Review Article

Pharmacotherapy of recurrent aphthous ulcers

Abstract

Aphthous ulcer is the most common type of ulcer affecting the oral cavity and is considered to be one of the most painful conditions. Treatment is often unsatisfactory. Newer treatment modalities are therefore being tried. Amlexanox and rebamipide are the approved drugs for painful aphthous ulcers and have been used in painful symptoms of acid peptic disease as prostaglandin enhancers. Safety and efficacy of the drugs used in the treatment of recurrent aphthous ulcers were evaluated and being used widely by most of the treating physicians choosing a modality of treatment of their experience. There is no proper treatment modality available till date. Various drugs and their efficacy with least adverse drug effects while treating the various aphthous ulcers are discussed.

Key words:
Erythema, lymphnodes, mucosa, recurrent aphthous ulce

Introduction

Recurrent aphthous ulcer (RAU) is characterized by spontaneously self-limiting ulcerations of the mucosa of the oral cavity. The lesions can be single or multiple and generally affect the tongue, floor of the mouth, cheeks, soft palate, fauces and gums which are the nonkeratinized parts of the oral mucosa. This pathology can be observed in 20–30% of the population and most commonly affects the higher social classes.[1,2] The highest incidence is among young people between 10 and 20 years of age, the severity and frequency of ulcers decreasing with age.[3,4] Genetic predisposition is also involved; if both parents suffer from recurrent aphthous ulcers, the probability of an early onset of such pathology is as high as 90%, but this probability falls to 10% if only one parent suffers from it.[5]

Recurrent aphthous ulcers can be divided into three categories depending on the characteristics of the ulcers: major, minor, and herpetiform.[6] The basic form is characterized by painful ulcers (>10 mm), which destroy the mucous membrane of deep ulcers located on the palate, tonsils, pharynx, or tongue, which generally heal scar formation within two weeks, but sometimes it can take several months. Recurrences can usually be seen every one-four months, but some patients with almost continuous ulcers.[7,8] Detailed medical history should be taken in each case of relapse thrush to rule out other diseases that may pose canker-like lesions, such as Behcet's syndrome, Crohn's disease, human immunodeficiency virus (HIV), and neutropenia.[4,9,10]

Etiology

The etiology of recurrent aphthous stomatitis is still not understood, although many predisposing and precipitating factors have been described: trauma, stress, changes in the immune system, sensitivity to certain types of food, or ingested substances such as preservative agents or the substances like cinnamaldehyde or sodium lauryl sulfate present in some toothpastes, iron, zinc, and vitamin deficiency.[11,12] The main pathogenetic event is the inflammatory response with production of inflammatory cytokines (IL2- IL12, IFN-γ), prostaglandin E2 (PGE2), and nitric oxide (NO).[13,14]

Aphthae more commonly affect young adults, and a familial tendency may exist.[15] Paradoxically, smoking offers a

Access this article online	
Website: http://www.cysonline.org	Quick Response Code
DOI: 10.4103/2229-5186.90889	

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somewhat protective effect against recurrent aphthae.[16] Infectious agents such as *Helicobacter pylori* and herpes simplex virus have been investigated, but the lack of association between RAU and the infectious agents has been consistently found in aphthous ulcers.[17] The lack of consistent studies regarding etiology has resulted in treatments that are largely empiric and aimed at symptom reduction.

Pathophysiology

The pathophysiology of aphthous ulcers is not clearly understood. Alteration of local cell mediated immunity is often encountered in patients with RAU. Systemic T- and B-cell responses have also been reported as altered in patients with RAU.[16] Histologically, aphthous ulcers contain a mononuclear infiltrate with a fibrin coating.[15] Three clinical presentations within RAU can be studied under separate headings.

Aphthous ulcer minor

This is the most common form, accounting for 80% of all cases. Oral mucosal ulcers which are discrete, painful, shallow, recurrent ulcers lesser than 1 cm in diameter characterize this form. Aphthous ulcer minor (MiAU) infrequently presents as a small single ulcer. Lesions heal without scarring within 7-10 days. The periodicity varies between individuals, with some having longer ulcer-free episodes and some never being free from ulcers.

Aphthous ulcer major

This is formerly known as periadenitis mucosa necrotica recurrens. This form is less common than the others and is characterized by oval ulcers greater than 1 cm in diameter. Occasionally Aphthous ulcer major (MaAU) be a relatively severe form, many major aphthae may be present simultaneously. Ulcers are large and deep, may have irregular borders, and may coalesce. Upon healing, which may take as long as six weeks, ulcers can leave scarring, and severe distortion of oral and pharyngeal mucosa may occur.

Herpetiform recurrent aphthous ulcer

This least common form (5-10% of cases) has the smallest of the aphthous ulcers, commonly less than 1 mm in diameter in size. The ulcers tend to occur in clusters that may consist of tens or hundreds of minute ulcers. Clusters may be small and localized, or they may be distributed throughout the soft mucosa of the oral cavity.[6]

The nonaphthous patient will experience oral mucosal trauma and the resultant ulceration is irregular in outline, shows minimal and short duration, which is an evidence of the cardinal signs of inflammation (heat, redness, swelling, pain, and loss of function) and resolves within a few days depending upon the severity of the initial soft tissue injury. The aphthous patient will follow a different route. The lesion will change within one to two days from the irregular traumatic ulcer to the typical regular outline of an aphthous lesion which will run the protracted course of an aphthous ulcer.

Physical or emotional stress is often reported by patients as associated with recurrent outbreaks.[18] Environmental factors are associated with recurrent aphthous ulcer. Local, chemical, or physical trauma may initiate ulcer development in patients who are susceptible. Allergy or sensitivity to chemicals or food additives may stimulate an outbreak. The role of microbial infection is debated.

Human immune virus (HIV) infection (associated with lesions) : Aphthous-like oral ulcerations involving all three types of recurrent aphthous ulcers are observed. Approximately 66% of patients who are HIV positive have herpetiform and major recurrent aphthous ulcers. Among individuals with HIV unlike others, the ulcerations may be present on both keratinized and nonkeratinized surfaces, making it even more critical to rule out opportunistic infections. Ulcerations should also be distinguished from those caused by HIV medications and fungal, viral, or bacterial infections by biopsy followed by histopathological examination.[19]

Epidemiology

RAU occur worldwide and are reported on every populated continent. RAU affects 2-66% of the international population.[20] They affect 20% of the population, with the incidence rising to more than 50% in certain groups of students in professional schools. Children from high socioeconomic groups may be affected more than those from low socioeconomic groups.[21]

Clinical Presentation

The accepted classification of aphthae is based on the three parameters of lesion size, duration and the presence of residual scarring.[22] Clinically, patients and clinicians are often able to map the sequence of presentation through resolution into the following stages: (i) prodromal – symptoms but without any visible clinical sign; (ii) pre-ulcerative – initial presentation, usually erythema and slight edema; (iii) ulcerative – formation of the epithelial defect; (iv) healing – symptom abatement and progressive healing; (v) remission – no evidence of lesions. The prodromal stage is infrequent and transient and heralds the early ingress of lymphocytes from the recirculating lymphocyte pool.

The severity and duration of any lesion that does progress to the ulcerative stage represents the period when the local vascular response has allowed the clinical development of redness and swelling. The cytotoxic process will lead to epithelial cell death and progression to the ulcerative

stage. The ulcerative stage is the dominant stage and noted particularly by the patient due to local pain. Early epithelial destruction and breakthrough causes a small clinical ulcer which rapidly progresses to the full size determined for that particular lesion, most frequently 0.3–0.5 cm in diameter. The lesion is umbilicated or crateriform with clear sharp raised margins and surrounding erythema and edema. The lesion is generally round to oval and the depressed central zone carries a pseudomembrane that corresponds to a scab on a similar skin lesion. It is useful to think of aphthae as regular lesions that present a typical structure as opposed to traumatic lesions that tend to be irregular in outline and with a less clinically obvious acute inflammatory component. The ulcerative stage lasts for three to seven days. The healing stage is identified by the abrupt cessation of pain and the appearance of granulations within the decreasing surface exudate. Healing progresses by secondary intention with ingrowth of marginal epithelium and gradual centripetal closure of the defect. The remission stage identifies the ulcer-free periods. This may be prolonged or short, regular or irregular, apparently spontaneous in progression to a preulcerative stage or triggered by an identifiable and sometimes predictable event, for example some dietary items and occasionally in the premenstrual phase.[23]

Lesions are non-vesicular and may be single or multiple (two to six) with several episodes a year. The submandibular, deep cervical and parotid lymph nodes may be palpable and sensitive depending upon the severity of individual lesions and the number present. Major aphthous ulceration (MaAU) lesions are generally greater than 1 cm in diameter, last four to six weeks without treatment and heal with scar formation. This level of ulcer involves the deep submucosa and subjacent tissues rather than being limited to the lamina propria and superficial submucosa as occurs with MiAU and hence the development of cicatrix. The duration, frequency of occurrence and associated level of morbidity reflect the overall severity of the condition compared with MiAU. Most commonly, MaAU are seen on the soft palate and fauces, tongue and buccal and labial mucosae. The ulcers are often multiple and asymmetrical. Like MiAU, they have a crateriform profile but on a more exaggerated basis and with an irregular margin. Patients typically experience severe pain and associated lymphadenopathy. Herpetiform recurrent aphthous ulcer (HAU) is a relatively rare form and presents as non-cluster pattern and non-vesicular lesions 1–3 mm in diameter as distinct from viral ulcers.[24] The number may reach 50–100 lesions with associated local pain. Characteristically, they involve the anterior part of the mouth, tip, lateral and ventral tongue and the floor of the mouth but rarely appear on the lips. The lesions will usually heal without scarring in 7–14 days. In contrast to herpes simplex virus primary infection, patients with HAU usually do not experience prodromal systemic symptoms (malaise, fever, pain) and do not have either vesicles or the extensive ulcerative gingival involvement.

Management of Recurrent Aphthous Ulcer

The successful management of RAU depends on a careful patient work-up and correct diagnosis including any features peculiar to a patient's presentation. It also requires patient understanding of the nature of the disease. A patient who leaves the consultation without an understanding of the nature of the condition and that it represents a specific disease like any other disease will not regard the condition as anything other than a mouth ulcer. The routine haematological screen covering complete blood examination, iron studies, folate and vitamin B12 for all patients presenting with RAU is required. Only a small number of patients show a specific anaemia or other haematological deficiency but their exclusion is an important part of the complete patient evaluation. Similarly, folate levels are an indicator of intestinal absorption function but patients are also questioned concerning any abdominal symptoms and particularly those without an identified cause.

Successful management of RAU is variable but, in most cases, a useful strategy can be tailored to the individual patient. It does require both patient compliance with instructions and an understanding and acceptance of the recurrent nature of this disease. Prior to commencing any treatment, the patient requires both an accurate diagnosis and an assessment of the level of morbidity. Those with extensive ulceration and particularly MaAU are generally not suitable for general practice management and require referral. Specific treatment for this heterogeneous group focuses on rapid symptom relief and lesion resolution and may involve systemic corticosteroids or other immunomodulatory agents. The current discussion will focus on various drugs used in the management of RAU.

Management of MiAU may be usefully divided into three phases: (1) symptomatic and supportive treatment; (2) specific treatment; (3) preventive treatment. Symptomatic and supportive treatment is selfexplanatory and focuses on the current level of patient morbidity. This phase is defined by the prescription of generally proprietary preparations that address the obvious and major concerns of the patient: (a) antiseptic/anaesthetic preparations; (b) adequate analgesia; (c) maintenance of fluid balance; (d) adequate dietary intake. It addresses the impact that RAU has both locally in the mouth and systemic morbidity and interference with systemic functions if present. This approach is somewhat traditional but, in combination with patient understanding of the specific disease of RAU, it reinforces the overall treatment strategy being proposed for an individual and, significantly, addresses the patients' pain.

Specific treatment of MaAU and HAU requires a recognition and acceptance of the immunopathogenesis of RAU, irrespective of the exacerbating factor(s) of a specific episode. The temporal sequence of lymphocyte migration

to the lesion site and subsequent cell mediated cytotoxic destruction of epithelial cells is being addressed in this stage. The aim is to prevent epithelial destruction and the most effective general strategy to date is the appropriate use of topical corticosteroids.[25] These have a broad based dampening effect on all immuno-competent cells as well as reducing tissue inflammation and edema. The specific agent employed will depend upon the number, size and duration of lesions but, for most patients, a betamethasone preparation is found to be effective.[26] The topical preparations seem to be the main agents used in the treatment of RAU, in particular with an anti-inflammatory action. Hence the topical steroids are frequently used in the management of RAU. Only one crossover, randomized controlled trial demonstrated a significant reduction in pain compared with placebo, but showed no reduction in the frequency of RAU occurrence.[27] However, for such agents to be effective, they should be easy to apply and maintain at the site of ulceration for a long period. Active ingredient must be released continuously to exhibit substantivity. Though the topical medications seem to be the first choice for the treatment of RAU, such preparations are having restrictions with respect to drug delivery and compliance with subsequent retention in the mucous membranes of the mouth. These features may have a significant impact on the efficiency of an agent and challenge the pharmaceutical industry for the appropriate drug development.

The commonly used agents are betamethasone, fluocinonide, fluocinolone, fluticasone, and clobetasol. These agents are found to be more effective than hydrocortisone and triamcinolone, but higher risk for adrenocortical suppression and predisposition to candidiasis. So in clinical practice triamcinolone or fluocinonide dental paste is used as topical application over the ulcers two-three times daily for five days. Clobetasol mouthwash and the dexamethasone elixir as mouthrinse reduce the period of persistence of aphthous ulcers and not the frequency of recurrence.[28]

Clinical experience shows that patients with MaAU and HAU will enter a phase of complete clinical remission following the medium-term use of a corticosteroid mouthrinse on a daily basis initially and then on a minimal maintenance dose over one to two months. This method of delivery is less readily controlled by both the clinician and the patient and hence the opportunity for both oral and systemic adverse reactions is increased. It is generally inappropriate for pediatric patients and those with general medical conditions likely to be steroid sensitive, as in diabetes and hypertension. Any suggestion of an infectious conditions either locally in the mouth or systemic is an absolute contra-indication. Clinicians may benefit from specific advice from an oral medicine specialist prior to considering this treatment.

Amlexanox 5% paste (Aphthasol) has been examined in several studies of the treatment of aphthous ulcers. The paste was applied to ulcers two to four times a day. Healing time was improved with this agent. In one large study, 21% of patients achieved complete healing at three days compared with 8% of untreated patients.[29,30]

Rebamipide, an amino acid analog of 2(1H)-quinolinone, had been in use for mucosal protection, healing of gastroduodenal ulcers and treatment of gastritis.[31] It is known for its action enhancing mucosal defense, scavenging free radicals and temporarily activating genes encoding cyclooxygenase-2.[32] Clinical and experimental data shows that rebamipide accelerates ulcer healing, improves scar quality and prevents ulcer recurrence. However, the mechanisms responsible for these rebamipide's actions must be elucidated by further studies. Rebamipide seems to act through activation in gastric epithelial cells of proangiogenic growth factor genes and a direct angiogenic action on microvascular endothelial cells.[33]

A range of immunomodulatory agents have been used against RAU over a much extended time. Most have achieved less success than the strategies proposed, other than in the small percentage of patients with refractory disease and particularly those with RAU that is related to a systemic condition. These medications, which include thalidomide, pentoxifylline, colchicines and etanercept, are being trialled successfully.[34-37]

Conclusion

Aphthous ulcers are a poorly understood clinical entity that cause significant pain in otherwise healthy patients. Several agents are helpful in the management of aphthous ulcers, including antibiotics, anti-inflammatories, immune modulators, local anaesthetics and alternative products. But the drugs amlexanox and rebamipide have the proven efficacy over other drugs in the prevention of recurrent benign aphthous ulcers of mouth. When ulcers are slow to heal or if associated systemic symptoms are present (e.g., uveitis, arthritis, fever, adenopathy), other more serious conditions should be ruled out. General medical practitioners have great expertise in the arena of preventive medicine and a compliant patient will receive every promised benefit from a detailed evaluation, individual preventive plan, early support, monitoring compliance and regular review. In many ways, RAU management is similar to preventive medicine as it manages a disease that often cannot be eradicated but can be controlled with careful attention to the management protocol.

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How to cite this article: Angeline Archana JP, Jesudoss Prabhakaran AC. Pharmacotherapy of recurrent aphthous ulcers. Chron Young Sci 2011;2:134-8.

Source of Support: Nil, **Conflict of Interest:** None declared