



Kobkan Thongprasom

Pregled učinkovitosti i nuspojava 0,1 %-tnog fluocinolon acetona u liječenju bolesti oralne sluznice

A Review of the Effectiveness and Side-Effects of Fluocinolone Acetonide 0.1% in the Treatment of Oral Mucosal Diseases

Zavod za oralnu medicinu, Stomatološki fakultet Sveučilišta Chulalongkorn u Bangkoku, Tajland
Oral Medicine Department, Faculty of Dentistry Chulalongkorn University Bangkok, Thailand

Sažetak

Topikalni steroidi naširoko se koriste u liječenju simptomatskih lezija oralne sluznice kako bi se smanjile bol i upala. Potentni topikalni steroidi, poput klobetazol propionata, flucinolon acetona (FA) i flucinonida, koriste se u liječenju tvrdokornih lezija oralne sluznice. U mnogim se izvještajima pokazalo da su navedeni steroidi učinkoviti u liječenju oralnih lezija uz malo popratnih pojava. U ovom preglednom radu opisuju se djelotvornost i popratne pojave korištenja FA 0,1 % u liječenju simptomatskog oralnog lihen planusa (OLP), oralne lihenoidne reakcije na lijekove (OLR-L), oralnog pemfigusa i eritema multiforme povezanog s herpesom (HAEM). FA 0,1 % pokazao se učinkovitim i sigurnim u liječenju pacijenata s multiplim sistemskim bolestima i trudnica s HAEM-om. Nadalje, taj topikalni steroid brzo smanjuje bol i upalu te pospješuje cijeljenje lezija bez ozbiljnih nuspojava, osim pseudomembranozne kandidijaze koja se jednostavno liječi. U nekim slučajevima dugoročna terapija FA-om 0.1 % rezultirala je hiperpigmentacijom u područjima zacijeljenih oralnih lezija, no takve hiperpigmentacije postupno su nestale nakon prestanka primjene topikalnog steroida.

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Prof. Kobkan Thongprasom
Chulalongkorn University
Faculty of Dentistry
Oral Medicine Department
Bangkok 10330, Thailand
Tel +66-2-2188942
Fax-77-2-2188941
kobkan.t@chula.ac.th

Ključne riječi

fluocinolon acetonid; nuspojave na lijekove; kandidijaza; eritema multiforme; oral lihen planus; pemfigus

Uvod

Tijekom proteklog desetljeća koristile su se različite terapije u liječenju teških ili kroničnih oralnih lezija, no potpuno izliječenje teško se postiže. Topikalni steroidi smatraju se terapijom izbora za oralne autoimune bolesti. Oni se naširoko koriste u liječenju simptomatskih oralnih lezija, poput tvrdokornih aftoznih ulceracija (1), oralnog lihen planusa (OLP) (2, 3), oralne lihenoidne reakcije na lijekove (OLR) (4), pemfigusa (5–7), mukozna membranoznog pemfigoida (8) i eritema multiforme povezanog s herpesom (HAEM-a) (9). Topikalni steroidi mogu se koristiti samostalno ili u kombinaciji sa sistemskim steroidima u liječenju teških bolesti oralne sluznice. Budući da su topikalni steroidi u izravnom kontaktu i penetriraju kroz mukozne membrane, mogu potaknuti njezino cijeljenje.

Flucinolon acetonid (FA) prvi put je sintetiziran 1959. na Odjelu za istraživanje Syntex laboratorija u Mexico Cityju. FA je sintetski derivat hidrokortizona koji se primarno koristi za liječenje upalnih promjena kože i smanjenje svrbeža. Supstitucija fluorina na položaju 9 u steroidnom prstenu povećava njegovu aktivnost (11) (Slika 1.). FA u orabazi (FAO) ili u otopini (FAS) koncentracije 0,1 % može se koristiti kao

Introduction

Over the past decade, various treatments have been used to treat chronic or severe oral lesions, however, a complete cure is difficult to achieve. Topical steroids are considered to be the first-line therapy for oral autoimmune diseases. These drugs have been widely used in the treatment of symptomatic oral lesions, such as recurrent aphthous ulceration (1), oral lichen planus (OLP) (2, 3), oral lichenoid drug reaction (OLDR) (4), pemphigus (5-7), mucous membrane pemphigoid (MMP) (8), and Herpes Associated Erythema Multiforme (HAEM) (9). Topical steroids can be used alone or combined with systemic steroids in the treatment of severe oral mucosal diseases. Since topical steroids directly contact and penetrate through the mucous membrane of erosive/ulcerative oral lesions, they can enhance lesion healing.

Fluocinolone acetonide (FA) was first synthesized in 1959 in the Research Department of Syntex Laboratories S.A. Mexico City, Mexico. FA is a synthetic hydrocortisone derivative primarily used to treat skin inflammation and relieve itching. The fluorine substitution at position 9 in the steroid nucleus ring greatly enhances its activity (11) (Figure 1). FA in orabase (FAO) or FA in solution (FAS) 0.1% can

alternativna terapija za tvrdokorne oralne lezije poput OLP-a, OLR-L-a, pemfigusa i HAEM-a kako bi se smanjile bol i upala. U ovom preglednom radu raspravlja se o učinkovitosti i nuspojavama terapije simptomatskih oralnih lezija FAO-om ili FAS-om. Opisuje se korištenje FAO-a ili FAS-a 0,1 % u liječenju različitih oralnih lezija.

Oralne lezije koje se liječe 0,1 %-tnim fluocinolon acetonom

Oralni lihen planus (OLP)

Godine 1985. predstojnik Zavoda za farmakologiju i oralnu medicinu Stomatološkog fakulteta Sveučilišta Chulalongkorn u Bangkoku na Tajlandu prvi put je pripremio 0,1 %-tnu otopinu topikalnog steroida FA, a 1988. pripremljen je i u orabazi 0,1 % (12). FA u otopini (FAS) bio je učinkovit u liječenju tvrdokornog ulcerativnog OLP-a kod 36-godišnje pacijentice (Slika 2. a). Lezije na bukalnoj sluznici gotovo su se potpuno povukle nakon dva tjedna primjene FAO-a 0,1 % (Slika 25.). Nadalje, 29-godišnja pacijentica došla je u Kliniku za oralnu medicinu s atrofičnim OLP-om na bukalnoj sluznici obostrano pri čemu lezije nisu odgovarale na prethodnu terapiju. Nakon liječenja FAO-om 0,1 % lezije na bukalnoj sluznici postupno su se smanjivale do potpunog povlačenja nakon 22 mjeseca (Slike 3.a i b). Dodatno, i FAO i FAS pokazali su dobre rezultate u liječenju OLP-a tijekom dvogodišnjeg praćenja (13). Međutim, u ovom istraživanju FAO 0,1 % pokazao se učinkovitijim u usporedbi s FAS-om 0,1 %.

U vezi s imunopatogenezi oralnog lihenusa otkrivena je ekspresija proupalnog citokina TNF- α u svakom slučaju oralnog lihenusa kod tajlandskih pacijenata, što upućuje na to da TNF- α igra važnu ulogu u imunopatogenezi OLP-a (14). Nakon liječenja lezija OLP-a FAO-om 0,1 % ponovno je uzeta biopsija istih lezija kako bi se istražila ekspresija TNF- α . Otkriveno je da je FAO 0,1 % izazvao smanjenje ekspresije u svakom slučaju. Stoga, FAO 0,1 % smanjuje upalni proces kod OLP-a potiskujući ekspresiju proupalnog citokina TNF- α .

Oralna lihenoidna reakcija na lijekove (OLR)

OLR je uobičajena lezija u tajlandskoj populaciji. Oralne manifestacije i patohistološke značajke ove lezije slične su onima OLP-a (15). Oralne lezije kod OLR-L-a pojavljuju se nakon uzimanja određenih lijekova i nestaju nakon prestanka uzimanja sumnjivog lijeka. Nije teško dijagnosticirati i liječiti OLR ako pacijent uzima samo jedan lijek (16). No, većina pacijenata uzima više lijekova i može biti teško odrediti koji je lijek izazvao reakciju (17). Potentni lokalni steroidi mogu se koristiti u liječenju OLR-a. Pacijentica u dobi od 72 godine, s anamnezom kardiomegalije, hipertenzije i dijabetesa melitusa, razvila je ozbiljnu OLR-u nakon injekcije inzulina s velikim lezijama koje su se pojavile obostrano na bukalnoj sluznici. Na desnoj strani pojavile su se bijele strije i krvarenje (Slika 4.a). Nakon zamjene inzulina za drugi tip, njezina bukalna sluznica u roku od 6 mjeseci terapije FAO-om 0,1 % vratila se u normalno stanje (Slika 4.b). Utvrđeno je da je FAO 0,1 % učinkovit u smanjenju boli i ubrzanju cijelje-

be used as an alternative treatment for recalcitrant oral lesions such as OLP, OLDR, pemphigus, and HAEM to reduce pain and inflammation. The present review discusses the effectiveness and side-effects of FAO/FAS in the treatment of symptomatic oral lesions. The use of FA as orabase (FAO) or solution (FAS) 0.1% in the treatment of various oral lesions is described.

Oral lesions that were treated using FA 0.1%

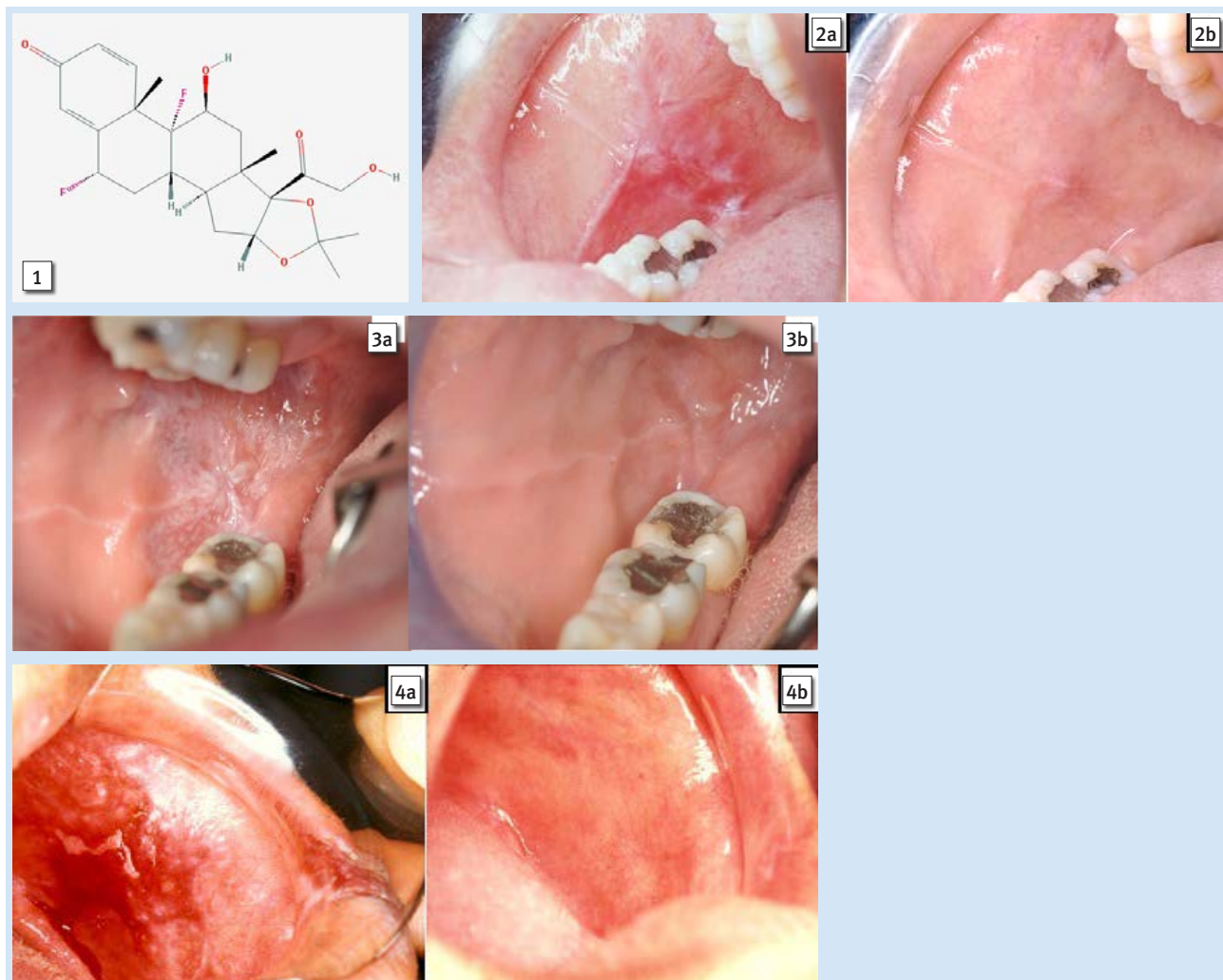
Oral lichen planus (OLP)

In 1985, topical steroid-FAS 0.1% was first prepared by the head of the Pharmacology and Oral Medicine Departments, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand, and later developed as FAO 0.1% in 1988 (12). FAO 0.1% was effective in the treatment of recalcitrant ulcerative OLP in a 36-year-old female (Figure 2a). Notably, the OLP lesions on her buccal mucosa showed nearly complete remission after 2 weeks of FAO 0.1% treatment (Figure 2b). Moreover, a 29-year-old female presented to the Oral Medicine Clinic with atrophic OLP on both buccal mucosae and these lesions were unresponsive to previous medications. After treatment with FAO 0.1%, the lesions on her buccal mucosa showed a gradual improvement until complete remission was seen at 22 months (Figure 3a, 3b). In addition, both FAO and FAS use resulted in improved results in the treatment of OLP during a 2 year-follow-up (13). However, in this study, FAO 0.1% was shown to be more effective compared with FAS 0.1%.

Regarding the immunopathogenesis of OLP, we found that the proinflammatory cytokine TNF- α was expressed in every case of OLP in Thai patients, indicating that TNF- α plays an important role in the immunopathogenesis of OLP in Thai patients (14). After treating their OLP lesions with FAO 0.1%, the same lesions were re-biopsied to investigate their TNF- α expression. We found that FAO 0.1% inhibited TNF- α expression in every case. Therefore, FAO 0.1% reduced the OLP inflammatory process by inhibiting the expression of the proinflammatory cytokine TNF- α .

Oral lichenoid drug reaction (OLDR)

OLDR is a common lesion in Thai patients. The oral manifestations and histopathological features of this lesion are similar to those of OLP (15). The oral lesions in OLDR erupt after taking a specific drug and resolve after withdrawing the suspected drug. It is not difficult to diagnose and treat OLDR if a patient is taking only one drug (16). However, most patients take multiple drugs and it can be difficult to withdraw the suspected drug (17). Potent topical steroids can be used in the treatment of OLDR. A 72-year-old female patient with a history of cardiomegaly, hypertension, and diabetes mellitus developed severe OLDR after an insulin injection, with severe lesions erupting on her bilateral buccal mucosae. White *striae* and excessive bleeding were seen on her right buccal mucosa (Figure 4a). After withdrawing the type of insulin injected and replacing it with another type of insulin, her buccal mucosa returned to normal state within 6 months of FAO 0.1% treatment (Figure 4b). FAO 0.1% was



- Slika 1.** Kemijska struktura fluocinolon acetonida
Figure 1 Chemical structure of fluocinolone acetonide
- Slika 2.a** Tvrđokorni ulcerativni OLP na bukalnoj sluznici desne strane koji nije odgovarao niti na jedan lijek.
Figure 2a Recalcitrant ulcerative OLP on the right buccal mucosa that was unresponsive to any medications.
- Slika 2.b** OLP lezija na bukalnoj sluznici desne strane gotovo se potpuno povukla nakon terapije FAO-om 0,1 % tijekom 2 tjedna.
Figure 2b OLP lesion on the right buccal mucosa showing nearly complete remission after treatment with FAO 0.1% for 2 weeks.
- Slika 3.a** Atrofični OLP na bukalnoj sluznici desne strane koji nije odgovarao na lijekove.
Figure 3a Atrophic OLP on the right buccal mucosa that was unresponsive to any medications.
- Slika 3.b** Lezije su se povukle nakon terapije FAO-om 0,1 % tijekom 22 mjeseca.
Figure 3b Lesions resolved after treatment with FAO 0.1% for 22 months.
- Slika 4.a** Bijele strije i krvarenje na bukalnoj sluznici desne strane.
Figure 4a White striae and severe bleeding seen on the left buccal mucosa.
- Slika 4.b** Nakon terapije FAO-om 0,1 % i promjene vrste inzulina koji je ubrizgavan, bukalna sluznica postala je normalna.
Figure 4b After a treatment with FAO 0.1% and changing the type of insulin injected, the buccal mucosa returned to normal.

nja lezija. Ovaj steroidni pripravak za topikalnu primjenu također je siguran za liječenje pacijenata s multiplim sistemskim bolestima (4).

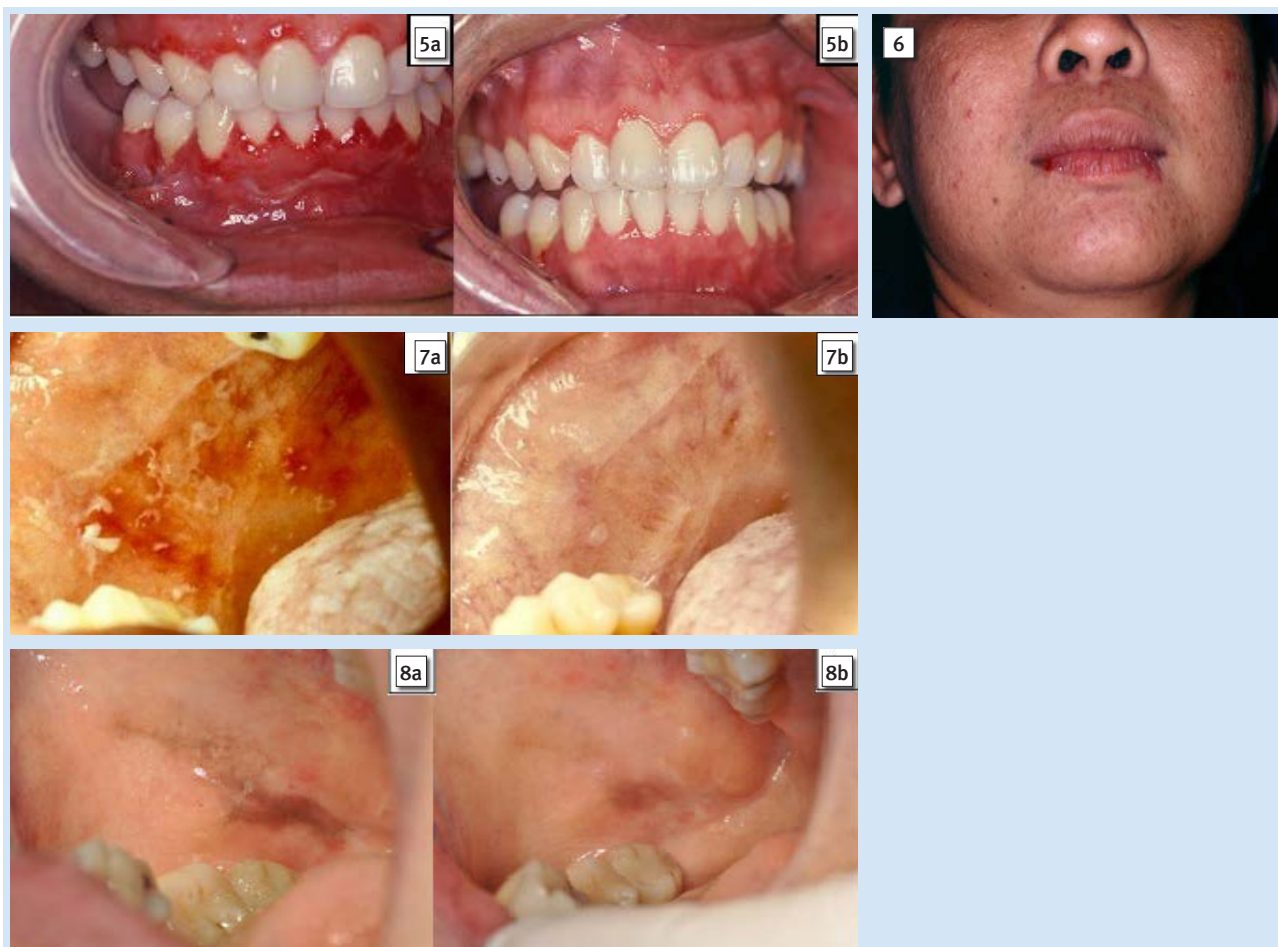
Oralni pemfigus

Pemfigus je autoimuna bolest čije oralne manifestacije obično prethode lezijama na koži. Gingiva je prvo i najčešće mjesto oralnih manifestacija pemfigusa (18). U liječenju oralnog pemfigusa koriste se sustavni steroidi. Međutim, kada se koriste u kombinaciji s lokalnim steroidima, sistemske doze mogu se smanjiti. Pacijentica u dobi od 35 godina došla je u Klinikum za oralnu medicinu s jakim boli i generaliziranim deskvamacijom epitela gingive koji se pojavio mjesec dana prije (Slika 5.a). Mjesec dana nakon kombiniranog lije-

found to be effective in rapidly reducing pain and enhancing lesion healing. This topical steroid formulation is also safe to use in treating patients with multiple systemic diseases (4).

Oral Pemphigus

Pemphigus is a fatal autoimmune disease the oral manifestations of which typically precede its skin lesions. The gingiva is the first and most common site of the oral manifestation of pemphigus (18). Systemic steroids have been used in the treatment of oral pemphigus. However, when used in combination with topical steroids, systemic steroid doses can be reduced. A 35-year-old female patient presented to the Oral Medicine Clinic with severe pain and generalized desquamative gingival epithelium for one month (Figure 5a).



Slika 5.a Teške generalizirane deskvamativne gingivne lezije kod pacijenta s pemfigusom.

Figure 5a Severe generalized desquamative gingival lesions in a patient with pemphigus.

Slika 5.b Lezije pemfigusa na gingivi gotovo su se potpuno povukle nakon terapije prednisonom 40 – 60 mg/dnevno i FAS-om 0,1 % tijekom 6 tjedana.

Figure 5b Pemphigus lesions on the gingiva showing nearly complete remission after treatment with prednisolone 40–60 mg/day and FAS 0.1% for 6 weeks.

Slika 6. Pacijentica s pemfigusom razvila je Cushingov sindrom koji obilježavaju mjesečevo lice, steroidne akne i hirsutizam nakon terapije sistemskim steroidima i FAS-om 0,1 % tijekom 6 tjedana.

Figure 6 Patient with pemphigus developed Cushing syndrome characterized by moon face, steroid acne, and hirsutism after treatment with a systemic steroid and FAS 0.1% for 6 weeks.

Slika 7.a Pseudomembranozna kandidijaza koja se razvila nakon terapije FAO-om 0,1 % tijekom mjesec dana.

Figure 7a Pseudomembranous candidiasis that developed after treatment with FAO for 1 month.

Slika 7.b Nakon terapije topikalnim protugljivičnim lijekom – mikonazol gel – bukalna sluznica se gotovo potpuno oporavila.

Figure 7b After treatment with topical antifungal- miconazole gel, the buccal mucosa showed nearly complete remission.

Slika 8.a Hiperpigmentacija na bukalnoj sluznici desne strane nakon terapije FAO-om 0,1 % tijekom 5 godina.

Figure 8a Hyperpigmentation on the right buccal mucosa after treatment with FAO 0.1% for 5 years.

Slika 8.b Hiperpigmentacija na bukalnoj sluznici desne strane postupno se povukla nakon 3 godine od prestanka korištenja FAO-a.

Figure 8b Hyperpigmentation on the right buccal mucosa gradually resolved within 3 years after discontinuing FAO 0.1% treatment.

čenja s 40 – 60 mg/dan prednizolona i topikalno primijenjenog FAS-a 0,1 % tri puta na dan na gingivu, lezije su pokazale gotovo potpunu remisiju (Slika 5.b). Nažalost, pacijentica je poslije razvila Cushingov sindrom: mjesečevo lice, steroidne akne i hirsutizam (Slika 6.). Njezin je liječnik postupno smanjio sistemsku dozu steroida i stanje joj se poboljšalo. Zanimljivo je da su se nakon dugotrajnog liječenja 43-godišnjeg pacijenta s pemfigusom FAS-om 0,1 %, u kombinaciji sa 60 mg prednizolona na dan, oralne lezije potpuno povukle nakon godinu dana (6). Štoviše, oralne lezije pemfigusa ostale su u potpunoj remisiji tijekom 12 godina praćenja bez ponovnog pojavljivanja ili bilo kakvih nuspojava.

One month after combined treatment with 40–60 mg/day prednisolone and topical FAS 0.1% three times/day on the gingiva, the lesions showed nearly complete remission (Figure 5b). Unfortunately, the patient subsequently developed Cushing syndrome: moon face, steroid acne, and hirsutism (Figure 6). Her physician gradually reduced the systemic steroid dose and her condition showed improvement. Interestingly, following long-term treatment of a 43-year-old male pemphigus patient with FAS 0.1% combined with 60 mg/day prednisolone, the oral lesions showed complete remission after 1 year (6). Moreover, his oral pemphigus lesions remained in complete remission during 12 years of follow-up without recurrence or any side-effects.

Erythema Multiforme povezana s herpesom (HAEM)

Multiformni eritem povezan s herpesom (engl. herpes associated erythema multiforme – HAEM) je atipična lezija uzrokovana infekcijom herpes simplex virusom i rijetko se pojavljuje u trudnica (9). FAO i FAS u koncentraciji od 0,1 % pokazali su se učinkovitim u liječenju bolnih oralnih ulkusa kod 28-godišnje trudnice s HAEM-om (9). Kratkotrajna terapija (2 tjedna) tim potentnim topikalnim steroidom brzo je smanjila bol s gotovo potpunim cijeljenjem lezije. FAO i FAS bili su učinkoviti i sigurni u terapiji HAEM-a kod ove trudnice koja je rodila zdravog dječaka. Nadalje, FAO i FAS su jeftini i u ovom slučaju bez popratnih pojava.

Nuspojave korištenja FAO-a/FAS-a

Tijekom liječenja oralnih lezija, kao što je OLP, FAO-om/FAS-om 0,1 %, uobičajena je pojava pseudomembranozna kandidijaza. Bijeli plakovi koji se mogu skinuti, mogu se razviti na bukalnoj sluznici nakon primjene FAS-a 0,1 % (Slika 7.a). Međutim, pseudomembranozna kandidijaza učinkovito se liječi lokalnim antimikoticima (Slika 7.b) (13, 19). U nekim slučajevima OLP-a, dugotrajno liječenje površinskim steroidom FAO 0,1 % izazvalo je hiperpigmentaciju na područjima prijašnjih oralnih lezija (Slika 8.a). Tijekom praćenja, mukozna hiperpigmentacija postupno je nestajala tijekom 3 godine nakon prestanka primjene toga lokalnog steroida (Slika 8.b).

Rasprava

FA 0,1 %, u otopini ili u orabazi, koristi se u liječenju različitih bolesti oralne sluznice. Štoviše, u sklopu dugoročnog praćenja pronađene su samo manje nuspojave, kao što su pseudomembranozna kandidijaza ili postupalna hiperpigmentacija. FA se može koristiti samostalno ili u kombinaciji sa sistemskim steroidima u liječenju teških oralnih lezija u pacijenata s multiplim sustavnim bolestima. Carrozzo i sur. naveli su da kombinacija sistemskih i visoko potentnih topikalnih steroida rezultira dobrom kontrolom takvih oralnih lezija (8). Utvrđeno je da je taj režim siguran i djelotvoran, uz manje popratne pojave tijekom ili nakon liječenja oralnih lezija u sklopu kratkoročnog i dugoročnog praćenja. Jedno je istraživanje pokazalo transmukoznu sistemsku apsorpciju potentnih topikalnih steroida, kao što je klobetazol (20). Stoga se preporučuje pažljivo praćenje pacijenata koji primaju kortikosteroidnu terapiju kako bi se izbjegli nepovoljni lokalni ili sustavni učinci. Međutim, zabilježene su neke nuspojave jakih lokalnih steroida, uključujući klobetazol propionat 0,05 % i betametazon, kao što je Cushingov sindrom (21).

U ovom preglednom radu, primjena FAS-a 0,1 % u kombinaciji s 40 – 60 mg prednisolona na dan tijekom jednog mjeseca u liječenju teškog oralnog pemfigusa rezultirala je Cushingovim sindromom. Stoga liječenje teških oralnih lezija sustavnim steroidima treba pomno pratiti i takve lezije treba liječiti stručnjak.

Prikaz slučaja pacijenta s HIV-om i OLR, koji je imao vrlo bolne erozivne lezije na oralnoj i bukalnoj sluznici, pokazao je da je pacijent dobro odgovorio na lokalnu terapiju FA-om 0,1 % (22). Topikalni steroid bio je učinkovit i ublažio je

Herpes Associated *Erythema Multiforme* (HAEM)

HAEM is an uncommon lesion caused by herpes simplex virus infection and is rarely found in pregnant women (9). FAO and FAS 0.1% were effective in treating severe painful oral ulcerations in a 28-year-old pregnant patient with HAEM (9). Short-term treatment (2 weeks) with this potent topical steroid rapidly reduced pain with nearly complete lesion healing. FAO and FAS 0.1% were effective and safe in the treatment of HAEM in this pregnant patient, who gave birth to a healthy son. Moreover, FAO and FAS 0.1% are low cost and without any side effects in this case.

Side-effects of FAO/FAS

During the treatment of oral lesions such as OLP with FAO/FAS 0.1%, pseudomembranous candidiasis eruption is common. White plaques that can be wiped off can develop on the buccal mucosa after treatment with FAS 0.1% (Figure 7a). However, pseudomembranous candidiasis is effectively treated with topical antifungal drugs (Figure 7b) (13, 19). In some OLP cases, long-term treatment with topical steroid-FAO 0.1% resulted in hyperpigmentation at the areas of previous oral lesions (Figure 8a). During the follow-up, the mucosal hyperpigmentation gradually resolved within 3 years after discontinuing this topical steroid (Figure 8b).

Discussion

FA 0.1%, both in solution or orabase forms, has been used in the treatment of various recalcitrant oral mucosal diseases. Moreover, only minor side-effects such as pseudomembranous candidiasis or post-inflammatory hyperpigmentation were found with FA use in our long-term observation. FA can be used alone or combined with systemic steroids in the treatment of severe oral lesions in patients with multiple systemic diseases. Carrozzo et al. suggested that the combination of systemic steroids and high potency topical steroids results in good control of these oral lesions (8). This regimen has been found to be safe and effective with only minor side-effects during or after the treatment of oral lesions in both short-term and long-term follow-up. One study showed the transmucosal systemic absorption of potent topical steroids, such as clobetasol (20). Thus, careful monitoring of patients receiving corticosteroid therapy is recommended to avoid adverse local or systemic effects. However, some side-effects of potent topical steroids, including clobetasol propionate 0.05% and betamethasone, such as Cushing's syndrome, have been reported (21).

In this review, FAS 0.1% in combination with 40–60 mg/day prednisolone for one month in the treatment of severe oral pemphigus resulted in Cushing's syndrome. Therefore, the treatment of severe oral lesions with a systemic steroid should be carefully monitored and these lesions should be treated by an expert.

A report of an HIV patient with OLR who had very painful erosive lesions involving the lip and buccal mucosa showed that this patient responded to topical FA 0.1% treat-

pacijentovu bol. Zanimljivo je da se pokazalo kako su lokalni steroidi, kao što je FA 0,1 %, klobetazol propionat 0,05 % i deksametazon 0,05 %, učinkoviti u liječenju težih lichenoidnih reakcija na lijekove bez ozbiljnih nuspojava u pacijenata s multiplim sustavnim bolestima tijekom 7-godišnjeg praćenja (4). Međutim, uloga određenog lijeka u patogenezi OLR-e može biti važna jer lijek djeluje kao antigen, potičući T-stanice. Antigen-specifične CD8+ citotoksične T-stanice zatim luče citokine, poput TNF- α ili interferona- α . Ti citokini zatim aktiviraju T-stanice i dendritičke stanice te aktiviraju apoptozu keratinocita bazalnih stanica, uzrokujući upalni imunski odgovor (23, 24).

Što se tiče hiperpigmentacija oralne sluznice, jedini rad o toj temi upućuje na to da hiperpigmentacija sluznice može biti sekundarni učinak lokalnog liječenja takrolimusom zbog povećanja broja melanocita i povećane proizvodnje melanina (25). Histopatološka slika hiperpigmentacije sluznice pokazala je porast broja melanocita i melanogeneze. Međutim, hiperpigmentacija je nestala kada je terapija završena, što je slično slučaju OLP-a liječenog FA-om u ovom radu.

Uz primjenu na oralnim lezijama, FA može imati i druge primjene. Istraživanje je pokazalo da FA potiče hondrogenozu mezenhimalnih matičnih/progenitorskih stanica u koštanoj srži povezanu s TGF- β , povećavajući razinu kolagena tipa II više od 100 puta u usporedbi sa široko rasprostranjenim lijekom, deksametazonom (26). Prema tome, FA/TGF- β 3 može se klinički primijeniti za povećanje učinkovitosti regenerativnih postupaka temeljenih na hondrogenoj diferencijaciji matičnih stanica. Također su zabilježeni učinci FA na formaciju tercijarnog dentina i oporavak ozlijeđene dentalne pulpe (27). Rezultati su pokazali da FA potiče proliferaciju stanica ljudske zubne pulpe (DPC), posebno subpopulacije CD146+. Pokazalo se da su stanice CD146+, stanice mezenhimske strome, sposobne za višelinijnsku diferencijaciju (28 – 30). Tako u oštećenoj pulpi CD146+ mogu proizvesti stanice koje se mogu diferencirati u odontoblaste za popravak oštećenja dentina i za rekonstituciju stanične populacije pulpe. FA inicira mineralizaciju DPC-a i ima potencijalnu ulogu u popravljaju oštećenog tkiva pulpe. FA može poboljšati zarastanje intraoralnih ozljeda poticanjem proliferacije i regeneracije stanica oralne sluznice. Potrebna su dodatna istraživanja o upotrebi FA u poticanju cijeljenja stanica oralne sluznice induciranjem ekspresije različitih citokina koji reguliraju molekule uključene u staničnu adheziju i formiranje izvanstaničnog matriksa (ECM) za učinkovito liječenje teških i tvrdokornih bolesti oralne sluznice.

Zaključak

FAO/FAS, u koncentraciji 0,1 %, učinkovit je u liječenju OLP-a, OLR, oralnog pemfigusa i HAEM-a. FAO/FAS 0,1 % brzo smanjuje bol i upalu. Taj topikalni steroid je jeftin i bez ozbiljnih nuspojava, osim pseudomembranozne kandidijaze koja se jednostavno liječi. Nadalje, FAO/FAS 0,1 % pokazao se sigurnim u liječenju pacijenata s višestrukim i različitim sistemskim bolestima te trudnica.

ment (22). This topical steroid was effective, and alleviated the patient's oral pain. Interestingly, a report showed that potent topical steroids such as FA 0.1%, clobetasol propionate 0.05%, and dexamethasone 0.05% were effective in the treatment of severe oral lichenoid drug reaction (OLDR) lesions without serious side-effects in patients with multiple systemic diseases during a 7-year follow-up (4). However, the role of a specific drug in the pathogenesis of OLDR may be important because the drug acts as an antigen, triggering T-cells. Antigen-specific CD8+ cytotoxic T cells then secrete cytokines, such as TNF- α or interferon- α . These cytokines subsequently activate T cells and dendritic cells and trigger basal cell keratinocyte apoptosis, causing an inflammatory immune response (23, 24).

Regarding oral mucosal hyperpigmentation, one observation report suggested that mucosal pigmentation could be a secondary effect of topical tacrolimus treatment due to an increase in the number of melanocytes and to an increased melanin production (25). Histopathology from the mucosal pigmentation showed an increase in melanocyte numbers and melanogenesis. However, the hyperpigmentation disappeared when the treatment was stopped, which is similar to the OLP case treated with FA in this review.

In addition to its use on oral lesions, FA may have other applications. A study found that FA strongly potentiated the TGF- β -associated chondrogenesis of bone marrow mesenchymal stem/progenitor cells, increasing the levels of collagen type II more than 100-fold compared with the widely used drug, dexamethasone (26). Thus, FA/TGF- β 3 may be clinically used to increase the efficiency of regenerative approaches based on the chondrogenic differentiation of stem cells. The effects of FA on reparative dentin formation and the recovery of injured dental pulp have also been reported (27). The results showed that FA promoted the proliferation of human dental pulp cells (DPCs), especially for the CD146+ subpopulation. CD146+ cells have been shown to be mesenchymal stromal cells capable of multilineage differentiation (28-30). Thus, in the injured pulp, an increase in CD146+ cells may provide cells that can differentiate into odontoblasts for repairing the dentin defect, as well as reconstituting the dental pulp cell population. Therefore, FA initiates mineralization by DPCs and has a potential role in repairing injured pulp tissues. FA may enhance oral lesion healing by promoting the proliferation and regeneration of oral mucosal cells. Future research on the use of FA in enhancing healing on the oral mucosal cells by inducing the expression of different cytokines that regulate molecules involved in cellular adhesion and extracellular matrix (ECM) formation is recommended for the effective treatment of severe and recalcitrant oral mucosal diseases.

Conclusion

FAO/FAS 0.1% is effective in the treatment of OLP, OLDR, oral pemphigus, and HAEM. FAO/FAS 0.1% rapidly reduces pain and inflammation. This topical steroid is low-cost (2 US\$/5 gm pack) with no serious side-effects other than easily treated pseudomembranous candidiasis. Moreover, FAO/FAS 0.1% was safe when used in treating patients with multiple or various systemic diseases and a pregnant patient.

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Abstract

Topical steroids have been widely used in the treatment of symptomatic oral lesions to reduce pain and inflammation. Potent topical steroids such as clobetasol propionate, fluocinolone acetonide (FA), and fluocinonide have been widely used in the treatment of severe oral mucosal lesions. Many reports have demonstrated that these steroids were effective in treating oral lesions with only minor side-effects. This review describes the effectiveness and side-effects of using FA 0.1% in the treatment of symptomatic oral lichen planus (OLP), oral lichenoid drug reaction (OLDR), oral pemphigus, and herpes associated *erythema multiforme* (HAEM). FA 0.1% was effective and safe in the treatment of patients with multiple systemic diseases and a pregnant patient with HAEM. Moreover, this topical steroid rapidly reduced pain, inflammation, and enhanced lesion healing with no serious side-effects other than pseudomembranous candidiasis, which is easily treated. In some cases, a long-term treatment with FA 0.1% resulted in hyperpigmentation at the areas of previously healed oral lesions; however, this hyperpigmentation was gradually resolved after discontinuing topical steroid treatment.

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Address for correspondence

Prof. Kobkan Thongprasom
Chulalongkorn University
Faculty of Dentistry
Oral Medicine Department
Bangkok 10330, Thailand
Tel +66-2-2188942
Fax-77-2-2188941
kobkan.t@chula.ac.th

Key words

Fluocinolone Acetonide; Drug-Related Side Effects and Adverse Reactions; Oral Candidiasis; *Erythema Multiforme*; Oral Lichen Planus; Pemphigus

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