Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Risk of Skin Necrosis Related to Injectable Vancomycin in Critically Ill Newborn Infants

Sixtine Gilliot (sixtine.gilliot.etu@univ-lille.fr)
Regional and University Hospital Centre Lille: Centre Hospitalier Universitaire de Lille
Mohamed Riadh BOUKHRIS
Regional and University Hospital Centre Lille: Centre Hospitalier Universitaire de Lille
https://orcid.org/0000-0002-1597-0320
Morgane Masse
Regional and University Hospital Centre Lille: Centre Hospitalier Universitaire de Lille
Laurent Storme
Regional and University Hospital Centre Lille: Centre Hospitalier Universitaire de Lille
Bertrand Decaudin
Regional and University Hospital Centre Lille: Centre Hospitalier Universitaire de Lille
Pascal Odou
Regional and University Hospital Centre Lille: Centre Hospitalier Universitaire de Lille
Kevin Le Duc
Regional and University Hospital Centre Lille: Centre Hospitalier Universitaire de Lille

Case report

Keywords: vancomycin, adverse drug event, neonatal intensive care, neonatal sepsis

Posted Date: March 6th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-281477/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Skin necrosis caused by the administration of vancomycin via a peripheral venous catheter is rarely diagnosed. We report a case of a male infant born at 30 weeks' gestational age who developed a skin necrosis, most probably related to vancomycin administration on a peripheral venous catheter. The frailty of this critically ill newborn probably increased its risk of exposition to adverse events. To prevent any damaging effect, the administration of vancomycin at a concentration lower than 2.5 mg/mL should be recommended when a central venous catheter is not available for the administration of injectable vancomycin in critically ill newborn.

Background

Vancomycin keeps on being widely used in the empiric probabilistic treatment of invasive bacterial infections in neonates to cover Gram-positive pathogens. Effectively, Staphylococcus Aureus and coagulase-negative staphylococci are among the most common pathogens leading to late-onset sepsis in neonates.[1] If the hindsight concerning the use of vancomycin is now important, the occurrence of adverse effects remains an issue in the neonatal therapeutic management.

The most common cutaneous adverse event related to the infusion of vancomycin is the Red man syndrome. Physiopathology is related to an anaphylactoid reaction, caused by the degranulation of mast cells and basophils, resulting in the release of histamine independent of preformed IgE or complement. Signs were reported to appear few minutes after an infusion started or early after its completion. To prevent its occurrence, international guidelines have warned that vancomycin should be administered diluted and infused over a period of at least 60 minutes or at a rate of 10 to 15 mg/min (≥ 1 hour per 1,000 mg) to minimize infusion-related adverse events.[2]

A less known adverse event related to the infusion of vancomycin in adults has been reported in the literature: skin necrosis.[3] We aim to promote awareness concerning the occurrence of a skin necrosis related to a 5mg/mL concentration of vancomycin infusion in a preterm infant.

Case Presentation

A male infant born at 30 weeks' gestational age with a birthweight of 1245 g was admitted to the neonatal intensive care unit (NICU) at Lille University Hospital in a context of induced-prematurity for a congenital cardiopathy. His hospitalization was marked by the apparition of infection leading to antibiotics injection. Intravenous vancomycin therapy started on the 6th day of life based on clinical symptoms of bacteremia. On the 8th day of life, the addition of many injectable continuous medications required the insertion of a peripheral venous catheter, dedicated to intermittent injections. The following drugs were infused through the catheter: piperacillin-tazobactam, furosemide, caffeine citrate, acetaminophen, hydrocortisone succinate and vancomycin. Vancomycin was administered two hours

after catheterization via a one-hour long infusion. Forty-eight hours later, a progressive skin necrotic lesion appeared one inch above the needle-site injection (shown in Fig. 1).

The intravenous line was immediately removed. A sterile gauze dressing was applied on the necrotic zone until its total regression. The case was declared to the Lille Regional Pharmacovigilance Centre (number LL20201014).

Discussion And Conclusions

Among the injectable medications administered via a peripheral venous catheter, vancomycin has been reported to irritate the vascular wall, due to its acid (2.8–4.5) pH. The vancomycin concentration of 5 mg/mL that was peripherally administered in our case is widely used in infants or neonates and had not yet been reported to be harmful. However, an in vitro study has demonstrated that 5mg/mL vancomycin induces a loss of viability of 50% of the initial pool of endothelial cells within 24 hours. Vancomycin may therefore damage endothelial cell significantly from a 2.5 mg/mL concentration.[4] A similar delay between administration of vancomycin and apparition of a skin lesion has been reported previously in an adult patient.[3]

It is of current knowledge that vancomycin is preferentially given continuously using a central catheter. In NICU, the central venous catheter is often dedicated to the administration of continuous low-rate medications and the peripheral venous catheter to the administration of intermittent injections. Concerning the injection of vancomycin, the loading dose is preferentially given on central catheter. However, it may be given via peripheral venous catheter when the use of numerous continuous medications and their potential incompatibilities with vancomycin require the use of independent peripheral lines. Otherwise, a peripheral administration of the loading dose of vancomycin will also be preferred if the only available central venous line is used to administer continuous injectable medications with narrow therapeutic ranges to the patient (i.e. insulin, norepinephrine, heparin injection) because of the high risk of increasing harmfully the administration rate of these latter drugs.

The frailty of critically ill newborns increases their risk of exposition to adverse events. Their inflammatory and hypercatabolic state influence the high susceptibility of this population to vancomycin endothelial toxicity. Endothelial toxicity of vancomycin must be considered as skin necrosis can be an entry point to a bacteremia and thus worsen the outcome of the vulnerable preterm newborn infants.

The combination of irritant intravenous drugs administered on a peripheral venous catheter, i.e. furosemide and caffeine in our case, may have enhanced the cumulative endothelial toxicity. If this co-toxicity has not been studied yet, a recent article tested the toxicity on endothelial cells viability when vancomycin was combined with piperacillin-tazobactam, revealing no excess cell death compared with the cell death rate from vancomycin alone.[5]

Finally, evidence suggests that presence of particles in infusion fluid was a major cause of chemical phlebitis,[6] supporting that use of in-line intravenous filters could reduce infusion particles.[7]

To prevent any damaging effect, the administration of vancomycin at a concentration lower than 2.5 mg/mL should be recommended when a central venous catheter is not available for the administration of injectable vancomycin. The combination of irritant injectable drugs administered on a peripheral venous catheter should be avoided even when rinsing is performed after each infusion, to limit the cumulative endothelial toxicity at the venous access point. The use of in-line intravenous filter must be considered for each antibiotic infusion in critically ill infants.

Declarations

Acknowledgements

We thank Benoit Catteau, MD, Pediatric Dermatologist, Louise Gaboriau and Sophie Gautier, PhD, Pharmacists in the Lille Regional Pharmacovigilance Centre, for their advice and expert opinion.

Statement of Ethics

The parents gave their written and informed consent to publish the case report, including the publication of the image.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

None declared

Author Contributions

S. Gilliot contributed to formal analysis, writing, review and editing of the final version.

R. Boukhris and K. Le Duc contributed to formal analysis, writing, review of the final version.

M. Masse, B. Décaudin, P. Odou, and L. Storme contributed to review of the final version.

References

1. Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath P. Neonatal sepsis: an international perspective. Arch Dis Child Fetal Neonatal Ed 2005;90(3):F220-4.
2. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2020;77(11):835-64.

3. Hoelen DWM, Tjan DHT, van Vugt R, Geert van der Meer Y, van Zanten ARH. Severe local vancomycin induced skin necrosis. Br J Clin Pharmacol 2007;64(4):553-4.
4. Drouet M, Chai F, Barthélémy C, Lebuffe G, Debaene B, Décaudin B, et al. Influence of Vancomycin Infusion Methods on Endothelial Cell Toxicity. Antimicrob Agents Chemother 2015;59(2):930-4.
5. Drouet M, Chai F, Barthélémy C, Lebuffe G, Debaene B, Décaudin B, et al. Endothelial Cell Toxicity of Vancomycin Infusion Combined with Other Antibiotics. Antimicrob Agents Chemother 2015;59(8):4901-6.
6. Campbell L. I.v.-related phlebitis, complications and length of hospital stay: 1. Br J Nurs 1998;7(21):1304-6, 1308-12.
7. Roberts JA, Taccone FS, Udy AA, Vincent J-L, Jacobs F, Lipman J. Vancomycin Dosing in Critically Ill Patients: Robust Methods for Improved Continuous-Infusion Regimens. Antimicrob Agents Chemother 2011;55(6):2704-9.

Figures

A

IV drugs	Concentrations (mg/mL)	8th day of life	9th day of life	10th day of life	11th day of life
Vancomycin	5	10 PM			
Acetaminophen	7.5	10 PM	11 AM – 11 PM	11 AM – 11 PM	
Caffeine	2.5		12 PM	12 PM	
Hydrocortisone hemisuccinate	2.5		12 PM – 8 PM	4 AM – 6 PM – 8 PM	
Furosemide	10		5 AM – 12 PM – 8 PM	2 PM – 6 PM – 10 PM	2 AM
Piperacilline/tazobactam	37.5		4 PM	12 AM – 8 AM – 4 PM	12 AM

B

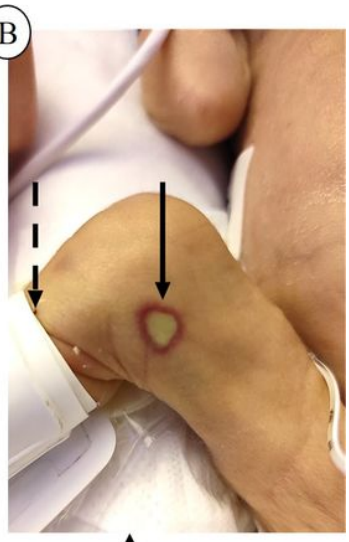

Figure 1

A. Daily chronology of injections on the peripheral venous catheter. B. Skin necrotic lesion related to vancomycin infusion appeared in the flow area of the vein of the right leg. The dotted arrow points out the injection site on the left and the plain arrow points out the skin necrosis area on the right. Legend: IV, intravenous.