Chapter

Corticosteroids in Oral Medicine Practice

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Abstract

Corticosteroids are one of the most useful and commonly prescribed drugs in oral medicine practice. They are hormones of the adrenal cortex with strong anti-inflammatory and immunosuppressive effects. Topical and systemic corticosteroids are used in the treatment of many diseases with oral mucosal manifestations such as oral lichen planus (OLP), pemphigus vulgaris (PV), pemphigoid, and systemic lupus erythematosus (SLE), as well as in the treatment of chemical injuries, traumatic lesions, recurrent aphthous ulcers (RAU), and many other. Rarely occurring side effects of topical steroid therapy are oral candidiasis and mucosal atrophy. Side effects occur more often with the systemic use of corticosteroids, such as adrenal insufficiency, hypertension, diabetes, infection, glaucoma, and osteoporosis. However, despite various side effects, corticosteroids still remain irreplaceable in the treatment of numerous diseases and conditions.

Keywords: corticosteroids, oral medicine, treatment, topical corticosteroids, systemic corticosteroids, oral mucosal diseases

1. Introduction

Corticosteroids are adrenal cortex hormones that have numerous physiological and pharmacological functions. The main actions of corticosteroids include maintenance of electrolytes, cardiovascular homeostasis, and functional status of skeletal muscles and nervous system [1]. The production of steroid hormones is under control of the hypothalamic-pituitary-adrenal axis. Hormones produced by the adrenal cortex are synthetic glucocorticoids, derivatives of hydrocortisone (cortisol), based on their natural chemical formula. Cortisol participates in the regulation of carbohydrate, fat, and protein metabolism and also plays a role in the body's response to a stressful situation [1].

Daily, the adrenal gland secretes between 24 and 30 mg of cortisol, while during stress it can produce up to 300 mg [1]. Doses of exogenous corticosteroids of 30 mg or more for 14 days or longer cause inhibition of the hypothalamic-pituitary-adrenal axis, and consequently it takes longer for the body to respond to a stressful

Anti-inflammatory effect	Immunosuppressive effect
• Inhibition of phospholipase A activation	• Decrease in the number of lymphocytes
• Prevention of leukocyte and macrophage migration	• Decrease in the amount of immunoglobulin
• Inhibition of fibroblast proliferation	• Reduction of the body's response to the antigen-antibody reaction
	• Inhibition of macrophage activity

Table 1.
Anti-inflammatory and immunosuppressive effects of corticosteroids.

situation [1]. The most important role of cortisol is gluconeogenesis, a process that increases the glucose level and the ability of the body to react in stressful situations [1]. Corticosteroids also have anti-inflammatory and immunosuppressive effects (**Table 1**) [1].

Considering the mentioned effects, corticosteroids are one of the most useful drugs in pharmacotherapy in general.

In regular clinical practice, corticosteroids have been used against a number of inflammatory and immune-mediated diseases and conditions for more than 50 years. In 1950, the Nobel Prize was awarded to Kendall, Reichstein, and Hench for the detection of these very important biologically active molecules [2].

Many diseases with oral mucosal manifestations such as oral lichen planus (OLP), pemphigus vulgaris (PV), mucous membrane pemphigoid (MMP), and systemic lupus erythematosus (SLE), as well as chemical injuries, traumatic lesions, and recurrent aphthous ulcers (RAU), are mostly successfully treated with corticosteroids.

The most commonly used systemic steroids are dexamethasone, prednisolone, methylprednisolone, and hydrocortisone [3]. Topical steroids commonly used in oral medicine practice are triamcinolone acetonide, clobetasol propionate, fluocinonide, and betamethasone [4]. While the use of topical corticosteroids is generally safe, systemic therapy needs some specific considerations, particularly in patients undergoing invasive dental procedures.

2. Topical corticosteroids

Corticosteroids are the gold standard for the management of many diseases in all medical areas. The use of corticosteroids has significantly improved treatment protocols for various oral diseases and conditions and has become indispensable in everyday clinical practice.

Topical corticosteroids are the first-line of therapy for patients with chronic inflammatory diseases of the oral mucosa. Most of such oral diseases can be controlled with topical high-potency corticosteroid preparations, which have been proven to be highly effective and have fewer side effects than systemic steroids [5]. Effect of topical steroid preparations involve vasoconstriction, reduced mast cell degranulation, and capillary permeability, causing a decrease in the amount of released histamine [3]. The formulations of topical steroids most commonly used in oral medicine practice are orabase ointments and aqueous solutions. The recommendation for using an orabase ointment is to apply a small amount of it to the lesion

area and not eat or drink for 30 minutes. It is advisable to use orabase ointments when treating small, solitary lesions and in cases where there are a few lesions that are easily accessible. Furthermore, lesions localized on the gingiva or palate can be treated with orabase ointments using customized trays, which allow excellent control of the time period in which the drug must come into contact with the lesion [4]. Benefits of using aqueous solutions are perfect control of time contact between lesion and drug and drug contact with all lesions regardless of their size and depth. Aqueous solutions are the formulations of choice for the treatment of large and extensive lesions. It is easier for the patients to use corticosteroids in the form of aqueous solutions than orabase ointments. The main disadvantage of using aqueous solutions is that even healthy oral mucosa comes into contact with the drug, increasing the risk of systemic absorption and ingestion [4].

The potency of topical steroids depends on the amount of vasoconstriction they produce. According to potency, topical corticosteroids are divided into mild, moderate, potent, and very potent preparations [4]:

Mild

- 1% hydrocortisone acetate
- 0.05% alclomethasone dipropionate
- 0.25% methylprednisolone acetate

Moderate

- 0.05% clobetasone butyrate
- 0.1% hydrocortisone butyrate
- 0.5% fluocortolone pivalate

Potent

- 0.025% beclomethasone dipropionate
- 0.05% betamethasone dipropionate
- 0.025% betamethasone benzoate
- 0.1% betamethasone valerate
- 0.1% diflucortolone valerate
- 0.025% flucinolone acetonide
- 0.05% fluticasone propionate
- 0.05% flucinonide

Very potent

- 0.05% clobetasol propionate
- 0.3% diflucortolone valerate
- 0.01% halcinonide.

Topical steroid preparations most often used in the treatment of oral mucosal diseases are clobetasol propionate, flucinonide, and triamcinolone acetonide [4]. These preparations belong to the group of potent and very potent topical steroid preparations.

2.1 Perilesional/intralesional corticosteroid injection

Perilesional/intralesional corticosteroid injection (P/ICI) is a form of topical application of the drug which ensures a high concentration of drug at the site of lesion. Although it is mentioned in the literature mainly as an intralesional injection, it is important to distinguish between the use of perilesional and intralesional corticosteroid injections. Perilesional injection is used in the treatment of major aphthous ulcers, decubitus, and other major erosions and is applied around the lesion. Furthermore, the intralesional injection is applied directly into the affected tissue, as in the case of orofacial granulomatosis.

This type of application has minimal systemic absorption and therefore no systemic side effects [6]. The most commonly prescribed drugs for P/ICI are triamcinolone and methylprednisolone [6]. Prior to P/ICI administration, a medical history must be taken from patients to rule out allergies and other medical issues that could affect the procedure. An insulin syringe is most suitable for the administration of P/ICI. Typically, 0.1–0.2 mL of the drug is injected at four sites around the lesion or directly into the lesion, with a total dose of 2 mL of the drug for each treatment session (**Figure 1a**, **b**). Before the application of P/ICI, local anesthesia can be used, which is mostly not the case due to similar pain when applying both drugs [7].

2.2 Side effects of topical corticosteroid therapy

Topical corticosteroids are applied directly to the oral mucosa with minimal systemic absorption, so side effects occur much less often than with systemic therapy, especially if the treatment is not prolonged. However, as a result of long-term use of topical preparations, local side effects such as oral candidiasis and atrophy of the oral mucosa have been described [8]. Oral candidiasis can be prevented by using antifungals or chlorhexidine mouthwash solutions [9].

In addition to the above, as a result of systemic absorption, cases of hirsutism and a moon face between the 4th and 6th week of therapy with topical steroid preparations have also been recorded in the literature [10]. Cases of dry mouth, bad taste and smell, swollen lips, and nausea are described less often [11].

Cases of hairy leukoplakia, hypersensitivity reactions of the oral mucosa, hemorrhagic effusions on the skin and mucous membranes, and iatrogenic Cushing's syndrome have also been described in the literature [12–15].

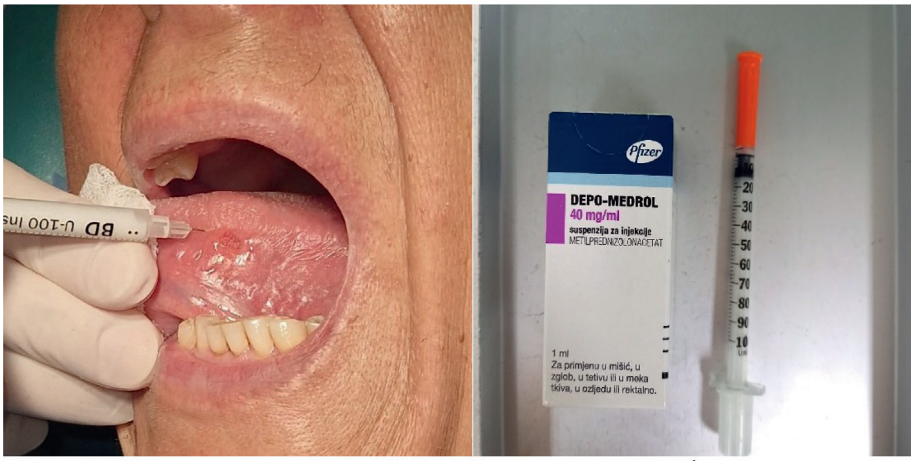

Figure 1.
(a and b) The use of perilesional injection with methylprednisolone and an insulin syringe for treatment of traumatic ulcer.

The mentioned side effects, such as Cushing's appearance and hirsutism, are related to systemic absorption due to long-term use of topical steroid preparations. However, it remains unclear whether the listed side effects occur as a result of direct absorption of the topical steroid preparation from the oral mucosa or as a result of unintentional ingestion, or are the result of potential risk factors such as the age of the patient, treatment method, use of additional drugs, time of application, localization, and size of the lesion, as well as the presence of more extensive ulcerations, which has not been investigated so far [15].

The most common and immediate side effects of P/ICI application are pain and bleeding. Less frequently, allergic reaction, infection, mucosal atrophy, and hypo- or hyperpigmentation can occur [7, 16].

3. Systemic corticosteroids

The use of systemic corticosteroids is reserved for severe, erosive, and stubborn cases of OLP, RAU, and MMP that do not respond to topical steroid therapy, as well as for PV lesions, and is prescribed according to a strict regimen with a gradual dose reduction [17].

The dose of systemic corticosteroids depends on the type and severity of the disease and the patient's individual response. Initially, relatively high doses are applied, which are significantly higher in severe acute forms than in chronic diseases. Prednisone and methylprednisolone are prescribed in doses of 1.5–2 mg/kg/day and after clinical improvement, the initial dose is gradually reduced. Depending on the clinical symptoms and the individual patient's reaction, the dose can be reduced to the lowest possible maintenance limit (5–15 mg of prednisone per day) in different time intervals [18]. Chronic diseases often require long-term treatment with low doses. General dosing guidelines in accordance with relevant literature data are presented in **Table 2** [18]. The most commonly used glucocorticoid for long-term control of oral diseases is prednisolone. Rarely, dexamethasone can be given, which is 5–6 times stronger than prednisolone; therefore, it

Dose	Dose mg/day	Dose mg/kg/body weight/day
High	80–100 (250)	1,0–3,0
Medium	40–80	0,5–1,0
Low	10–40	0,25–0,5
Very low	1,5–7,5 (10)	–/–

Table 2.
Dosing guidelines for systemic corticosteroids (prednisolone).

is given in a much lower dose. Dexamethasone is not appropriate for long-term systemic administration because its long action does not allow the hypothalamic-pituitary-adrenal (HPA) axis to recover [19].

Dose reduction begins when the desired clinical effect has been achieved. Furthermore, if the daily dose is divided into several individual doses, the evening dose is reduced first, and then, if applicable, the midday dose. Initially, the dose is reduced in slightly larger steps, and from a value of about 30 mg per day downward, in smaller steps. The clinical picture of the disease determines whether the treatment should be stopped completely or whether a maintenance dose is required [18]. With careful disease monitoring, the following scheme can be applied as an orientation for dose reduction (**Table 3**) [18].

3.1 Side effects of systemic corticosteroid therapy

Systemic corticosteroid therapy has significantly more serious and frequent side effects than topical preparations. Long-term use of systemic corticosteroids causes suppression of the adrenal gland, which leads to a life-threatening condition called adrenal crisis, characterized by hypotension, nausea, cardiovascular collapse, stroke, coma and, in the most serious cases, death [1]. In addition to the adrenal crisis, long-term use of systemic steroid therapy can cause a number of side effects, such as:

- Cushingoid appearance—moon face, hirsutism, bison hump, central obesity
- Skin atrophy, capillary fragility, and tendency to bruises
- Loss of muscle mass
- Gastritis, ulcers, bleeding from the gastrointestinal tract
- Osteoporosis

>30 mg	reduction by	10 mg	every 2–5 days
30–15 mg	reduction by	5 mg	every week
15–10 mg	reduction by	2,5 mg	every 1–2 weeks
10–6 mg	reduction by	1 mg	every 2–4 weeks
< 6 mg	reduction by	0,5 mg	every 4–8 weeks

Table 3.
Dose reduction scheme for systemic corticosteroids.

- Hypertension
- Hyperglycemia
- Headaches
- Cataracts
- Immunosuppression
- Mood changes [1].

The irreversible side effect of long-term use of systemic corticosteroid therapy is osteoporosis, a condition that increases the risk of developing bone fractures. Densitometry, serum calcium levels, phosphorus, and 25-hydroxyvitamin D should be performed in these patients to avoid possible complications during invasive dental procedures [19]. The European League Against Rheumatism (EULAR) group has given recommendations for monitoring and prophylaxis for long-term glucocorticoid treatment [20], but data from the literature suggest that monitoring of these patients should be improved in daily practice [21]. In addition to systemic corticosteroid therapy, a patient should receive antacids and a proton pump inhibitor as prophylaxis against peptic ulceration, and all other parameters should be adequately followed-up, such as blood pressure, glucose, and eye survey [20].

Adrenal insufficiency, Cushing's syndrome, diabetes, hypertension, and osteoporosis are potential problems that may require modification of the dental procedure. Therefore, dental care modifications in patients on long-term systemic corticosteroid therapy will be mentioned in the following text.

4. Recommendations for the dental management of patients receiving systemic corticosteroid therapy

In everyday clinical practice, systemic corticosteroids are used in the treatment of a number of inflammatory and immune-mediated diseases and conditions, including autoimmune diseases and prevention of transplant rejection. During stress, in healthy individuals the level of cortisol normally doubles, while in the case of adrenal insufficiency, a sufficient amount cannot be produced. Therefore, in these patients, in stressful situations (during acute infection, surgery, trauma, sudden interruption of long-term therapy, or in a patient exposed to a strong physical or psychological stress), a life-threatening condition, an adrenal crisis, can develop [1].

Patients with Addison's disease, other forms of adrenal gland insufficiency, and patients on systemic steroid therapy for more than 3 weeks are at risk of developing an adrenal crisis. (7.5 mg/day prednisone) [1]. There is a lack of more recent agreed positions regarding the dental management of patients on systemic corticosteroid therapy. The primary reference that dentists usually follow is Gibson et al. [22] or the integrated clinical environment (ICE) Health Systems platform guidelines [23].

Before stressful procedures, major surgeries, or procedures under general anesthesia:

- If patient has been taking more than 7.5 mg of prednisone per day for more than 3 weeks and the procedures are performed within 3 weeks of discontinuation of corticosteroids, the patient should be given an earlier maintenance dose in the morning before the procedure.

- If patient is currently on more than 7.5 mg of prednisone, a double daily dose is given on the day of the procedure and an additional single dose on the first postoperative day if pain is present.

- When the patient is taking the medicine every other day, the procedure is performed on the day of taking the medicine, in a double dose [24, 25].

Routine dental procedures, including minor surgical procedures (simple extractions, biopsy, minor periodontal surgery ...) performed under local anesthesia:

- Do not require additional corticosteroid administration if the patient is on a daily maintenance dose higher than 7.5 mg of systemic prednisone or uses corticosteroids every other day.

- In patients who take corticosteroids every other day, the procedure is performed on the day of drug intake.

- If patient has been taking more than 7.5 mg of prednisone per day for more than 3 weeks, and minimally stressful procedures are performed within 2 weeks of corticosteroids discontinuation, the patient should be given previous maintenance dose in the morning before the procedure [24, 25].

Recently published Addison's Self-Help Group guidelines suggest that patients with adrenal insufficiency or who are at risk of adrenal insufficiency should receive 100 mg of hydrocortisone intramuscularly before all dental extractions [26].

These guidelines completely invalidate the dentist's assessment of the invasiveness of the procedure, and it is known that most tooth extractions and similar interventions are considered minor procedures that do not result in significant stress. When there are concerns, it is rational to consult with endocrinologist.

Dental procedures should be done in the morning, within 2 hours of taking the regular therapeutic dose. It is also important to reduce stress as much as possible with sedation, prevent intraoperative pain (long-acting local anesthetic) and ensure adequate postoperative analgesia [24, 25].

5. Conclusion

Topical and systemic corticosteroids are one of the most common drugs used in oral medicine practice for the treatment of a large number of oral mucosal diseases. Due to their anti-inflammatory effect, they are used to reduce edema and pain in many acute and chronic conditions. In addition, they also have an immunosuppressive effect, so long-term use, especially of systemic corticosteroids can cause a series of side effects, some of which are even life-threatening. Despite unwanted side effects and caution when prescribing, the use of corticosteroids has no alternative in clinical practice for many conditions.

Conflict of interest

The authors declare no conflict of interest.

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