Arch Health Invest (2021)10(9):1525-1529
https://doi.org/10.21270/archi.v10i9.5249

Clinical Case

Chemical injury induced by the use of topical imiquimod: case report

Lesão química induzida pelo uso de imiquimode tópico: relato de caso

Lesión química inducida por el uso de imiquimodos tópicos: reporte de caso

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Abstract

Chemical injury consists in damage caused by a substance when it comes into contact with living tissue. Certain drugs can cause this type of lesion in the oral mucosa. Imiquimod (INN) is an example. Erythema, edema, vesicles, erosions, ulcerations and inflammatory reactions are among the adverse effects associated with the use of INN. Nevertheless, since its effects disappear when terminating treatment, INN is still considered an essential drug in the treatment of condyloma acuminata, actinic cheilitis, superficial basal cell carcinoma and molluscum contagiosum. The objective of this work is to report a clinical case of a 34-year-old male patient presenting a symptomatic lesion on the lower and upper lip mucosa; while including a literature review on potential adverse effects when prescribing topical INN 5% for the oral mucosa.

Descriptors: Pharmaceutical Preparations; Mouth Mucosa; Drug-Related Side Effects and Adverse Reactions.

Resumo

Introdução: As lesões químicas consistem em alterações causadas por substâncias que causam danos ao entrar em contato com tecidos vivos. Alguns medicamentos podem causar esse tipo de lesões na mucosa oral, sendo o imiquimode (IMI) um exemplo deles. Dentre os efeitos adversos associados ao uso do IMI estão eritema, edema, vesículas, erosões, ulcerações e reações inflamatórias. Apesar disso, o IMI ainda é considerado um poderoso fármaco no tratamento de lesões, como condiloma acuminado, queilite actínica, carcinoma basocelular superficial e molusco contagioso, já que seus efeitos desaparecem ao interromper o tratamento. Objetivo: relatar o caso clínico de um paciente do sexo masculino, de 34 anos de idade, que possuía uma lesão sintomática em mucosa labial inferior e superior; além de fazer uma revisão de literatura sobre os possíveis efeitos adversos do IMI tópico 5% aplicado em mucosa oral.

Descritores: Preparações Farmacêuticas; Mucosa Bucal; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos.

Resumen

Introducción: las lesiones químicas consisten en cambios causados por sustancias que causan daños cuando entran en contacto con tejidos vivos. Algunas drogas pueden causar este tipo de lesión en la mucosa oral, siendo el imiquimod (IMI) un ejemplo de ellas. Entre los efectos adversos asociados con el uso de IMI se encuentran eritema, edema, vesículas, erosiones, ulceraciones y reacciones inflamatorias. A pesar de esto, el IMI todavía se considera un fármaco poderoso en el tratamiento de lesiones, como el condiloma acuminado, la queilitis actínica, el carcinoma basocelular superficial y el molusco contagioso, ya que sus efectos desaparecen cuando se interrumpe el tratamiento. Objetivo: informar el caso clínico de un paciente masculino de 34 años que tenía una lesión sintomática en la mucosa del labio inferior y superior; Además de revisar la literatura sobre los posibles efectos adversos del IMI tópico 5% aplicado a la mucosa oral.

Descriptores: Preparaciones Farmacéuticas; Mucosa Bucal; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos.

INTRODUCTION

Chemical lesions in the oral mucosa are associated with numerous agents, including medications, non-pharmacological substances, illicit drugs, and dental materials[1]. Such injuries when related to medications can be classified as adverse reactions. Clinically, regardless of the associated aggressor agent, chemical lesions are often similar in appearance; presenting mucosal destruction that ranges from superficial epithelial desquamation to a deeper and more extensive involvement of the epithelium and the underlying submucosal connective tissue[1-3]. A multitude of medications that patients take to control illness can also exposes them to the risk of developing adverse reactions[4].

Imiquimod (INN) is a topical immunomodulatory drug that works by activating the Toll-like receptor-7 (TLR-7), resulting in pro-inflammatory cytokine and chemokine release, strengthening of the acquired immune system, activation of T lymphocytes, and other immune responses which help to control intracellular viruses, tumors, and parasites[5]. The US Food and Drug Administration indicates INN for the treatment of warts, superficial and small basal cell carcinomas (< 2 cm), and actinic keratosis to within a contiguous area of 25 cm^2[2,6].

Despite the fact that INN is considered a proven chemotherapy, there are few studies on application in the oral mucosa. The most common adverse effect related to the use of INN in the oral mucosa is local irritation, including

erythema, ulceration, and pain[7,8]. The aim of this study is to report a clinical case of chemical injury resulting from treatment with topical INN, and perform a literature review on adverse effects involving the oral mucosa. The case report demonstrates the need for medical awareness and clear patient guidance concerning dose limitations when prescribing a specific therapy such as INN.

CLINICAL CASE

A 34-year-old male patient sought clinical care complaining of a symptomatic lesion in the lower and upper labial mucosa with approximately one month of evolution. During the anamnesis, the patient reported that the appearance of the lesion began after applying INN 5% cream (Aldara) prescribed by a dermatologist as treatment for a white, plaque-shaped, asymptomatic lesion located on the lower lip. The medication was used according to the dermatologist's instructions: applied to the lesion, three times a week. The patient also commented that the lesion symptoms started about 15 days after the first applications, which were continuing. Soon, the symptoms increased to the point of making it difficult to eat, causing weight loss “a few kilos”. This motivated him seek care at a stomatology clinic. Clinically, the lesion presented an extensive area of ulceration and erosion which extended throughout the upper and lower labial mucosa with redness of the lower lip (Figure 1A and B).

Figure 1. Clinical aspect of the chemical lesion showing areas of Erythema, edema, erosions and ulcerations in (A) Upper lip and (B) Lower lip.

The patient was normal-systemic and presented no other notable changes. In view of what had been reported, with clinical and physical examination, a diagnosis was made of chemical injury induced by the use of topical INN. In the presence of such lesions and the patient's comorbidity, it was decided to request suspension of INN; with prescriptions of oral prednisone (40 mg: one 20mg tablet every 12 hours for seven days) and topical clobetasol propionate to be applied to the injury three times a day for seven days. At the first follow-up visit, (one week after the initial visit), a significant improvement in the clinical condition was observed. The lesions on the upper lip had healed, and those on the lower lip were beginning the healing process (Figure 2A and B).

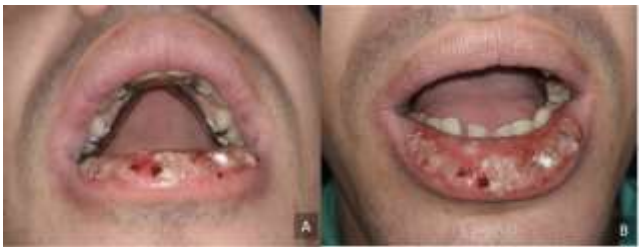

Figure 2. Clinical aspect of the chemical lesion after 1 week of treatment as systemic and topical corticosteroids. (A) Upper lip showing complete resolution; (B) Lower lip in the healing process.

It was decided to decrease the prednisone dosage to 20mg (one tablet a day, for 7 days) and to continue using topical clobetasol propionate. At the second follow-up visit, (the second week of treatment), the use of systemic corticosteroids was suspended, leaving only topical corticosteroids for another week. The patient presented significant improvement with only a few areas still in the process of healing (Figure 3A). After three weeks of treatment and total resolution of the clinical picture, the treatment was finished and medication was suspended (Figure 3B).

Figura 3. (A) Clinical aspect of the lesion on the lower lip after 2 weeks of treatment with topical corticosteroids and showing the final healing phase. (B) Complete remission of the chemical lesion after 3 weeks of treatment with topical corticosteroids.

DISCUSSION

INN, considered a topical chemotherapy, is an agonist of the TLR-7, and belongs to the imidazoquinolines family which act as immunomodulators[8-14]. INN stimulates an immune response by inducing, synthesizing and releasing monocyte/macrophage-derived cytokines, such as interferon, tumor necrosis factor (TNF), interleukins (IL) IL-1, IL-6, IL-8, and IL-12, as well as prostaglandin E2 and IL-10 (dominant TH1 cytokine pattern)[13], acting directly on cellular immunity, through induction of indirect antiviral and anticancer activities[10,13-15].

INN is marketed as a white or slightly yellowish cream 5% (Aldara® - 3M), and is used successfully to treat certain skin pathologies, such as superficial basal cell carcinoma, Bowen's disease, superficial squamous carcinoma, malignant superficial melanomas, actinic keratosis, and genital warts. It is contraindicated in patients with hypersensitivity to INN or to any other component of the

formula[11,16]. Dosage and method of administration differ according to clinical indication. There is no published pharmacokinetic data on mucosal application of INN and in general, oral application of imiqumod is prohibited[17]. However, intraoral application of INN has been successfully used for oral leukoplakia and intraoral melanoma with no systemic side-effects[18].

Given local administration, systemic side effects are rare and local reactions are more frequent. These include: edema, itching, burning sensation, bleeding, gallbladder, abrasions, crusts, hardening, tenderness, pain, eczematization, erosion, ulceration and induction of other dermatoses. Also, these effects are usually resolved upon interruption of treatment[7,8,10,11,14,19]. Though only a small amount of the drug is expected to reach systemic circulation, unusual systemic side effects have been reported including: headache, upper respiratory tract infection, gastrointestinal symptoms and certain non-dermatological disorders (neuropathic pain, thyroiditis, abnormal liver function, etc. [7,8,10,11,13-15,19-27]

In the present case, the oral mucosa was the only affected site, a chemical lesion that brought a certain comorbidity to the patient, presenting extensive areas of ulceration, erosion, edema and erythema covering the entire length of the lower lip and part of the upper lip; and causing local itching, burning, irritation and pain.

Though INN has already proven its effectiveness, its use in oral mucosa is not considered common[28]. Some case reports in the literature emphasize this potential for adverse effects. Currently, there are some studies reporting adverse effects resulting from the use of INN to treat oral lesions (Table I). Of the reported adverse effects, some presented a higher degree of comorbidity than others. However, due to the small number of cases reported, it is not possible to confirm a direct relationship between the mode of application and the intensity of the adverse reactions.

In the cases reported by Esquivel et al.[8] and Barikbin et al.[7], INN was respectively used as a treatment for oral lesions in human papillomavirus (HPV) and multifocal epithelial hyperplasia; the posology consisted of seven applications per week. In these cases, erythema and erosions were predominantly reported. Lesions were located on the gums, tongue, palate, cheek and labial mucosa; the effects coincided with the areas of application.

As reported by Mcdonalds et al.[23], Chakrabarty et al.[10] and Gencoglan et al.[19], in cases using INN to treat actinic cheilitis and lichen planus, undesirable reactions were observed upon five applications, among them, aphthous ulcers, crust, erythema, itching, irritation, burning, and pain. Brown et al.[20], Chakrabarty et al. [10] and Ermertcan et al.[22], in cases of actinic cheilitis and micro-invasive squamous cell carcinoma, (being treated with just two applications of INN per week), ulcers, erythema and irritation were reported as adverse effects.

Table 1. Cases of adverse effects involving the oral mucosa induced by the use of topical INN

Year	Reference	Oral injury	INN posology 5%	Adverse reactions
2000	Rinne et al.	Papilloma	3x a week for 12 weeks.	Burning and erythema.
2002	Smith et al.	Actinic cheilitis	3x a week for 4 weeks.	Inflammation in different degrees of severity and edema.
2003	Wenzel et al.	Oral florid papilomatosis	3x a week for 4 months (2 weeks yes, 2 weeks no).	Severe irritation, erosion and pain.
2005	Chakrabarty et al.	Actinic cheilitis	3x a week for 3 weeks plus 5x a week for 1 week.	Edema and aphthous ulcers.
2005	Chakrabarty et al.	Actinic cheilitis	3x a week for 3 weeks.	Aphthous ulcers.
2005	Chakrabarty et al.	Actinic cheilitis	2x a week for 5 weeks.	Aphthous ulcers.
2009	Yasar et al.	Multifocal epithelial hyperplasia	3x a week for 16 weeks.	Burning, erosion and headache.
2010	Mcdonald et al.	Actinic cheilitis	5x a week for 6 weeks.	Erythema, ulceration, crust and pain.
2011	Kwon et al.	Verrucous Carcinoma	3x a week for 8 weeks.	Erythema, crust with exudation and pain.
2011	Kwon et al.	Verrucous Carcinoma	3x a week for 7 weeks.	Erythema and crust.
2011	Gencoglan et al.	Lichen planus	5x a week for 2 weeks	Prominent erosion and crust.
2011	Sotiriou et al.	Dysplasia	3x a week for 4 weeks.	Itching, burning, erythema, edema, erosions and ulcerations.
2013	Emertcan et al.	Microinvasive squamous cell carcinoma	5x a week for 2 weeks.	Burning and irritation.
2014	Brown et al.	Actinic cheilitis	2x a week for 3 weeks.	Liqueinoid reaction
2014	Barikbin et al.	Multifocal epithelial hyperplasia	7x a week for 16 weeks.	Erythema and erosion
2015	Esquivel et al.	Oral HPV lesions	7x a week for 5 weeks	Erosion
2020	Present case	Actinic cheilitis	3x a week for 4 weeks	Itching, burning, erythema, edema, erosions and ulcerations.

Other reports relate adverse reactions such as aphthous ulcers, erosions, edema, itching, pain, and burning when INN was prescribed at three applications per week, (the therapeutic dosage adopted in the present case)[10,11,13-15,25,26].

Adverse effects affecting the oral mucosa were more intense following INN treatment of lesions such as actinic cheilitis; other lesions presented milder manifestations. From a universe of 64 cases, 16 presented either moderate or severe reactions, of which 14 were characterized as actinic cheilitis lesion. Thus, the majority of the cases reporting severe adverse reactions in the literature were actinic[10,13,20,23]. According to some authors, serious adverse events are secondary to systemic absorption and are related to the mechanism of action of the drug through activation of pathological cytokines[29,30].

In the present case, upon complete resolution of the chemical lesions caused by the use of INN, an incisional biopsy of the initial lesion was realized that confirmed the diagnosis of actinic cheilitis, and also that the use of INN in actinic cheilitis causes more severe adverse manifestations.

In most cases reported in the literature, treatment with INN is interrupted upon facing an adverse reaction. Treatment is thus postponed until the condition improves. In the present case, (where the patient continued to use the INN cream), this did not occur. The existing chemical lesion worsened without improvement in the condition and patient weight loss also resulted for not being able to eat properly.

CONCLUSION

Thus, we conclude that the topical INN generally presents few local adverse effects. However, in cases of actinic cheilitis it can induce more significant reactions. In the present case and in other similar case reports, the most common local reaction is characterized as chemical injury induced by the use of a specific medication.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interests.

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Received 01/12/2020
Accepted 18/07/2021