A Case of Metronidazole Injection Infiltration Without Sequelae

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Abstract

Purpose: This report describes a case of metronidazole injection infiltration which contrasts the sole other case report in the literature at this time, as the patient described herein experienced mild signs and symptoms with prompt resolution and no significant sequelae. **Summary:** The patient experienced metronidazole injection infiltration during administration open to gravity via an 18-gauge peripheral catheter in the left brachial vein. The site was examined at bedside within approximately 30 minutes of the incident and was noted to be slightly edematous, erythemic, and painful in terms of a 5.5 × 6.6-cm area. No blanching, blister formation, induration, skin discoloration, or diminished capillary refill were observed. The event was conservatively managed in the form of catheter discontinuation and marking of the affected area with a patient skin marker, as hyaluronidase was not administered due to a product osmolarity of ~314 mOsm/L and pH of 5.8. A bedside evaluation the next morning revealed full resolution of the previously described symptoms. The patient was discharged from the facility 11 days later without further complications from the infiltration event. **Conclusion:** We describe a case of metronidazole injection infiltration which did not require pharmacologic or nonpharmacologic interventions and resulted in complete resolution. This case supplements the current literature by contrasting the sole other case report which resulted in profound necrosis near the intravenous access site. This case suggests metronidazole infiltrations may not require clinician alarm or treatment if events occur under circumstances similar to that which is presented.

Keywords

metronidazole, infusions (intravenous), extravasation of diagnostic and therapeutic materials, infiltration, case reports

Introduction

Complications of intravenous medication therapy include infiltration and extravasation—two terms often used synonymously despite having distinct characteristics. Although the magnitude of tissue damage associated with extravasations can vary due to a multitude of factors, significant extravasations are often noted to involve vesicle formation, necrosis, and sometimes more severe complications such as skin grafting and amputation.^{1–5} A number of medication properties composing a “vesicant” contribute to extravasation injury, as cytotoxic mechanisms, vasoconstrictive properties, hyperosmolarity, pH extremes, or other unknown irritant properties play key roles.^{2–10} Infiltrations, on the contrary, involve agents without these potentiating factors and may include fluids such as lactated ringers, isotonic concentrations of sodium chloride, and a variety of medications. Infiltrations still pose a risk for complications, as certain volume-dependent issues can arise such as compartment syndrome.^{3,4} Although clinicians can potentially predict severity of extravasation injury based upon cytotoxic or vasoconstrictive mechanisms, it is largely unknown what drug osmolarities and pHs should warrant concern. Another confounding element includes the fact that

in many cases, determination of whether or not an agent is considered a “vesicant” is based upon one or several case reports. It is difficult to extrapolate information from these case reports given inherent heterogeneity of the situations in terms of patient, drug product, and drug administration factors. This, combined with publication bias of clinical sequelae, may result in falsely heightened alarm and even overtreatment should suspected “extravasation” occur.

Based upon a search of the biomedical literature as well as pharmaceutical organization conference abstracts, only a singular case report involving metronidazole injection infiltration was identified.¹¹ This patient experienced profound gangrene involving the dorsum of the right hand and a considerable amount to four fingers. Given the lack of cases

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Figure 1. Intravenous medications administered during emergency department encounter.

involving metronidazole infiltration available at this time, we report a case which contrasts the limited but seemingly concerning profile of this medication.

Case Presentation

The patient, a 38-year-old Caucasian female (weight approximately 63 kg), presented from an outside facility with left upper quadrant pain and concern for pancreatitis versus bowel perforation. The patient had a history significant for a perforated gastrointestinal ulcer, peptic ulcer disease, and a partial colectomy and cholecystectomy in 2014. She reported 10 out of 10 left-sided abdominal pain for the past three or four days with worsening pain today including radiation to her chest. She also reported bright green emesis 10 times since earlier that morning. Review of systems was positive for fever, chills, activity change, and appetite change. She had leukocytosis (white blood cell: 18.7 K/ μ L), computed tomography denoting edema near the duodenum, and a small amount of pneumoperitoneum. Therefore, she was initiated on intra-abdominal antimicrobial therapy consisting of intravenous metronidazole and levofloxacin.

The emergency department registered nurse caring for the patient called the clinical pharmacist in the emergency department at 21:36 PM regarding infiltration of intravenous metronidazole injection (500 mg in 100-mL sodium chloride). This product was initiated at 21:28 open to gravity, and thereby faster than the standard 60-minute infusion time, through an 18-gauge peripheral catheter in the left brachial vein. Based upon product remaining, 50 mL was estimated as a conservative volume of medication which had infiltrated (estimated administration rate $\sim$ 375 mL/h). Levofloxacin 750 mg in 150-mL dextrose 5% water was administered successfully open to gravity via this same access site prior to metronidazole starting at 21:00 and ending at an estimated time of 21:20 (estimated rate of $\sim$ 450 mL/h). The intravenous catheter was confirmed to be patent during and after administration of levofloxacin by the registered nurse. Other therapies administered via this

Figure 2. Metronidazole infiltration site (L brachial vein) at 22:00.

intravenous catheter during the emergency department stay are denoted in Figure 1.

Based upon bedside examination at approximately 22:00, the site was found to be slightly edematous and erythemic (Figures 2 and 3). The involved site measured approximately 5.5×6.6 cm. There were no observed blanching, blister formation, induration, skin discoloration, or diminished capillary refill. The patient reported some pain at the catheter site, but no coolness, burning, numbness, or warmth. The Infiltration/Extravasation Scale was utilized to stratify the patient's event and was found to be a 2 out of 4.^{1,12} Interventions performed included catheter discontinuation, cleansing of the catheter site with alcohol, marking of the infiltration site with a patient skin marker, and patient education on alarm symptoms of infiltration such as extension of edema, erythema, decreased range of motion, and diminished sensation. The decision was made to not treat the site with hyaluronidase due to an estimated osmolarity of $\sim$ 310 mOsm/L and a pH of 5.8 (pH range: 4.5-7).¹³ The recommendation provided to the treatment team consisted of monitoring the left brachial infiltration site at least every two hours for the next 24 hours. No specific recommendations were made with regard to thermal compresses or extremity elevation. Replacement intravenous catheter access was obtained via the right internal jugular vein in the emergency department.

Figure 3. Metronidazole infiltration site (L brachial vein) at 22:00 (site marked).

Figure 4. Metronidazole infiltration site (L brachial vein) at 09:00 next morning.

Shortly after the metronidazole infiltration event, the patient was evaluated by the colorectal surgery service and taken to the operating room due to concern for perforation of a gastric ulcer. There, an exploratory laparotomy and Graham patch closure of a gastric ulcer were performed. And, the remaining metronidazole therapy was not continued. Approximately 12 hours after the infiltration event, a bedside evaluation of the site by the same clinical pharmacist was performed with seemingly full regression of edema and erythema (Figure 4). The patient denied pain at the intravenous access site and no ecchymosis, necrosis, or dermal discoloration were found. Extremity elevation and thermal application are believed to have not occurred between the infiltration event and reevaluation. She was ultimately discharged 11 days later after postoperative complications consisting of left-sided pleural effusion status post image-guided thoracentesis as well as achievement of goals for oral intake and pain management.

Discussion

We describe an infiltration case report involving metronidazole injection which was managed with neither pharmacologic (eg, hyaluronidase) nor nonpharmacologic (eg, thermal compresses and elevation) treatment and showed marked improvement by 12 hours after insult. Strengths of this case include the fact that detailed information is available with regard to all medications administered via the implicated intravenous catheter including drug product concentrations. Similarly, a bedside clinical emergency medicine pharmacist was able to assess, evaluate, and document all details pertinent to the event nearly immediately after it occurred. In addition, this patient stayed under direct observation within the health system for 11 days after the infiltration event which provides a reasonably long-term period for the basis of outcome assessment. Although delayed complications have been previously described with extravasation events as a whole, we are not familiar with any cases where marked improvement was observed shortly after the event and prior to future significant sequelae. One large limitation of this case is the fact that the exact volume of metronidazole infiltration is not known; however, at bedside, the clinical pharmacist and registered nurse were able to approximate the implicated volume as being 50 mL. Another limitation is that other medications were administered via the same intravenous catheter site including levofloxacin immediately prior to metronidazole administration; however, vessel patency was confirmed prior to metronidazole administration. If the patient had experienced a significant negative outcome, the administration of levofloxacin immediately prior to metronidazole would have raised some question as to which drug was the culprit.

The management of infiltrations and extravasation events should often be patient-centered and individualized based upon reported symptoms, comorbidities, drug product properties, volume which infiltrated, and any clinical findings. Upon assessment of the metronidazole injection physiochemical properties consisting of an osmolarity close to isotonic (~ 310 mOsm/L) and a pH of 5.8 (range: 4.5-7), as well as the fact that the patient had relatively mild symptoms (slight erythema/edema/pain), it was decided that the risk for significant injury was low and no treatment was initiated. Much of the data utilized for theoretical cutoffs of concern for drug product osmolarity and pH are based upon conflicting phlebitis studies involving prolonged infusions in animal and human models.¹⁴⁻¹⁹ It is therefore not known what threshold should be used for consideration of hyaluronidase administration, generally speaking, for a hyperosmotic agent extravasation. Models have suggested that prolonged infusions with agents >600 mOsm/L cause phlebitis, but again, this cannot be extrapolated to extravasation events. Past case reports of dextrose 10% water (osmolarity ~ 505 mOsm/L) extravasations have been described in the literature with consequential morbidity; however, dextrose 10% solutions

inherently have a pH of 4.5 (range: 3.2-6.5), so it is unknown whether injury is due to the osmolarity, pH, or some other factor.²⁰ Similar to osmolarity, the pH at which clinicians should be alarmed is also largely unknown; however, it is generally accepted that alkaline solutions are relatively more caustic to tissues than acidic fluids.⁴

It should be noted that only one other case report involving intravenous metronidazole injection infiltration was identified in the literature via a PubMed and International Pharmaceutical Abstracts inquiry.¹¹ This case involved a 45-year-old patient who was placed on intravenous metronidazole and intravenous ampicillin therapy for antimicrobial therapy targeted against abdominal pathogens. This patient experienced an estimated 50-mL volume of metronidazole infiltration similar to our described case and subsequently developed “full blown gangrene” of the dorsal portion of his right hand and a large portion of 4 out of 5 digits within a day after the event. All laboratory markers were normal, and aspirin, pentoxifylline, and nifedipine were employed to mitigate the extensiveness of gangrene development. The authors should be commended for publishing the first identified case report involving metronidazole injection infiltration, as it is clear that more case reports and case series would contribute to the knowledge of metronidazole infiltrations. However, there are several aspects of information which would be of value for full understanding and evaluation of the reported metronidazole infiltration event. First, medication factors such as the dose, concentration, and solution vehicle of metronidazole therapy would give clinicians a sense as to the drug product’s osmolarity and potential for extravasation injury from a hyperosmolarity standpoint. Also, it is unclear whether the medications presented encompass all medications which were administered via the implied access site. Of course, if the intravenous access site had been utilized for other medication therapy, these would need to be considered in terms of potential culprit agents. The authors only comment on the fact that ampicillin and intravenous fluids were administered via an alternate access site, and it seems probable that a patient presenting with profound emesis and diarrhea potentially received other intravenous agents to aid symptom control during the inpatient admission including at least antiemetics. If by chance, promethazine was administered intravenously during the hospitalization and prior to the development of gangrene, we would consider this to be the most likely cause of the outcomes based upon past case reports.²¹⁻²³

Conclusion

We describe a case of metronidazole injection infiltration which did not require pharmacologic or nonpharmacologic interventions and resulted in marked resolution shortly after the event. This case supplements the current

literature by contrasting the sole other case report which resulted in profound necrosis near the intravenous access site. This case suggests intravenous metronidazole injection infiltrations may not require clinician alarm or treatment if events occur under circumstances similar to that which is presented.

Declaration of Conflicting Interests

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