Topical metronidazole for arterial insufficiency ulcers

BARBARA KAPLAN, PharmD
LEO B. GIBSON, JR, DO

The use of topical metronidazole has been limited to the treatment of acne rosacea, infected foot ulcers associated with diabetes mellitus, varicose veins, postirradiation ulcers, and dental conditions since the Food and Drug Administration approved the drug in 1988. Because of this agent's apparent effectiveness in treating anaerobic bacterial infections in such ulcers, the authors believed that treatment of arterial insufficiency ulcers with a solution of topical metronidazole would be a rational approach. They describe a 30-year-old man in whom bilateral lower extremity cellulitis developed as a result of arterial insufficiency. The patient's ulcers were unresponsive to intravenously administered antibiotics and whirlpool therapy. However, when a topical solution of metronidazole was administered, the ulcers began to heal and epithelialization at the ulcer sites occurred. The authors review others' studies concerning clinical use of topical metronidazole and suggest that further study is warranted. To the authors' knowledge, topical metronidazole solution for the treatment of arterial insufficiency and venous stasis ulcers has not been previously reported.

(Key words: Arterial insufficiency ulcers, topical metronidazole, lower extremity cellulitis treatment, metronidazole solution)

Dr Kaplan is assistant professor of clinical pharmacy and clinical assistant professor of family medicine, and Dr Gibson is an assistant professor of family medicine, West Virginia University–Charleston Division.

Correspondence to Barbara Kaplan, PharmD, Department of Clinical Pharmacy, School of Pharmacy, Robert C. Byrd Health Sciences Center, West Virginia University–Charleston Division, 3110 MacCorkle Ave, SE, Charleston, WV 25304.

Topical metronidazole gel was approved by the Food and Drug Administration (FDA) in late 1988. Even though topical metronidazole had FDA labeling only for the treatment of acne rosacea, the drug has been used to treat infected foot ulcers associated with diabetes mellitus, ulcers associated with varicose veins, postirradiation ulcers,[1] and dental conditions (for example, alveolar osteitis).[2] In addition, it has been designated an orphan drug by the FDA for use in the treatment of grade III and IV anaerobically infected decubitus ulcers.[3] Because of topical metronidazole's apparent effectiveness in treating anaerobic bacterial infections in such ulcers, we believed that extrapolation of these results to the treatment of arterial insufficiency ulcers was rational. Thus, we report a case in which topical metronidazole aqueous solution was used for the treatment of arterial insufficiency ulcers of the lower extremity.

Report of case

A 30-year-old man was seen in the emergency department with bilateral foot pain with redness and swelling of 2 weeks' duration. The patient had had a history of recurrent problems with his lower extremities since an airplane crash 7 years earlier in which he suffered extensive burns that required multiple surgeries and skin grafting. Approximately 1 week before hospital admission, bilateral cellulitis of the leg and foot with ulcerations was diagnosed, and the patient was placed on oral cephalexin and twice-daily whirlpool therapy. These treatment modalities did not alleviate symptoms.

The patient's medical history was significant for multiple infections and multiple surgeries on both feet since the airplane crash. In addition, the patient had had an Achilles tendon removed, all

toes amputated on the right foot, and all but the great toe amputated on the left. He had undergone multiple split-thickness skin grafting on the right forearm and legs. The patient had no other medical illnesses and was taking no medications except the antibiotic cephalexin and hydrocodone/acetaminophen for pain.

Physical examination revealed the man to have discomfort but no acute distress. The right forearm had multiple skin grafting sites; the right foot was significant for all toes having been amputated. There was extensive scarring, and the skin was hard and scaly secondary to what was thought to be arterial insufficiency. There was a small ulcer on the right arch, there were no palpable pulses, and the left lower extremity was red and swollen with a 3-cm ulceration on the dorsal aspect of the left foot which contained moderate necrotic tissue. There was also a 3-cm ulceration on the medial aspect of the left great toe which was very painful to palpation and contained foul-smelling necrotic tissue. The skin was hard and scaly, with multiple skin graft sites that were well healed and no palpable pulses; neurologically, the patient was intact. There was no visible granulation tissue within any of the ulcer sites.

The patient was hospitalized to receive intravenous (IV) antibiotics. He received ciprofloxacin IV empirically and wet-to-dry dressing changes twice daily in which a solution of metronidazole prepared with 0.6% hypotonic saline solution (2.5 g of metronidazole per liter of solution) was used. After the application of metronidazole topically, the arterial insufficiency ulcers began to improve within 48 hours. This improvement was evidenced by disappearance of the odor, removal of the necrotic tissue, and the appearance of healthy granulation tissue with minimal fibrinous exudate. Also, after 4 days, the beginning of epithelialization at the ulcer margins was noticed. The patient also received twice-daily whirlpool therapy. For pain, he received extended-release morphine sulfate and immediate-release morphine sulfate on an "as needed" basis. These medications controlled his pain very well.

Cultures from the affected foot grew gram-positive cocci, which were noted to be *Staphylococcus aureus*, which was sensitive to the ciprofloxacin (minimum inhibitory concentration <1). X-ray studies of the patient's lower extremities showed chronic changes, but there was no evidence of osteomyelitis. Specifically, the x-ray results indicated that there had been fusion of the first metatarsophalangeal joint with some surgical clips at the level of the great toe and in the proximal tarsal region. The distal fifth metatarsal had some deformity consistent with previous surgery at that site. In addition, there was bony fusion of the cuneiforms and cuboid. Results of other laboratory studies done throughout the patient's hospital stay were essentially unremarkable.

After 5 days' administration of IV antibiotics, it was decided that the patient had greatly improved and was stable enough to be switched to oral ciprofloxacin and discharged. Two weeks after discharge, the patient was seen at follow-up. His lesions continued to improve while the topical metronidazole dressings and oral ciprofloxacin were maintained. His ulcers had decreased markedly and healthy granulation tissue was noted; there was no exudate or odor. There was further evidence of epithelialization at the ulcer margins.

Discussion

The topical metronidazole formulation was developed as the result of concerns over possible toxicity from long-term oral therapy. Although the exact mechanism of antimicrobial action has not been fully elucidated, metronidazole is bactericidal, amebicidal, and trichomonacidal.[4] In general, metronidazole's spectrum of activity covers most obligately anaerobic bacteria and many protozoa, but it is inactive against most aerobic or facultatively anaerobic bacteria, fungi, and viruses.[5,6] Metronidazole does not appear to be appreciably absorbed systemically after topical application to the skin.[5] However, in cases in which some systemic absorption has been reported, the proposed mechanism of action is that the metronidazole is probably absorbed percutaneously as unchanged drug, metabolized in the liver, and then excreted in the urine.[7]

Bower and associates[8] conducted a double-blind, placebo-controlled trial in 11 patients with malodorous fungating tumors. Patients received either 0.8% metronidazole gel, 1 g per square centimeter of lesion, or placebo gel daily for 6 days. This course was followed by an open assessment period of 5 days when all patients received active gel. Odor was graded daily by the patient and by one investigator at home visits by means of visual analogue scales rated 0 to 10. Of the nine patients who completed the study, each received 5 or 11 days of 0.8% metronidazole gel therapy and, in every case, there was subjective improvement in odor as assessed by both patient and medical staff. The authors concluded that daily cleaning and redressing for 7 days followed by a 5-day course of topical 0.8% metronidazole, applied daily at a dose of 1 g per square centimeter of lesion, is recommended for palliation of offensive-smelling tumors because it is safe, effective, and less toxic than orally administered metronidazole.

Witkowski and Parish[9] report successful treatment of 10 putrid-smelling decubitus ulcers with metronidazole gel. The purpose of their study was to determine if anaerobic bacteria could be cultured from putrid-smelling decubitus ulcers and if eliminating this odor was associated with eradication of these organisms. Twenty-six isolates were removed from the 10 decubitus ulcers before treatment. The most common organisms included *Staphylococcus aureus*, group D *Streptococcus, Proteus mirabilis, Pseudomonas aeruginosa, Actinobacter* species, *Escherichia coli,* and *Bacteroides* species. After 5 days of treatment with metronidazole gel, all cultures were negative for anaerobes; however, the list of aerobes recovered was the same as before treatment. Additionally, the putrid odor was eliminated from all ulcers (elimination of odor was often noted within 36 hours of beginning treatment), all ulcers showed a decrease in the amount of drainage, progression of tissue necrosis was stopped, no apparent increase in crater occurred, and new granulation tissue was beginning to appear in all the treated ulcers. The authors concluded that although topical metronidazole gel should not be considered a panacea for the treatment of decubitus ulcers, it is very effective in eliminating anaerobic organisms and the associated odor.

Finally, McMullen[10] used a 1% metronidazole solution in four patients with foul-smelling ulcerating skin lesions that had been unresponsive to traditional wound and room deodorizers. The solution was prepared by crushing oral metronidazole tablets and mixing them with sterile normal saline solution to equal either 200 mL or 500 mL[3]. The solution was irrigated into the fistula with a 200-mL syringe. In all patients, significant reduction or elimination of odor was reported within 24 hours of initiation of treatment. In fact, three patients also had slight improvements in wound appearance and a decrease in pain. The author concluded that topical metronidazole was useful for the treatment of malodorous ulcerated skin lesions in patients with nonresectable malignancies.

To our knowledge, use of topical metronidazole solution for the treatment of arterial insufficiency or venous stasis ulcers has not been reported previously. However, because of the potential for anaerobic bacterial infections in such ulcers, it appeared rational to attempt to treat this patient with topical metronidazole. In this particular case, the patient's ulcers did not improve with appropriate oral or IV antibiotics, but only began to heal once the wet-to-dry metronidazole solution dressings were applied. Although, further study is warranted, it appears that the topical metronidazole was successful in resolving this patient's arterial insufficiency ulcers.

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