Azithromycin Extravasation in a Pediatric Patient

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Objective: To report a case of azithromycin infiltration and extravasation in a pediatric patient.

Case Summary: A 12-month-old African American male, between chemotherapy cycles for acute myelogenous leukemia, self-dislodged his central venous catheter. A peripheral catheter was placed in the right dorsal hand and, 2 days later, azithromycin for injection infiltrated at the infusion site. Several bullae formed in the first web space and a few areas of epidermolysis, each <2 cm wide, later appeared on the forearm. Treatment included warm compresses, adaptee dressing, topical antibiotics, splint placement, and arm elevation. Four months after the incident, there was no visible impairment or restriction to the toddler's use of the right hand or arm. The only residual finding was an area of hypopigmented skin in the dorsal web between the first and second fingers.

Discussion: As of February 10, 2005, this is the first case published in the English-language literature describing intravenous azithromycin infiltration and extravasation. Infiltration occurs generally by 3 mechanisms. These include the catheter dislodging or causing a hole in the vessel wall, intravenous fluid irritating the vessel wall leading it to rupture or leak, or backflow of intravenous fluid through the catheter insertion site.

Conclusions: Complications can occur secondary to intravascular therapy, including extravascular extravasation. In this case, infiltration and extravasation injury were probably related to azithromycin. Immediate detection and treatment are critical to decrease morbidity associated with infiltration events.

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Intravascular therapy is essential for providing nutrition, medications, electrolytes, blood products, chemotherapy, and fluids to hospitalized patients, especially in infants and children. It has been estimated that around 80% of hospitalized patients will receive intravenous therapy.[1] Venous access devices or central venous catheters (CVCs) are vital in the treatment of children with malignancies.[2]

Despite the benefits of intravascular therapy, complications can occur, including extravascular infiltration. The incidence of pediatric peripheral intravenous infiltration ranges from 11% to 23%.[3] Children and neonates are likely to have less phlebitis and more infiltrations versus adults, possibly due to proportionally smaller vessels that are more likely to react and venoconstrict.[1] Younger children are particularly at risk, as they cannot describe or pinpoint painful sensations.[4]

Infiltration involves intravenous fluid leaking out of the vessel into surrounding tissue. Extravasation occurs when the intravenous fluid causes tissue damage through localized increased pressure and chemical irritation.[3] After infiltration, the area often hardens and an ulcer may form. The area may heal slowly or progress to an area of severe necrosis. The severity of the extravasation event is proportional to the volume and concentration of the infiltrated drug and its properties, the site of the reaction, and the degree of soft-tissue uptake.[5] We present an extravasation probably secondary to azithromycin infiltration in a pediatric patient.

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CASE REPORT

A 12-month-old, 9-kg African American male with acute myelogenous leukemia (9:11 translocation) was admitted on December 26, 2001, for intravenous induction chemotherapy according to Children's Cancer Group protocol CCG-2961 (unpublished data). The institutional review board approved the protocol, and the parents provided written informed consent. He had received cycle 2 of the protocol, which consisted of idarubicin, dexamethasone, cytosine arabinoside, 6-thioguanine, etoposide, and daunorubicin 15 days earlier, and was awaiting recovery of his blood counts which, on February 19, 2002, were white blood cells $1.8 \times 10^3/mm^3$, hemoglobin 7.2 g/dL, and platelets $60 \times 10^3/mm^3$. The absolute neutrophil count was 20 cells/mm^3 and serum creatinine level was 0.3 mg/dL.

On January 14, the patient had a left subclavian percutaneous 5-French double-lumen CVC placed. He pulled out this catheter on February 17. A temporary peripheral catheter was placed that day into the right dorsal hand, until a central catheter replacement could be scheduled. On February 19, the patient was receiving multiple antimicrobials for neutropenic fever and, due to persistent fever, intravenous azithromycin and vancomycin were empirically added to the existing antibiotic regimen of intravenous imipenem/cilastin and metronidazole and oral itraconazole and trimethoprim/sulfamethoxazole. Metronidazole was started on February 8 and imipenem/cilastin was started on February 6; both had last been infused at least 6 hours previously with no complications. Hydration fluid consisting of dextrose 5%/NaCl 0.45% with potassium chloride 20 mEq/L was continuously infusing at 35 mL/h. The nurse, verified the azithromycin prescription as 105 mg in 53 mL of dextrose 5% in water, resulting in a drug concentration of 2 mg/mL, to be infused over 60 minutes before administering the drug to the patient. The infant's peripheral catheter in the right dorsal hand was patent before azithromycin administration.

The nurse noted infiltration into the dorsal aspect of the right hand at the completion of the azithromycin infusion, discontinued the hydration fluid, and paged the medical team. The radial pulse could not be detected on manual examination. The right arm was newly firm and distended from fingertips to the shoulder and cool to the touch, with no bruising or bleeding. The child's fingertips blanched when compressed with a one-second capillary refill. Several bullae had formed on the distal arm. Doppler examination showed strong ulnar and brachial pulses. The arm had no evidence of arterial vascular compromise. Warm compresses were applied to the right arm to facilitate diffusion of fluid, and the peripheral catheter was removed.

In the early morning of February 20, repeat Doppler examination revealed strong ulnar, radial, and brachial pulses. The right arm was still firm and swollen; warm compresses were continued. The plastic surgery service verified multiple intact blisters above the dorsal first web space and wrist with warm digits, normal capillary refill, full passive range of motion, and no signs of compartment syndrome. Intervention with Adaptic dressing (Johnson & Johnson, Arlington, TX), topical bacitracin, splint placement in the volar position, and elevation were implemented.

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The radial pulse could not be detected on manual examination.

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On February 22, the blisters were still intact and the arm was less edematous. Cellulitis was not detected. However, there were a few areas of epidermolysis, each <2 cm in size, on the forearm. Over the next week, swelling in the arm decreased and no new epidermolysis or cellulitis occurred. Continued intervention included topical bacitracin to the intact first dorsal web blister and topical silver sulfadiazine to the open wrist blister.

The affected areas continued to improve. The first dorsal web blister opened on March 3 and showed pink re-epithelialized skin underneath. Splint and dressing changes were discontinued on March 7. Four months after the incident, there was no visible impairment or restriction to the toddler's use of the right hand or arm. The only residual finding was an area of hypopigmented skin in the dorsal web between the first and second fingers.

Discussion

In this patient, azithromycin had been dosed according to the American Society of Health-System Pharmacists: Pediatric Injectable Drugs (PID) recommendations[6] and was infusing at the PID and manufacturer's adult recommended concentration and rate of 2 mg/mL over one hour.[7] The pH range of azithromycin in dextrose 5% in water ranges from 6.4 to 6.8,[8] which is unlikely to have contributed to the catheter failure. The replacement fluids had been continuously infusing for over one week without complications, are compatible with intravenous azithromycin, and therefore are also unlikely to have contributed to the catheter failure.[1] No medication had been infused for at least 6 hours, and the intravenous infusion site was patent before azithromycin administration.

The use of intravenous macrolides, specifically erythromycin, is associated with an increased risk of throm-

bophlebitis.[9-10] Intravenous azithromycin is better tolerated, but pharmacokinetic data in pediatric patients are lacking.[12] The manufacturer reports that the safety and efficacy of intravenous azithromycin in patients <16 years of age have not been established. Adverse effects from azithromycin intravenous infusion in adults have included pain at the injection site and local inflammation in 6.5% and 3.1% of patients, respectively.[7] The incidence of pain and inflammation is similar at the manufacturer's 2 recommended concentrations and rate of infusion (2 mg/mL over 1 h or 1 mg/mL over 3 h). In the manufacturer's clinical trials, adults uniformly experienced local site pain and inflammation upon receiving azithromycin at concentrations >2 mg/mL.

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The use of intravenous macrolides, specifically erythromycin, is associated with an increased risk of thrombophlebitis.

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Infiltration occurs generally by 1 of 3 mechanisms. The first involves the catheter dislodging or producing a hole in the vessel wall, either during catheter insertion or adjustment. The second involves the catheter and/or the intravenous fluid irritating the vessel wall, leading it to rupture or leak, which can occur especially with hyperosmolar solutions or large-gauge catheters. The third involves the backflow of intravenous fluid through the catheter insertion site due to increased intravascular resistance,[3] possibly from venoconstriction induced by the intravenous fluid.[1]

Symptoms associated with infiltration may include local burning, sometimes severe in nature, erythema, and edema. Other signs of potential infiltration include a lack of blood return in the intravenous catheter and decreased or absent free flow from intravenous fluids.[5]

It is recommended that, after infiltration, catheters be removed immediately. The first catheter of therapy for a non-vesicant infiltration is elevation of the extremity. Application of warmth allows fluid distribution, although moist heat can trap caustic fluids, inducing progressive damage. Regular assessment of the infiltration site should continue after catheter removal. Initial signs may not be an accurate predictor of subsequent damage to the subcutaneous tissue. Cellulitis, scarring, loss of function, nerve damage, and/or contractures can result.[3] A reference for the management of chemotherapy infiltration is available.[13]

Different methods are available to reduce infusion failure. These include minimizing length of individual infusion sites to 48–72 hours, using solutions of neutral pH, and utilizing in-catheter filters. Pharmacologic methods used with variable success for non-vesicant medications include admixture of heparin, corticosteroids, and vasodilators into the infusion solution.[1]

The etiology of azithromycin infiltration in this pediatric patient is unknown. It may have included catheter dislodgement from patient activity or movement and/or vessel wall irritation. Pediatric peripheral catheters remain in place until patency is lost; our patient's peripheral catheter had been in place 48 hours at the time of the event.

No previous reports of azithromycin infiltration and/or extravasation were noted in a MEDLINE search in July 2003. There were also no published recommendations regarding treatment of azithromycin infiltration. An objective causality assessment using the Naranjo algorithm revealed that the infiltration and extravasation injury was probably related to azithromycin.[14] The patient was supportively treated with repeated warm compresses, splint placement, and elevation. He has recovered without apparent permanent disability.

Conclusions

Complications can occur secondary to intravascular therapy, including extravascular extravasation. In this case, infiltration and extravasation injury were probably related to azithromycin. Immediate detection and treatment are critical to decrease morbidity associated with infiltration events. ≏

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