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# Assessment of Pizotifen efficacy in the management of recurrent aphthus stomatitis - A double blind trial -

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## Abstract

Recurrent aphthus ulceration (RAU) is one of the most common and troublesome oral lesions, as they are extremely painful and recurrent, no single preparation is uniformly effective in the treatment of this condition.

A double blind cross-over trial assessed the value of pizotifen in reducing the severity of pain, duration and frequency of ulcers in a group of recurrent aphthus ulcer patients. Active & placebo preparation were used for a period of 4 weeks each; 42 patients completed the use of both preparations.

20 patients out of 28 patients on pizotifen therapy experienced a decrease in the severity of pain as well as decrease in the duration of each attack, where as 18 patients in the same group reported reduction in the frequency of the disease.

Pizotifen reduced pain severity, duration and frequency of oral ulcerations in the examined group

## Introduction

Recurrent aphthus ulceration is one of the most common oral lesions seen by the dentist in every day practice. As many as 20% of adults suffer from aphthus stomatitis or canker sore [1]. These lesions may be associated with certain systemic conditions like: Iron, folate or vit.B12 deficiency, inflamed bowel, Behcet's disease, hypersensitivity to food or medications, HIV infections and in conditions predisposing to neutropenia [2] Clinically, single or multiple round or oval grayish ulcers develop on the lips, buccal mucosa and the tongue. These ulcers resolve in 10-14 days only to recur at a late date, and with advancing age, recurrent episodes become less frequent, and most of the population becomes disease free [3]. These ulcers are extremely painful and recurrent.

Diagnosis is established by the history, appearance and recurrence pattern of the lesions after the exclusion of other known causes of oral ulceration in which specific treatment may be appropriate [4,5].

Etiology of these lesions is still unknown, but suspected in the etiology& pathogenesis are mycoplasma and cell-mediated immune reactions[1].So, in the absence of complete understanding of the nature of these lesions, treatment remains symptomatic, and no definitive therapy is available [6].

Many empirical treatments have been used, and the management is largely directing towards reducing or alleviating the suffering that

accompanies this condition. The availability of multiple drug preparation including local anesthetic gels, topical analgesics, anti-inflammatory agents &antibiotics (such as tetracycline) and antiseptics in the form of chlorhexidine [7,8]. This evidence supports the fact that no single preparation is uniformly effective, however, it has been shown that systemic and topical treatment with corticosteroids can be a very useful modality in the control of this lesion, but the use of steroids in patients with pre-existing systemic disease is very dangerous, in addition to the known side effects of this drug.

Pizotifen (Sandomigran Sandoz) presents a possible recent addition to the therapeutic regiment of this troublesome condition. It is an antaminic characterized by polyvalent inhibitory effect on biogenic amines such as serotonin &histamin. Pizotifen is antihistamine and serotonin antagonist structurally related to the tricyclic antidepressants [9]. This drug is used nowadays in the prophylactic treatment of migraine.It contains ergotamine tartarate (1 mg)& caffeine (100 mg); as ergotamine prevents attacks of migraine & other vascular headaches by its specific vasotonic action& distended external arteries, while caffeine accelerates the absorption of ergotamine [9] .The indications of pizotifen are mainly for Acute attacks of migraine & other vascular headaches, while the contra-indications are in peripheral vascular disorder, pregnancy & lactation, sever hypertension and hepatic& renal failures. Side effects of pizotifen are mainly nausia, dizziness, and weakness in the extremities, abdominal pain, increased appetite and weight gain. However, if any symptoms such as tingling in the fingers or toes occur, the drug should be discontinued [9]. The initial dose is 2 tabs (each Tablet of 0.5mg) daily, then increased to 3 tabs daily in case of subsequent attacks. Maximum dose per day for adults is 6 tabs and for children are 3 tabs [9]. The purpose of this study was to assess the efficacy of systemic pizotifen in a double blind fashion in patients with recurrent aphthus ulceration.

## Materials & Methods

42 patients suffering from recurrent aphthus stomatitis. Their age range was 16-65years (mean age: 32.6 years), they were 17 female (mean age: 34.8 years) and 25 male (mean age 30.4 years) patients. They were selected from oral medicine clinic at the college of Dentistry, Baghdad University, to participate in a double cross over trial with pizotifen.

All patients had been screened and shown to have no correctable causes of oral ulceration such as nutritional deficiencies or food allergy, otherwise excluded from the study. They suffered from their ulcers for 1 - 8 years (mean duration: 4.6 years).34 patient of them had minor aphthae, while 5 patients had major aphthae and 3 patients had herptiform ulcers.

All patients selected for this study had not responded to other treatment modalities. 28 patients in the study group took 1.5mg of pizotifen (3 Tablets of 0.5mg, t.d.s) while 14 patients took placebo Tablets (control) for 4 weeks (sucary1 Tablets of low calories sweetener, Abott laboratories),

All patients were asked to take no other medications for 10 weeks before or during the course of the study.

Patients were examined, and data collected included frequency, number, severity, size and duration of the lesion, the information's were recorded on a diary form and medications were also recorded (Fig.1).

Patients who failed to respond to this initial 4 weeks trial of pizotifen and or placebo were switched to the alternative treatment The responses to pizotifen therapy were determined by: Assessment of clinical findings (including any alteration in the healing time of the area(s) involved), Changes in the length of time free of disease, patient's subjective assessments of symptoms, and occurrence of side effects.

## Results

20 patients out of 28 patients on pizotifen therapy experienced a decrease in the severity of pain as well as decrease in the duration of each attack, where as 18 patients in the same group also reported reduction in the frequency of the disease.6 patients remained completely unchanged in regard to pain severity, and disease duration & frequency. Only 2 patients reported increase in these parameters, (Table 1).

At the end of this trial, 8 patients in this group became completely free of the disease and were not crossed over to placebo.5 patients with recurrent aphthus ulceration in the control group were not crossed over to pizotifen since they reported a decrease of pain severity, duration and frequency (Table 2).

Another attack of these ulcerations had not occur during the time of this study After one year follow-up of 20 patients who completed the trial on pizotifen, we found that 13 of them continued to show a dramatic improvement in the symptoms, and they had not required further treatment, three patients were dropped from the study because of failure of follow-up Only 4 patients remained unchanged in regard to duration and frequency of the attack (Table 3) and needed just a course of pizotifen (1-1.5 mg ) daily for 3 days in order to bring the disease under full control.

A qualitative analysis of the data showed a greater reduction in the severity of pain, duration and frequency of the disease when pizotifen is used; this represents a beneficial carry-over effect.

### Side effects:

Minor side effects were reported in 6 patients out of 28 patients, change in taste, drowsiness was the most commonly reported side effects. Abdominal pain, increased appetite and skin rash were also seen in 2 patients. All blood counts remained within normal limits.

## Discussion

This double blind cross over trial with pizotifen in patient with recurrent aphthus ulceration confirms the superiority of this drug over placebo and supports the preliminary finding from uncontrolled trial in which significant clinical benefits was obtained in nine out of twelve patients with recurrent aphthus ulceration [10]. Two of the remaining three patients had partial improvement of the symptoms.

Patients who entered in this study have management problems, some of them had either failed to the conventional therapy with anti-inflammatory and or antimicrobial agents, other patients had used cortisone in moderate to high doses both systemically and topically with limited improvement apart from the side effects developed in those patients.

The results of the present investigation were rather dramatic, as 13 of the patients who had very troublesome ulcerations, with an average of 3 - 4 attacks per month, showed significant improvement which

needed no further treatment, while the rest experienced fewer and milder attacks that required no additive treatment a part from a single course of pizotifen (0.5-1.5 mg) daily for 3 days which were strong enough to abort the attack or alleviate the symptoms.

We believed that the exact mechanism by which pizotifen benefits our patients is thorough its inhibitory effect on the chemical mediators of pain such as histamine, serotonin and trypytamine because it is an antihistamine & serotonin antagonist, thus reducing the discomfort & duration of lesions experienced by the patients. Another very important point is that patients responding to pizotifen tends to remain free of the disease for prolong periods of time even upon cessation of treatment. This is one of the major advantages of pizotifen over other treatments modalities. Regarding side effects, they were few, occurred in only 6 patients, and none was sever enough to jeopardize the clinical benefits obtained from this drug.

Sedation may be experienced at the beginning of the treatment, which may be well tolerated by some patients. Otherwise it can be avoided by decreasing the drug gradually or taking the drug at bed time. Two patients developed abdominal pain &skin rash, in these patients, therapy was temporarily stopped. The appetite stimulating effects of pizotifen may lead to increases body weight.

As we couldn't find any previous studies regarding the application of pizotifen for the treatment of recurrent aphthus ulceration or even other conditions of the oral cavity so we can mention that this study is the first of its kind. However further studies on the application of such drug for the treatment of other oral diseases is necessary in the future.

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Figure 1: Patients diary information record

-Please Indicate the location of your mouth ulcer .

-Please indicate the duration that the ulcer(s) stay in your mouth: 1…30 day.

-Please indicate the pain severity from your mouth ulcers in response to treatment, by ticking the appropriate box:

**Increased Unchanged Decreased**

-Please indicate any alteration in the healing time of your ulcers, by ticking the appropriate box .

**Increased Unchanged Decreased**

-Please indicate whether you experienced any change in the frequency of your mouth ulcer by ticking the appropriate box

**Increased Unchanged Decreased**

- Please indicate whether you experienced any change in the symptoms:

**Increased Unchanged Decreased**

-If you have experienced any side effects this week please state:

Table 1: Disease response in double blind trial with pizotifen for 28 patients with recurrent aphthus ulceration, (during study):

| Response | Increased | Unchanged | Decreased |
|---|---|---|---|
| **Pain severity** | **2** | **6** | **20** |
| **Disease duration** | **2** | **6** | **20** |
| **Disease frequency** | **2** | **8** | **18** |

Table 2: Disease response in double blind trial with placebo (control) for 14 patients with recurrent aphthus ulceration, (during study):

| Response | Increased | Unchanged | Decreased |
|---|---|---|---|
| **Pain severity** | --- | **9** | **5** |
| **Disease duration** | --- | **9** | **5** |
| **Disease frequency** | --- | **9** | **5** |

Table 3: Disease response to pizotifen for 20 patients with recurrent aphthus ulceration (1 year follow up):

| Response | Increased | Unchanged | Decreased |
|---|---|---|---|
| **Pain severity** | --- | --- | **20** |
| **Disease duration** | --- | **4** | **13** |
| **Disease frequency** | --- | **4** | **13** |