ACCIDENTAL OVERDOSE OF VANCOMYCIN IN PRETERM TWINS

Vancomycin is a glycopeptide antibiotic agent that is mainly used for the treatment of infections caused by multiresistant staphylococci and enterococci. Important adverse reactions of vancomycin are nephrotoxicity and ototoxicity and to a minor degree hematotoxicity and retinotoxicity.[1–5] These side effects are considered to appear after long term treatment or in combination with other antibiotics, especially aminoglycosides.[6, 7] Only a few reports of acute toxicity of vancomycin alone have been published. The red man syndrome (RMS, also known as red neck syndrome or red person syndrome) is a reaction after vancomycin administration that manifests as flush, pruritus, hypotension and tachycardia.[7–11] It is self-limited and rarely requires intensive care treatment. We describe two preterm twins who accidentally received an overdose of vancomycin as a bolus intravenous injection.

Case report. After an uneventful pregnancy a female and a male twin were delivered vaginally from a 22-year-old Caucasian second gravida in the 35th week of gestation. The birth weights were 1985 and 2390 g, and the APGAR scores were 5/7/9 and 6/8/9, respectively. The children initially presented with grunting, cyanosis and intercostal retractions. Because of respiratory insufficiency both newborns were artificially ventilated, and the chest radiographs showed linear shadowing compatible with congenital pneumonia. Antibiotic therapy with piperacillin (100 mg/kg/d) and cefotaxime (100 mg/kg/d) was started. White blood cell count and C-reactive protein values were normal. Respirator-assisted ventilation was stopped 13 and 16 h after birth, respectively.

On the 6th day of antibiotic treatment, vancomycin was administered, by error as a single 1-min dose intravenously to both babies. The dosages were 38 and 35 mg/kg, respectively. After a few minutes both newborns developed a flushed face and trunk and peripheral cyanosis. Capillary refill time was prolonged. Apnea and hypoxemia (oxygen saturation between 60 and 64%, measured by transcutanous pulse oximetry) were noted. Repeated bradycardia (40 to 60 beats/min) appeared and systolic blood pressure dropped 10 mm Hg. Oxygen was delivered immediately to both infants. Blood gas analyses showed metabolic acidosis, characterized by a blood pH of 7.29 and 7.24 and a base excess of −10.5 and −10.9 mmol/l, respectively. After 30 min clinical signs and symptoms of RMS as well as the metabolic acidosis disappeared. The next morning, 9 h after administration, the vancomycin serum concentrations were 32 and 34.5 mg/l, respectively.

Funduscopic examination on Day 19 after the event revealed no retinal damage. Ototoxicity was ruled out by regular otoacoustic emissions registered on the same day. Repeated blood cell counts demonstrated no abnormalities. Clinically no renal dysfunction was obvious; especially no edema was observed. Serum creatinine values were normal for both infants. The glomerular filtration rate, estimated with the Schwartz formula,[12] was also normal in both infants (29.4 ml/min/1.73 m^2 in the male twin and 34.6 ml/min/1.73 m^2 in the female patient on Day 9). No proteinuria was present before the vancomycin administration. Semiquantitative urinary dipstick analysis showed no proteinuria, but an urinary protein electrophoresis revealed tubular proteinuria. Proteinuria was paralleled by an elevated activity of the tubular enzyme *N*-acetyl-beta-D-glucosaminidase (NAG) in the urine for 16 days. Two days after vancomycin administration NAG was 38.2 U/mmol creatinine and 46 U/mmol creatinine, respectively (normal range, <20 U/mmol creatinine). One week later proteinuria resolved completely and NAG excretion returned to normal values.

Discussion. The presented cases focus attention on the infusion speed and the large dosage of vancomycin administered. Vancomycin was erroneously administered as a rapid intravenous injection.[9] The rapid administration is considered by most authors to be the most likely cause of the RMS, although RMS can be observed when vancomycin is administered for longer than 60 min.[8, 11, 13–18] The red man syndrome is not considered as a true drug allergy because patients who develop RMS on one occasion will not necessarily do so on a subsequent administration of vancomycin, if the infusion time is prolonged.[19] A review of 11 children with RMS after vancomycin administration compared with 11 age-matched children without RMS showed that the children in the first group had shorter infusion periods although these were not statistically significant.[20] Polk et al.[21] reported that the administration of 1000 mg of vancomycin was significantly more often followed by RMS than giving a 500-mg dose when the infusion period was 1 h in both groups.

The pathophysiology of RMS is considered to be a vancomycin-induced histamine release from mast cells, provoking hypotension, flushing and tachycardia. Polk et al.[21] determined plasma concentrations of histamine after vancomycin administration in healthy volunteers. Patients with RMS had dose-dependent increases in histamine concentrations, and the severity of reaction correlated with increasing plasma histamine values. Wold and Stanley[22] were able to prevent hypotension in laboratory animals by administering a histamine antagonist before infusion of the vancomycin. O'Sullivan et al.[23] found only a minimal increase in serum histamine in RMS caused by vancomycin. Sahai et al.[24] were also able to prevent RMS by antihistamine pretreatment.

Levy et al.[20] investigated retrospectively 11 children (among them 1 preterm), who developed RMS after vancomycin administration. Only the preterm child had marked hypotension. Bradycardia, as observed in our patients, has not been reported whereas 4 of 11 children showed tachycardia.[20] Lacoutre et al.[10] observed severe hypotension in 2 preterm infants. One of them developed tachycardia, and the other showed no change in heart rate. Other than these 2 reports, RMS in preterm infants has not been reported. The observation of bradycardia in our patients cannot be explained. In rats, as shown by Cohen et al.,[25] vancomycin exhibits a direct frequency-depressing effect on the cardiac function. Whether this might also play a role in humans is unknown.

The second aspect of this report is the fact that vancomycin was not only administered too rapidly but was also given in a 3-fold elevated dose. In our patients we measured vancomycin

concentrations 9 h after the antibiotic drug had been injected.[15, 26] Alpert et al.[27] showed that in neonates, despite administration of recommended dosages of vancomycin, up to 70% had plasma values greater than desired, which was attributed to the immature kidney function in these patients.[28] Reports of acute toxicity after single overdose of vancomycin in neonates and preterm infants are rare. Tissing et al.[29] reported the case of a preterm baby that became oliguric and had a rise in serum creatinine 24 h after administration of an appropriate dose of vancomycin. However, the child also received tobramycin treatment. Because the serum concentration of tobramycin was normal and the vancomycin value elevated, the reaction was considered to be caused by the latter drug. After withdrawal of both drugs, clinical signs and laboratory changes returned to normal. Brainstem audiometry was normal. Burkhart et al.[30] described an infant who was treated for necrotizing enterocolitis with intravenous vancomycin which was inadvertently administered six times in a 20-fold overdose. The child showed only altered renal function, which returned to normal after multiple doses of oral activated charcoal. A volume exchange transfusion failed to decrease serum values. Brainstem audiometry at Day 3 was normal. Odio et al.[7] reported four older children who had >2-fold elevated serum creatinine concentrations after receiving normal doses of vancomycin. All of them were also being treated with an aminoglycoside antibiotic. Renal function returned to normal after the treatment.

Considering these few reports nephrotoxicity is the most common finding in overdosage of vancomycin in pediatric patients. It appears to be reversible in all children reported. In our patients we found only a minimal reduction of the creatinine clearance, calculated with the Schwartz formula, which serves only as an estimation of renal function. The tubular pattern in the urine protein electrophoresis and the elevated NAG concentration returned rapidly to normal. It is unclear whether this renal tubular damage was a direct toxic effect of vancomycin or caused by the transient relatively mild depression of the circulation and renal hypoperfusion during the occurrence of the RMS. No other toxic effects were noted.

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