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ORIGINAL ARTICLE

Efficacy and safety of topical diltiazem 2% in anal fissure

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KEYWORDS
Anal fissure;
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Abstract
Objectives: To evaluate the effectiveness and safety of 2%diltiazem ointment in the treatment of anal fissure. To analyse the relationship between healing and diagnosis, and duration of the treatment, and the number of applications.
Methods: A prospective observational study of all patients diagnosed with anal fissure that began treatment with topical diltiazem between January and June in 2007. Diltiazem ointment was prepared in the Pharmacy Service. Effectiveness and safety were assessed by a telephone survey conducted with each patient after 8 weeks of treatment, adding it to the patient's clinical records. The variables that were analysed were healing, adverse effects, diagnosis, duration of treatment, and number of applications, among others. Follow-up was carried out for up to 1 year until complete healing of the fissure. The data analysis was carried out by descriptive statistics, crosstabs, and χ^2.
Results: A total of 70 patients were included in the study and anal fissure healed in 48.6% of them. Healing occurred in 54.5% of patients with anal fissure and in 33.3% of patients with anal fissure and haemorrhoids. Some adverse effects occurred in 30%of patients. Therapy was abandoned due to adverse reactions for 5.7%. The fissure was cured for 60% of patients who underwent treatment for a month or more. More than twice-daily applications did not lead to improved healing. There were no significant statistical differences in these results.
Conclusions: Despite not having found statistical differences between the analysed variables, treatment of anal fissures with 2% diltiazem ointment has avoided surgery in nearly 50% of patients, with few adverse effects.

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PALABRAS CLAVE
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Diltiazem;
Efectividad y seguridad;
Estudio observacional

Efectividad y seguridad de diltiazem 2% tópico en fisura anal

Resumen
Objetivo: Evaluar la efectividad y la seguridad de la pomada de diltiazem al 2%en el tratamiento de la fisura anal. Analizar la relación entre la cicatrización de la fisura y diagnóstico, duración del tratamiento y número de aplicaciones.
Métodos: Estudio prospectivo observacional de todos los pacientes diagnosticados de fisura anal que comenzaron tratamiento con diltiazem tópico entre enero y junio de 2007. La pomada de diltiazem al 2% se preparó como fórmula magistral en el servicio de farmacia. La efectividad y la seguridad se evaluó mediante encuesta telefónica a cada paciente tras 8 semanas de tratamiento, completándose con la historia clínica del paciente. Las variables analizadas fueron cicatrización, efectos adversos, diagnóstico, duración del tratamiento y número de aplicaciones, entre otras. Se realizó seguimiento hasta resolución de la fisura hasta un período de 1 año. El análisis de los datos se realizó mediante estadística descriptiva y frecuencia, tablas de contingencia y χ^2.
Resultados: Se incluyó a un total de 70 pacientes y se produjo cicatrización en el 48,6% de éstos. Cicatrizó en el 54,5% de los pacientes con fisura anal y en el 33,3% con fisura anal y hemorroides. El 30% experimentó efectos adversos. El 5,7% abandonó el tratamiento por reacción adversa. La fisura cicatrizó en el 60% de los pacientes que estuvieron más de 1 mes en tratamiento. No hubo más cicatrización con más de 2 aplicaciones diarias. En ninguno de estos resultados hubo diferencias estadísticamente significativas.
Conclusiones: A pesar de no encontrarse diferencias significativas entre las variables estudiadas, el tratamiento de la fisura anal con la pomada de diltiazem al 2% ha evitado la intervención quirúrgica casi en un 50%de los pacientes, con efectos adversos poco frecuentes.

Introduction

Anal fissure is a fissure associated with intense spasming of the internal anal sphincter, with clinical symptoms of proctalgia and rectal bleeding, and results in changed work and social patterns combined with, on a personal level, fear and preoccupation.[1-3] It constitutes one of the most frequent proctologic problems in the western population. It is equally prevalent among both sexes and is displayed mainly in young patients and middle age adults, although it can affect all ages.[4] Its most frequent location (90%) is the midline in the posterior plane, and another, less common location (10%) is the anterior midline.[5] The classic symptoms are anal pain, rectal bleeding, and pruritus ani. The pain is characteristically sharp, often intense, and can last from minutes to several hours, during and/or following defecation. The rectal bleeding usually consists of clear, red blood discharge, generally in small quantities and is not mixed with faeces. The chronic phase of the lesion may involve the onset of pruritus and/or mucosal or mucopurulent secretion.[6] Its diagnosis is simple and is based on clinical history: past medical history, clinical symptoms, and examination.[7]

The aim of the treatment is to reduce the hypertonia with a decrease in pressure in the anal canal and to improve local vascularisation, breaking the vicious circle of anal pain, spasming of the sphincter, and ischaemia, allowing healing and recovery from the fissure.[8,9] Treatment has undergone significant developments in recent years, and there are various treatment options listed in the bibliography, such as hygiene and dietary recommendations, surgical, and pharmacological treatment.[10,11]

Lateral internal sphincterotomy is the treatment of choice for anal fissure. It is a simple method which shows a high rate of recovery. However, the definitive section of the anal sphincter produces irreversible rates of incontinence in differing degrees between 0%and 66%[10,12] In addition, clinical manometric studies have demonstrated that there is a group of patients with certain contributing factors associated with anal fissure without associated hypertonia in which there is a greater risk of residual incontinence following surgery. Therefore surgical sphincterotomy should be avoided as an initial treatment option and should be considered as the next step in cases of relapse or among selected patients who do not display incontinence risk factors.[9-16]

In the search for alternative forms of treatment which do not result in residual incontinence, different pharmacological treatments have been tested to find the cure for anal fissure. The mechanism consists of bringing about a temporary or reversible relaxation of the internal sphincter, sufficiently long enough to allow the healing of the fissure, but with the subsequent recuperation of normal basal anal tone, thereby avoiding incontinence.[17] This treatment option is known as reversible chemical sphincterotomy.[18] Among those used, the most popular are: a local injection of botulinum toxin; nitric oxide liberators in topical form; and calcium-channel blockers.[19]

The calcium antagonists applied topically or orally which have mainly been tested are nifedipine and diltiazem. They act by blocking calcium channels, reducing sphincter spasming and thereby resulting in a greater blood flow in the internal anal sphincter.[20]

The objective of our study was to assess the efficacy and safety of diltiazem 2% ointment in the treatment of anal fissure in our hospital centre, as well as to analyse the relationship between the healing of the fissure and the diagnosis, the duration of the treatment and the number of applications.

Methods

An observational prospective study was undertaken, which included all of the patients diagnosed with acute and chronic anal fissure in a third level hospital, who began treatment with diltiazem 2% ointment between January 1 and June 30, 2007. Patients under the age of 18 years were excluded.

Preparation of diltiazem 2% ointment

The diltiazem 2% ointment was prepared as a magistral formula in the Pharmacy Department. It was produced from diltiazem HCl (Fagron Ibérica), liquid vaseline (Acofarma), and white vaseline (Acofarma). For 100 g of ointment 2 g of diltiazem hydrochloride, 2 g of vaseline oil and white vaseline were weighed in sufficient quantities for 100 g. The diltiazem 2% ointment was repackaged in aluminium tubes of 30 g and conserved at room temperature, protected from light, with an expiry date of 3 months.[21]

Dispensation information and record for diltiazem 2%

Following the medical prescription of topical diltiazem and the informed consent of the patient, the diltiazem ointment was dispensed. At the first dispensation, the pharmacist issued a leaflet produced by the pharmacy department (Annex 1), and informed the patients of its expiry date, conservation, mode of application, and possible adverse effects.

At the beginning of treatment, the personal and dispensation details of all external patients were recorded in the dispensation programme database for outpatients available in the hospital, for their corresponding dispensation, entering into records and subsequent follow-up. In this way all the patients diagnosed with anal fissure who began treatment with topical diltiazem during the months of the study and who complied with the inclusion criteria were selected.

Assessment of the efficacy and safety of diltiazem 2%

A questionnaire was designed (Annex 2) which included all of the sociodemografical variables and all variables related to the disorder, the treatment and the clinical response. A telephone survey was carried out on each patient after 8 weeks of treatment. This was completed retrospectively, based on the corresponding clinical history of the patient. A follow-up was undertaken until recovery from the fissure, by means of either healing with diltiazem, or surgery, up to a maximum period of 1 year.

The main efficacy variable was the result of the treatment, defined as recovery (total healing of the fissure), surgery and non-recovery (fissure not healed or surgery not undertaken at the end of the study). The main safety variable was the onset or otherwise of classic adverse effects (headache and hypotension). Other studied variables were the associated presence or otherwise of haemorrhoids, the number of daily applications of the ointment, the duration of treatment in weeks, the subjective evaluation of relief of symptoms experienced after 8 weeks of treatment by means of a scale numbered from 1 to 5 (1 = very poor; 2 = poor; 3 = average; 4 = good; 5 = very good), the onset of other adverse reactions different from the usual ones and the abandonment or otherwise of the treatment due to the onset of side effects.

Statistical analysis

A database for the analysis of all of the variables of the study was designed using the SPSS version 12.0 (©2003 SPSS inc) computer programme. Descriptive and frequency statistics of the variables of the study were carried out. The association between the variable healing was compared with the main qualitative variables of the study (diagnosis, duration of treatment, and number of applications) by means of contingency tables and χ^2 with the significance level established at $P<.05$.

Results

A total of 70 patients were included (37 men), 57 of whom (81.4%) were diagnosed with anal fissure and 13 (18.6%), with anal fissure with haemorrhoids. The average age was 49.04 (45.53-52.55) years. As regards the symptoms prior to beginning treatment, 100% were experiencing pain, 58.6% (41 patients) were experiencing irritation, and 75.7% (53 patients), rectal bleeding.

Of the 70 patients, 13 (18.6%) were applying the ointment once per day, 55 (78.6%) twice per day, and only 2 patients (2.9%) 3 times per day, with an average duration of treatment of 6.16 (5.15-7.16) weeks.

As regards the outcome variable, healing occurred in 34 patients (48.6%) while 33 of them underwent surgery (47.1%). Of the total patients treated, 3 were not cured nor operated on during the study period; therefore they were not taken into account in the rest of the results.

With regard to relief of the symptoms experienced after 8 weeks of treatment with topical diltiazem and with respect to the scale of subjective evaluation, 5 (7.1%) responded "very poor"; 4 (5.7%), "poor"; 13 (18.6%), "average"; 25 (35.7%), "good"; and 23 (32.9%), "very good."

Twenty-four patients (30%) experienced some form of side effect related to the treatment. With respect to the classic adverse reactions to diltiazem, 6 patients (8.6%) of the total experienced headache and one of them (1.4%) experienced hypotension. Other various noted side effects were: an allergic reaction in 3 patients (4.3%), irritation in 10 (14.3%), dizziness in 2 (2.9%),

facial flushing in 1 (1.4%), and local heat in 1 (1.4%). Only 4 patients (5.7%) abandoned the treatment due to an adverse reaction: 1 due to experiencing an allergic reaction (abandoned treatment after 2 weeks) and the remaining 3 due to irritation upon application (abandoned treatment after 2 or 3 weeks), and they underwent surgery.

As regards the relationship between the diagnosis and healing of the fissure, the data is shown in Figure 1. The anal fissure was healed in 30 of the 55 patients diagnosed with anal fissure (54.5%), and only in 4 of the 12 diagnosed with anal fissure with haemorrhoids (33.3%), although a statistically significant difference between both diagnoses has not been obtained (P=.183).

The results obtained with regard to association between the duration of the treatment and the healing or otherwise of the fissure are shown in Figure 2. The patients were divided into 2 groups: those who were treated with diltiazem for a period of equal to or less than 4 weeks, and those who were treated for over 4 weeks. Of those treated for 1 month or less (42 patients), the fissure was healed in 19 (45.2%), and of those who were in treatment for a longer period (25 patients), 15 (60%) were healed, and no significant differences were found between both groups (P=.242).

Upon comparison of the number of daily applications of the ointment with the healing of the fissure, the vast majority (79.1%) followed the usual dosage instructions and applied twice per day; of this group, the fissure healed in 49.1% Of the 2 patients who applied 3 times per day, in one the fissure eventually healed and in the other it did not (the latter had surgery scheduled since before starting treatment with topical diltiazem). No significant differences were found between both groups (P=.746).

In order to better evaluate the efficacy of the treatment a subgroup was created which excluded those patients who had surgery scheduled before starting treatment with diltiazem and those who were less than 1 month in treatment, given that the standard duration used in the bibliography is 4 to 8 weeks. A total of 55 patients were taken into account. The most noteworthy fact is that of the 100%of the cured patients, 60%were diagnosed with anal fissure, while the other 40% had anal fissure with haemorrhoids. However, on application of the χ^2 test corrected by Fisher's exact test, no statistically significant difference was obtained between both diagnoses (P=.304).

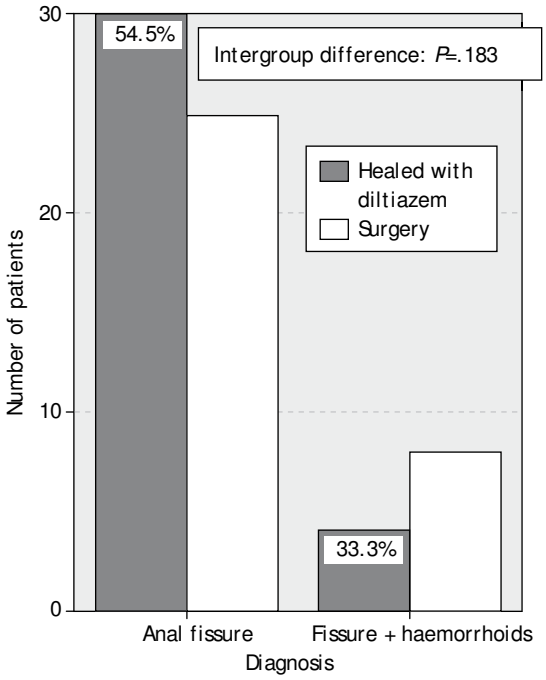

Figure 1 Percentage of patients operated on and cured according to the diagnosis.

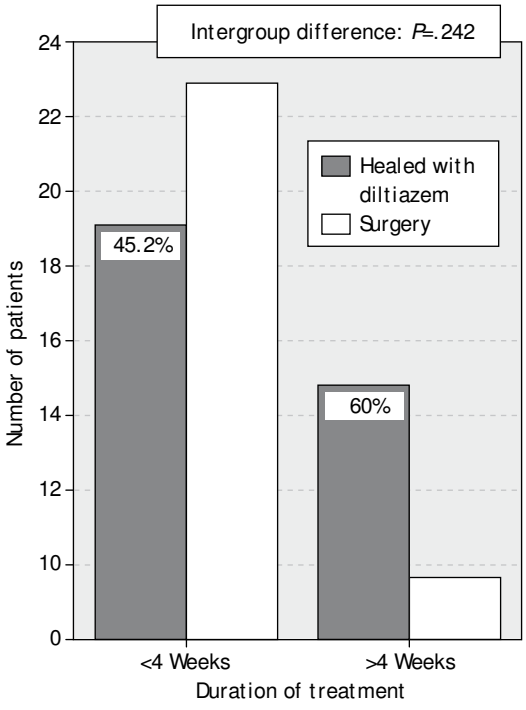

Figure 2 Percentage of patients operated on and cured according to the duration of treatment with diltiazem.

Discussion

Lateral internal sphincterotomy is one of the treatment options described and accepted as the treatment of choice for chronic anal fissure, since it reduces sphincter hypertonia, allowing a reduction in proctalgia and thereby promoting healing of the fissure. However, it is not without complications, especially changes in faecal incontinence, which explains why in the last 50 years the most successful treatment for anal fissures remains a matter of considerable debate. A consensus has still not been reached on the matter, and every day new molecules are researched, both topical and oral, to treat this common disorder.

Among the oral and topical treatments produced in the context of chemical sphincterotomy of anal fissures, the use of botulinum toxin has created new perspectives in the treatment of anal fissures; however, studies regarding the most effective dosage, its location, the number of injections, the duration of the treatment, and the long-term results, are still necessary. As regards the rest of the treatments,

mainly derived from nitric oxide liberators and calcium antagonists, there is a discrepancy in the results pertaining to their efficacy.

Treatment with diltiazem is associated with an initial healing rate of between 65% and 95% in the treatment of chronic fissures, with no significant side effects. However, oral treatment has resulted in unacceptable rates of nausea, vomiting, and headaches; therefore the majority of publications refer to diltiazem 2% in ointment form, applied twice daily. Studies have been undertaken which compare diltiazem with nitroglycerine, and both are equally effective; however, nitroglycerine is associated with more side effects (headaches and irritation).[22-24]

This study, from the point of view of the results of effectiveness of diltiazem ointment, ranks slightly below other published studies. The fissure was healed in 48.6% of patients, and 47.1% underwent surgery. Nash et al 25 carried out a study similar to our own (112 patients treated with diltiazem 2% ointment applied twice per day) with a healing rate of 66%

With regard to adverse effects, our study demonstrates that treatment with topical diltiazem is safe. Only 8.6% of patients experienced headaches and only 1.4% experienced hypotension, which are considered the most common side effects; various other side effects were experienced by 24.3%. The adverse reactions were a cause of the abandonment of treatment only in 5.7% of patients. Nash et al[25] obtained a similar percentage of adverse effects (approximately 20% of patients). This low frequency of headaches is probably related to the form of administration (applied directly onto the fissure and not around the anus, which is generally recommended) and with the recommended precaution using a disposable glove for its application, to avoid any minimal contact with the patient's skin, and therefore, its absorption.

With regard to the rest of the results obtained in our study, one may conclude that the fissures are more likely to heal when unaccompanied by haemorrhoids; that application more frequent than twice per day does not influence an improved level of healing; and that prolonging treatment over 1 month seems to produce improved healing (although there is no significant statistical difference, perhaps due to the difference in the number of patients that make up the groups, which means that they are not comparable between themselves).

As regards the follow-ups, they must be carried out on a long-term basis, as late relapses and recoverable incontinence can be detected as time passes. This fact is reflected in examples such as progressive recurrence with follow-up periods of over 1 year in around 50% of patients treated with botulinum toxin, according to Arroyo et al[26,27] and 11%45% of patients with reversible incontinence 6 years after the sphincterotomy, published by Nyam et al.[28] Therefore, definitive conclusions must not be drawn from short to mid term studies.

The lack of long-term follow-up periods which could detect relapses and the difficulties in carrying out telephone interviews (although the details of the interview were confirmed with the clinical history) could be considered among the limitations of our study.

In the future, similar studies, with some differences in the methodology, could focus on comparing the type of fissure (anterior or posterior), recording the causes of failure of the treatment with topical diltiazem (side effects, persistent symptoms, lack of healing, etc), carrying out longer-term follow-ups for all patients on an equal basis (cured or otherwise). The studies could thereby allow conclusions to be drawn on relapses, or take a control group treated with topical nitroglycerine and comparing both topical treatments.

Another field which merits future research would be evaluating the initial response to diltiazem 2% as a factor predicting curability. In this sense, Placer et al[29] concluded that a poor response in the first week resulted in failure of the treatment, avoiding the necessity of prolonging the treatment.

In conclusion, the treatment of the anal fissure with topical diltiazem in our hospital has avoided surgery in almost 50% of the patients, with infrequent, slight and tolerable adverse effects. Despite no significant differences being found between the studied variables, the results suggest that treatment was more effective in patients who did not have haemorrhoids associated with the anal fissure and in those whom the duration of treatment was longer than 4 weeks.

We believe that further studies with the different methods of treatment, surgical and non-surgical, are necessary, in order to construct a treatment algorithm which would result in an improved approach to anal fissures.

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Annex 1 Information sheet issued to patients treated with topical diltiazem

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DILTIAZEM 2% OINTMENT

Which conditions or disorders is this medication prescribed for?

Diltiazem is used topically to treat anal fissure, among other conditions. Diltiazem belongs to a class of medication known as calcium-channel blockers. It works by relaxing the blood vessels and muscles.

How should this medication be used?

Diltiazem is packaged in aluminium tubes of approx. 30 g. Take a small amount, approximately the size of a grain of rice, and apply it using a latex glove or with a cotton bud over the fissure. Use the medication exactly as indicated. Do not use more or less than the indicated dosage or more frequently than prescribed by your doctor.
Follow the instructions that have been issued to you in the consultation carefully and ask your doctor or pharmacist if there is anything you do not understand.

What other use does this medication have?

It is used in tablet form, taken orally, in the treatment of cardiovascular diseases. This medication may also be prescribed for other uses; ask your doctor or pharmacist for more information

Which special precautions should I follow?

Before beginning to take diltiazem:

- Tell your doctor or pharmacist if you are allergic to diltiazem or to any other medication.
- Tell your doctor or pharmacist which medication, with and without prescription, you are taking, especially medication for the heart and for blood pressure such as beta-blockers, digoxin (Lanoxin), quinidine (Quinaglute, Quinidex), and diuretics; carbamazepine (Tegretol); cimetidine (Tagamet); cyclosporine (Neoral, Sandimmune); fentanyl (Duragesic); medication for treating depression; medication for treating glaucoma (increased pressure in the eye); theophylline, and vitamins.
- Tell your doctor if you have, or have had at any time, a heart, liver, or kidney condition.
- Tell your doctor if you are pregnant, if you have plans to become pregnant, or if you are breast-feeding. If you become pregnant while taking this medication, call your doctor immediately.
- If you are going to undergo any type of surgery, including dental surgery, tell your doctor or dentist that you are taking diltiazem.

(Continues next page)

Annex 1 Information sheet issued to patients treated with topical diltiazem *(Continuation)*

What special diet should I follow while taking this medication?

If your doctor prescribes you with a diet, follow the instructions exactly.

What should I do if I forget to apply a dose?

Apply the dose you have forgotten as soon as you remember, however, if it is time to apply the next dose, skip the one you forgot and continue with your regular dosage. Do not take a double dose to compensate for the one you have forgotten.

What are the side effects which this medication could cause?

Although side effects are not common with this medication, there is a possibility they could occur.

Tell your doctor if any of the following symptoms becomes severe or does not disappear:

- Dizziness or nausea.
- Hot flushes (sensation of excessive heat).
- Cephalea (headache).
- Extreme tiredness.
- Slower heartbeat than normal.
- Upset stomach.
- Loss of appetite.
- Vomiting.
- Diarrhoea.
- Constipation.
- Stomach ache.
- Sensation of dryness in the mouth.
- Difficulty getting to sleep or staying asleep.

If you experience any of the following symptoms, call your doctor immediately:

- Inflammation of the face, eyes, lips, tongue, arms, or legs.
- Difficulty breathing or swallowing.
- Fainting.
- Skin rash (eruptions of the skin).
- Yellowish discoloration of the skin or eyes.
- Fever.
- Increase in the frequency or intensity of chest pain (angina).

How should this medication be stored?

Keep this medication in its packaging, properly closed and out of reach of children. Store it at room temperature and away from excessive heat and humidity (not in the bathroom). Dispose of any medicine which has expired or is no longer in use. Consult your pharmacist about appropriate disposal of medication.

Annex 2 Telephone questionnaire designed to assess the response to diltiazem after 8 weeks of treatment

DILTIAZEM 2% FOLLOW-UP SURVEY

Questionnaire No.: _____ **Date:** _____

Patient details:

Surname 1: _____ Surname 2: _____ First name: _____

NHC: _____ Telephone: _____

Sex: _____ Age: _____

Diagnosis:

Anal fissure/anal fissure + haemorrhoids

Symptoms prior to treatment:

Pain Yes/No

Irritation/pruritus Yes/No

Rectal bleeding Yes/No

Treatment with diltiazem 2%:

- No. of applications per day
- Relief of symptom: 1 2 3 4 5
  (1 = very poor; 2 = poor; 3 = average; 4 = good; 5 = very good)
- Adverse effects:

Headache Yes/No

Hypotension Yes/No

- Other adverse effects:
- Abandonment of treatment due to onset of adverse effects: Yes/No:
- Healing of the fissure: Yes/No:
- Surgery after treatment with diltiazem: Yes/No:
- Surgery scheduled prior to beginning treatment: Yes/No: