

BRIEF RESEARCH REPORT

Oxycodone in the Long-Term Treatment of Chronic Pain Related to Scleroderma Skin Ulcers

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Abstract

Objective. To demonstrate the efficacy and safety of long-term therapy with oxycodone in severe pain of scleroderma skin ulcers.

Design. Open study.

Setting and Patients. Twenty-nine consecutive patients, referred to our Rheumatology Unit during 2006, affected by systemic sclerosis complicated by painful long-standing skin ulcers entered in the study. In all cases, pain was classified as severe according to World Health Organization guidelines, and oxycodone chlorhydrate (Oxycontin®; Mundipharma Pharmaceuticals, Milan, Italy) was administered at the dosage of 10–20 mg twice daily for a mean period of 7.9 ± 3.2 standard deviation months.

Outcome Measures. To evaluate the efficacy and safety of opioid therapy, the following parameters were recorded at standard time intervals: visual analog scale (VAS) pain, Pittsburgh sleep quality index (PSQI), hours of sleep per night, Health Assessment Questionnaire-Disability index, analgesics use (rescue therapy), side effects, vital signs, routine laboratory assessment.

Results. After 1 month of therapy, all patients experienced relief of pain (VAS decreased from 93.8 ± 8.72 to 56.7 ± 10.4 , $P < 0.0001$), and better quality of sleep (total hours of sleep increased from 3.68 ± 1.28 to 5.27 ± 0.75 , $P < 0.0001$; PSQI

decreased from 9.72 ± 3.95 to 3.37 ± 1.04 , $P < 0.0001$). These parameters further improved after 3 months of therapy and remained stable during the follow-up; moreover, an increase of daily dosage of oxycodone was never required. The observed side effects were always transient and mild; only constipation, when present, was persistent.

Conclusion. Oxycodone showed to be effective and safe in the treatment of pain due to severe scleroderma skin ulcers; contemporarily, it markedly improved the patient's compliance to local wound care procedures.

Key Words. Oxycodone; Pain; Skin Ulcers; Systemic Sclerosis; Scleroderma

Introduction

Systemic Sclerosis (SSc) is an autoimmune disease, characterized by progressive fibrosis of the skin and internal organs due to diffuse immune-mediated microangiopathy [1]. Skin ulcers represent one of the most frequent complications of the disease; they are slow-healing ischemic lesions, characterized by severe chronic pain, often resistant to traditional treatments. Moreover, they are frequently complicated by infections, gangrene, and consequent amputation, which severely affect the quality of life of these patients and are responsible for disability. Systemic therapy (i.e., calcium-channel blockers, prostanoids, anti-endothelin receptors) may limit the incidence of small ulcers, whereas they are scarcely effective on most severe skin lesions. The pain relief provided by standard therapy (i.e., nonsteroidal anti-inflammatory drugs [NSAIDs], tramadol) is often inadequate or dose limited by side effects.

Moreover, pain control is fundamental for the wound care procedures in SSc patients, increasing treatment adherence and compliance to skin ulcers dressing changes.

Opioids have been defined effective and safe in the treatment of chronic cancer pain [2]; their efficacy was demonstrated even in chronic noncancer pain conditions [3]. However, the use of oral opioids in SSc patients was limited to tramadol [4]. Among opioid analgesics, the oxycodone, derived from alkaloid thebaine, was described as a drug well absorbed orally, with higher bioavailability than morphine [5].

This open study evaluated the efficacy and safety of oxycodone as supportive therapy in severe pain related to scleroderma skin ulcers.

Patients and Methods

Twenty-nine SSc patients (24 women and 5 men; mean age 52.3 ± 12.9 standard deviation [SD] years), referred to our Rheumatology Unit during 2006, were consecutively included in the study. All patients satisfied the preliminary American College of Rheumatology (ACR) classification criteria for SSc [6]. In all cases, the disease was complicated by long-standing, painful skin ulcers resistant to both NSAIDs and tramadol therapy, at the maximum recommended doses. Pain was classified as severe, according to World Health Organization guidelines in all subjects [7]. The oxycodone chloridrate (Oxycontin® controlled-release tablets; Mundipharma Pharmaceuticals) was taken twice a day to assure 24 hours pain control. At the beginning, the lowest dose of medication (10 mg twice daily) was administered in all cases, and progressively adjusted in order to obtain a complete pain relief. All patients continued systemic (calcium-channel blockers and/or prostanoids) and local (surgical debridement and moist dressing) standard therapies for skin scleroderma ulcers.

Patients have been provided with a diary to record the following symptoms daily: self-evaluation of pain at the same time in the evening, using a visual analog scale (VAS) [8], eventual use of other analgesics, hours of sleep per night, eventual side effects. Health Assessment Questionnaire-Disability Index (HAQ-DI) [9] was administrated baseline and at the end of treatment, while Pittsburgh Sleep Quality Index (PSQI) questionnaire [10] was administrated baseline, after 1 month, and at the end of the treatment. The latter self-rate questionnaire is an effective tool able to differentiate poor from good sleepers by measuring both quality and quantity of sleep, therefore it was previously used in patients with chronic noncancer pain [11] and fibromyalgia [12].

Safety of oxycodone was evaluated by patient's records of side effects, while vital signs and laboratory parameter variations were monitored at each monthly visit.

All data were analyzed by paired Student's *t*-test.

Results

All patients treated with oxycodone experienced a significant reduction of the skin ulcers-related pain. On the whole, mean oxycodone dosage varied from 20 to 40 mg/day, administered for a period of 7.9 ± 3.2 SD months. After the first month of therapy, pain VAS decreased from 93.8 ± 8.72 to 56.7 ± 10.4 ($P < 0.0001$), total hours of sleep increased from 3.68 ± 1.28 to 5.27 ± 0.75 ($P < 0.0001$), while PSQI decreased, from 9.72 ± 3.95 to

3.37 ± 1.04 ($P < 0.0001$), suggesting a better quality of sleep. Additional analgesic therapy was necessary in 11/29: 6/11 assumed NSAIDs, 2/11 morphine, 3/11 paracetamol plus codeine.

After 3 months of therapy, further clinical improvement was observed: the pain VAS reduced to 42.9 ± 14.9 , the mean total hours of sleep per night was 6.10 ± 0.85 and the PSQI 3.37 ± 1.04 . Eight patients needed additional therapy: NSAIDs in 5/8 and paracetamol plus codeine in 3/8. The HAQ-DI decreased from 1.1 ± 0.67 (baseline) to 0.46 ± 0.46 at the last patients' evaluation, when complete relief of the pain was obtained and oxycodone was discontinued.

Of interest, with oxycodone treatment the patient's compliance to the local wound management, specially to surgical debridement, markedly improved. In addition, we observed a progressive reduction of patient's analgesic consumption during the ulcer treatments.

No patient experienced severe adverse events related to the treatment, neither physical examination nor laboratory parameter alterations were noticed during the entire period of observation. Mild side effects, namely itch, nausea, and/or dizziness, were referred by 9/29 (31%) patients, while 15 subjects (51.7%) reported constipation after 1 month of treatment. This latter symptom was controlled with psyllium fiber supplementation and, only in some cases, with laxatives.

Finally, no patient presented the abstinence phenomenon after treatment discontinuation.

Discussion

The results of our preliminary study suggested that long-term treatment with oxycodone represent an important approach to the scleroderma skin ulcers, responsible for severe chronic pain and marked reduction of patients' quality of life. In addition, the treatment was well tolerated and permitted a better local management of ulcers, mainly with regards to the surgical debridement.

Adequate pain control is a primary goal in the management of SSc patients complicated by skin ulcers, but standardized analgesic strategies are not available for this condition. Opioids are accepted and used for the treatment of moderate to severe pain in chronic cancer and noncancer pain [2,3]. This study preliminary evaluated the effect of oxycodone in patients with painful, long-lasting scleroderma skin ulcers, without important side effects.

Oxycodone may represent an ideal analgesic drug for the treatment of nonmalignant chronic pain, frequently observed in several rheumatic diseases, because of the long duration of action, minimal side effects [13], and reasonable costs.

The usefulness of oxycodone therapy in reducing chronic rheumatic pain with only mild toxicity was firstly demonstrated in 1998 by Steven et al. [14], and confirmed by Jamison et al. in patients with chronic noncancer back pain [15]. A more recent randomized, controlled trial with oxycodone in patients with osteoarthritis and moderate to severe pain, resistant to standard therapy, demonstrated a significant pain control and improvement of physical activity [16].

Chronic pain management in scleroderma patients is poorly investigated, even though it is a common symptom, mainly in patients with skin ulcers [17,18]; Georges et al. demonstrated that scleroderma digital ulcers may influence both mental and physical component score of SF-36, severely affecting the patient's quality of life, particularly for resistant chronic pain [19].

The usefulness of analgesic substances applied topically to painful skin lesions complicating different conditions, including scleroderma, has been investigated, namely the use of cream containing benzydamine in patients with pressure sores and a mixture of diamorphine in pressure sores or malignant skin ulcerations [20,21]. These observations were not confirmed by recent randomized, controlled trial evaluating the effect of topical morphine in chronic skin lesions [22].

Similarly, in our previous clinical experience topical opioids scarcely affected painful scleroderma skin lesions. Moreover, as the pain from skin ulcers is often resistant to conventional analgesic therapy (NSAIDs, tramadol), an aggressive therapeutic approach is required.

In conclusion, our study suggests that long-term use of oral oxycodone is effective and safe in maintaining analgesia in patients with scleroderma skin ulcers; not secondarily it may be crucial for an adequate local wound care.

References

- 1 Ferri C, Valentini G, Cozzi F, et al. Systemic Sclerosis Study Group of the Italian Society of Rheumatology (SIR-GSSSc). Systemic sclerosis: Demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine* 2002;81:139–53.
- 2 Hanks GV, Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: The EAPC recommendations. *Br J Cancer* 2001;84:587–93.
- 3 Breivk HB. Opioids in chronic non-cancer pain, indications and controversies. *Eur J Pain* 2005;9:127–30.
- 4 Guseva NG, Alekperov RT, Anikina NV. Tramadol in the vascular pains of patients with systemic scleroderma and other rheumatic diseases. *Ter Arkh* 1994;66:20–4.
- 5 Pöyhiä R, Seppälä T, Olkkola KT, Kalso E. The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. *Br J Clin Pharmacol* 1992;33:617–21.
- 6 Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis. *Arthritis Rheum* 1980;23:581–90.
- 7 World Health Organization. *Cancer Pain Relief*, 2nd edition. Geneva: WHO; 1996.
- 8 Steen VD, Medsger TA Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum* 1997;40:1984–91.
- 9 Poole JL, Steen VD. The use of the Health Assessment Questionnaire (HAQ) to determine physical disability in systemic sclerosis. *Arthritis Care Res* 1991;4:27–31.
- 10 Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- 11 Sayar K, Arikian M, Yontem T. Sleep quality in chronic pain patients. *Can J Psychiatry* 2002;47:844–8.
- 12 Osorio CD, Gallinaro AL, Lorenzi-Filho G, Lage LV. Sleep quality in patients with fibromyalgia using the Pittsburgh Sleep Quality Index. *J Rheumatol* 2006;33:1863–5.
- 13 Levy MH. Advancement of opioid analgesia with controlled-release oxycodone. *Eur J Pain* 2001;5(suppl A):113–16.
- 14 Steven RY, Maren LM, Sharon RW. Codeine and oxycodone use in patients with chronic rheumatic disease pain. *Arthritis Rheum* 1998;9:1603–12.
- 15 Jamison RN, Raymond SA, Slawsky EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. *Spine* 1998;23:2591–600.
- 16 Markenson JA, Croft J, Zhang PG, Richards P. Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *Clin J Pain* 2005;21:524–35.
- 17 Carriera PE. "Quality of pain" in systemic sclerosis. *Rheumatology* 2006;45:1185–6.

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- 18 Benrud-Larson LM, Haythornthwaite JA, Heinberg LJ, et al. The impact of pain and symptoms of depression in scleroderma. *Pain* 2002;95:267–75.
- 19 Georges C, Chassany O, Toledano C, et al. Impact of pain in health related quality of life of patients with systemic sclerosis. *Rheumatology* 2006;45:1298–302.
- 20 Jepson BA. Relieving the pain of pressure sores. *Lancet* 1992;339:503–4.
- 21 Back IN, Findlay I. Analgesic effect of topical opioids on painful skin ulcers. *J Pain Symptom Manage* 1995;10:493.
- 22 Welling A. A randomised controlled trial to test the analgesic efficacy of topical morphine on minor superficial and partial thickness burns accident and emergency departments. *Emerg Med J* 2007;24:408–12.