

Original Article

Randomized Single-Blind Trial of Topical Ketanserin for Healing Acceleration of Diabetic Foot Ulcers

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Abstract

The objective of this study was to determine the efficacy of topically applied ketanserin for healing acceleration of diabetic foot ulcers. From August 1993 to September 1994, 140 NIDDM patients entered a randomized single-blind trial of topical ketanserin (Sufrexal, Janssen Pharmaceuticals; n = 69) vs. normal saline (labeled here as placebo; n = 71). All patients were subjected to surgical debridement of necrotic tissue and lavage with normal saline. Wounds were <100 cm² in area. Persons with NIDDM and foot ulcers Wagner 2 and 3 with a median of 8 (interquartile range 4 - 26) weeks duration were included. Ulcer area was measured at 0, 4, 8 and 12 weeks. The groups were similar in age, sex, years of diabetes duration, obesity, ulcer Wagner type, number of previous amputations

and surgical debridements during this hospital stay. Average percent reduction in ulcer area at 12 weeks was 87% for ketanserin vs. 63% for placebo (p <0.001). The regression equations for the least-squares fit to the area (y) against time (x) data points were $y = 43.46 - 3.181x$ (r = -0.995) for ketanserin and $y = 39.46 - 2.016x$ (r = -0.999) for placebo (p <0.01). The 95% confidence limits for slopes were -3.181 ± 0.98 and -2.016 ± 0.15 . Thus, average daily reduction in ulcer area was 4.5 mm²/day for ketanserin vs. 2.88 mm²/day for placebo.

In conclusion, topical ketanserin significantly accelerated wound healing in diabetic neurotrophic foot ulcers when applied as part of a comprehensive healing program. (*Arch Med Res* 1996; 27:95)

KEY WORDS: Diabetic foot ulcers; Ketanserin; Wagner classification.

Introduction

The health care costs and lethality of people with NIDDM treated at the Instituto Mexicano del Seguro Social increased, at the national level, during the period

of 1980 -1986 (1,2). NIDDM patients in Mexico frequently demand primary care and ophthalmological outpatient treatment and are the main source of chronic renal failure and nontraumatic amputations (3,4). Data from the international literature indicate that 10 - 30% of these types of patients are discharged with diabetic foot ulcers in varying degrees of tissue involvement (1,5) from the hospital. Patients with diabetic foot ulcers are generally subjected to a comprehensive treatment pro-

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gram of surgical debridement of necrotic tissues, protective dressings, and resting of injured area, among other measures, such as systemic antibiotics and surgical revascularization when indicated. Several additions to accelerate healing are under study and include a variety of growth factors (6), cultured human dermis (7), hyperbaric oxygen (8) and pentoxifylline (9).

Ketanserin is a synthetic compound initially introduced as a hypotensive agent (10) and later utilized for the treatment of nondiabetic (11) and diabetic ulcers through systemic administration (12,13). It is a serotonergic₂-receptor antagonist that inhibits platelet aggregation, blocks vasoconstriction, restores erythrocyte deformability and improves tissue perfusion (12,14). A ketanserin ointment, prepared in an antiseptic and hydrophilic gel of polyethyleneglycol, has now been made available for topical application. Based on the above, we reasoned that the topical use of ketanserin, after surgical debridement, would be advantageous in reducing both the risk of overt systemic adverse reactions and the practical problems of a long IV infusion while retaining its local beneficial effects. Thus, to evaluate the efficacy of topical ketanserin on size reduction of diabetic foot ulcers, a randomized prospective simple-blind study was undertaken.

Materials and Methods

Local NIDDM patients with neurotrophic nonhealing foot ulcers are usually referred to us (the National Medical Center of Veracruz, Mexico of the Instituto Mexicano del Seguro Social) by our peripheral medical offices. After initial history and physical examination, most of our patients undergo the common comprehensive treatment of systemic antibiotics (when indicated), weight avoidance and surgical debridement and lavage under regional anesthesia. Ulcers are then classified according to Wagner (15): Grade 0, intact skin; Grade I, superficial ulcer; Grade II, deep ulcer; Grade III, osteomyelitis and/or deep abscess; Grade IV, forefoot gangrene; and Grade V, hindfoot gangrene. Succinctly, Wagner type 2 lesions affect soft tissues and type 3 also involve bone. Osteomyelitis is diagnosed at the surgical step (or during later care) by periosteal disruption and bone darkness or frailty. The present study contemplated a single selection criterion of patients with Wagner 2 and 3 (with minor bone involvement) ulcers taking into consideration possible usefulness of results to the clinically oriented health care practitioner after hospital discharge (1-2 weeks). Baseline population measures were performed on the first day of the hospital stay. All patients required hospital care for 1) surgical debridement of necrotic tissues, 2) aggressive parenteral antimicrobial treatment, 3) foot rest and 4) correction of fasting hyperglycemia caused by sepsis. From August 1993 to September 1994, 161 of these types of patients were initially

selected for the study by alternate assignment to ketanserin or placebo (normal saline) groups simply following their time of presentation and were voluntarily blinded about differences in treatment (medical personnel were obviously aware). We were not able to obtain the polyethyleneglycol gel for placebo because this product was not available. Ketanserin treatment started as early as the day following initial surgical debridement. After 2 weeks, 21 patients (13%) abandoned the study for personal reasons and their initial data were not included. Sixty-nine and 71 patients (ketanserin and placebo groups, respectively) completed the full length of the study (12 weeks). All patients received systemic antibiotics and pentoxifylline at a dose of 1200 mg/day. Ulcers had a median duration of 8 weeks (interquartile range, 4 - 26 weeks) and were on the surface of the foot. Ulcer dressings were removed every day (by hospital staff), wounds were inspected, cleaned with normal saline (referred to as placebo) or a topical 2% ketanserin ointment (Sufrexal, Janssen Pharmaceuticals) was added, applied covering the depth of the lesion. Ulcers were then covered with dry gauze dressings. Ulcer size was estimated by measuring its two perpendicular horizontal diameters with a metric ruler at 0, 4, 8, and 12 weeks thereafter. Measurements obtained at each assessment period were used to quantify ulcer size and percent reduction was calculated. Sitting blood pressure, complaints about general status and compliance of weight avoidance were taken (with reinforcement of the latter) at these 4-week-period intervals. Blood samples to determine preprandial serum glucose levels were taken at the follow-up intervals. After hospital discharge, those patients with metabolic instability were excluded and those with mean fasting plasma glucose concentration <160 mg/dl were considered as being clinically well and under reasonable control (16). Preprandial glucose levels below 160 mg/dl fall into a range (173 - 144 mg/dl) of poor and good control (16). All patients received this care in a comprehensive outpatient management facility until their complete resolution, but we only documented the immediate effects of ketanserin in accelerating wound size reduction. The benefits of normal glucose obtained concentration by intensive control over traditional goals are beyond the purpose of this trial.

Neuropathic assessment by electromyographic sensory testing, nerve conduction and autonomic studies was not performed since diabetic neuropathy in this population was obviously present in its two modalities, motor and sensorial, causing this syndrome, its diagnosis being clinically established by foot deformity, dryness and loss of pain or sensory perception.

For statistical analysis, the significance level was set at the traditional 5% level and sample size was required to have 80% power to detect differences. Since most reports on ulcer acceleration healing have obtained about 50% improvement over control and a 50% area healing

with the usual comprehensive treatment (P_1), we calculated a P_2 of 75% ($P_2 = 0.5 + 0.5 [1 - 0.5]$) and a minimum sample size of 65/group was obtained (17). Values of Chi-squared with Yates' correction for 2x2 tables and of variance ratios for natural and treatment analysis of variance were calculated. Simple regression was performed for variables such as ulcer size and time assuming a dependent relationship of ulcer size during the time period of examination. The 5% critical value for t with $n-2$ df ($n = 4$) was used to fit confidence limits around the sample slopes. The p value for slope difference was determined by the Student's t test (two-tailed). The protocol was approved by the Investigation Committee according to our institutional guidelines.

Results

Patients included in the study or control group were similar in age, sex, years of known diabetes duration, obesity, ulcer Wagner type, previous amputations, and number of surgical debridements during hospital stay. Almost one-third of the ulcers for each group were Wagner 3 grade with contiguous minor bone affection that resolved easily with surgical debridements. Cigarette smoking was somewhat higher ($p = 0.043$) in the study group (Table 1). Ulcer sizes were similar in both groups at 0 and 4 weeks ($p > 0.05$) and significantly smaller ($p < 0.001$) for the ketanserin group at 8 and 12 weeks (Table 2). Nevertheless, the average percent re-

Table 1

Baseline Demographic and Clinical Characteristics of NIDDM Patients with Foot Ulcers Treated With or Without Ketanserin

Characteristic	Ketanserin n=69	Placebo n=71	P Value
Age (Yr)	59.7 ± 10.7 ¹	60.7 ± 12.1	NS ²
Sex			
Masculine	31 (44.9)	28 (39.4)	NS ³
Feminine	38 (55.1)	43 (60.6)	
Years of Diabetes duration	23.3 ± 26.5	21.7 ± 9.5	NS ⁴
Cigarette Smoking +	39 (56.5)	27 (38)	0.043 ³
Obesity	20 (28.9)	23 (32.3)	NS ³
Wagner type			
2	44 (63.7)	50 (70.4)	NS ⁴
3	25 (36.3)	21 (29.6)	
Number of previous amputations	0.5 ± 0.6	0.6 ± 0.7	NS ²
Number of surgical debridements	1.6 ± 0.69	1.5 ± 0.75	NS ⁴

¹Values are means ± SD or actual (percent) + Cigarette smoking was defined as > 1 cigarette/day, and Obesity defined as BMI > 27 kg/m.

NS = nonsignificant.

²Student's t test.

³chi squared and Yates' correction.

⁴Kruskal-Wallis.

Table 2
Wound Area

Weeks	Ketanserin		Placebo		P Value ¹
	Area (cm ²)	Mean Reduction (%)	Area (cm ²)	Mean Reduction (%)	
0	44.75 ± 20.8 ²	0	39.70 ± 17.9	0	NS
4	29.71 ± 16.8	34.4	31.10 ± 32.9	12	NS
8	16.20 ± 11.1	65.3	23.22 ± 12.3	42.7	<0.001
12	6.84 ± 6.5	87	15.45 ± 10.4	62.8	<0.001

¹For area values between both groups at each assessment period.

²Means ± SD (Student's t test).

duction in ulcer area ($[A_1 - A_2] [100]/A_1$) showed higher percentages for the ketanserin group as early as the 4th week with a sustained difference of 22 - 23% up to the 12th week where the values were 87 and 63% ($p < 0.001$) for ketanserin and placebo groups, respectively (Table 2). The actual size areas were used for simple regression analysis and the least-squares model was fitted to the data. The equations found were $y = 43.46 - 3.181x$ ($r = -0.995$) and $y = 39.46 - 2.016x$ ($r = -0.999$) for ketanserin and placebo, respectively (Figure 1). The calculation of the 95% confidence limits for slopes gave values of $-3.181 ± 0.985 [4.166-2.196]$ and $-2.016 ± 0.15 [2.166-1.866]$. The rate of ulcer healing was significantly better for ketanserin than placebo ($p < 0.01$).

Finally, throughout the study, local or systemic (e.g., arterial hypotension and mood disorders) adverse effects were not detected, no lesion changed to a more serious stage and there was no arterial obstruction, no gross vascular insufficiency or mortality. No patients were excluded from the study due to metabolic disturbances. Mean fasting glucose concentrations in ketanserin group was of $139 ± 10.2$ and $144 ± 9.6$ at 8 and 12 weeks, respectively. Those for placebo groups were 137.1 and $142 ± 8.2$.

Discussion

Wound healing is a complex process where many different molecular factors play important roles (4). At this interaction level, serotonin appears to be negatively involved since, besides the clinical changes observed by means of ketanserin (11-14), it increases vascular permeability (18) and inhibits vessel cells migration (19). Although ketanserin appears to be more modest in its variety of actions than a complete platelet releasate, the results of this study indicate that it can have a place in the already accepted comprehensive healing program. In an effort to obtain an idea of its relative efficacy and with the

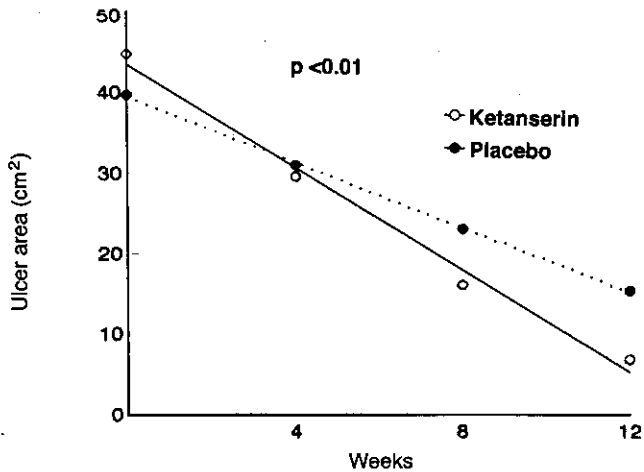


Figure 1. Least-squares fitted to wound area against time values. See text for details.

high correlation coefficients obtained here, we first calculated the average daily reduction in ulcer area from the slopes of Figure 1. The values were 4.5 mm²/day for ketanserin and 2.88 mm²/day for placebo. Since the protocol previously designed had the statement of concluding measurements at the endpoint of 12 weeks, ketanserin treatment was discontinued and patient care was continued conventionally, before the analysis results were known by the authors. Therefore, we then used the regression lines to predict, under the statistical uncertainty, the values of time that we would expect to correspond to a complete ulcer healing. The predicted times were 14 weeks for ketanserin and 20 weeks for placebo. Overall, these four values looked grossly similar to those reported by Steed et al. (6). The final situation, in this respect, obviously requires a direct comparison. But even if ketanserin would demonstrate to be somewhat inferior to the releasate, the latter is expensive, cannot be prepared in minor medical centers, and the surveillance of plasma-transmitted diseases (although legally stated) is problematic in many medical settings.

Another limitation of this trial was that area surface, and not volume, determined ulcer size reduction. The real importance of this issue must be stated precisely, because some clinicians felt that these lesions frequently have the tendency to close over at the surface leaving an unhealed base, and often these surface margins will need to be resected in order to promote healing of the base. We did not find a published controlled trial that confirms this empirical observation. Total wound healing is obviously the purpose of every diabetic foot treatment, but since its complete resolution depends on multiple and heterogeneous conditions and not only on the ketanserin activity, we focused our attention on its efficacy in accelerating wound size reduction. This advantage of ketanserin activity could be important when applied as part of an adjuvant comprehensive healing program to improve some or all of those heterogeneous conditions. However,

this heterogeneity increased the problems to define variables, the majority of them have controversial issues about its association to wound healing in NIDDM (20-22). Although it is commonly believed that wound healing in diabetes is impaired, there has been little published data to document or define this ambiguous phenomenon. Pecoraro et al. (21) found that many of the variables suggested as specific impediments to tissue repair do not interfere in wound healing of diabetic foot ulcers, including some variables used in our trial and others not considered by us. Age, average duration of ulcers, initial size of ulcers, intensive treatment to achieve normal glucose level concentrations, HbA1c and severity of chronic complications are independent of ulcer healing in NIDDM (16,21). These aspects decrease the need of controlling all possible variables to validate results in wound healing trials heavily dependent on controlling variables and the recruitment of comparable treatment groups (7). The same ulcer size at baseline and randomization reduced variability in wounds and the chances for such differences to affect healing rates. Analysis of demographic factors of the patients and their wounds demonstrated that the treatment groups were comparable in all variables except for an increased smoking rate favoring the placebo group. Since current smoking is independent to ulcer healing (18,19), it caused no bias in this assay. The various statistical analyses provide assurance that the differences found between the treatment groups were not due to differences in the patients or their wounds. Therefore, we think that our results could serve as a basis for both further studies of this serotonin₂-receptor antagonist and new, more effective similar agents.

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