

Transdermal Nifedipine for Wound Healing: Case Reports

Introduction

We are treating a number of patients with difficult-to-heal wounds that are refractory to standard forms of treatment, and we are seeing positive results with the addition of transdermal nifedipine to our traditional course of therapy. This is illustrated in the following case reports.

Case 1

A 43-year-old woman with a history of juvenile diabetes mellitus for many years presented 7 years ago with significant diabetes breakdown that included macular degeneration, neuroretinal and vascular problems, diabetic neuropathy, and a nonhealing wound on the right heel. The patient was unable to perceive sensation in her foot and had actually walked through the skin of her heel so that bone was exposed. The vascular supply to the area was extremely poor as a result of the chronic diabetes, and osteomyelitis was noted in the calcaneus. Maggots were applied to debride the necrotic tissue to ensure the salvage of the maximum quantity of viable tissue, after which a limb-salvage procedure consisting of insertion of an external fixator and application of a cross-leg flap was initiated. Three weeks later during a follow-up procedure, it was noted that the wound had healed, but several other breakdowns on both legs necessitated continuing treatment that included a whittling away of osteomyelitic bone and debridement of nonviable soft tissue. In the interim, the patient had become dialysis dependent. Because of the extended healing time required by the recurring wounds, long-term repeated hospitalizations, and wound care, we decided to use transdermal nifedipine to accelerate healing by inducing localized vasodilation without systemic effects. A dosage of 80 mg nifedipine (1 mL of 8% nifedipine in Pluronic® lecithin organogel [PLO]) was prescribed to be administered by the patient twice a day. The gel was dispensed in a 30-mL syringe.

The patient began using the gel on February 10, 1999, and we observed a decrease in healing time (depending on wound size) from as long as 4 to 5 months to within 6 to 8 weeks. No adverse effects were observed with this therapy. Our concern was the potential for rapid systemic absorption and blood-pressure complications; however, none was noted in the course of therapy. Because the patient is still ambulatory, she continues to experience repeated tissue breakdown on both feet. She is now on a waiting list to undergo both a kidney and pancreas transplant, and we continue to treat repeated breakdowns with nifedipine and routine therapy to facilitate having closed wounds in time for the kidney and pancreatic transplantation.

Case 2

An 8-year-old boy with a clubfoot was referred by an orthopedic surgeon. The patient had undergone a foot-straightening procedure 2 years earlier; however, good union of the bones had not been achieved, and a linear hypertrophic scar contracture had de-

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veloped over the medial aspect of the foot that pulled the foot out of alignment. In addition, a number of other medial and lateral scars on the patient's foot included a large hypertrophic scar on the lateral side, which compromised blood supply to the area. To correct this problem and release the contracture, it was necessary to insert

Figure 1



Note the gray, dusky skin (the area treated) above the lower vertical incision and to the left of the upper incision.

Figure 2



Approximately 10 to 14 days after the initiation of therapy with nifedipine. The gray skin color (Figure 1) is more pink, which indicates renewed vascularization of the compromised area. The incisions are healing.

a tissue expander in the scar, which was on the dorsum of the foot. This was accomplished, and the expander was left in place for 4 days.

Bowing of the foot and the tightness of the scar over the integral port of the expander caused a pressure necrosis of the skin over the dorsum within 4 postoperative days (Figure 1). When the expander was removed, the area was treated with transdermal nifedipine to accelerate wound healing and prevent the formation of another hypertrophic scar so that a second tissue expander could be inserted in the same area (Figure 2). We also did not want to protract the orthopedic procedure. A nifedipine 2% (20 mg/mL) PLO gel was

prescribed for application (~ 1 mL twice a day) by the patient's mother. Daily whirlpool therapy was also prescribed in addition to gel application twice a day. After 3 weeks of following this regimen, complete healing was observed (Figures 3 and 4).

Approximately 10 weeks was allowed for healing, after which the patient underwent the second insertion of an expander. Four weeks after that procedure, weekly expansion was initiated for 4 to 6 weeks. The large scar on the side of the foot was excised by an orthopedic surgeon. In March of 1999, the bones were refractured, repinned, and straightened; a multiple W-plasty was performed that created a zigzagged scar intended to heal in a nonlinear manner to distribute forces along a greater surface area; a rotation flap was applied; and the foot was immobilized in a cast. The cast was cut 1 week after surgery so that the wound could be examined. Areas with vascular compromise were observed; this was not unexpected because of the nature of the multiple procedures that had been performed. Transdermal nifedipine was again prescribed as previously described, and complete wound healing occurred in 3 to 4 weeks. The patient is now ambulatory with a straightened foot.

Figure 3



After several weeks of continuous therapy with nifedipine.

Figure 4



The patient was recuperating at home when this photo was taken. Proper healing had occurred, and the skin color eventually returned to normal.

Discussion

Nifedipine, a calcium channel blocker used as an antianginal, prevents the development of both motor deficits and sensory nerve-conduction-velocity deficits in streptozotocin-diabetic rats.¹ The exact mechanism of action remains to be determined. The beneficial effects of nifedipine without concomitant changes in nerve hypoxic resistance or capillarization have been observed. It has been suggested that the drug-induced blocking of calcium influx into vascular smooth muscle may lead to reduced vascular tone,^{2,3} which could increase nerve blood flow.⁴ We believe that the same smooth muscle relaxation occurs in the skin vasculature and creates a localized peripheral vasodilation and increased flow to the localized area, which accelerates epithelialization and possible microvascular neogenesis.

Theoretically, nifedipine could lower blood pressure and cause bradycardia and related symptoms, but we have seen no evidence of adverse effects in these 2 patients. The patient described in Case 2 was monitored vigilantly for such changes by his pediatrician during treatments. In addition, other patients (even a non-compliant diabetic with uncontrolled blood pressure) have exhibited no evidence of lowered blood pressure with this treatment. The transdermal application that has been used appears to result in little-to-no systemic absorption when applied as prescribed. One effect has been noted: dryness of the skin in the area surrounding the wound. However, we consider this to be a good sign because it suggests vasodilatation and epidermolysis in the healed areas. We have considered such skin dryness as a criterion in the assessment of the effects of dilation.

Because the nifedipine in a traditional PLO gel is somewhat

tacky, a vanishing penetrating transdermal cream that provides a more elegant and patient-acceptable preparation is now being substituted as the base. That cream is slightly more emollient than nifedipine in PLO gel and may cause fewer signs of dryness.

Because the preparation is light sensitive, it is dispensed in an amber plastic bag in which the product is to be stored. The patient is instructed to apply the preparation with a finger cot or a plastic-wrapped finger to minimize possible systemic absorption.

This therapy has proven so efficacious that transdermal nifedipine is now considered another part of our therapeutic armamentarium for limb salvage in a variety of patients.

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