Chronic Ulcers Caused by Injection of Substances

Healing Aided by Naltrexone

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Obesity, insulin-dependent diabetes mellitus, a sedentary lifestyle, and chronic ulceration can all be complicated by refractory substance abuse. A case is presented featuring significant improvement of these parameters and others, including successful resolution of the refractory ulceration after control with naltrexone hydrochloride implants. The case is important both as a novel form of treatment for ulcer healing in drug-dependent persons, and for potential pathophysiological insights to wound healing that might be suggested by the likely mechanisms of action of naltrexone.

REPORT OF A CASE

A 54-year-old man, 174 cm tall and weighing 117 kg (body mass index, calculated as weight in kilograms divided by height in meters squared, 38.6), with poorly controlled insulin-dependent diabetes mellitus and a long history of severe polydrug abuse (including benzodiazepines, cannabis, and heroin, 1-3 g/d for a total of 33 years, currently prescribed methadone hydrochloride, 70 mg/d) presented with a 10-month history of severe open purulent sores on the backs of his hands, heels, and feet. The ulcers had not responded to numerous treatments with antibiotics, dressings, bismuth paste, bandages, or topical colloidal gels and foams. Ulcer dressings were changed daily or 3 times weekly as prescribed by the local wound clinic. His medications included insulin, atenolol, aspirin, ramipril, simvastatin, and metformin hydrochloride.

On physical examination, the patient had multiple ulcers on all 4 distal limbs. The ulcers, which were extensive and sloughing, extended to the deep dermis, occurred on the dorsum of the hands, heels, feet, and Achilles tendon. Bare tendon was not exposed. The ulcers were related to his substance injections and developed as a natural progression of “puffy hand syndrome,” in which missed injections into the veins had caused local abscesses and finally frank ulceration (Figure 1). Continued injection into the hyperemic inflamed tissue resulted in the present ulceration. He was hypertensive with a blood pressure of 161/72 mm Hg.

SOLUTION

After a preliminary period of detoxification, naltrexone implants were inserted to control the drug addiction. The

Therapeutic Challenge

Chronic ulceration of the extremities is a difficult problem in unfit obese medical patients. This was intensified in our patient by poorly controlled insulin-dependent diabetes mellitus, polydrug abuse, and the chaotic lifestyle accompanying such disorders. Both medical and topical treatments and dressings had been applied for 10 months, but relentless deterioration was observed.

Figure 1. Deep sloughy ulcer on the back of both hands 2 days before the first naltrexone hydrochloride implant.
Naltrexone has been used for a variety of indications within addiction medicine, including the management of dependencies (eg, alcohol, opiates, gambling, self-mutilation, and miscellaneous problems). It has also been studied in experimental animals on corneal and gastrointestinal ulcers, but to our knowledge, its application to the studied in experimental animals on corneal and gastrointestinal ulcers, but to our knowledge, its application to the patient was treated under the legal framework of the Special Access Scheme in Australia, which allows compassionate access to unlicensed drugs and therapeutic devices for patients with life-threatening conditions. Naltrexone had been used previously for a similar problem in 2005 and resulted in rapid healing of hand and foot ulcers over a 2-month period. Rapid healing of the ulcers also occurred on this occasion in response to his initial treatment with 5.6 g naltrexone hydrochloride implants (Shenzhen Civil Life Science Co, Shenzhen, China). The first series of naltrexone implants induced only partial healing. However, when the patient required a higher dose of implant to gain full control of his drug use, the ulcers rapidly healed over 13 weeks without any special further treatment (Figure 2). The second group of implants were inserted 2 weeks after the first and were the same type as the first, with the addition of a 1- to 3-month naltrexone implant from Psychological Addiction Treatment Services, Sydney, Australia. The patient’s medical treatment remained unchanged. No local or topical treatment was used beyond simple wound dressings.

Figure 2. Complete ulcer healing 85 and 71 days after naltrexone hydrochloride implant insertion.

COMMENT

Naltrexone has been used for a variety of indications within addiction medicine, including the management of dependencies (eg, alcohol, opiates, gambling, self-mutilation, and miscellaneous problems). It has also been studied in experimental animals on corneal and gastrointestinal ulcers, but to our knowledge, its application to the common and severe clinical problem of refractory chronic ulceration has not previously been described. Clearly, control of injected drug use was an important contributing factor to the rapid resolution of the ulceration in this case. A substantial literature has described the capacity of opiates to inhibit cell growth in virtually all tissues and of naltrexone to stimulate such growth. Moreover, naltrexone stimulates tissue growth in the basal state, indicating that tissue growth and, presumably, stem cell replicative activity, are under tonic opioid inhibition. The inhibitory effect of opiates on tissue growth has been shown to be blocked by naltrexone, confirming that their actions occur via the well-known opioid receptors, which are found on many cell types, including stem and progenitor cells, at least of the neural lineage.

Classical literature and modern literature have described suppression of immune responses by opiates and the compensatory immune stimulation, which is suppressed by naltrexone. Drug-dependent patients have many causes for immune stimulation. Inmate stem cell regenerative potential in such patients is likely to be depressed both by the direct inhibition of the stem and progenitor cell cycling, by immune mechanisms impeding cell growth, and by an interactive effect of the immune system on stem cell processes. Because both stem cell inhibitory and immunocompromise-immunostimulation states exist in patients such as the one described herein, it is likely that wound healing is impaired. Deficits of tissue growth have been documented in various tissues, such as teeth and hair, and the present study suggests that the skin is also involved in such defects.

It is noteworthy that this study describes the second documented occasion on which such healing occurred in response to naltrexone implant therapy in this patient. On the previous occasion, multiple naltrexone implants from Go Medical in Perth, Western Australia, were used. This dramatic response was therefore not thought to be related to any particular formulation of naltrexone, but was thought to be related to the reliable delivery of the drug from a long-term sustained-release preparation.

It would seem that the repeated observations made in this case merit further trials of naltrexone therapy in challenging patients with complex clinical presentations including diabetes mellitus, obesity, medical conditions, circulatory disorders, and substance abuse and with various other conditions predisposing to chronicity of ulceration refractory to conventional treatment modalities.

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**Archives Web Quiz Winner**

**Congratulations to the winner of our January quiz, Dr Rameshwar Gutte, Department of Dermatology, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, India. The correct answer to our January challenge was scurvy. For a complete discussion of this case, see the Off-Center Fold section in the February Archives (Masferrer E, Canal L, Álvarez A, Jucglá A. Gingival hypertrophy and anemia. *Arch Dermatol*. 2009;145[2]:195-200).

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