renal function and a documented loss of high-frequency hearing. The charcoal hemoperfusion appeared to decrease the apparent vancomycin half-life from 145 h the day before the procedure to 12.5 and 11.1 h during the first and second charcoal hemoperfusion sessions, respectively. No rebound effect was observed with the vancomycin levels 24 h after completion of the hemoperfusion. Vancomycin clearance parameters were not reported in this case. This patient suffered both a loss of high-frequency hearing and worsened renal function, with serum creatinine level rising from the baseline of 309 µmol/L to 548 µmol/L just before initiation of the charcoal hemoperfusion. The hearing loss resolved after 6 months, but the renal deterioration persisted, rendering the patient dependent on dialysis.[6]

Goebel and colleagues[7] described the effects of continuous venovenous hemodiafiltration with a high-flux membrane as an intervention for vancomycin overdose. Their patient was a 6-day-old full-term boy with anuric renal failure (serum creatinine 354 µmol/L), hypoplastic left kidney, and pulmonary hypoplasia. The patient was started on vancomycin for presumed sepsis and inadvertently received a 100 mg/kg IV dose, which resulted in a random serum vancomycin level of 240 mg/L approximately 15 h after the drug was given. The patient was reported to have experienced short bradycardic episodes but no other observable changes in clinical status. Continuous venovenous hemodiafiltration was initiated and continued for 41 h, at which time the serum vancomycin level had decreased to 30.7 mg/L. The vancomycin elimination half-life during the procedure was 14.59 h. Peritoneal dialysis was resumed upon discontinuation of the procedure, with little decrease in vancomycin concentrations over the subsequent 60 h. The patient's final clinical outcome was not reported. This report and the case described by Panzarino and colleagues[6] demonstrate effective means of removing vancomycin, in facilities that are adequately equipped, for patients with preexisting renal dysfunction.

Muller and colleagues[8] reported the clinical course of preterm twins (35 weeks gestation), weighing 1985 and 2390 g, who received rapid (over 1 min) IV bolus vancomycin doses of 38 and 35 mg/kg, respectively. The patients suffered flushed face and trunk, peripheral cyanosis, apnea, hypoxemia, repeated bradycardia, hypotension, and metabolic acidosis. Nine hours after administration of the vancomycin, drug levels were 32.0 and 34.5 mg/L, respectively. Glomerular filtration rate was determined to be normal, and ototoxicity was ruled out. Tubular proteinuria was detected on urinary electrophoresis. The proteinuria resolved within 1 week after the overdose. No specific intervention was undertaken in these cases. Relative to the overdoses in

Table 1: Temporal Relationship Between Vancomycin Overdose and Change in Serum Creatinine (SCr) Level

Reference	Time After Overdose (days*)	Vancomycin Level (mg/L)	SCr Level (µmol/L)
Burkhart et al[4]	0 (before overdose)	ND	27
	1	ND	54
	1.5	267	61
	3	427	ND
	3.5	ND	123
	4.5	187	123
	5	ND	106
	6.5	ND	62
Kucukguclu et al[5]	1 h	165.7	ND
Panzarino et al[6]	"Baseline"	ND	309
	1†	338 (5 h after third dose)	424 (23 h after baseline)
	2	268	468
	3	216	450
	4	193	521
Goebel et al[7]	"Baseline"	ND	354 (subsequent values not reported)
Muller et al[8]	ND	ND	ND; patients' SCr was "normal day 19 after the overdose"

ND = no data reported.
* Unless specified otherwise.
† Vancomycin q6h x 3 doses.

previous reports, the overdose in these preterm twins was small. The rate of drug administration and subsequent histamine release, consistent with red man syndrome, were hypothesized to be the major contributors to the patients' adverse clinical consequences.

In our case, which involved a 10-fold vancomycin overdose, no specific intervention was undertaken. The paucity of reports of acute vancomycin toxicity in neonates and the heterogeneous nature of the cases reviewed make it difficult to determine what constitutes a serious vancomycin overdose and when, or what type of, intervention would be optimal. Patients with preexisting renal dysfunction may be at greater risk for further toxic effects and thus might benefit from interventions such as charcoal hemoperfusion or continuous venovenous hemodiafiltration. The contribution of enterally administered activated charcoal remains questionable. We had the benefit of documented patient-specific pharmacokinetic parameters, which indicated that at baseline our patient had a vancomycin half-life of approximately 4 h. Thus, it was anticipated that the drug would be eliminated relatively quickly, even if some degree of renal impairment were to occur. We observed a rapid postoverdose rise in serum creatinine level. Similar creatinine elevations were documented in some of the previous case reports (Table 1). Our patient's rise in creatinine level could not be attributed to the early postoperative episodes of hemodynamic instability, hypotension, or hypovolemia, as all measured renal parameters remained within normal limits, without a rising trend, for 10 days after the surgery, up to and including the day of the accidental overdose. The mechanism of vancomycin nephrotoxicity remains uncertain. Some animal data suggest that entry of vancomycin through the renal basolateral membrane and the subsequent effects on organic cation transport may play a role in the renal toxicity of the drug.[12] Our patient appeared to have made a complete recovery from any adverse effects of the vancomycin overdose without specific therapeutic intervention.

References

1. Wandstrat TL, Phelps SJ. Vancomycin dosing in neonatal patients: the controversy continues. *Neonatal Netw* 1994;13:33-9.
2. Nahata MC. Lack of nephrotoxicity in pediatric patients receiving concurrent vancomycin and aminoglycoside therapy. *Chemotherapy* 1987;33:302-4.
3. Leader WG, Chandler MHH, Castiglia M. Pharmacokinetic optimization of vancomycin therapy. *Clin Pharmacokinet* 1995;28:327-42.
4. Burkhart KK, Metcalf S, Shurnas E, O'Meara O, Brent J, Kulig K, et al. Exchange transfusion and multidose activated charcoal following vancomycin overdose. *Clin Toxicol* 1992;30:285-94.
5. Kucukguclu S, Tuncok Y, Hasan O, Guven H, Uguz A, Maltepe F. Multiple-dose activated charcoal in an accidental vancomycin overdose. *Clin Toxicol* 1996;34:83-6.
6. Panzarino VM, Feldstein TJ, Kashtan CE. Charcoal hemoperfusion in a child with vancomycin overdose and chronic renal failure. *Pediatr Nephrol* 1998;12:63-4.
7. Goebel J, Ananth M, Lewy JE. Hemofiltration for vancomycin overdose in a neonate with end-stage renal failure. *Pediatr Nephrol* 1999;13:423-5.
8. Muller D, Hufnagel M, Suttorp M. Accidental overdose of vancomycin in preterm twins. *Pediatr Infect Dis J* 1999;18:744-5.
9. Davis RL, Roon RA, Koup JR, Smith AL. Effects of orally administered activated charcoal on vancomycin clearance. *Antimicrob Agents Chemother* 1987;31:720-2.
10. el-Sayed YM, Niazy EM, Tawfik AF, al-Dardiri MM. Effect of oral activated charcoal on vancomycin clearance in rabbits with acute renal failure. *Drugs Exp Clin Res* 1993;19:19-24.
11. Schaad UB, McCracken GH, Nelson JD. Clinical pharmacology and efficacy of vancomycin in pediatric patients. *J Pediatr* 1980;96:119-26.
12. Sokol PP. Mechanism of vancomycin transport in the kidney: studies in rabbit renal brush border and basolateral membrane vesicles. *J Pharmacol Exp Ther* 1991;259:1283-7.

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