IV Ciprofloxacin-Induced Phlebitis: Investigating the Impact of Pharmaceutical and Process-Related Factors on Patient Safety

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Abstract

Transient phlebitis is a rare but notable adverse reaction that can occur following intravenous administration of various medications, including ciprofloxacin, an antibiotic recognized for its broad-spectrum activity. This case report discusses a 48-year-old male patient with poorly controlled type 2 diabetes who developed phlebitis after receiving undiluted ciprofloxacin via a peripheral intravenous line. Symptoms emerged within 24 hours, characterized by swelling and redness at the injection site, prompting the discontinuation of the medication. Analysis revealed that improper dilution and rapid infusion rate were major factors contributing to the development of phlebitis. This underscores the importance of adhering to guidelines provided in product information leaflets for intravenous drug preparation and administration. This case emphasizes the critical need for healthcare professionals to follow recommended protocols to reduce the risk of infusion-related complications, especially in patients with underlying comorbidities.
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Keywords: Thrombophlebitis; Ciprofloxacin; Adverse Drug Reaction

Introduction

Transient phlebitis is a rare adverse reaction which has been reported after intravenous injection of some medications including morphine, pethidine, meperidine, propofol, diphenhydramine, and antibiotics with highest risk for dicloxacillin and erythromycin, cefuroxime, cloxacillin and aminoglycosides (1–5). Phlebitis is an inflammatory reaction in the vascular endothelium, and tunica intima of the vein, and is associated with erythema, pain, warmth, tenderness, and swelling of the vein. Various risk factors can be involved in the occurrence of this complication which can be categorized to product-related factors (such as pH, osmolarity, presence of particulate matters, and intrinsic properties of the drug substance), infusion process-related factors (such as dilution of the infusing medication, rate of infusion, intravenous catheter placement site and technique and duration of catheterization), and patient-related factors (such as the patients' comorbidities) (1,2,5–8). Usually, symptoms completely resolve by discontinuing the causative medication. The exact mechanism of transient reactive phlebitis is unknown (7). However, previous studies have hypothesized several possible mechanisms such as direct hypersensitivity caused by the medication, damage to endothelial cells associated with the acidic pH, IgE-mediated histamine release, local mediator release, direct activation of C-nociceptors and activation of the kallikrein-kinin system with the release of bradykinin (3,7,9). Ciprofloxacin is a broad-spectrum antibiotic belonging to the fluoroquinolone class antibiotics, which was patented by Bayer A.G. in 1983 and subsequently approved by the US Food and Drug Administration (FDA) in 1987. This antibiotic, as one of the most successful and widely used compounds in the class of fluoroquinolones, has since been marketed worldwide and is now known under more than 300 different proprietary names worldwide for different indications such as urinary tract infections, pyelonephritis, bone and joint infections, skin infections, nosocomial pneumonia, lower respiratory tract infections, and inhalational anthrax post-exposure in adult and pediatric patients (10–14). Ciprofloxacin is available in multiple dosage forms including tablets, extended-release tablets, capsules, oral suspension, ophthalmic and

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otic drops, and intravenous solutions. Injectable solutions of ciprofloxacin are available in 200mg and 400mg doses which are in forms of 200mg/100mL and 400mg/200mL ready-for-use infusion solution, and 200mg/20mL and 400mg/40mL concentrate for solution for injection. The concentrate for solution for injection preparations such as ciprofloxacin 200mg/20mL must be diluted before use. In case of using concentrated solutions, the intravenous dose should be prepared by aseptically withdrawing the concentrate from the vial and diluting with a suitable and compatible intravenous solution to a final concentration of 1–2 mg/mL (10). The prepared solution should be infused over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place and preferably through CV-lines (10). If the concomitant use of IV ciprofloxacin and another drug is necessary, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug (10). Moreover, it is very important that the intended injection solution have the quality characteristics of a sterile pharmaceutical product such as safety, sterility, absence of pyrogens, absence of particulate matter, isotonicity, compatibility and stability (15). IV Ciprofloxacin contains lactic acid as a solubilizing agent and the pH range is 3.5 to 4.6 for the 0.2% ready-for-use infusion solutions and 3.3 to 3.9 for the concentrated form according to USP-NF 2023 (10). Intravenous infusion of ciprofloxacin could be associated with hypersensitivity reactions, and infusion site reactions (e.g., phlebitis, thrombophlebitis) (10). Thrombophlebitis is a rare adverse drug reaction reported with ciprofloxacin, and there are only few case-repots of ciprofloxacin induced phlebitis in the literature so far, to the best of our knowledge. According to these case reports, development of thrombophlebitis following ciprofloxacin intravenous injection could be related to different factors including underlying comorbidities of the patient, characteristics of product (e.g., pH and osmolality), medication error (e.g., dilution method, intravenous catheter insertion site and technique and dwelling time) (7,9). Recognizing the key associated factors helps to prevent and control this rare complication.

Case presentation

We present the case of a 48-year-old male patient with a weight of 70 kg and a history of poorly controlled type 2 diabetes. He was diagnosed with lower limb cellulitis and was hospitalized at a tertiary hospital, Karaj, Iran. Diagnosis and management of the case seemed challenging due to the patient's history of poorly controlled diabetes. The antibiotic regimen for the patient included ciprofloxacin 200 mg IV infusion twice per day plus clindamycin 600 mg IV infusion three times per day. The antibiotic therapy was initiated with Ciprox® (ciprofloxacin as lactate manufactured by Ronak pharmaceutical co.), 200 mg/20 mL concentrate for solution for intravenous injection, administered via a peripheral line on the patient's right arm, twice daily. The day after the first dose injection, phlebitis had been noticed with clinical manifestations including swelling of the vein, localized redness, and pain. The injection line was changed to the left hand, but phlebitis appeared on the left hand as well. Ciprofloxacin treatment was stopped after the appearance of clinical symptoms and topical NSAIDs were used for symptom management. According to our follow-ups, we found out that Ciprox® concentrate for solution for IV infusion was injected directly to a peripheral line on right arm without any further dilution within only 20 minutes. According to the product information leaflet, Ciprox® should be diluted with a suitable solution such as Normal saline to the concentration of 1-2mg/mL. If prepared according to this method, the final pH and osmolarity will be in the appropriate range. The product-related factors, including pH, osmolality and particulate matter were reviewed in the analysis sheet of the reported batch number of the product and repeated to ensure accuracy, and all of the critical quality attributes were approved based on USP-NF limits. Since the product passed the relevant tests in terms of pharmaceutical properties, the occurrence of phlebitis due to problems in the manufacturing process of the medicinal product was ruled out. In this case, our analysis suggests that the primary factor contributing to the complication was the failure to dilute the concentrated solution before administering it intravenously at a rapid rate (nearly 20 drops/min). In addition, the peripheral vein chosen for puncture was too small and tortuous, causing the medication to become temporarily concentrated locally within blood vessels. which can be quite irritating, and can easily cause phlebitis.

Discussion

Intravenous administration of antibiotics is a known risk factor for transient phlebitis. According to literature, dicloxacillin, erythromycin, cefuroxime, cloxacillin and aminoglycosides have the highest risk for antibiotic induced phlebitis most probably due to chemical irritation of the endothelium (4, 16). While ciprofloxacin-induced phlebitis can be attributed to the innate properties of the drug substance, it is crucial not to overlook other factors that may contribute to the development of phlebitis. Adherence to aseptic techniques and the therapeutic principles, and correct nursing measures are necessary to reduce the incidence of this complication. As mentioned earlier, inappropriate dilution of infusing medication and high rate of infusion are two important factors in the occurrence of phlebitis (7). Parenteral fluoroquinolones

have significant direct harmful effect on endothelial cell function and dilution of the concentrate solution may reduce the risk of this effect (16). The dilution of the concentrated injection solution of ciprofloxacin should be done exactly according to the instructions provided on the product information leaflet of the medicine by a healthcare professional. Also, it is important to choose a suitable injection site, such as a large vein for injection and the infusion rate should be strictly controlled (3, 8, 9). Overall, some of the most suggested conditions to reduce the risk of phlebitis associated with intravenous ciprofloxacin include correct dilution of the concentrated medication, slowing the rate of infusion, and preferably using larger veins through central line for intravenous infusion (3, 7–9). In addition, educating healthcare professionals and the proper explanations to the patient are particularly important.

Conflict of interest:

This article discusses phlebitis associated with IV Ciprofloxacin, a product developed and marketed by Ronak company. The authors are affiliated with Ronak Company and hold various roles within the organization. Despite this affiliation, every effort has been made to present the information in this article objectively and transparently, grounded in the best available data.

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