GRADUATION PROJECT

Degree in Dentistry

STEROIDS PRESCRIPTIONS AT SPANISH DENTAL OFFICES: A CROSS-SECTIONAL STUDY

Madrid, academic year 2024/2025

Identification number: 103

ABSTRACT

Introduction: Steroids can be prescribed to treat systemic and local diseases, e.g., allergic, inflammatory, pain, etc. The first dental use of corticosteroids was in 1951. Because of their effectiveness, steroids usage has been growing since 1998. However, in dentistry, steroids are not much prescribed probably because of fear of possible side effects. **Objectives:** To analyze steroid prescriptions in Spanish dental offices: indications, the most frequently used, and prescribing information of the medications. **Methodology:** This cross-sectional study aims to investigate the prescription of steroids in Spanish dental offices. A questionnaire (in which consisting 14 questions concerning information about dentists and dental practices and the use of steroids) was designed according to the objective of this study. The survey period is from December 2024 to 31 January 2025. Data collected were analyzed and the results of the analysis were discussed. Ethical guidelines were strictly followed and participant autonomy was respected. **Results**: 50 dentists filled in questionary and one was dropped out: Two-thirds of Spanish dentists have prescribed local and systemic steroids for the treatment of oral diseases. The primary objective of their use is to control postoperative inflammation and swelling after oral surgery. Prednisone is the steroid of choice for Spanish dentists followed by dexamethasone. Most of Spanish dentists learn how to use steroids in the postgraduate education. **Conclusions:** Steroids are drugs not commonly prescribed by Spanish dentist: it is important that dentist should know well indications and the risks of these drugs and consider them is good alternative to NSAID.

KEYWORDS

Dentistry; Spain; Steroids; Frequency; Indications

RESUMEN

Introducción: Los esteroides que se pueden recetar para tratar enfermedades sistémicas y locales, como alérgicas, enfermedades inflamatorias, dolor, etc. El primer uso de corticosteroides en odontología fue en 1951. Debido a su eficacia, su uso ha ido en aumento desde 1998. Sin embargo, en odontología, probablemente a su desconocimiento o al miedo a sus posibles efectos secundarios, los corticoides no son prescritos tan frecuentemente como podrían ser. **Objetivos:** Analizar la prescripción de corticoides en las consultas odontológicas españolas: indicaciones de los medicamentos, esteroides más utilizados e información de prescripción. **Metodología:** Este estudio transversal tiene como objetivo investigar la prescripción de corticoides en las consultas dentales españolas. Se diseñó un cuestionario (con 14 preguntas sobre información sobre dentistas, consultas dentales y el uso de esteroides) de acuerdo con el objetivo de este estudio. El periodo de la encuesta fue de diciembre de 2024 al 31 de enero de 2025. Se analizaron los datos recopilados y se discutieron los resultados. Se siguieron estrictamente las normas éticas y se respetó la autonomía de los participantes. **Resultados:** 50 dentistas rellenaron la encuesta. Uno fue excluido del análisis. Dos tercios de los dentistas españoles han prescrito esteroides locales y sistémicos para el tratamiento de enfermedades bucodentales. El objetivo principal de su uso es controlar la inflamación y la hinchazón postoperatorias tras la cirugía oral. La prednisona es el corticoide de elección entre los dentistas españoles seguido de dexametasona. La mayoría de los dentistas encuestados aprendieron el manejo de los corticoides en estudios postgrado. **Conclusiones:** Los corticoides es un grupo de fármacos que no son frecuentemente prescritos por los dentistas españoles. Es importante que los dentistas conozcan bien las indicaciones y los riesgos de uso de estos fármacos y considerarlos como una buena alternativa a los AINEs.

PALABRAS CLAVE

Odontología; España; Corticoides; Frecuencia; indicaciones

INDEX

1. INTRODUCTION

Steroids are commonly indicated in the treatment of allergic, inflammatory, and autoimmune diseases, pain, edema, and lockjaw. (1) Because of steroid effectiveness, there has been a trend toward increased use of steroid treatment since 1998. (2) Importantly, prolonged use of steroids may depress the normal function of the adrenal cortex, which produces steroids, and lead to withdrawal syndrome. (3) Hence, dentists should be familiar with the indications, contraindications, drug interactions, pharmacodynamics, and pharmacokinetics of steroid drugs. Also, dentists need to consider the patient's general health condition, systemic problems, allergy, etc. Detailed medical history, current medications, and correct diagnosis are important to consider before prescribing steroid therapy. (4) All these factors indicate that it is important to investigate steroid prescriptions.

1.1 Classification, functions, and chemical structures of steroids

Steroids are endogenous endocrine hormones. Structurally, these hormones have four rings including a core phenanthrene ring with an attached pentane ring, creating the sterane backbone (Fig.1) (5). In mammals, steroid hormones can be grouped into six main families based on their structural features and biological roles (Fig. 2) (5). These families include estrogens and progestins (female sex hormones), androgens (male sex hormones), mineralocorticoids (like aldosterone), glucocorticoids (such as cortisol), and vitamin D. Bile acids, which share a structural link to cholesterol, are considered a seventh steroid category. Steroid structures can vary due to the addition of hydroxyl or carbonyl groups, introducing double bonds, or including heteroatoms, each following particular organic nomenclature rules. Asymmetric carbons in steroids play a crucial role in distinguishing stereoisomers. For instance, the orientation of the hydroxyl group in epimers (such as 3α- or 3β-ol) can alter steroid function. Additionally, asymmetry at the ring junctions affects the steroid's shape and the type of ring fusion (cis or trans), impacting its overall three-dimensional configuration (6).

In living organisms, hormones serve as key regulatory agents, facilitating communication and control of essential processes within and between cells and tissues, thereby connecting all organs in the body. Endocrine hormones, in particular, travel through the bloodstream to enable communication between cells and organs separated by large distances. Hormones fall into two main types based on their solubility. Hydrophilic hormones primarily act on cell surfaces by binding to protein receptors embedded in the plasma

membrane. Conversely, hydrophobic hormones circulate bound to carrier plasma proteins, freely diffusing across cell membranes to activate specific intracellular receptors (7).

Cholesterol is the precursor for all types of steroids (5). The metabolism of cholesterol produces cortisol in the adrenal gland (8). Steroid hormones (including cortisol, aldosterone, estradiol, and testosterone) are synthesized from cholesterol in specialized endocrine cells in organs such as the adrenal gland, ovaries, and testes (7). These hormones are released into the bloodstream as needed, allowing them to move freely into cells, where they bind to nuclear receptors in the cell nucleus. These multi-domain ligand-dependent transcriptional regulators then alter the expression of hundreds to thousands of specific target genes in the genome, modulating a wide array of cellular functions and then regulating various physiological processes (7,9).

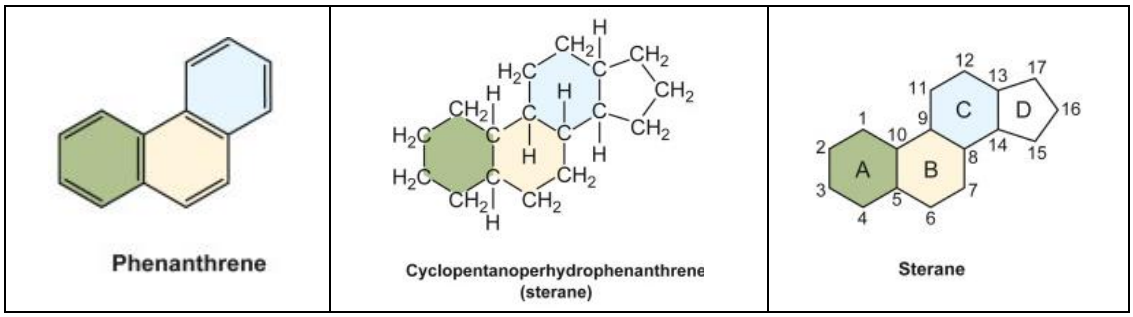

Fig. 1. Steroids originate from a phenanthrene ring and have a common ring structure. In its fully hydrogenated form, this configuration is known as cyclopentano-perhydrophenanthrene, and also referred to as the sterane ring structure (5).

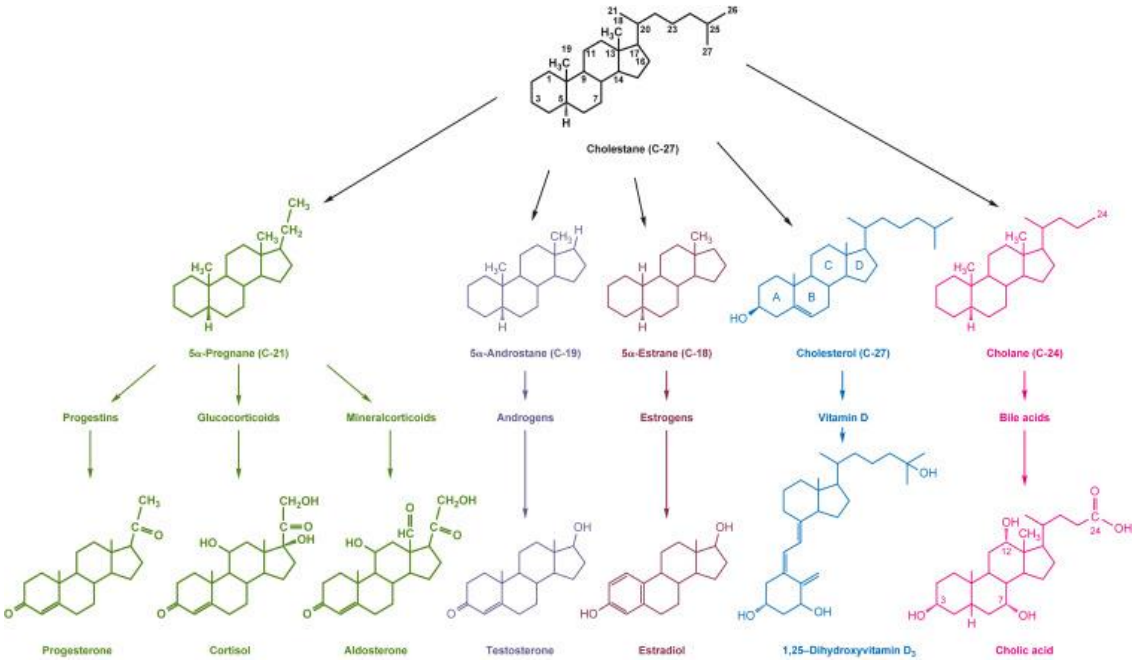

Fig. 2. The seven main steroid classes (bottom row) are derived structurally from the base compound cholestane (top row) (5).

1.2 Mechanism of action of steroids

Corticosteroids are important therapeutic agents used to treat allergic and inflammatory disorders or to suppress undesirable or inappropriate immune system actions. The term corticosteroid is used clinically to describe agents with glucocorticoid activity. Cortisol is an endogenous glucocorticoid, named for its effects on glucose metabolism, but it also exerts corticosteroids' other immunological actions. Various other hormones, including the mineralocorticoid, aldosterone, and male and female sex hormones, are produced through the common cholesterol metabolism pathway. This common pathway and structural similarities among the hormones help to explain some of the side effects and adverse reactions associated with pharmacologic doses of cortisol and its synthetic analogs (10).

Corticosteroids are crucial, life-saving medications when strong anti-inflammatory or immunosuppressive effects are required. They act at multiple points within the inflammatory pathway, which increases their effectiveness. To work, the corticosteroid molecule has to cross cell membranes and attach to glucocorticoid receptors, triggering a conformational shift in the receptor (10). This receptor-steroid complex enters the cell nucleus, dimerizing and binding to glucocorticoid response elements (Fig. 3) (10). Glucocorticoid response elements are linked to genes that either suppress or enhance transcription, leading to RNA and protein synthesis - processes referred to as transrepression and transactivation, respectively (8). In the end, these agents work to inhibit transcription.

In essence, these agents suppress transcription factors that regulate the production of pro-inflammatory mediators, affecting cells such as macrophages, eosinophils, lymphocytes, mast cells, and dendritic cells (11,12). Another vital effect is the inhibition of phospholipase A2, which produces numerous inflammatory mediators (13).

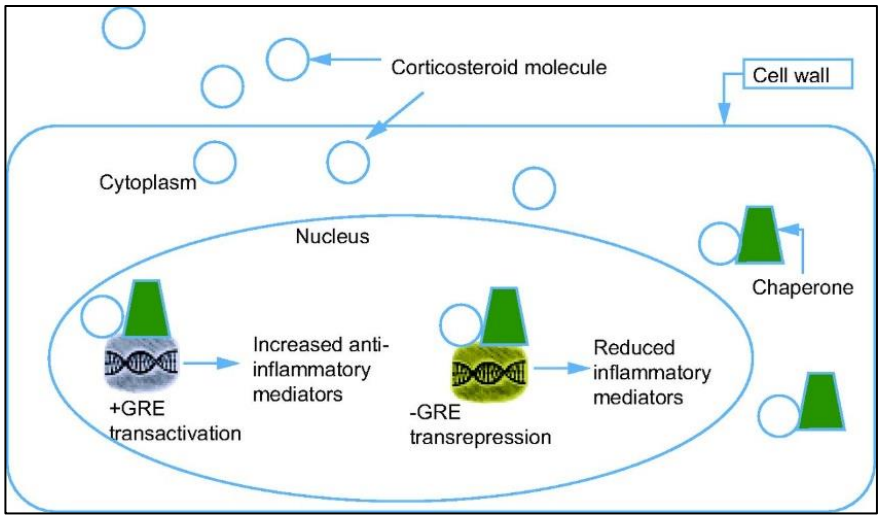

Fig. 3. Mechanism of action for corticosteroids (10). GRE, glucocorticoid response element.

Cortisone and prednisone, two corticosteroids widely used in clinical practice, contain a ketone group at carbon 11 and must undergo hepatic conversion to their activated hydroxyl forms, hydrocortisone and prednisolone, respectively (14). Hydrocortisone is the clinical term for cortisol. Various corticosteroid agents have been formulated for topical applications, including creams, ointments, enemas, eye drops, nasal sprays, oral inhalers, and joint injections. These are biologically active due to the hydroxyl group at carbon-11.

Adding ester groups at carbons 16 and 17 and hydrophobic groups at carbons 20 and 21 enhances binding affinity for the glucocorticoid receptor. For synthetic corticosteroids, adding a halogen and a double bond between carbons 6 and 9 boosts potency and resistance to metabolic breakdown. These structural changes enhance specificity for the glucocorticoid receptor, prolong receptor occupancy, increase lipophilicity, and decrease water solubility (15). These features are desirable pharmacologic properties to enhance efficacy and safety.

Systemic corticosteroid therapy is most commonly delivered through oral, intravenous, or intramuscular routes, depending on the urgency and nature of the treated condition. Short-term corticosteroid use can be critical in acute or life-threatening situations, providing rapid anti-inflammatory and immunosuppressive effects that stabilize patients and prevent further complications. However, prolonged use of systemic corticosteroids, even at minimal doses, poses a risk of serious side effects, including osteoporosis, weight gain, increased infection susceptibility, hypertension, and glucose intolerance, among others. These risks often outweigh the benefits. Therefore, systemic corticosteroids are rarely the first line of treatment for chronic conditions where long-term management is necessary

(16). However, in certain autoimmune and immunologic diseases (such as severe forms of rheumatoid arthritis, lupus, and vasculitis) systemic corticosteroids may be necessary when alternative therapies fail to provide adequate control or when the disease activity is high. In such cases, physicians aim to use the lowest effective dose for the shortest duration possible, often supplementing with other immunosuppressive agents to reduce the need for corticosteroids over time. This approach helps to balance the need to use corticosteroids for immediate disease control with the need to minimize long-term health risks associated with chronic steroid use (10).

Clinically used systemic glucocorticoids are listed in Table 1 (10). It is noteworthy that prednisone requires hepatic conversion to prednisolone to become active. Even in the presence of significant liver dysfunction, this conversion rate remains nearly 100%, making the effects of these two agents almost identical. Cortisone (an inactive corticosteroid) also requires conversion to its active form (hydrocortisone) in the liver, but this activation is limited in patients with impaired liver function. Thus, liver function impairment affects its efficacy. Glucocorticoid products can be classified based on characteristics such as the duration of suppression of the hypothalamic-pituitary-adrenal axis (17).

Table 1. Properties of systemic corticosteroids (10)

Medication	Anti-inflammatory Potency (relative)	Equivalent potency (mg)	Duration of effect (hypothalamic-pituitary-adrenal axis) (h)	Mineralocorticoid potency (relative)
Short acting				
Hydrocortisone	1	20	8-12	1
Intermediate acting				
Prednisone	4	5	18-36	0.8
Prednisolone	4	5	18-36	0.8
Methylprednisolone				
Long acting	5	4	18-36	0.5
Dexamethasone	25	0.75	>36	0

1.3 Indications for steroid use

Since their discovery, corticosteroids have become a staple of care in nearly every field of medicine and can be administered through various routes. They are synthetic analogs of

natural adrenal cortex hormones, including glucocorticoids and mineralocorticoids, with each synthetic hormone possessing a unique balance of these properties. Glucocorticoids primarily impact metabolism and offer immunosuppressive, anti-inflammatory, and vasoconstrictive effects, while mineralocorticoids regulate electrolytes and water balance through ion transport in the kidney tubules (18).

"Corticosteroids" usually refer to glucocorticoids, essential stress hormones that regulate multiple physiological processes vital for survival. Corticosteroids rank among the most prescribed drugs globally, with a market exceeding 10 billion US dollars annually. In the United Kingdom, about one percent of adults are taking oral glucocorticoids at any given time. They are prescribed for numerous conditions, which can be broadly grouped into infectious and inflammatory disorders, allergic and autoimmune diseases, adrenal disorders, shock, hypercalcemia management, water regulation, hypoglycemia treatment, excess adrenocortical secretion suppression, graft rejection prevention, and specific neurological, hematologic, and dermatologic conditions (16).

Table 2. Common clinical uses of corticosteroids (16)

Field	Indications
Allergy and Pulmonology	1. Asthma
	2. Chronic obstructive pulmonary disease (COPD) exacerbations
	3. Anaphylaxis
	4. Urticaria, rhinitis
	5. Pneumonitis
	6. Sarcoidosis
	7. Interstitial lung disease
Dermatology	1. Contact dermatitis
	2. Pemphigus vulgaris
Endocrinology	1. Adrenal insufficiency
	2. Congenital adrenal hyperplasia
Gastroenterology	1. Inflammatory bowel disease
	2. Autoimmune hepatitis
Hematology	1. Hemolytic anemia
	2. Leukemia
	3. Lymphoma

	4. Ldiopathic thrombocytopenic purpura
Rheumatology	1. Rheumatoid arthritis
	2. Systemic lupus erythematosus
	3. Polymyositis
	4. Dermatomyositis
	5. Polymyalgia rheumatica
Ophthalmology	1. Uveitis
	2. Keratoconjunctivitis
Other	1. Organ transplantation
	2. Antenatal lung maturation
	3. Nephrotic syndrome
	4. Cerebral edema
	5. Multiple sclerosis

1.4 Side effects of steroids

Chronic use of systemic corticosteroids carries numerous significant risks of adverse effects and toxicities, impacting nearly every organ system and metabolic process in the body (19). The risk of adverse effects from corticosteroid use depends on factors like dose, treatment duration, and the specific corticosteroid chosen. Although short-term systemic corticosteroids were previously considered relatively safe, recent studies question this view. Chronic use, even at normal physiological doses, is known to cause significant adverse effects, with suppression of the hypothalamic-pituitary-adrenal (HPA) axis being a major and serious outcome associated with other toxicities. The likelihood of HPA axis suppression varies with dose, duration, timing of administration, corticosteroid type, and delivery method. For long-term use, localized or topical corticosteroids are preferred when suitable, especially for conditions involving the skin, respiratory system, musculoskeletal system, eyes, ears, nose, throat, and intestines (18).

Short-term corticosteroid use has been associated with disturbances in normal bodily functions, though it was not previously thought to cause lasting effects. These short-term impacts can include hyperglycemia, blood pressure fluctuations, edema, gastrointestinal bleeding, psychiatric issues, delayed wound healing, infection risks, and electrolyte imbalances. However, a recent study on over a million patients revealed that 21% received a short-term corticosteroid prescription within the past year, often for allergies, upper

respiratory infections, or spine issues (20). Within 30 days of treatment, there was an elevated risk of severe outcomes such as sepsis, venous thromboembolism, and fractures, highlighting the need for a more detailed investigation into short-term corticosteroid risks (20).

Glucocorticoids naturally play a critical role in metabolic and immune regulation. However, long-term corticosteroid use brings serious and predictable side effects, including HPA axis suppression, osteoporosis, immune suppression, muscle wasting, and physical changes. The range of systemic corticosteroid side effects is vast, affecting nearly all organs and body systems. Many of these adverse outcomes are due to disruption of normal HPA axis functions, and common side effects are summarized in Table 3 (10).

Table 3. Common side effects of corticosteroids due to HPA axis disruption (10)

Classification	Adverse effects
Metabolic	Hyperglycemia, weight gain, fluid retention, electrolyte imbalances (e.g., hypokalemia).
Endocrine	Hypothalamic-pituitary-adrenal (HPA) axis suppression, risk of adrenal insufficiency.
Musculoskeletal	Osteoporosis, muscle wasting, avascular necrosis, myopathy.
Immune	It increased infection risk due to immunosuppression.
Gastrointestinal	Increased risk of peptic ulcers and gastrointestinal bleeding.
Psychiatric	Mood changes, insomnia, and psychosis in severe cases.
Dermatologic	Skin thinning, delayed wound healing, easy bruising, acne.
Cardiovascular	Hypertension, dyslipidemia, increased risk of cardiovascular events.

1.5 Steroids in dentistry

The first research article about the general use of corticosteroids in dentistry was published by Strean in 1951 (21). Traditionally, dentists use systemic (oral and injectable) and topical steroids to treat various inflammatory and immune-mediated oral diseases, e.g., oral lichen planus, aphthous stomatitis, pemphigus vulgaris, mucous membrane pemphigoid, oral submucous fibrosis, Bell's palsy, temporomandibular disorders, etc. Glucocorticoids reduce all forms of inflammation and allergic reactions by inhibiting white blood cell function, stabilizing lysosomal membranes, blocking plasminogen activation, and decreasing the production of inflammatory mediators like prostaglandins and leukotrienes. These corticosteroids include hydrocortisone, prednisone, triamcinolone, dexamethasone,

clobetasol, and mometasone. Glucocorticoids impact the metabolism of lipids, carbohydrates, proteins, calcium, and electrolytes.

Recurrent aphthous stomatitis (RAS) is a chronic inflammatory disorder of the oral mucosa with an unclear cause (22). Major aphthae usually appear on mucosa overlying minor salivary glands, often emerging after puberty and involving areas such as the lips, soft palate, and throat. Topical corticosteroids are the primary treatment for RAS (23,24), with short-term systemic steroids reserved for more severe cases. In severe cases, high-potency topical steroids such as fluocinonide, betamethasone, or clobetasol can be applied directly to the lesion using gauze. For continuous ulceration without remission periods, intralesional injections of betamethasone, dexamethasone, or triamcinolone may be necessary (24).

Corticosteroids (such as prednisone, prednisolone) are also used in dentistry to treat autoimmune derived oral diseases (e.g., lichen planus, pemphigus) (25,26). For instance, prednisone 10-20 mg/day can be prescribed to treat moderate lichen planus, and 35 mg/day to treat severe cases. For the treatment of pemphigus vulgaris, oral prednisolone 1-1.5 mg/kg/day is administered (25,26).

Temporomandibular joint disorders (TMD) include a range of conditions that impact either the temporomandibular joint itself (intraarticular) or the surrounding muscles (extraarticular) (27,28,29). Typical symptoms include pain, joint clicking or popping sounds, restricted jaw movement, and tenderness near the ear area (30). TMD treatment aims not to provide a cure but to improve jaw function, alleviate pain, enhance quality of life, and prevent the condition from worsening (31). Unlike NSAIDs, corticosteroids block the inflammatory process at an earlier stage by inhibiting phospholipase, which prevents the production of arachidonic acid. This action disrupts the inflammatory pathway more effectively than NSAIDs, leading to a stronger impact on inflammatory mediators (32).

Sixty years after the introduction of steroid use into dentistry, the prevention and control of post-dental operation pain became one of the areas of focus in dental research. Research in various countries, e.g., Brazil, had concluded that dexamethasone can reduce post teeth extraction pain effectively (33,34).

The study from Zardo et al. (33) evaluated and compared the effectiveness of etoricoxib and dexamethasone for preventing and controlling postoperative pain following mucogingival surgery. It showed that a single, preemptive dose of either etoricoxib or dexamethasone can effectively reduce postoperative pain after mucogingival surgery and be considered a viable protocol for pain management in these cases (33).

Another study comparing the efficacy of preemptive ibuprofen and dexamethasone protocols for pain prevention or control after surgical implant placement (34) concluded that dexamethasone (a steroid) is as effective as ibuprofen (a non-steroid anti-inflammatory agent) for preventing or controlling postoperative pain and discomfort after surgical implant placement (34).

Both studies concluded that dexamethasone and ibuprofen are equally effective for managing postoperative pain in oral surgeries, making each a viable option for pain control protocols in these settings.

Hypothesis

Spanish dentists fully understand the effectiveness and value of steroids as medicinal drugs and use them efficiently in the dental office.

2. OBJETIVE

To analyze steroids prescriptions in Spanish dental offices: steroid indications, the most frequently used steroids, and their prescribing information.

3. MATERIAL AND METHODS

This “Final Degree Project” intended to investigate the prescription of steroids at Spanish dental offices in different provinces through a voluntary and anonymous questionnaire to ensure confidentiality, and reduce bias. In the research process, the ethical guidelines were followed and ethical approval was requested.

A questionnaire to evaluate steroidal use in Spanish dental offices was created using Microsoft Forms (annex 1). This questionnaire contained 14 questions: six of them were questions about demographic (i.e., age, gender, experience, and field of specialization of the responding dentists); whereas the other eight questions were based on previous prescription information attributes, such as the frequency of steroids prescriptions, the kinds of steroids prescribed, their dose, etc. Only dentists who actually practiced in Spain

were included. It was expected that the responding dentists would contribute truthful insights informed by their experience and practice.

The questionnaire was approved by the Dentistry Department, Universidad Europea de Madrid (approval code: OD.003/2425) and the Research and Ethics Committee, Universidad Europea de Madrid (approval code: 2024-921).

Subsequently, the digitized (online) questionnaire was made available to the Spanish dentists, who were from different provinces. At the same time, the questionnaire was delivered in person to some dentists for completion between December 2024 and 31 January 2025.

After all the questionnaires were returned, the data were described using frequency tables and analyzed using descriptive statistics.

4. RESULTS

As of 31 January 2025, 50 responses were received. As the title indicates, this research focuses on Spanish dentists. One of respondents was from Mexico. Hence, the effective number of respondents in the sample was 49. All of them recognized that they were voluntary participants in this survey.

• The characteristics of the participants

- 19 (38.8%) of the 49 dentists in this study were male and 30 (61.2%) were female.

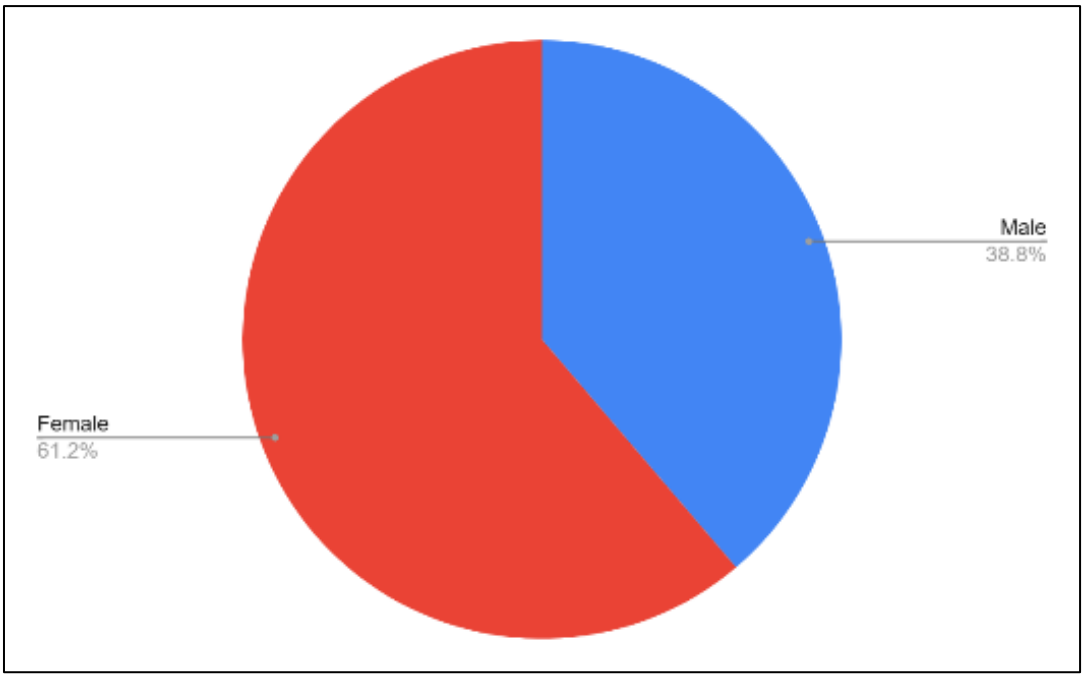

Fig. 4. the male/female ratio is 38.8%：61.2%.

- Their age ranged from 26 to 67 years old. The youngest dentist had 3 years working experience, and the two 67-year-old dentists had worked 36 and 37 years, respectively. The following two charts (Figs. 5 and 6) summarize the ages of the dentists and their years of dental practice.

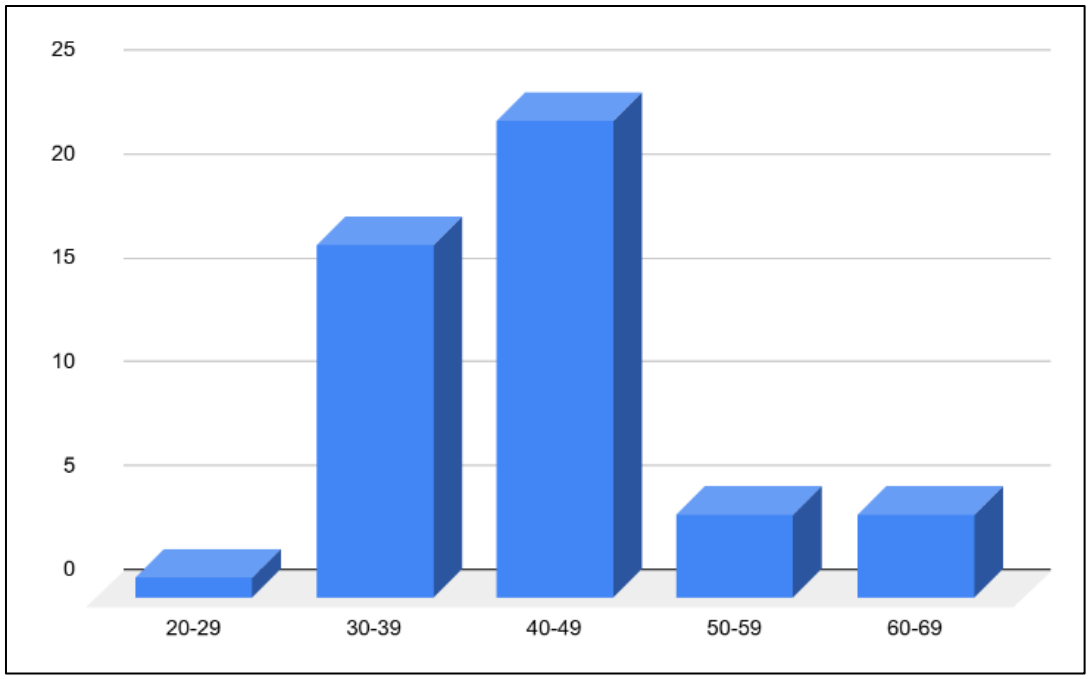

Fig. 5. The ages of the dentists.

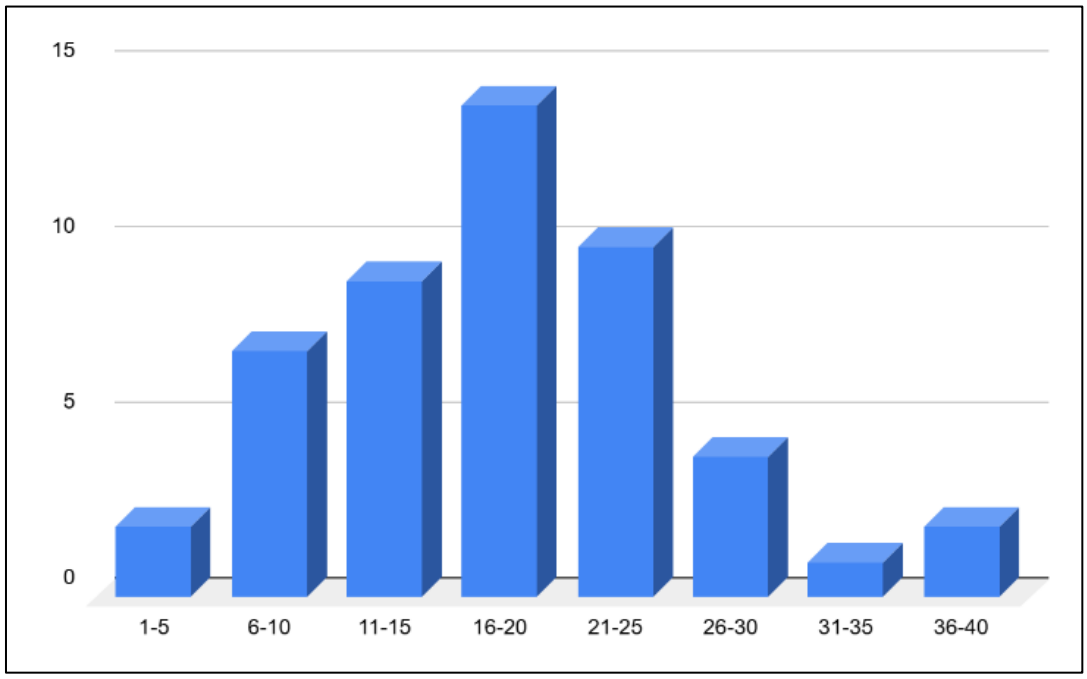

Fig. 6. The years of dental practice.

- All participants were from various provinces in Spain: 36 (73.5%) from Madrid; 4 (8.2%) from Barcelona; and one each from Toledo, Alicante, Segovia, Las Palmas, Cuenca, Sevilla, Teruel, Gipuzkoa, and Almería.

- Figure 7 indicates that participants practiced in a wide range of specialties, covering almost every profession in dentistry: general dentistry in 33 (28.4%), oral implantology in 21 (18.1%), oral surgery in 20 (17.2%), endodontics in 14 (12.1%), periodontics in 10 (8.6%), pediatric dentistry in 8 (6.9%), oral medicine in 8 (6.9%), and orthodontics in 2 (1.7%).

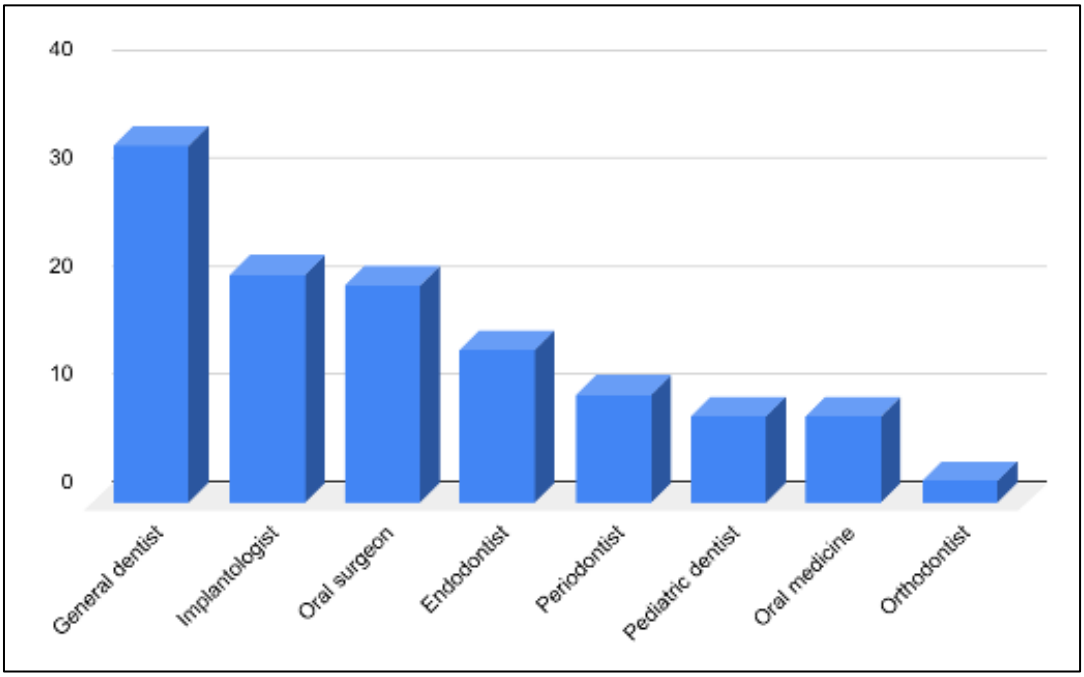

Fig. 7. The specialties of the participants.

- **Prescribing of steroids at Spanish dental offices**

- According to their responses, 23 dentists used topical or local steroids occasionally; 11 dentists used them sometimes; 3 dentists used them often, and 12 dentists never used them (Fig. 8).

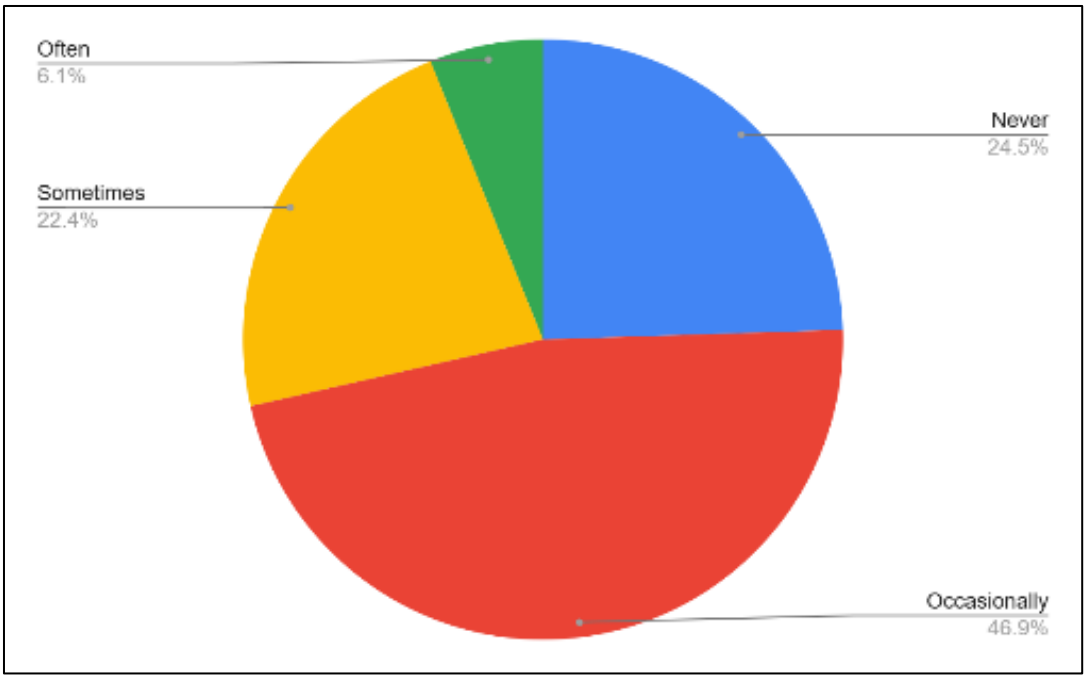

Fig. 8. The frequency of prescribing topical or local steroids for use inside the mouth.

- Regarding prescription of systemic steroids (pills or injections), 12 dentists never used systemic steroids, 19 dentists used them occasionally, 13 dentists used them sometimes, and 5 dentists used them often (Fig. 9).

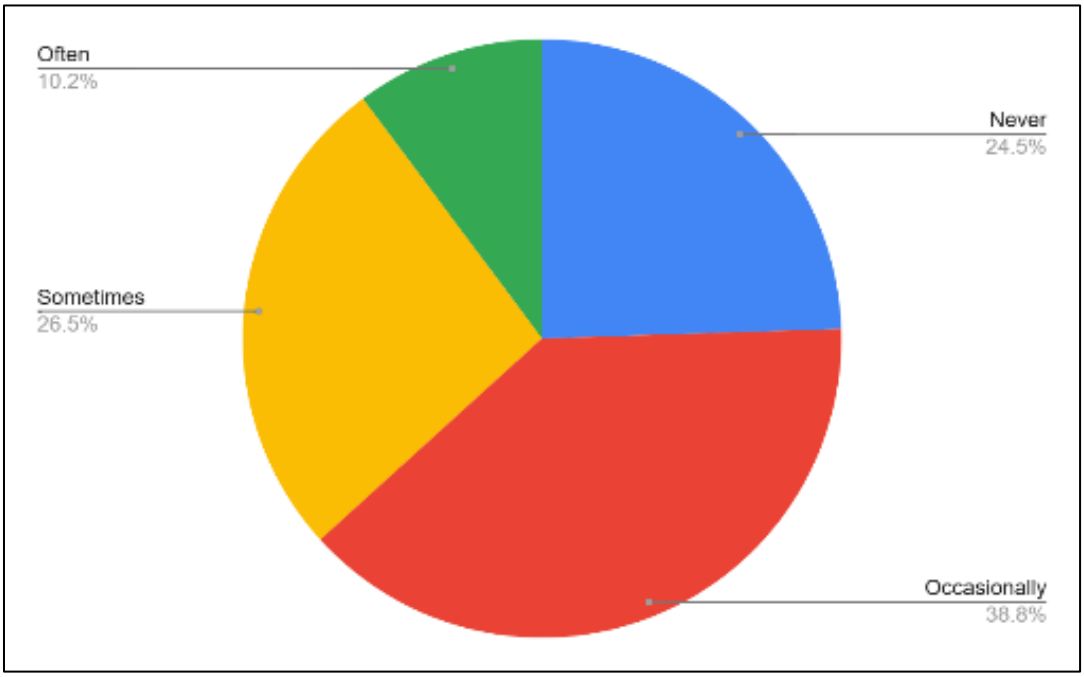

Fig. 9. The frequency of prescription of systemic steroids.

• The indications for prescribing steroids at Spanish dental offices

- Figure 10 summarizes the reasons for prescribing steroids. The main reason was "postoperative swelling and inflammation control after oral surgery". The other reasons (2-6) were as follows:

1. Postoperative swelling and inflammation control after oral surgery, e.g. implantation, third molar surgery, etc.: 32 (40.5%)
2. Oral inflammatory conditions such as lichen planus, erythema multiforme, etc.: 18 (22.8%)
3. Oral autoimmune pathologies such as pemphigus vulgaris, etc.: 10 (12.7%)
4. Aphthous ulcers: 8 (10.1%)
5. Temporomandibular joint disorders: 3 (3.8%)
6. Never prescribed steroids: 8 (10.1%)

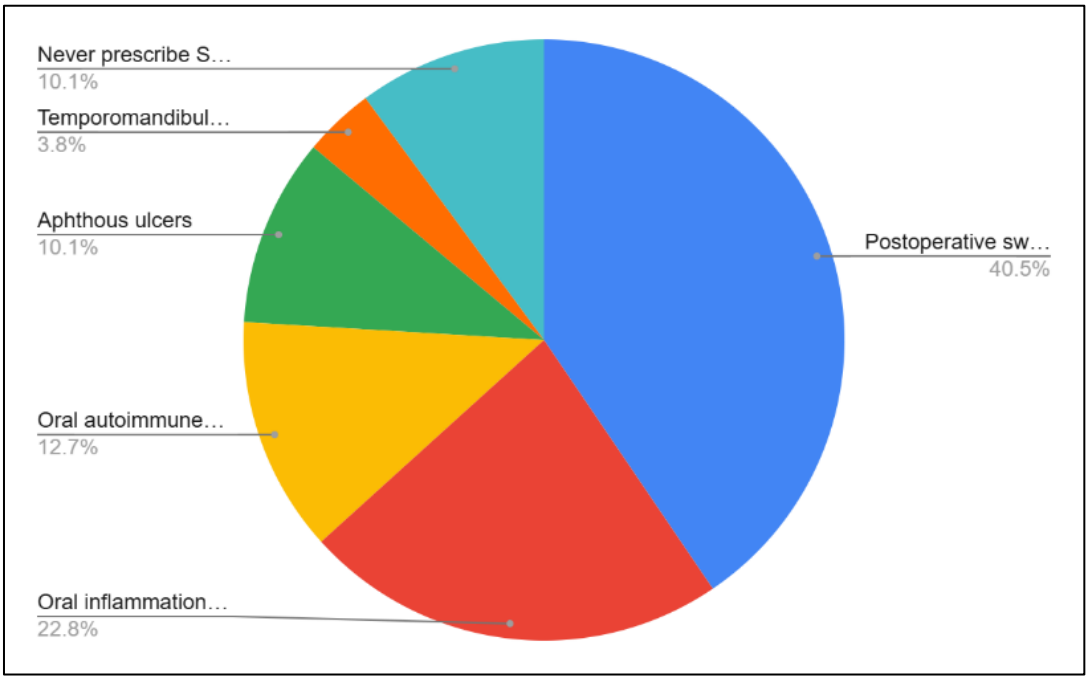

Fig. 10. The indications for steroids prescription.

- The steroids that the dentists prescribed included:

1. Prednisone: 27 (35.1%)
2. Dexamethasone: 17 (22.1%)
3. Prednisolone: 11 (14.3%)
4. Betamethasone: 11 (14.3%)
5. None of the above: 11 (14.3%)

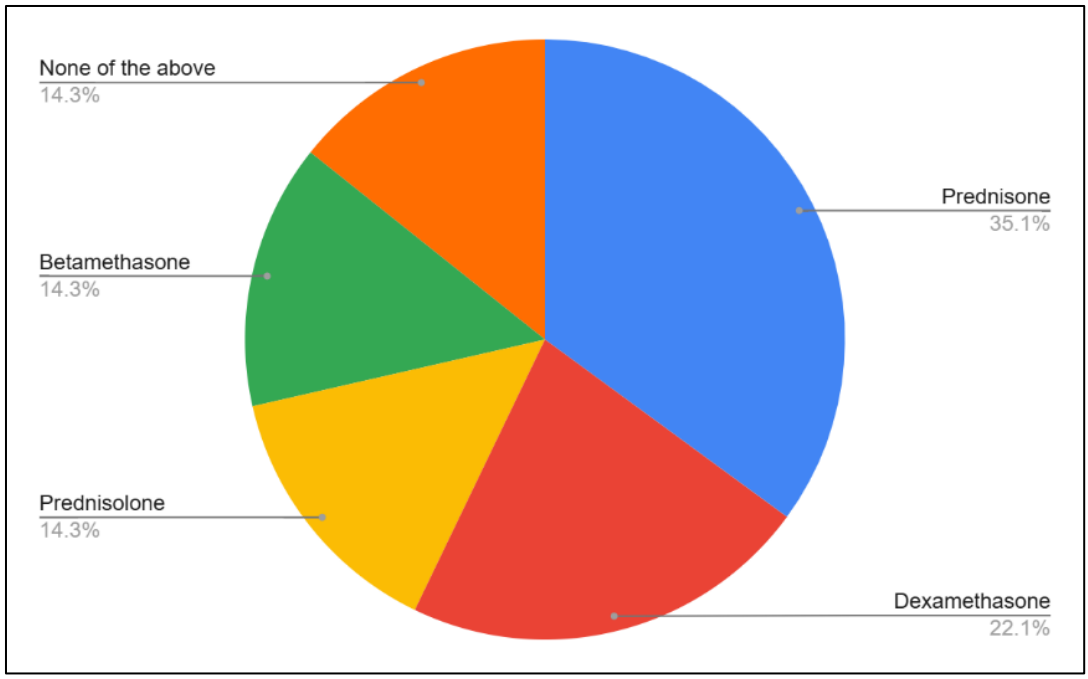

Fig. 11. The steroids that the dentists prescribed.

- Although many steroids can be used to treat disease, the most prescribed steroids were prednisone and dexamethasone (Fig. 12):

  1. Prednisone: 19 (38.8%)
  2. Dexamethasone: 9 (18.4%)
  3. Prednisolone: 4 (8.2%)
  4. Betamethasone: 2 (4.1%)

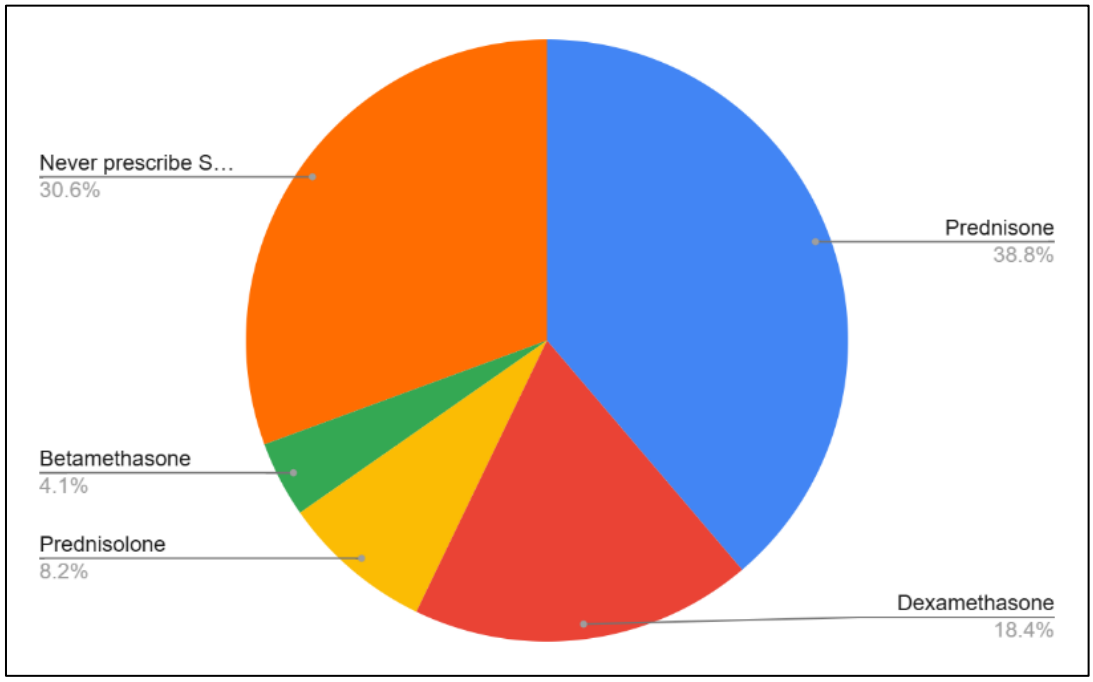

Fig. 12. The most common steroids prescribed by participating dentists.

- Steroids were prescribed between 1 to 7 days by 42 (93.3%) dentists, whereas they were prescribed between 7 to 14 days by only 3 (6.7%) dentists.

- The majority of the participating dentists (25 dentists, 39.1%) learned how to use steroids in postgraduate school, the rest learned elsewhere: 17 dentists (26.6%) in undergraduate school, 8 dentists (12.5%) at conferences and scientific meetings, and 5 dentists (7.8%) from colleague. There were 6 dentists (9.4%) who answered "I do not prescribe corticosteroids because my patients do not have dental pathologies that require corticosteroids as treatment", and 3 dentists (4.7%) who admitted that they didn't prescribe corticosteroids because they really don't know how steroids are used (Fig. 13).

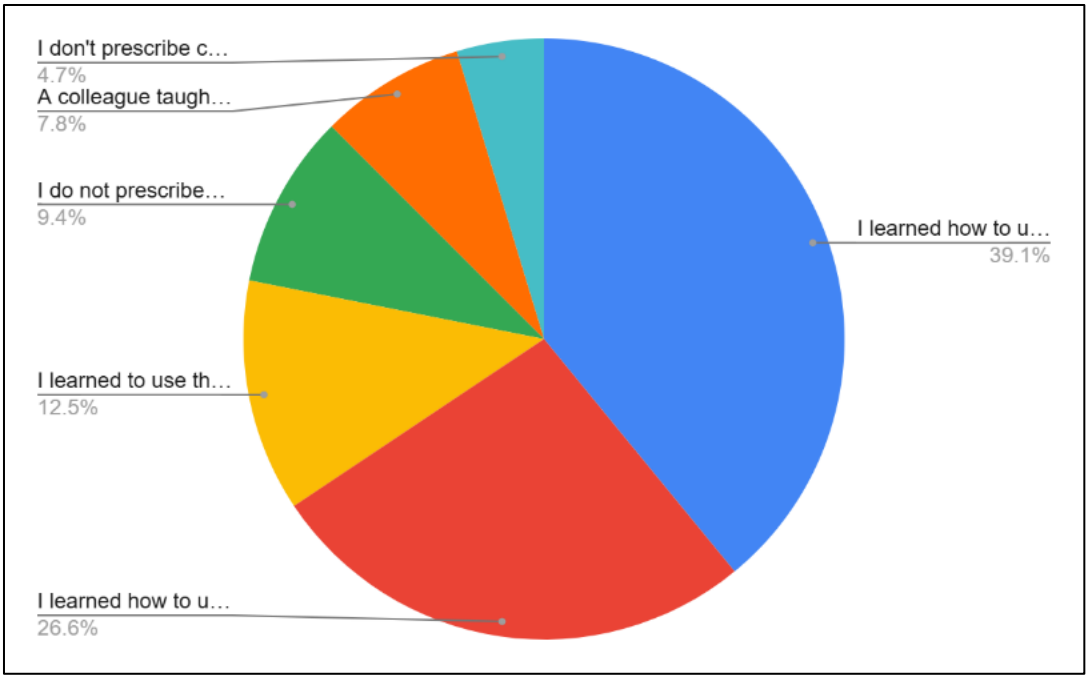

Fig. 13. Where steroids use for therapeutic management was learned.

- For those dentists who had never prescribed steroids, we asked whether they knew any dental colleagues who prescribed steroids. A majority of them (32 dentists) answered "yes", and 7 dentists answered "no".

5. DISCUSSION

In this study, we observed that approximately 75% of Spanish dentists prescribe steroids (most of them; occasionally or sometimes and few of them (6,1%) frequently). However, we have not found similar studies in medical literature that allows us to make comparisons.

The second objective of this study was to explore the indications for steroid use among Spanish dentists. Our study shows that the main reason for steroid use among most Spanish dentists (40.5%) is the management of postoperative swelling and inflammation control after oral surgery followed by oral inflammatory (22,8%) and autoimmune diseases (12,7%) that matches with studies published in other countries.

Although NSAIDs are the group of first choice to treat postsurgical oral inflammation, dentist should keep in mind always the possibility of prescribing steroids, even with high dose but short duration. Some recent published studies show that a postoperative steroid such as dexamethasone is effective to reduce postoperative complications after major oral surgeries. (33,34,36) In 70% of patients, pain is reduced on the second postoperative day, with a 12 mm reduction in edema noted. (36) It is not surprising that 40.5% of our participating dentists prescribed steroids for management of postoperative swelling and inflammation after oral surgery, e.g., implant, third molar, etc.

Our research revealed that prednisone (35.1%) and dexamethasone (22.1%) are the two most frequently prescribed steroid in Spanish dental offices that matches with other dental studies published (33,34) in the prevention and treatment of inflammation after surgery.

Steroids are commonly indicated for allergic processes as they have very powerful antiallergic effects. They are also prescribed for treat inflammation, autoimmune diseases, pain, edema, and lockjaw. (1) As far as treatment of systemic disease is concerned, oral steroids are widely used in western European countries. In a study of more than 700,000 patients with active asthma in France, Germany, Italy, and the UK, 44% of the patients were prescribed steroids to manage the disease. (37)

The 10 most commonly prescribed steroids for medical reasons in 2022 are listed below: (38)

1	Prednisone	29.70%
2	Triamcinolone acetonide	13.50%
3	Methylprednisolone	13.40%
4	Clobetasol propionate	5.60%
5	Hydrocortisone	4.80%
6	Dexamethasone	3.70%

7	Clotrimazole-betamethasone	2.80%
8	Prednisolone sodium phosphate	2.50%
9	Prednisolone	2.00%
10	Neomycin-polymyxin-dexamethasone	1.80%

Whereas in 2024, the most commonly prescribed steroids in dental treatments are prednisone, dexamethasone, betamethasone, etc. (39,40) that matches with our results. Although the classic steroid used in dentistry was prednisone (basic steroid with intermediate power), in last years, mainly in third molar surgery and due to increase of dental implant surgery, dexamethasone; an extremely powerful steroid, is more common prescribed in dentistry comparing with medicine prescriptions in which it represents 6th position (38) In this regard, knowledge and experience may play an important role in choosing the dosage. In fact, Kiran et al. remind the health providers that it is crucial to understand the indications, contraindications and special precautions before prescribing steroids. (41) They also stress that clinician must be mindful of adjusting dosage based on the disease process and patient condition and response.

Finally, our last objective was knowing where dentists adquire knowledge in the using of steroids and most of them responded after graduating. It will be interesting to review pharmacological training during bachellor period in order to get that all dental students adquired skill for using steroids before finishing their dental grade.

Limitations of the study:

The objective of this study was to analyze the steroid prescriptions at Spanish dental offices. The number of years of working experience of each participant varied between 3 and 37. These numbers suggest that all respondent dentists had sufficient experience to answer this questionnaire. Moreover, the participating dentists were highly skilled in one or more of most of the dental specialties. Hence, their answers could be considered as representative. However, due to the limitation of time and sample size, the results may not be conclusive. I intended to analyze which specialists prescribed topical or local steroids most frequently. However, most of the responders specialized in several areas of dentistry. For instance, three of these dentists used steroids frequently or often: the first person worked in the field of “general dentistry, implantology, oral surgery, and endodontics”; the second person worked in “periodontistry, implantology, oral surgery, oral medicine, and general dentistry”;

the third was an “oral surgeon, and general dentist”. The multidisciplinary nature of these dentists’ practices made the analysis impossible. Nevertheless, this study may serve as a cornerstone for further research.

6. CONCLUSIONS

1. To justify the hypothesis of this study, we observed that around 75% of Spanish dentists occasionally or sometimes prescribe local or systemic steroids in their treatments.
2. The main medical reason for prescribing steroids in the majority of Spanish dentists (40.5%) is to reduce inflammation after aggressive dental procedures or surgeries.
3. The most frequently prescribed steroid in Spanish dental offices is prednisone (35.1%), followed by dexamethasone (22.1%).
4. In Spain, postgraduate school was the most common way where dentists learnt how to manage steroids (39,1%).

7. SUSTAINABILITY

Due to the increasing usage of steroids for medical and dental treatments, properly prescribing this medicine has become increasingly important. This research may spur the review of dental education at both the undergraduate and postgraduate levels. Also, it may offer some ideas for future professional conferences as venues for providing the latest information to dental practitioners. Most importantly, self-improvement may be important to dental practitioners. Afterall, the safety of medication is a primary concern of treatment. We did not include the dosages prescribed in our investigation. Moreover, we should have included treatment outcome information in our questionnaire. Further research may include these perspectives and furnish information that can be used by dental professionals as a steroid prescription reference.

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9. ANNEXES

Annex 1

PRESCRIPTION OF CORTICOSTEROIDS IN SPANISH DENTAL OFFICES: Cross-sectional study

QUESTIONNAIRE FOR THE COMPLETION OF A FINAL DEGREE PROJECT IN DENTISTRY AT THE EUROPEAN UNIVERSITY OF MADRID

This questionnaire is part of the Final Degree Project in Dentistry of the European University of Madrid entitled PRESCRIPTION OF CORTICOSTEROIDS IN SPANISH DENTAL OFFICES: A CROSS-SECTIONAL STUDY and directed by Professor Dr. Emilio Pintor Holguín. The purpose of this work is to find out about the prescription of corticosteroids in Spanish dental offices: their frequency, indications as well as the most commonly used drugs, their routes of administration and the duration of treatment. The information will be collected through a brief survey. Your participation in this study is free and voluntary, and you may request to be excluded from it, without prior justification or harm to you. The information collected will be confidential and will not be used for any other purpose outside of this research and derived from investigative disclosure. The data collected will be completely anonymous. No personal identifying data will be requested. The data collected in the survey will be treated in accordance with the provisions of Organic Law 3/2018, of December 5, on the Protection of Personal Data and the Guarantee of Digital Rights. For the purposes of the provisions of the regulations of Organic Law 3/2018, of December 5, on the Protection of Personal Data and the Guarantee of Digital Rights, you are informed and expressly consent to the use of the data provided in the survey, for the purposes indicated above.

This consent is granted without prejudice to all the rights that assist you in relation to the aforementioned regulations, and there is the possibility of accessing the information provided, rectification, cancellation and opposition at any time you wish. To do so, you must write to the tutor Prof. ○○○○○

Do you consent to participate in the survey as a volunteer so that the results of the survey may be used in the Final Degree Project entitled PRESCRIPTION OF CORTICOSTEROIDS IN SPANISH DENTAL OFFICES: A CROSS-SECTIONAL STUDY?

○ Yes

○ No

2. Sex of the dentist

○ Male

○ Female

3. Age of the dentist

4. Years of clinical practice (as a dentist)

5. Province where the dental office where you work is located

6. Dental specialty you practice (choose one or several answers if necessary)

☐ General dentist

☐ Periodontist

☐ Orthodontist

☐ Pediatric dentist

☐ Endodontist

☐ Implantologist

☐ Oral surgeon

☐ Oral medicine

7. How often do you prescribe TOPICAL/LOCAL corticosteroids in the oral cavity in your dental practice?

○ Never

○ Occasionally

○ Sometimes

○ Often

8. How often do you prescribe SYSTEMIC corticosteroids (tablets or injections) in your dental practice?

○ Never

○ Occasionally

○ Sometimes

○ Often

9. If you prescribe CORTICOSTEROIDS to your patients, what are the INDICATIONS? (choose one or several answers if necessary)

☐ Aphthous ulcers

☐ Oral inflammation: such as lichen planus, erythema multiforme, etc.

☐ Oral autoimmune pathology: pemphigus vulgaris, etc.

☐ Temporomandibular joint disorders

☐ Postoperative swelling and inflammation control after oral surgery. E.g. implant, third molar, etc.

☐ Never prescribe Steroids

10. Which of the following corticosteroids have you ever prescribed?

☐ Prednisone

☐ Prednisolone

☐ Dexamethasone

☐ Betamethasone

☐ None of the above

11. Which of the following corticosteroids has been prescribed most frequently? (you can choose one or several answers)

○ Prednisone

○ Prednisolone

○ Dexamethasone

○ Betamethasone

○ None of the above

12. When you prescribe a corticosteroid to your patients, what is the usual duration of treatment?

○ less than 7 days

○ between 8 and 14 days

○ more than 14 days

13. Where did you learn the therapeutic management of corticosteroids?

☐ I don't prescribe corticosteroids because I don't really know how they are used.

☐ I do not prescribe corticosteroids because my patients do not have dental pathologies that require corticosteroids as treatment.

☐ I learned how to use them during my undergraduate training.

☐ I learned how to use them during my post-graduate training.

☐ I learned to use them in conferences or scientific meetings.

☐ A colleague taught me how to use them.

14. If you do not use/prescribe corticosteroids, do you know any dentist who does? If you are going to mark YES, we would appreciate it if you could forward this questionnaire to them.

○ Yes

○ No

Annex 2

Universidad Europea

Comisión de Investigación

Villaviciosa de Odón, 29 de noviembre de 2024

Estimado/a investigador/a,

La Comisión de Investigación de la Escuela de Doctorado e Investigación, una vez revisada la documentación e información, remitida por el investigador responsable con fecha 05/11/2024 9:43:21, relativa al proyecto abajo indicado, autoriza su desarrollo en la Universidad Europea.

Título del proyecto:	Prescripción de corticoides en las consultas dentales españolas
Tipo de proyecto:	TFG
Investigador/a responsable:	[redacted]
Código CI:	2024-921
Código OTRI:	Sin especificar
Código Departamento:	OD.003/2425
Dictamen:	APROBADO

Atentamente,

Universidad Europea
ESCUELA DE DOCTORADO E INVESTIGACIÓN

Fdo. Óscar García López

Director de la Escuela de Doctorado e Investigación

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Annex 3

BJP British Journal of Pharmacology

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www.brjpharmacol.org

Themed Issue: Respiratory Pharmacology

REVIEW

Glucocorticosteroids: current and future directions

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asthma; COPD; inflammation; p38 MAP kinase; histone deacetylase; steroid resistance; oxidative stress; β_2-adrenoceptors

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Glucocorticoids are the most effective anti-inflammatory therapy for asthma yet are relatively ineffective in chronic obstructive pulmonary disease. Glucocorticoids suppress inflammation via several molecular mechanisms. Glucocorticoids suppress the multiple inflammatory genes that are activated in chronic inflammatory diseases, such as asthma, by reversing histone acetylation of activated inflammatory genes through binding of ligand-bound glucocorticoid receptors (GR) to co-activator molecules and recruitment of histone deacetylase-2 to the activated inflammatory gene transcription complex (*trans*-repression). At higher concentrations of glucocorticoids GR homodimers interact with DNA recognition sites to activate transcription through increased histone acetylation of anti-inflammatory genes and transcription of several genes linked to glucocorticoid side effects (*trans*-activation). Glucocorticoids also have post-transcriptional effects and decrease stability of some pro-inflammatory mRNA species. Decreased glucocorticoid responsiveness is found in patients with severe asthma and asthmatics who smoke, as well as in all patients with chronic obstructive pulmonary disease. Several molecular mechanisms of glucocorticoid resistance have now been identified which involve post-translational modifications of GR. Histone deacetylase-2 is markedly reduced in activity and expression as a result of oxidative/nitrative stress so that inflammation becomes resistant to the anti-inflammatory actions of glucocorticoids. Dissociated glucocorticoids and selective GR modulators which show improved *trans*-repression over *trans*-activation effects have been developed to reduce side effects, but so far it has been difficult to dissociate anti-inflammatory effects from adverse effects. In patients with glucocorticoid resistance alternative anti-inflammatory treatments are being investigated as well as drugs that may reverse the molecular mechanisms of glucocorticoid resistance.

LINKED ARTICLES
This article is part of a themed issue on Respiratory Pharmacology. To view the other articles in this issue visit http://dx.doi.org/10.1111/bph.2011.163.issue-1

Abbreviations
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GR, glucocorticoid receptor; GRE, glucocorticoid response element; HDAC, histone deacetylase; ICS, inhaled corticosteroids; JNK, c-Jun *N*-terminal kinase; MAPK, mitogen-activated protein kinase; MKP, MAP kinase phosphatase; MIF, macrophage migration inhibitory factor; NF-κB, nuclear factor-κB; PI3K, phosphoinositide-3-kinase; TNF, tumour necrosis factor

Introduction

Glucocorticosteroids (also called glucocorticoids, corticosteroids or steroids) are the most effective anti-inflammatory drugs available for the treatment of many chronic inflammatory and immune diseases, including asthma. However, a minority of patients with these diseases show little or no response even to high doses of glucocorticoids. Several other inflammatory diseases, including chronic obstructive pulmonary disease (COPD), interstitial pulmonary fibrosis and cystic fibrosis, appear to be largely glucocorticoid-resistant.

Both asthma and COPD involve chronic inflammation of the respiratory tract, with the activation and recruitment of many inflammatory cells and orchestrated by a complex network of inflammatory mediators (Barnes, 2008a,b). However, there are differences in the nature of this inflammation and its inflammatory consequences between these diseases and perhaps this is best demonstrated by the differing response to glucocorticoids, which is excellent in most patients with asthma but very poor in most patients with COPD. There is now a much better understanding of how glucocorticoids suppress chronic inflammation in asthma

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ARTICLE OPEN

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A retrospective database study of oral corticosteroid and bisphosphonate prescribing patterns in England

Christos V. Chalitsios[1✉], Dominick E. Shaw[1] and Tricia M. McKeever[2]

Exposure to oral corticosteroids (OCS) is associated with an increased risk of osteoporosis and fragility fractures. Guidelines suggest bisphosphonate (BP) therapy as the first-line treatment of glucocorticoid-induced osteoporosis (GIOP). This population study used publicly available data, including prescription annual cost analysis and monthly practice-level data. Our aim was to examine the prescribing of OCS and BP at practice level and investigate reasons for variation using a mixed-effect negative binomial regression analysis. There was a rise in OCS and BP prescriptions of 55% and 1200% from 1998 to 2018, respectively. Of the 6586 included practices, the median (IQR) of OCS and BP prescriptions were 120.8 (84.8–160.4) and 107.7 (73.8–147.4) per 1000 patients, respectively. Asthma and chronic obstructive pulmonary disease (COPD) were significantly associated with OCS use ($p < 0.0001$), but only COPD was associated with BP use ($p < 0.0001$). Higher OCS prescribing rates were associated with higher BP prescribing rates (5th to 1st quintile—IRR = 1.99; 95% CI: 1.88–2.10). Practice list size, deprivation and advanced age were all associated with both drugs ($p < 0.0001$). In conclusion, although OCS use is positively associated with BP prescription, variation among practices and CCGs exists. The variation in prescribing suggests there is still a need to improve GIOP prevention.

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INTRODUCTION

Oral corticosteroids (OCS) (glucocorticoids) are used to treat chronic conditions including autoimmune,[1] and respiratory diseases.[2,3] Asthma and COPD are two of the most common indications for prolonged OCS use (more than 90 days).[4] Both short-term (5–90 days) and prolonged exposure to OCS can lead to deleterious effects[5,6] including bone loss resulting in osteoporosis and fragility fracture.[7] Bone loss is substantial and rapid during the first months of the OCS treatment.[8] Patients with severe asthma exposed to prednisolone 5 mg per day are more likely to be diagnosed with osteoporosis (OR = 6.5) and have a fracture (OR = 1.5) compared to those without asthma.[9] After OCS initiation, spine fracture risk increases by 55% with exposure at doses as low as prednisone 2.5 mg per day, whereas hip fracture risk goes up by 50% among patients exposed to 2.5–7.5 mg per day.[10,11]

Fragility fractures are also associated with substantially increased healthcare costs, morbidity, and mortality,[12,13] and guidelines suggest all patients exposed to any dose of OCS for more than 3 months should be considered for BP therapy to prevent glucocorticoid-induced osteoporosis (GIOP).[14,15] The bisphosphonate class is effective in reducing bone loss and fragility fracture risk.[16,17] Despite this, only a minority of patients with increased fragility fracture risk receive appropriate therapy.[18,19] There are no specific guidelines for GIOP in asthma or COPD and the size of the potential problem is not well established.

We are unaware of any published U.K. research investigating the trends in OCS and anti-GIOP therapy (BP) prescribing. Our aim was to comprehensively assess OCS and BP prescribing patterns, at practice level, using primary care data from England and to investigate factors associated with their prescribing, in order to gain a better understanding of prescribing enabling us to reduce prescribing variation and optimise GIOP prevention.

RESULTS

Practice characteristics

In our analysis, we included 195 Clinical Commissioning Groups (CCGs) containing 6586 practices after the exclusion of 507. In 2018, the median (IQR) OCS and BP prescriptions per 1000 patients was 120.8 (84.8–160.4) and 107.7 (73.8–147.4), respectively. The characteristics of practices are summarised in Table 1.

Long-term patterns and ratio between OCS and BP prescriptions

Prednisolone was the most frequently prescribed OCS. There was a steady increase in OCS prescriptions over time (Fig. 1a). In 1998, there were 95 OCS prescriptions per 1000 population increasing to 140 in 2018 (55% rise). The cost of OCS was £250 per 1000 population until 2006, with a noticeable increase up to just less than £2000 the following years (Supplementary Fig. 1).

There was an increase in bisphosphonate prescribing rates over time (Fig. 1b). In 1998, there were 10 BP prescriptions per 1000 population, while the total prescriptions reached 120 in 2018 (1200% increase). The most prescribed bisphosphonate was alendronic acid. BP cost peaked at £3200 per 1000 population in 2005; however, there was a reduction to £101 by 2018 (Supplementary Fig. 1).

There were 0.99 OCS prescriptions per 1 BP item in 2015; however, this relationship changed slightly to 1.16 by 2018 (Table 2).

Variations among practices and CCGs for OCS and BP items

In 2018, there was a significant variation between OCS ($m = 129.6$, $SD = 38.9$) and BP ($m = 118.5$, $SD = 34.2$) prescription per 1000 patients; $t = 6.27$, $p < 0.0001$. OCS prescription varied between 48 and 239 and BP ranged from 38 to 207 prescriptions per 1000 patients across CCGs. Sixty out of 195 CCGs prescribed less OCS

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Review Article

Management Of Dental Patients On Corticosteroid Therapy

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ABSTRACT:
Many dental patients are receiving long-term systemic corticosteroid therapy. The corticosteroids act as double edged sword that is it helps in the dental treatment as well as also has a profound systemic effect on patients taking this medication for a long term. This article enlightens about the management of the patient receiving such medication and requiring dental therapy, the guidelines and handling the adverse effects. It also briefs about the use of Corticosteroids in certain dental procedures.
Keywords: Corticosteroids, adrenal atrophy, management, dental procedures, anxiety control, steroid therapy.

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INTRODUCTION

Corticosteroids and their synthetic analogues are commonly used for their potent anti-inflammatory and immunosuppressive properties in the treatment of a variety of medical conditions characterized by chronic inflammatory and immune phenomena.[1][2]Prolonged therapy with corticosteroids may produce many diverse side effects as well as depress normal function of the adrenal cortex. Every practicing dentist must have a basic understanding of adrenal physiology and the body's response to exogenous corticosteroids in order to properly manage dental patients who are receiving systemic corticosteroid medications. The purpose of this article is to review these topics, with focus on the management of dental patients receiving corticosteroid therapy.

PHYSIOLOGY OF CORTISOL

Adrenal cortex secretes three types of hormones: glucocorticoids, androgens, and mineralocorticoids. These are related to the body's response to stress and the physiological response of the vascular system to tissue damage [3][4]. A total of 24–30 mg/day of cortisol is secreted by the adrenal gland in normal adults[5]. However, during periods of stress, this secretion level can spike up to300 mg/day[6]. Diurnal variations; the response of individuals to stress; and the effectiveness of control mechanisms involving the hypothalamus, pituitary gland and adrenal glands play a central role in regulating the daily secretion level of cortisol.

When high doses of corticosteroids equivalent to >30 mg of cortisol are administered for two weeks, these regulatory mechanisms may be altered and may return to normal only over a period of up to one year. Meanwhile, the body's capacity to react to stress can recover in just 15–20 days[5][7]. A total of 10–20 mg/day of cortisol is secreted, with almost 50% of this being secreted in the early hours of the day[6].

FEEDBACK MECHANISM

The secretion by adrenal cortex is controlled by Feedback system of HYPOTHALAMUS-PITUITARY-ADREANAL AXIS.

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STEROIDS APPLICATION IN ORAL DISEASES

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ABSTRACT

Steroids are substances that are naturally produced in the body. Steroids are produced by the adrenal glands which are small glands lying above the kidneys. It may regulate our immune system, balance the intake of salt and water in our bodies. Steroid helps in reducing inflammation. Most common types of steroids that are used in dentistry are hydrocortisone, dexamethasone, methylprednisolone and prednisolone. In dentistry, apart from surgeries, steroids are widely used and accepted mode of treatment for oral mucosal lesions such as oral lichen planus, oral submucous fibrosis, erythema multiforme, pemphigus vulgaris, pemphigoid and mucocele. This review discusses about the steroids application in oral diseases

KEYWORDS:Steroids, Hydrocortisone, oral lichen planus, oral submucous fibrosis, erythema multiforme

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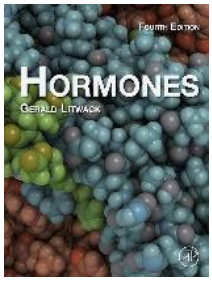

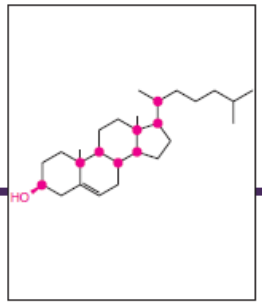

Chapter 2

Steroid Hormones: Chemistry, Biosynthesis, and Metabolism

I. INTRODUCTION

A. General Comments

This chapter deals with the structural chemistry and biosynthetic pathways of the major classes of steroid hormones. All have a complicated structure of fused rings which can be modified by functional group substitution at many points. Furthermore, the presence of asymmetric carbon atoms introduces steric modifications and isomeric possibilities. The reader will find it prudent to first grasp the essential features of the steroid structures and relationships before attempting to delve into a consideration of their specific hormonal activities in later chapters. Then, when so doing, it may be helpful to turn back to the appropriate portion of this chapter to further heighten understanding of the structures of the hormones under review.

B. Historical Perspective

The first steroid hormone, estrone, was isolated in 1929 at a time before the characteristic ring structure of the steroid nucleus had been elucidated. Today well over 230 naturally occurring steroids have been isolated and chemically characterized. In addition, an uncountable number of steroids and steroid analogs have been chemically synthesized and evaluated for their drug properties.

The development of our modern understanding of hormones and the science of endocrinology has closely paralleled studies on the isolation, chemical characterization, and synthesis of steroids and the subsequent elucidation of their pathways of biosynthesis and catabolism. The foundation of many of these developments with steroid hormones is to be found in a lengthy series of papers authored by Professor Adolf O. R. Windaus' chemistry laboratory in Gottingen, Germany (1925–1935[1]) that led to the structural determination of cholesterol. This was an extraordinarily challenging problem given the limitation that the techniques of nuclear magnetic resonance spectroscopy (NMR), mass spectrometry, and ultraviolet (UV) and infrared (IR) spectroscopy were not available at that time. Instead, the structure was determined through elaborate classical organic chemistry manipulations, which involved the conversion of the compound under study to known reference compounds. At the present time, application of the powerful separation techniques of high-performance liquid chromatography (HPLC) or gas chromatography, combined with the use of continuous on-line monitoring by mass spectrometry with computer-assisted data storage and analysis, frequently permit unequivocal structural determinations on impure samples that contain less than 1 ng of the steroid of interest.

[1] The Nobel Prize in Chemistry in 1928 was awarded to Adolf Windaus "for the services rendered through his research into the constitution of the sterols and their connection with the vitamins."

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30 YEARS OF THE MINERALOCORTICOID RECEPTOR

Evolution of the mineralocorticoid receptor: sequence, structure and function

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Abstract

The mineralocorticoid receptor (MR) is descended from a corticoid receptor (CR), which has descendants in lamprey and hagfish, cyclostomes (jawless fish), a taxon that evolved at the base of the vertebrate line. A distinct MR and GR first appear in cartilaginous fishes (Chondrichthyes), such as sharks, skates, rays and chimeras. Skate MR has a strong response to corticosteroids that are mineralocorticoids and glucocorticoids in humans. The half-maximal responses (EC50s) for skate MR for the mineralocorticoids aldosterone and 11-deoxycorticosterone are 0.07 nM and 0.03 nM, respectively. EC50s for the glucocorticoids cortisol and corticosterone are 1 nM and 0.09 nM, respectively. The physiological mineralocorticoid in ray-finned fish, which do not synthesize aldosterone, is not fully understood because several 3-ketosteroids, including cortisol, 11-deoxycortisol, corticosterone, 11-deoxycorticosterone and progesterone are transcriptional activators of fish MR. Further divergence of the MR and GR in terrestrial vertebrates, which synthesize aldosterone, led to emergence of aldosterone as a selective ligand for the MR. Here, we combine sequence analysis of the CR and vertebrate MRs and GRs, analysis of crystal structures of human MR and GR and data on transcriptional activation by 3-ketosteroids of wild-type and mutant MRs and GRs to investigate the evolution of selectivity for 3-ketosteroids by the MR in terrestrial vertebrates and ray-finned fish, as well as the basis for binding of some glucocorticoids by human MR and other vertebrate MRs.

Key Words
- corticosteroid receptor evolution
- mineralocorticoid receptor evolution
- glucocorticoid receptor evolution
- lamprey
- cartilaginous fishes

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Journal of Endocrinology

Introduction

In this special issue of JOE, we celebrate the thirtieth anniversary of cloning of the mineralocorticoid receptor (MR) in the Evans laboratory at the Salk Institute (Arriza *et al.* 1987). This was an impressive achievement. Indeed, it was not an easy task, as the MR was the last cloned receptor from the adrenal and sex steroid receptor family, which also includes the glucocorticoid receptor (GR), progesterone receptor (PR), androgen receptor (AR) and estrogen receptor (ER) (Evans 1988, Markov *et al.* 2009, Baker *et al.* 2015). The MR and other steroid receptors belong to the nuclear receptor family, a diverse group of transcription factors that arose in multicellular animals, which have key roles in the physiology of humans and other vertebrates (Markov *et al.* 2009, Bridgham *et al.* 2010, Huang *et al.* 2010, Baker *et al.* 2013). A 3-ketosteroid receptor (SR) ancestor of the MR, GR, PR and AR first

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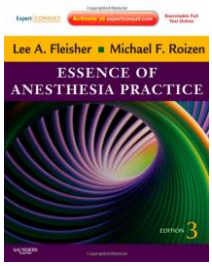

Hormone Replacement Therapy (HRT)

Edgar Pierre
Nicole D. Martin

DRUGS

Uses

- To treat the physiologic and physical manifestations of hypoestrogenism due to hypogonadism or primary ovarian failure
- To prevent or alleviate the signs and symptoms assoc with surgical or age-related menopause incl vaginal dryness, urogenital atrophy, irritability, depressed mood, osteoporosis, hyperlipidemia, CV disease, and vasomotor symptoms incl hot flashes
- A generic term that encompasses the use of unopposed estrogen therapy and combinations of estrogens and progestins

Perioperative Risks

- Increased risk for coagulopathy due to changes in coagulation and fibrinolytic pathways
- Within the first year of use, can cause a slight increase in coagulation factors II, VII, IX, X and XII, while decreasing the anticoagulation factors Protein C, Protein S, and antithrombin III, enhancing clot formation
- When used in combination with a progestin, may result in decreased levels of plasminogen-activator inhibitor protein-1 (PAI-1) resulting in increased fibrinolysis and prolonged bleeding

Worry About

- Increased risk of thrombosis incl DVT, pulm embolism, stroke, and myocardial infarction with estrogen replacement therapy if used without concomitant aspirin therapy (can be continued thru day of surgery for all but plastic, eye, and some neurologic operations).
- Increased risk of fibrinolysis and prolonged bleeding with combination estrogen-progestin
- Alterations in drug metabolism due to induction of various cytochrome P450 CYP isozymes
- Changes in drug distribution as a result of increased hepatic production of serum binding proteins

Overview/Pharmacology

- HRT provides low dosages of one or more estrogens, often in combination with progesterone or a chemical analogue, called a progestin.
- Conjugated estrogens and synthetic progestins have been most commonly used in HRT.
- Estrogens: A group of 18-carbon steroid compounds that occur naturally in three major forms: estrone, estradiol, and estriol. All steroids contain 4 condensed rings, designated A-D. The phenolic A ring is the principal structural feature that is responsible for selective, high-affinity binding to the estrogen receptors. As with most steroid hormones, estrogens can diffuse readily across cell membranes. Once within the cell, they bind and activate estrogen receptors that in turn up-regulate gene expression. Estrogen receptors are abundant throughout the body and can be found in the female reproductive tract, mammary glands, hypothalamus, endothelial cells, vascular smooth muscles, lung, brain, and bone.
- Progestins: A family of 21-carbon steroids that are synthetic derivatives of the 19-nortestosterone structure. Designed to have progestinic effects similar to progesterone, progestins work by binding to an intracellular progesterone receptor resulting in transcriptional activation. Physiologic actions incl endometrial proliferation, suppression of uterine contractility, mammary gland development, and thickening of endocervical gland secretions.

Drug Class/Mechanism of Action/Usual Dose

- Classified as steroid hormones, estrogens and progestins bind to specific receptors and have widespread effects on many tissues in the body.
- Various formulations are available for oral, parenteral, transdermal, or topical administration.
- To reduce the risks of HRT, lower-dose estrogen therapy regimens are preferred over high-dose therapy. The typical daily oral dose of conjugated estrogen is 0.625 mg, however, initial treatment should start at a dose of 0.3 mg/d and dose adjustments made based on clinical response. Additional available dosages are 0.9, 1.25, and 2.5 mg.
- The most commonly prescribed progestin is medroxyprogesterone acetate. It is typically given in a cyclic regimen (5–10 mg/d) or continuous regimen (2.5mg/d). Better choice is a micronized progestin (Prometrium, for example) which doesn't oppose the effect of estradiol on arterial function.

DRUG EFFECTS

System	Effect	Assessment by Hx	PE	Test
HEENT	Retinal vascular thrombosis, ↑ corneal curvature, ↑ lacrimal secretion	Changes or loss of vision, contact lens intolerance	Pale retina with cherry red macula, retinal hemorrhages	Ophthalmologic exam
CARDIO	Fluid retention, Htn improved lipoprotein profiles: ↑ HDL, ↓ LDL	Swelling and wt gain, Htn	Edema	Physical exam, BP, lipid profile
GI	Pancreatitis, N/V, gallstone formation	Abd pain, intolerance to fatty foods	RUQ or epigastric pain	Amylase, lipase, alk phos, RUQ U/S, bilirubin
HEPAT	Adenoma enlargement cholestasis	Abd pain, yellowing of skin	Hepatomegaly, jaundice	RUQ US, LFTs, bilirubin
GU	Abn uterine bleeding, changes in cervical secretions, increase in fibroid size, vaginal candidiasis	Vaginal bleeding, vaginal discharge, vaginal itching/burning	Enlarged lobulated uterus, vaginal discharge	Gynecologic exam, GYN US, KOH prep
HEME	Increased coagulation if not given with concomitant aspirin increased fibrinolysis	DVT, PE, MI, CVA Prolonged bleeding	LE swelling, SOB, CP, neuro deficits	PT/PTT, D-dimer, duplex US, CT angio fibrinogen, antithrombin III, Protein C
DERM	Chloasma, melasma, rashes, alopecia, hirsutism	Skin and hair changes	Hyperpigmentation, erythema, papules, nodules, hair changes	Dermatologic exam

Key References: Brunton L, Parker K, et al. *Goodman & Gilman's manual of pharmacology and therapeutics*. McGraw Hill Companies. 2008:993–1006.

Perioperative Implications

Preoperative Concerns

- Changes in angiotensin-aldosterone system may result in elevated BP and/or renal failure.
- Increased risk for thrombosis if not given with concomitant aspirin. Pts undergoing procedures assoc with moderate to high risk for venous thromboembolism should stop hormone therapy at least 4 to 6 wk prior to surgery. Rigorous prophylaxis for DVT must be observed in the periop period.
- The risks assoc with temporary D/C of hormone therapy incl withdrawal bleeding, hot flashes, and other menopausal symptoms.

Induction/Maintenance

- Alterations in the activity of various cytochrome P450 CYP isozymes may require dose adjustment of hepatically cleared drugs.
- HRT may induce metabolism of drugs which are glucoronidated, incl some benzodiazepines and analgesics.
- Progestin metabolite, allopregnanolone, may affect the excitability of neurons through direct modulation of the GABA-A receptors exerting hypnotic/sedative, anxiolytic, and anesthetic.

Postoperative Period

- Increased risk for thrombosis extends into the postop period. A higher suspicion for postop DVT, pulm embolism, stroke, and myocardial infarction must be maintained. Restart or continue aspirin which should be always given concomitantly unless contraindicated.
- Activation of fibrinolytic pathways in pts using combined estrogen-progestin replacement therapy may result in postop bleeding.

Anticipated Problems/Concerns

- Coagulopathy, esp. increased risk for thromboembolism, remains a top concern for women using HRT.

Inhaled Corticosteroids in Lung Diseases

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Inhaled corticosteroids (ICSs) are used extensively in the treatment of asthma and chronic obstructive pulmonary disease (COPD) due to their broad antiinflammatory effects. They improve lung function, symptoms, and quality of life and reduce exacerbations in both conditions but do not alter the progression of disease. They decrease mortality in asthma but not COPD. The available ICSs vary in their therapeutic index and potency. Although ICSs are used in all age groups, younger and smaller children may be at a greater risk for adverse systemic effects because they can receive higher mg/kg doses of ICSs compared with older children. Most of the benefit from ICSs occurs in the low to medium dose range. Minimal additional improvement is seen with higher doses, although some patients may benefit from higher doses. Although ICSs are the preferred agents for managing persistent asthma in all ages, their benefit in COPD is more controversial. When used appropriately, ICSs have few adverse events at low to medium doses, but risk increases with high-dose ICSs. Although several new drugs are being developed and evaluated, it is unlikely that any of these new medications will replace ICSs as the preferred initial long-term controller therapy for asthma, but more effective initial controller therapy could be developed for COPD.

Keywords: asthma; asthma control; asthma guidelines; β-adrenergic agonists; corticosteroids

HISTORICAL PERSPECTIVE

Corticosteroids are widely used in the treatment of lung diseases. Their efficacy comes from their broad antiinflammatory and immunosuppressive effects. Systemic corticosteroids were first shown to be effective in the treatment of acute asthma in 1956 (1). Since then, numerous studies have confirmed the effectiveness of systemic corticosteroid therapy in managing acute and chronic asthma. Since the mid-1990s, several studies have demonstrated their efficacy in acute exacerbations of chronic obstructive pulmonary disease (COPD) (2).

Beclomethasone dipropionate (BDP) was introduced in the early 1970s as the first inhaled corticosteroid (ICS) to show enhanced topical to systemic activity (i.e., therapeutic index) (3). Subsequently, studies have documented the effectiveness and limited adverse effects of ICSs for decreasing morbidity and mortality from asthma (4, 5). However, ICS therapy in COPD has been controversial (6, 7). Six ICSs are available for use in the United States: BDP, flunisolide, budesonide (BUD), fluticasone propionate (FP), mometasone furoate, and ciclesonide.

MECHANISM OF ACTION

Corticosteroids have many cell- and tissue-specific antiinflammatory effects that have been extensively described (8). The corticosteroid enters the cell cytoplasm and binds with the inactive glucocorticoid receptor complex. Consequently, the activated glucocorticoid receptor binds to DNA at the glucocorticoid response element sequence and promotes synthesis of antiinflammatory proteins (transactivation) and inhibits transcription and synthesis of many proinflammatory cytokines (transrepression) (8). Transactivation is also responsible for many adverse systemic effects of corticosteroids. Corticosteroids also reduce the number of T lymphocytes, dendritic cells, eosinophils, and mast cells in airways and reduce inducible nitric oxide production (8).

PHARMACOKINETICS

The pharmacokinetics and pharmacodynamics of the available ICSs have been extensively reviewed elsewhere (9–11). Table 1 presents the factors that determine "clinically comparable doses" for efficacy and the therapeutic index of the ICSs. The delivery device can alter efficacy and therapeutic index (9–12). Therapeutic index is improved by decreased oral bioavailability, increased systemic clearance, and prolonged residence time in the lung secondary to increased lipophilicity, which results in increased volume of distribution (Table 1) (9–11). Even ICSs with a greater therapeutic index produce systemic effects when administered in the high-dose range as defined by the guidelines (Table 2) (4).

Younger and smaller children may be at a greater risk for adverse systemic effects because they can receive higher mg/kg doses of ICSs when administered by metered-dose inhaler (MDI) and valved holding chambers (VHCs), particularly with the newer static free VHCs, compared with older children (13, 14).

PHARMACODYNAMICS

As with other drugs whose mechanisms are receptor mediated, corticosteroids exhibit a log–dose linear effect; thus, the clinical dose response is often described as flat because doubling the dose is relatively ineffective in producing significant changes in outcomes (9, 10, 15). The ICS dose response is further complicated because the various measures of response (lung function, bronchial hyperresponsiveness, asthma symptom control, exacerbations, sputum, and exhalation markers of inflammation) are downstream events from the direct antiinflammatory

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The science of steroids

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ABSTRACT

Steroids are complex lipophilic molecules that have many actions in the body to regulate cellular, tissue and organ functions across the life span. Steroid hormones such as cortisol, aldosterone, estradiol and testosterone are synthesised from cholesterol in specialised endocrine cells in the adrenal gland, ovary and testis, and released into the circulation when required. Steroid hormones move freely into cells to activate intracellular nuclear receptors that function as multi-domain ligand-dependent transcriptional regulators in the cell nucleus. Activated nuclear receptors modify expression of hundreds to thousands of specific target genes in the genome. Steroid hormone actions in the fetus include developmental roles in the respiratory system, brain, and cardiovascular system. The synthetic glucocorticoid steroid betamethasone is used antenatally to reduce the complications of preterm birth. Development of novel selective partial glucocorticoid receptor agonists may provide improved therapies to treat the respiratory complications of preterm birth and spare the deleterious effects of postnatal glucocorticoids in other organs.

1. Introduction

Steroids are complex four-ringed organic molecules that serve many roles and functions in multicellular organisms. They are structural components of cell membranes exemplified by the important dietary steroid cholesterol and have many functional regulatory roles as modified structural forms of cholesterol to function as endogenous endocrine hormones. In all organisms, hormones *in vivo* play key regulatory roles in mediating communication and regulation of important functions and processes within and between cells, and across tissues, to connect all organs of the body [1]. Endocrine hormones circulate in the bloodstream and allow communication between cells and organs separated by relatively large distances. Hydrophilic or water-soluble hormones act primarily at the cell surface by binding to protein receptors embedded in the plasma membrane. In contrast, hydrophobic hormones circulate primarily bound to carrier plasma proteins and are able to freely defuse across cell membranes to activate specific intracellular hormone receptors [1].

This review will focus on the biology and actions of the lipophilic steroid hormones and some of the important synthetic steroid compounds, developed over the past 50 years to treat human disease, that act as specific agonists or antagonists to steroid hormone receptors *in vivo*. It will summarize current knowledge on the action of physiological steroid hormones in fetal development and the use of synthetic steroids to treat the postnatal complications associated with preterm birth.

2. Steroid biosynthesis and turnover

All steroids in the body are derived from cholesterol via a tightly regulated biosynthetic enzymatic pathway that operates predominantly in specific endocrine organs, including the adrenal gland, ovary, and testis. Further modifications of the steroid structure and resulting function can occur in many tissues and organs of the body such as in the liver, skin epidermis, brain and prostate [2].

In the steroidogenic cells of the adrenal gland, ovary and testis, cholesterol is first converted to pregnenolone by the cholesterol side-chain cleavage enzyme, $P450_{SCC}$, a cytochrome P450 enzyme, and this step represents the key regulatory point for synthesis of the majority of endogenous steroid hormones. Most of the enzymes in the steroid biosynthetic pathway are either cytochrome P450 enzymes or specialised hydroxysteroid dehydrogenase (HSD) enzymes, which belong to the short-chain alcohol dehydrogenase reductase (SDR) enzyme super family [3].

Adrenal steroid biosynthesis occurs in the outer cortex of the adrenal gland. The cortex is divided into three layers where specific

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Clinical Pharmacology of Corticosteroids

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Corticosteroids have numerous applications in treating inflammation and diseases of immune function based on their significant anti-inflammatory and immunosuppressive effects. Corticosteroids modulate immune function through various effects in the nucleus of numerous cells. When used in pharmacologic doses to suppress allergic responses or inflammation, these agents can cause numerous adverse effects associated with an excess of glucocorticoid activity. Prolonged use (>2 wk) results in suppression of the hypothalamic-pituitary-adrenal axis, which requires tapering of doses. Dosing strategies for systemic corticosteroids are designed to minimize the risk for hypothalamic-pituitary-adrenal axis suppression. Topical administration of corticosteroids, including oral inhalation, is often used to avoid the significant adverse effects associated with chronic use. Inhaled corticosteroids are potent synthetic agents that exert their actions locally in the airways but can cause systemic effects based on several factors that influence systemic bioavailability. Inhaled corticosteroids are the cornerstone of asthma therapy and important options for COPD in patients who experience frequent exacerbations. By the nasal route, they are the most effective therapy for treating moderate-to-severe allergic rhinitis. *Key words: COPD; asthma corticosteroids; lung disease.*
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REVIEW

How Do Corticosteroids Work in Asthma?

Peter J. Barnes, DM, DSc, and Ian M. Adcock, PhD

Clinical Principles

Asthma is the most common chronic disease in westernized countries.

Patients with asthma have an underlying chronic inflammation of the airways characterized by activated mast cells, eosinophils, and T-helper 2 lymphocytes. This results in increased responsiveness of the airways to such triggers as exercise, allergens, and air pollutants.

This chronic inflammation underlies the typical symptoms of asthma, which include intermittent wheezing, coughing, shortness of breath, and chest tightness.

Corticosteroids are the most effective treatment for asthma, and inhaled corticosteroids have become first-line treatment for children and adults with persistent symptoms.

Corticosteroids suppress the chronic airway inflammation in patients with asthma, and the molecular mechanisms involved are now being elucidated.

Physiologic Principles

Inflammation in asthma is characterized by the increased expression of multiple inflammatory genes, including those encoding for cytokines, chemokines, adhesion molecules, and inflammatory enzymes and receptors.

Increased expression of inflammatory genes is regulated by proinflammatory transcription factors, such as nuclear factor-κB and activator protein-1. These bind to and activate coactivator molecules, which then acetylate core histones and switch on gene transcription.

Corticosteroids suppress the multiple inflammatory genes that are activated in asthmatic airways by reversing histone acetylation of the activated inflammatory genes.

This mechanism acts by binding of the activated glucocorticoid receptors to coactivators and recruitment of histone deacetylases to the activated transcription complex.

Understanding how corticosteroids work in patients with asthma may help in designing novel corticosteroids with less systemic effects, as well as novel anti-inflammatory approaches.

These molecular mechanisms of action of corticosteroids may also help elucidate the molecular basis of chronic inflammation and why corticosteroids are ineffective in patients with steroid-resistant asthma and with chronic obstructive pulmonary disease.

Corticosteroids (or glucocorticosteroids) are widely used to treat various inflammatory and immune diseases. The most common use of corticosteroids today is in the treatment of asthma, and inhaled corticosteroids have become established as first-line treatment in adults and children with persistent asthma, the most common chronic inflammatory disease. Recent developments in understanding the fundamental mechanisms of gene transcription (see Glossary) have led to major advances in understanding the molecular mechanisms by which corticosteroids suppress inflammation. This may have important clinical implications, as it will lead to a better understanding of the inflammatory mechanisms of many diseases and may signal the future development of new anti-inflammatory treatments. The new understanding of these new molecular mechanisms also helps explain how corticosteroids switch off multiple inflammatory pathways; in addition, it provides insights into why corticosteroids fail to work in patients with steroid-resistant asthma and in patients with chronic obstructive pulmonary disease (COPD).

The Molecular Basis of Inflammation in Asthma

All patients with asthma have a specific pattern of inflammation in the airways that is characterized by degranulated mast cells, an infiltration of eosinophils, and an increased number of activated T-helper 2 cells (see Glossary) (1). It is believed that this specific pattern of inflammation underlies the clinical features of asthma, including intermittent wheezing, dyspnea, cough, and chest tightness. Suppression of this inflammation by corticosteroids con-

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REVIEW

A Review on the Safety and Efficacy of Inhaled Corticosteroids in the Management of Asthma

Qian Ye · Xiao-Ou He · Anthony D'Urzo

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ABSTRACT

Asthma is a chronic inflammatory disease characterized by symptoms of cough, dyspnea, chest tightness, and wheeze. Inhaled corticosteroids (ICS) have been recommended as initial therapy in the treatment of persistent asthma in all guidelines, as they have been shown to reduce morbidity and mortality. However, high-dose regimens and long-term use of ICS may be associated with a variety of side effects, similar to those observed with systemic corticosteroid therapy. These side effects include impaired growth in children, osteoporosis, fractures, glaucoma, cataracts, and skin thinning. The current recommendations on ICS use in asthma management will be reviewed in this article with a view to highlight treatment strategies that strike an optimal balance between safety and efficacy.

Keywords: Add on therapy; Airway inflammation; Asthma; Dose–response; Efficacy; Inhaled corticosteroids; Mechanism of action; Pathophysiology; Safety; Side effects

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INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by varying degrees of bronchoconstriction and airway hyperresponsiveness leading to classic symptoms of airway obstruction that is often reversible.

The first asthma management guidelines were published in the mid 1980s in Australia and New Zealand. Since then, the Global Initiative for Asthma (GINA), the National Asthma Education and Prevention Program (NAEPP), the Canadian Thoracic Society (CTS), and the British Thoracic Society guidelines have become available for implementation and dissemination [1].

Current treatment of asthma is aimed at reducing the severity of symptoms day-to-day and minimizing future risks including severe exacerbations, hospitalizations, and death. Inhaled corticosteroids (ICS) are the mainstay of controller therapy and are the standard of care in long-term asthma treatment. ICS has been

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Steroids: Pharmacology, Complications, and Practice Delivery Issues

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ABSTRACT

Background: Since their identification nearly 80 years ago, steroids have played a prominent role in the treatment of many disease states. Many of the clinical roles of steroids are related to their potent antiinflammatory and immune-modulating properties.

Methods: This review summarizes the basic pharmacology, complications, and practice delivery issues regarding steroids.

Results: Clinically relevant side effects of steroids are common and problematic. Side effects can occur at a wide range of doses and vary depending on the route of administration. The full spectrum of side effects can be present even in patients taking low doses.

Conclusions: Practitioners must be aware that these drugs might exacerbate a preexisting condition or present a new medical condition. Knowledge of the clinical implications of prescribing these agents is critical.

INTRODUCTION

Since their identification in 1935, steroids have served a wide range of uses. Initially, these isolates from adrenal glands were thought to be useful only in patients suffering from Addison disease.[1] Today, many of the clinical roles of steroids are related to their potent antiinflammatory and immune-modulating properties. Clinically relevant side effects of steroids are common and problematic, ranging from a minor case of acne to Cushing syndrome that can result in diabetes mellitus and potentially life-threatening heart disease if untreated.[2] Side effects can occur at a wide range of doses and vary depending on the route of administration.[1]

The term *steroid* applies to a wide range of molecules with varying physiological effects. More specifically, corticosteroids are a class of chemicals encompassing both laboratory-synthesized and naturally produced hormones. Glucocorticoids, in general, regulate metabolism and inflammation; mineralocorticoids regulate sodium and water levels. Corticosteroids fall along a spectrum from exclusively glucocorticoid effects to exclusively mineralocorticoid effects, and steroid compounds are selected based on their appropriateness for a given treatment. For example, although a compound may possess potent antiinflammatory properties, it may additionally have mineralocorticoid activity that adversely affects blood pressure.

CORTICOSTEROID METABOLISM AND CLINICAL ROLE

Although corticosteroid metabolism is complicated by enzyme induction, protein binding, molecular interconversion, and interaction with endogenous cortisol, corticosteroids are generally metabolized by the hepatic P450 system.[3] Direct application (eg, topical, intraarticular, inhaled, or epidural) of these agents to sites of inflammation bypasses the liver and its first-pass effect.

Chronic oral glucocorticoid use is common in patients with rheumatoid arthritis, chronic obstructive pulmonary disease, systemic lupus erythematosus, inflammatory bowel disease, and asthma.[4] Side effects of chronic use include bruising, muscle weakness, weight gain, skin changes, sleep disturbances, cataracts, and pathologic fractures.[4] Glucocorticoid administration can also have psychiatric side effects: mood disorders, anxiety, delirium, and panic

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Symposium on Steroid Therapy

Corticosteroid Physiology and Principles of Therapy

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ABSTRACT

The adrenal cortex secretes glucocorticoids (GC), mineralocorticoids (MC) and androgens. GC maintain homeostasis, MC regulate fluid and electrolyte balance and adrenal androgens contribute to development of secondary sexual characteristics. Pharmacologic GC therapy is frequently indicated in the pediatric age group. Besides having many important side effects, prolonged high dose systemic GC therapy has a suppressive effect on endogenous steroid production. Therefore, GC therapy should be withdrawn gradually and stopped based on assessment of hypothalamo-pituitary-adrenal (HPA) axis recovery. Patients with HPA axis suppression require physiological replacement of GC along with enhancement of doses during periods of stress. Due to its immunosuppressive effects, issues about safety and efficacy of live virus vaccines in patients receiving systemic high dose GC therapy must be borne in mind. **[Indian J Pediatr 2008; 75 (10) : 1039-1044]**
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Key words: *Corticosteroid; Hypothalamo-pituitary-adrenal axis; Replacement dose; Stress dose*

Corticosteroids (CS) are an important class of naturally occurring and synthetic steroid hormones that affect virtually every aspect of human physiology. They are a common part of our prescriptions, sometimes in physiological doses and sometimes for pharmacological therapy. CS therapy affects endogenous CS production and has a suppressive effect on hypothalamo-pituitary-adrenal (HPA) axis. This chapter deals with principles of endogenous steroidogenesis and CS therapy including actions of CS, agents used in CS therapy, dosing and withdrawal regimes, stress dosing and immunisation related issues.

The adrenal cortex and HPA axis

The adrenal cortex consists of three zones. The *zona glomerulosa*, located immediately beneath the capsule, synthesizes aldosterone, the most potent mineralocorticoid (MC) in humans. The *zona fasciculata* (middle zone) produces cortisol (hydrocortisone), the principle circulating glucocorticoid (GC). Adrenal androgens are secreted by both *zona fasciculata* and *zona reticularis* (innermost zone).

GC secretion is regulated by adrenocorticotrophic hormone (ACTH), produced in the anterior pituitary and released in secretory bursts throughout the day and night. ACTH production is in turn driven by corticotrophin releasing hormone (CRH) from the hypothalamus. Pulses of ACTH occur every 30-120 minutes. Varying amplitude of ACTH pulses leads to the normal diurnal rhythm of cortisol production. Plasma cortisol is highest in the early morning, low in the afternoon and evening, and lowest 1 or 2 hours after sleep begins. Cortisol has a negative feedback on ACTH and CRH production. Thus when GC production is impaired as in Addison disease, ACTH is elevated. Similarly, excess GC (either endogenous or exogenous) suppresses ACTH.

In contrast to the ACTH driven GC pathway, MC synthesis is regulated mainly by the renin-angiotensin system and by potassium levels in blood, with ACTH having only a short term effect. This is the reason why patients with primary adrenal insufficiency require both GC and MC for treatment, whereas hypopituitarism patients with ACTH deficiency require only GC and no MC replacement.

The mechanism of regulation of adrenal androgens is not completely understood. Adrenarche, the onset of adrenal secretion of dehydroepiandrosterone and androstenedione, is a maturational process and usually sets in prior to the onset of puberty.

Endogenous steroidogenesis

The substrate for steroid production is cholesterol. It is mobilised from the outer to the inner mitochondrial membrane (by the *steroidogenic acute regulatory* (StAR) protein), where it is converted to pregnenolone (Figure 1). ACTH regulation of StAR protein is the rate limiting step in adrenal steroidogenesis.

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Inhaled corticosteroids: potency, dose equivalence and therapeutic index

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Corticosteroid, dose equivalence, inhaled, potency, therapeutic index

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Glucocorticosteroids are a group of structurally related molecules that includes natural hormones and synthetic drugs with a wide range of anti-inflammatory potencies. For synthetic corticosteroid analogues it is commonly assumed that the therapeutic index cannot be improved by increasing their glucocorticoid receptor binding affinity. The validity of this assumption, particularly for inhaled corticosteroids, has not been fully explored. Inhaled corticosteroids exert their anti-inflammatory activity locally in the airways, and hence this can be dissociated from their potential to cause systemic adverse effects. The molecular structural features that increase glucocorticoid receptor binding affinity and selectivity drive topical anti-inflammatory activity. However, in addition, these structural modifications also result in physicochemical and pharmacokinetic changes that can enhance targeting to the airways and reduce systemic exposure. As a consequence, potency and therapeutic index can be correlated. However, this consideration is not reflected in asthma treatment guidelines that classify inhaled corticosteroid formulations as low-, mid- and high dose, and imbed a simple dose equivalence approach where potency is not considered to affect the therapeutic index. This article describes the relationship between potency and therapeutic index, and concludes that higher potency can potentially improve the therapeutic index. Therefore, both efficacy and safety should be considered when classifying inhaled corticosteroid regimens in terms of dose equivalence. The historical approach to dose equivalence in asthma treatment guidelines is not appropriate for the wider range of molecules, potencies and device/formulations now available. A more robust method is needed that incorporates pharmacological principles.

Introduction

Glucocorticosteroids are natural and synthetic analogues of the hormones secreted by the hypothalamic–anterior pituitary–adrenocortical (HPA) axis which have anti-inflammatory activity. It is a widely held assumption that the therapeutic index of synthetic glucocorticoids, generally termed corticosteroids, cannot be improved by increasing their potency via enhanced glucocorticoid receptor binding affinity. This is probably valid for systemically administered corticosteroids, unless selectivity for glucocorticoid receptors *vs.* nontarget receptors is greatly increased, as the efficacy and safety are both attributable to circulating drug concentrations and common receptor interactions [1]. However, a similar rationale is commonly adopted for inhaled corticosteroids, where potency is not considered to affect the topical efficacy to systemic activity ratio [2], with efficacy and potency differences being overcome by giving larger doses of the less potent drug [3].

There are several reasons why this rationale may not be valid for inhaled corticosteroids. First, they exert their anti-inflammatory activity at the site of action in the airways, which is not in equilibrium with the downstream systemic drug concentrations responsible for the unwanted systemic effects [4]. Secondly, it assumes that increasing inhaled corticosteroid potency is not associated with changes in other features of the molecule [5]. However, in reality, the molecular structural features that increase glucocorticoid receptor binding affinity and selectivity also result in physicochemical and pharmacokinetic changes that together may potentially enhance targeting to the airways and reduce systemic exposure.

Currently, there are eight inhaled corticosteroid molecules approved for clinical use that span a wide range of potency and other attributes. This article explores the relationship between inhaled corticosteroid potency and therapeutic index

Potency and molecular structure

Beclomethasone dipropionate (BDP) was introduced in 1972 as the first synthetic corticosteroid asthma controller medication administered via the inhaled route [6]. At the time, it was heralded as a major breakthrough that freed asthma sufferers from the fear of the adverse effects

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Corticosteroids

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Continuing Education Activity

Corticosteroids are drugs used in the management and treatment of almost all areas of medicine. This activity outlines the indications, action, and contraindications for corticosteroids as a valuable agent in managing numerous disorders. This activity will highlight the mechanism of action, adverse side effects profile, and other key factors (e.g., off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, relevant interactions) of corticosteroid usage.

Objectives:

- Describe the mechanism of action of corticosteroids.
- Summarize the potential adverse effects associated with corticosteroids.
- Review the toxicity profile of corticosteroids.
- Explain some interprofessional team strategies for improving care coordination and communication to advance the management of patients on corticosteroids and improve outcomes.

Access free multiple choice questions on this topic.

Indications

Since their discovery, corticosteroids have been used in almost all areas of medicine and by nearly every route.[1] Corticosteroids are synthetic analogs of the natural steroid hormones produced by the adrenal cortex and include glucocorticoids and mineralocorticoids. The synthetic hormones have varying degrees of glucocorticoid and mineralocorticoid properties. Glucocorticoids are predominantly involved in metabolism and have immunosuppressive, anti-inflammatory, and vasoconstrictive effects. While mineralocorticoids regulate electrolytes and water balance by affecting ion transport in the epithelial cells of the renal tubules.[2]

The term corticosteroids in practice, however, is generally used to refer to the glucocorticoid effect. Glucocorticoids are primary stress hormones that regulate a variety of physiologic processes and are essential for life.[3] Corticosteroids are among the most widely prescribed drug classes worldwide, with an estimated market of more than 10 billion USD per year.[4] An estimated one percent of the total adult population in the United Kingdom receives oral glucocorticoids at any one time.[5] Indications for corticosteroid therapy include hundreds of conditions. These indications can very generally group into infectious and inflammatory disorders, allergic and autoimmune diseases, shock, lowering of hypercalcemia, promotion of water excretion, treatment of pathologic hypoglycemia, suppression of excess adrenocortical secretion, prevention of graft rejection, neurological disorders, hematologic disorders, skin disorders, and corticosteroid replacement therapy.[6][7]

They have both endocrine and nonendocrine indications. Their endocrine role is often in the diagnosis of Cushing syndrome or the management of adrenal insufficiency and congenital adrenal hyperplasia. Their nonendocrine role regularly takes advantage of their potent anti-inflammatory and immunosuppressive effects to treat patients with a wide range of immunologic and inflammatory disorders. Corticosteroids are used at physiologic doses as replacement therapy in cases of adrenal insufficiency and supraphysiologic doses in treatments for anti-inflammatory and immunosuppressive effects.[2]

Review Article

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Corticosteroids: Clinical Pharmacology and Therapeutic Use

Stephen L. Swartz and Robert G. Dluhy

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Summary

The widespread use of corticosteroids in clinical practice emphasises the need for a thorough understanding of their metabolic effects. In general, the actions of corticosteroids on carbohydrate, protein, and lipid metabolism result in increased hepatic capacity for gluconeogenesis and enhanced catabolic actions upon muscle, skin, lymphoid, adipose and connective tissues. Because of the morbidity associated with steroid therapy, the clinician must carefully consider in each case the gains that can reasonably be expected from corticosteroid therapy versus the inevitable undesirable side effects of prolonged therapy. Thus, it is important to remember that the enhanced anti-inflammatory activity of the various synthetic analogues of cortisol is not dissociated from the expected catabolic actions of glucocorticoid hormones.

Replacement therapy with physiological doses of cortisol in primary or secondary adrenal insufficiency is intended to simulate the normal daily secretion of cortisol. Short term, high dose suppressive glucocorticoid therapy is indicated in the treatment of medical emergencies such as necrotising vasculitis, status asthmaticus and anaphylactic shock. With improvement of the underlying disorder, the steroid dosage can be rapidly tapered and then discontinued over a 2 to 3 day period. Long term, high dose suppressive therapy is often commonly used to treat certain diseases (see sections 4.7.2 and 4.7.3). In this setting, suppression of the hypothalamic-pituitary-adrenal axis may persist for as long as 9 to 12 months following steroid withdrawal if steroid doses are administered in the supraphysiological range for longer than 2 weeks. In general, higher doses, longer duration of usage, and frequent daily administration are all correlated with the severity of pituitary ACTH suppression.

When steroid therapy is to be withdrawn, gradual tapering of the dosage is necessary; the steroid dosage should also be given as a single morning dose if possible. Rapid or total withdrawal of the steroid therapy may be associated with exacerbation of the underlying disease or with a steroid withdrawal syndrome. An additional important point to remember in any withdrawal programme is that the steroid dosage should be appropriately increased for an exacerbation of the underlying disease or for intercurrent major stress. Alternate day therapy is recommended as a steroid maintenance programme for patients requiring high dose glucocorticoid therapy over a prolonged period of time. Thus, it is usually employed to maintain a therapeutic benefit which had previously been established by daily steroid treatment.

Complications resulting from corticosteroid therapy include: (1) proximal muscle weakness; (2) osteopenia; (3) unmasking of latent diabetes mellitus; (4) sodium retention and/or elevation of mean arterial blood pressure; (5) adverse psychiatric reactions; (6) development of glaucoma; and (7) reactivation of latent infections (such as tuberculosis).

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Corticosteroids-Mechanisms of Action in Health and Disease

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SYNOPSIS

Glucocorticoids are primary stress hormones that regulate a variety of physiologic processes and are essential for life. The actions of glucocorticoids are predominantly mediated through the classic glucocorticoid receptor (GR). Glucocorticoid receptors are expressed throughout the body, but there is considerable heterogeneity in glucocorticoid sensitivity and biological responses across tissues. Ligand-activated GR induces or represses the transcription of thousands of genes through direct binding to DNA response elements, physically associating with other transcription factors, or both. The conventional belief that glucocorticoids act through a single GR protein has changed dramatically with the discovery of a diverse collection of receptor isoforms. These GR variants are derived from a single gene by alternative splicing and alternative translation initiation mechanisms. Moreover, posttranslational modifications of these GR isoforms further expand the heterogeneity of glucocorticoid signaling. In this chapter, we provide an overview of the molecular mechanisms that regulate glucocorticoid actions, highlight the dynamic nature of hormone signaling and discuss the molecular properties of the GR isoforms.

Keywords

glucocorticoid; glucocorticoid receptor; glucocorticoid signaling; hypothalamic-pituitary-adrenal axis; isoforms; phosphorylation and polymorphism

INTRODUCTION

Corticosteroids are a class of steroid hormones released by the adrenal cortex, which includes glucocorticoids and mineralocorticoids[1]. However, the term "corticosteroids" is generally used to refer to glucocorticoids. Named for their effect in carbohydrate metabolism, glucocorticoids regulate diverse cellular functions including development, homeostasis, metabolism, cognition and inflammation[2]. Due to their profound immune-

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CONFLICT OF INTEREST STATEMENT
The authors declare that they have no relevant conflicts of interest.

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Clinical Reviews

Therapeutic Recommendations

Side Effects of Corticosteroid Therapy

Alan L. Buchman, M.D., M.S.P.H.

Abstract

Background: Corticosteroids have been used for the treatment of inflammatory bowel disease since the late 1940s. Upwards of 80% of patients may respond acutely to treatment with these medications, although 20% or more may be refractory and others become dependent on corticosteroid use to suppress disease activity. Side effects in the acute situation are relatively minor, although significant side effects (e.g., psychosis) have been encountered; the long-term use of corticosteroids is more problematic. This creates a milieu for the potential for serious and irreversible problems. These side effects are discussed in detail. The side effects from corticosteroids emulate from exogenous hypercortisolism, which is similar to the clinical syndrome of Cushing's disease. **Study:** PubMed search for years 1966–2000, author's personal manuscript/abstract files, and citations of known references. **Conclusion:** Short-term corticosteroid use is associated with generally mild side effects, including cutaneous effects, electrolyte abnormalities, hypertension, hyperglycemia, pancreatitis, hematologic, immunologic, and neuropsychologic effects, although occasionally, clinically significant side effects may occur. Long-term corticosteroid use may be associated with more serious sequale, including osteoporosis, aseptic joint necrosis, adrenal insufficiency, gastrointestinal, hepatic, and ophthalmologic effects, hyperlipidemia, growth suppression, and possible congenital malformations.

Key Words: Corticosteroids—Side effects.

SIDE EFFECTS ENCOUNTERED WITH SHORT-TERM USE OF CORTICOSTEROIDS

Cutaneous

Cutaneous manifestations of hypercortisolism include truncal obesity, acanthosis nigricans (a velvety, thickened, hyperpigmented plaque that usually occurs on the neck or in the axillary region), acne, ecchymoses after minor trauma, hyperpigmentation, hirsutism, petechia, and striae.[1,2] Corticosteroids may inhibit fibroblast growth and collagen synthesis by decreasing hydroxyproline production, which leads to decreased structural stability of connective tissue.[3] With the possible exception of striae, all symptoms are completely reversible upon discontinuation of corticosteroids.

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Hypokalemia

Hypokalemia is a well-recognized side effect of corticosteroid therapy and is probably related to the mineralocorticoid effect of hydrocortisone, prednisone, and prednisolone; dexamethasone has no mineralocorticoid effect. Hypokalemia may also occur (although rarely) with the use of topical (per rectum) corticosteroid use.[4]

Myopathy

Myopathy was first described in association with hypercorticalism in 1932 by Cushing.[5] There are two recognized forms: acute and chronic. Acute myopathy may in part be caused by hypokalemia, although corticosteroids (especially massive dosages) may have a direct affect on skeletal muscle. Both proximal and distal muscle weakness occur acutely, usually with an associated and significant elevation in serum creatinine phosphokinase, which is indicative of focal and diffuse muscle necrosis; rhabdomyolysis may result.[6] Severity of the myopathy correlates with the elevation in creatinine phosphokinase in the absence of renal failure. Type IIB fiber (fast twitch) atrophy also occurs. This may take between 6 weeks and several months to resolve, even after the discontinuation of corticosteroids.[7,8] In the more chronic form of myopathy, weakness is more insidious in onset and primarily involves proximal muscle groups, the creatinine phosphokinase is typically normal or only slightly elevated, and there is no predilection for type II muscle fibers, although focal and diffuse muscle necrosis may still be evident on biopsy. Although there is not a direct correlation with dosage, patients who receive small amounts of prednisone (i.e., ≤10 mg/d) are unlikely to develop myopathy. Muscle biopsy is recommended in patients who require long-term corticosteroid treatment that develop weakness during therapy.

Corticosteroids affect skeletal muscle directly by interference with oxidative phosphorylation, inhibition of protein synthesis, and impairment of muscle membrane excitability.[9–11] The impairment of muscle membrane excitability occurs primarily because amino acid uptake and the incorporation into proteins is decreased but also because the activity of myofibrillar proteinases is increased.[12] Of note is that type II fibers have more active protein synthesis than type I fibers and they have relatively little myofibrillar ATPase. Probably because an exercised muscle has the most

Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study

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ABSTRACT

OBJECTIVE

To determine the frequency of prescriptions for short term use of oral corticosteroids, and adverse events (sepsis, venous thromboembolism, fractures) associated with their use.

DESIGN

Retrospective cohort study and self controlled case series.

SETTING

Nationwide dataset of private insurance claims.

PARTICIPANTS

Adults aged 18 to 64 years who were continuously enrolled from 2012 to 2014.

MAIN OUTCOME MEASURES

Rates of short term use of oral corticosteroids defined as less than 30 days duration. Incidence rates of adverse events in corticosteroid users and non-users. Incidence rate ratios for adverse events within 30 day and 31-90 day risk periods after drug initiation.

RESULTS

Of 1 548 945 adults, 327 452 (21.1%) received at least one outpatient prescription for short term use of oral corticosteroids over the three year period. Use was more frequent among older patients, women, and white adults, with significant regional variation (all P<0.001). The most common indications for use were upper respiratory tract infections, spinal conditions, and allergies. Prescriptions were provided by a diverse range of specialties. Within 30 days of drug initiation, there was an increase in rates of sepsis (incidence rate ratio 5.30, 95% confidence interval 3.80 to 7.41), venous thromboembolism (3.33, 2.78 to 3.99), and fracture (1.87, 1.69 to 2.07), which diminished over the subsequent 31-90 days. The increased risk persisted at prednisone equivalent doses of less than 20 mg/day (incidence rate ratio 4.02 for sepsis, 3.61 for venous thromboembolism, and 1.83 for fracture; all P<0.001).

CONCLUSION

One in five American adults in a commercially insured plan were given prescriptions for short term use of oral corticosteroids during a three year period, with an associated increased risk of adverse events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Complications with chronic use of corticosteroids include a wide spectrum of effects on the cardiovascular, musculoskeletal, digestive, endocrine, ophthalmic, skin, and nervous systems

However, the potential risks associated with the use of short term oral corticosteroids and their overall use in a general population has not been fully characterized

WHAT THIS STUDY ADDS

This study of 1.5 million privately insured adults (18-64 years) in the US found that one in five patients in an outpatient setting used short term oral corticosteroid over a three year period (2012-14)

Within 30 days of corticosteroid initiation, the incidence of acute adverse events that result in major morbidity and mortality (sepsis, venous thromboembolism, fracture) increased by twofold, to fivefold above background rates

Greater attention to initiating prescriptions of these drugs and monitoring for adverse events may potentially improve patient safety

Introduction

Corticosteroids are powerful anti-inflammatory drugs that have been used to treat a variety of diseases for over seven decades, dating back to their introduction for rheumatoid arthritis in 1949.[1-5] A strong driver of corticosteroid use is the potent symptomatic relief they give many patients. Yet long term use of corticosteroids is generally avoided, given the risks of serious acute complications such as infection, venous thromboembolism, avascular necrosis, and fracture, as well as chronic diseases such as diabetes mellitus, hypertension, osteoporosis, and other features of iatrogenic Cushing's syndrome.[6-18] Indeed, corticosteroids are one of the most common reasons for admission to hospital for drug related adverse events,[19] and optimizing their long term use has been a major focus for clinical guidelines across diverse specialties for many years.[20-26]

In contrast with long term use, however, the risk of complications from short term use is much less understood, and evidence is generally insufficient to guide clinicians. In the outpatient setting, brief courses of oral corticosteroids are often used to treat conditions with clearly defined inflammatory pathophysiology for which there is clinical consensus for efficacy, such as asthma, chronic obstructive lung disease, rheumatoid arthritis, and inflammatory bowel disease.[27-31] Yet anecdotally corticosteroids are also used often in the short term to treat many other prevalent conditions where evidence is lacking, such as non-specific musculoskeletal pain and rashes. Despite such pervasive indications for use of oral corticosteroids, little is known about the prescribing patterns of short term use of these drugs in the general adult population, or their potential harm.

In this study we characterized short term use of oral corticosteroids in a contemporary outpatient population, and the risk of acute adverse events. We describe those who use oral corticosteroids in the short term in an outpatient setting and then report (absolute) incidence rates of adverse events in users and non-users. We chose three acute events listed as adverse

Chapter 6

66 Years of Corticosteroids in Dentistry: And We Are Still at a Cross Road?

Wei Cheong Ngeow, Daniel Lim and Nurhalim Ahmad

Additional information is available at the end of the chapter

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Abstract

Most of the corticosteroids prescribed in dentistry are for topical applications or short-term usage, rarely for its systemic effects or for long-term consumption, as in the treatment of some medical conditions. Among the various specialties in dentistry, oral and maxillofacial surgery, oral medicine and endodontics are the more frequent users of corticosteroids. Corticosteroids are used in oral and maxillofacial procedures to reduce associated post-operative inflammation. The most researched outcome on the use of corticosteroids in oral and maxillofacial surgery revolves around their impact to reduce post-operative pain, swelling and trismus. Topical corticosteroids, on the other hand, are effective in treating various oral mucosal lesions including oral ulcerations and oral presentations of auto-immune diseases. Corticosteroids are also used as part of the treatment of temporomandibular joint disorders. Intracanal placement of corticosteroids is used in endodontic treatment. This chapter reviews the use of corticosteroids in the three specialties of dentistry as mentioned.

Keywords: corticosteroids, dentistry, oral and maxillofacial surgery, oral medicine, endodontology

1. Introduction

Corticosteroids is one well-known anti-inflammatory group of drugs that is listed in the Dental' Practitioners' Formulary. Among the various specialties in dentistry, oral medicine, oral and maxillofacial surgery and endodontics are the more frequent users of corticosteroids. Most of the corticosteroids prescribed in dentistry are for topical applications or short-term usage, rarely for its systemic effects or for long-term consumption, as in the treatment of some medical conditions. Five years ago, a chapter entitled "The role of Corticosteroids in today's Oral and

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REVIEW

Recurrent Aphthous Stomatitis☆

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KEYWORDS
Recurrent aphthous stomatitis;
Aphthae;
Oral ulcers;
Periodic fever syndrome

Abstract Recurrent aphthous stomatitis is a chronic inflammatory disease of the oral mucosa. It is characterized by painful mouth ulcers that cannot be explained by an underlying disease. Recurrent oral mucosal ulcers require a proper differential diagnosis to rule out other possible causes before recurrent aphthous stomatitis is diagnosed. The condition is common, with prevalence rates ranging from 5% to 60% in different series. Its pathogenesis is unknown, but multiple factors are considered to play a part. There are no standardized treatments for this condition and none of the treatments are curative. The goal of any treatment should be to alleviate pain, reduce the duration of ulcers, and prevent recurrence.

PALABRAS CLAVE
Aftosis oral recidivante;
Afta;
Ulceras orales;
Síndrome periódico;
Mucosa oral

Aftosis oral recidivante

Resumen La aftosis oral recidivante es una enfermedad inflamatoria crónica de la mucosa oral. Se caracteriza por presentar úlceras dolorosas en la cavidad oral sin que se encuentre una enfermedad subyacente que lo justifique. Ante la aparición de úlceras recidivantes en la mucosa oral habrá que realizar un correcto diagnóstico diferencial y descartar otras causas antes de llegar al diagnóstico de aftosis oral recidivante. Se trata de una enfermedad frecuente, según la población estudiada se han documentado prevalencias entre el 5 hasta el 60%. Su patogenia es desconocida pero se considera multifactorial. El tratamiento no está estandarizado, y no hay un tratamiento curativo, se pretende disminuir el dolor durante el brote, acortar la duración del mismo y evitar la aparición de nuevas lesiones.

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Review Article

Recurrent aphthous stomatitis — Etiology, serum autoantibodies, anemia, hematinic deficiencies, and management

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KEYWORDS
Recurrent aphthous stomatitis;
Gastric parietal cell antibody;
Thyroglobulin antibody;
Thyroid microsomal antibody;
Hematinic deficiency

Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal diseases characterized by recurrent and painful ulcerations on the movable or nonkeratinized oral mucosae. Clinically, three types of RAS, namely minor, major, and herpetiform types, can be identified. RAS more commonly affects labial mucosa, buccal mucosa, and tongue. Previous studies indicate that RAS is a multifactorial T cell-mediated immune-dysregulated disease. Factors that modify the immunologic responses in RAS include genetic predisposition, viral and bacterial infections, food allergies, vitamin and microelement deficiencies, systemic diseases, hormonal imbalance, mechanical injuries, and stress. Our previous study found the presence of serum gastric parietal cell antibody, thyroglobulin antibody, and thyroid microsomal antibody in 13.0%, 19.4%, and 19.7% of 355 RAS patients, respectively. We also found anemia, serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia in 20.9%, 20.1%, 4.8%, 2.6%, and 7.7% of 273 RAS patients, respectively. Therefore, it is very important to examine the complete blood count, serum autoantibody, hematinic, and homocysteine levels in RAS patients before we start to offer treatments for RAS. Because RAS is an immunologically-mediated disease, topical and systemic corticosteroid therapies are the main treatments of choice for RAS.

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The diagnosis and management of recurrent aphthous stomatitis

A consensus approach

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ABSTRACT

Background. Recurrent aphthous stomatitis, or RAS, is a common oral disorder of uncertain etiopathogenesis for which symptomatic therapy only is available. This article reviews the current data on the etiopathogenesis, diagnosis and management of RAS in a primary care setting.

Methods. The authors reviewed publications on Medline from 1995 through 2000, the period since the last major reviews were published.

Results. RAS may have an immunogenetic background owing to cross-reactivity with *Streptococcus sanguis* or heat shock protein. Predisposing factors seen in a minority include haematinic (iron, folate or vitamin B12) deficiency, stress, food allergies and HIV infection. While topical corticosteroids remain the mainstay for therapy, a number of other immunomodulatory modalities now are available.

Conclusions. There is still no conclusive evidence relevant to the etiopathogenesis of RAS, and therefore therapy can attempt only to suppress symptoms rather than to address the basic issues of susceptibility and prevention.

Clinical Implications. In the majority of patients, symptomatic relief of RAS can be achieved with topical corticosteroids alone, with other immunomodulatory topical agents or by combination therapy.

ARTICLE 4

Recurrent aphthous stomatitis, or RAS, is a common condition in which recurring ovoid or round ulcers affect the oral mucosa. It is one of the most painful oral mucosal inflammatory ulcerative conditions and can cause pain on eating, swallowing and speaking.[1] This article is based on the outcome of a consensus conference between the American Academy of Oral Medicine and the European Association of Oral Medicine, held in Montreal, Canada, in 2001, and summarizes the current data on the etiopathogenesis, diagnosis and management in a primary dental care setting.

There is no conclusive evidence regarding the etiopathogenesis of recurrent aphthous stomatitis, so therapy can attempt only to suppress symptoms.

CLINICAL FEATURES OF RAS

The onset of RAS usually is during childhood, with a tendency for ulcers to diminish in frequency and severity with age.[2] In about 80 percent of patients with RAS, the condition develops before 30 years of age; onset in later years suggests a possibility of definable predisposing factors leading to RAS or that the ulceration is not simple RAS, but rather a part of a more complex disorder such as Behcet's syndrome.

A prodrome of localized burning or pain for 24 to 48 hours can precede the ulcers. The lesions are painful, clearly defined, shallow, round or oval, with a shallow necrotic center covered with a yellow-grayish pseudomembrane and surrounded by raised margins and erythematous haloes. The pain lasts for three to four days, at which point early epithelialization can occur.

Clinical presentations of RAS. RAS has three clinical presentations (Table 1).

Minor aphthae. Minor aphthae (also called Mikulicz's aphthae or mild aphthous ulcers) account for 75 to 85 percent of all cases of RAS.[2] Minor aphthae can involve

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REVIEW ARTICLE

Oral Lichen Planus–A Brief Review on Treatment Modalities

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ABSTRACT

Lichen planus is an autoimmune-mediated chronic inflammatory disease of unknown etiology, but studies have reported the role of cytotoxic T cells responsible for the disruption of basal keratinocytes and also causing the clinical symptoms. It is commonly seen in adults, with rare occurrence in children. It clinically manifests on the skin and oral mucosa, with skin lesions healing faster than the oral lesions. To obtain a diagnosis, a complete history and characteristic clinical features are usually sufficient for diagnosis, but there are certain other lesions like lichenoid reaction, contact sensitivity, white sponge nevus, pemphigoid and lupus erythematosus that show similar clinical characteristics, hence the need for histopathological evaluation using standard criteria given by Krutchkoff or World Health Organization (WHO). The treatment administered is always for eliminating symptoms and discomfort of the patients. A variety of pharmacological and natural alternatives have been used, along with frequent follow up visits in case of a tropic and erosive lichen planus. The purpose of this paper is to review the current trends in the management of oral lichen planus.

Keywords: Lichen planus, Management, Update.

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INTRODUCTION

Oral lichen planus (OLP) is a chronic mucocutaneous disease of multifactorial etiologies with Wilson first describing it in 1869. It was suggested by authors to an autoimmune disease triggered by antigens in the form of extrinsic or intrinsic factors that activate the lymphocytes and releases cytokines that are directed against the basilar keratinocytes leading to their apoptosis. It was seen to affect 0.5–1% of the worldwide population and 0.1–1.5% prevalence in India.[1]The condition affects the cutaneous or mucosal areas or both, where 50% of individuals with cutaneous lichen planus had oral mucosal lesions, and about 25% presented with, oral mucosal lesions alone.[2] It was seen most commonly in adults and had a female predilection.[3]

An OLP commonly affects the buccal mucosa, gingiva, and the tongue, with an uncommon presentation on the palate.[4] It is usually seen as multiple lesions, bilaterally present in the mouth persisting for a longer duration of up to 25 years in comparison to the cutaneous counterpart.[5,6] It shows a chronic course having periods of dormancy and flare-ups with spontaneous remissions rarely seen.[7]

Andreasen[2] divided oral lichen planus into six clinical types: reticular, plaque-like, papular, erosive, bullous, and atrophic types where erosive and atrophic types caused discomfort and painful symptoms. On clinical examination, in the absence of the reticular type which is easily identifiable, the other types of oral lichen planus requires histopathological evaluation for a definite diagnosis. This is done using WHO criteria (2003) for diagnosis of OLP, that includes clinical criteria's, histopathological criteria's and final differentiation of lichen planus from lichenoid lesions.[8]

An OLP is a disease with a potential for malignant transformation. It has been noted that the rate of malignant transformation has decreased from 5.9% in 1924 to 0.5–1.1% in 2017.[9] However, this possibility may be reduced by patient counseling, consumption of a healthy diet and avoiding carcinogens.[10] The standard protocol for the management of oral lichen planus includes symptomatic relief with no complete cure. Various alternatives have been applied in the management which suggests the inadequacy of any single drug to provide relief. The present article hereby provides an overview of different treatment modalities in the management and the advancements made in obtaining control over the symptoms of OLP.

The OLP could be symptomatic (erosive, atrophic and bullous types) or asymptomatic (reticular or plaque types). The symptomatic oral lichen planus can cause a burning sensation, severe pain, inability to speak and swallow, which is seen to be the chief complaint of the patient requiring symptomatic relief[11] while the asymptomatic forms do not require pharmacological interven-

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Review Article

Applications of corticosteroids in oral diseases – A narrative review

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ABSTRACT

Background: The anti-inflammatory and immunomodulatory properties of corticosteroids aids in the treatment of oral diseases both topically and systemically. Furthermore, its significance in medical emergencies like adrenal crisis and anaphylactic shock cannot be understated. **Aim:** The purpose of the current review article was to provide and simplify the application of steroids used in oral mucosal diseases. **Methods:** An online search was conducted using databases such as PubMed, Web of Science, Scopus, and Google Scholar to find articles with the terms "corticosteroids", "oral medicine", "recent advancements", "dental applications", "oral lichen planus", "oral submucous fibrosis", and "oral aphthous ulcers". **Results:** A total of 34 articles were included and analyzed for this review. **Conclusion:** The overall effectiveness of medications depends on knowledge of the illness process, accurate diagnosis, and periodic follow-up.

Key words: Corticosteroids, oral lichen planus, oral sub mucous fibrosis, recurrent aphthous stomatitis

INTRODUCTION

East Germany was the first to explore the use of testosterone on their Olympic weightlifters in the 1940s. Philip Hench, Edward Kendall, and Tadeus Reichstein received the Nobel Prize in medicine and physiology in 1950 for their "investigations of the hormones of the adrenal cortex."[1] Corticosteroids are well known for their actions by inhibiting the inflammatory process and its immunological effects since decades. This nature of steroids regulates the body's defense responses.[2] Normally, the adrenal gland produces 24–30 mg of cortisol per day and up to 300 mg when under stress. The body's circadian rhythm regulates the release of cortisol, which is also governed by a negative feedback process involving the pituitary, brain, and adrenal glands. Estrogens, androgens, progestogens, glucocorticoids, and mineralocorticoids are the several subtypes of steroid hormones. The two main corticosteroids in humans which are normally secreted are hydrocortisone in a daily dose of 10–20 mg/kg and aldosterone at 0.125 mg/day. The glucocorticoids, androgens, and mineralocorticoids are the three hormone families that the adrenal cortex produces. Corticosteroids have been used both topically and systemically in an array of oral diseases and conditions

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Nonsurgical Management of Temporomandibular Joint Arthropathy

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KEYWORDS

• TMJ • TMD • Arthopathy • Orofacial pain • Arthritis • Diagnosis • Management

KEY POINTS

- The management of a TMJ arthropathy is dependent on an accurate diagnosis that helps understand the etiology of the condition.
- There are many non-surgical treatment options available with proven efficacy, which can be initiated while patients complete the diagnostic work up of their TMJ arthropathies.
- The majority of patients with a TMJ arthropathy will have symptomatic relief with non-surgical treatment modalities, which often include a combination of patient education, occlusal appliance therapy, pharmacotherapy, physical therapy, and behavioral therapy.
- For patients with persistent symptoms of TMJ arthralgia or limited range of motion after completing conservative, non-surgical treatment, a surgical consultation is recommended for further evaluation and possible intervention.

CASE REPORT

A 24-year-old woman presented to the orofacial pain clinic with the chief complaint of jaw locking and pain. She stated that her symptoms began about 4 months prior during a visit with her primary care physician when she opened her mouth wide during evaluation of a sore throat and her jaw became locked in an open position. The open lock persisted for approximately 2 hours before she was seen by her dentist, who helped manually reposition her jaw. Following this initial locking episode, she developed a persistent, dull ache of her jaw, localized to her bilateral masseter and preauricular areas. The symptoms were constant but fluctuated in severity, with

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REVIEW

Management of pain in patients with temporomandibular disorder (TMD): challenges and solutions

This article was published in the following Dove Press journal:
Journal of Pain Research

Alfonso Gil-Martínez[1–3]
Alba Paris-Alemany[1–4]
Ibai López-de-Uralde-Villanueva[1–3]
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Abstract: Thanks to advances in neuroscience, biopsychosocial models for diagnostics and treatment (including physical, psychological, and pharmacological therapies) currently have more clinical support and scientific growth. At present, a conservative treatment approach prevails over surgery, given it is less aggressive and usually results in satisfactory clinical outcomes in mild–moderate temporomandibular disorder (TMD). The aim of this review is to evaluate the recent evidence, identify challenges, and propose solutions from a clinical point of view for patients with craniofacial pain and TMD. The treatment we propose is structured in a multimodal approach based on a biobehavioral approach that includes medical, physiotherapeutic, psychological, and dental treatments. We also propose a new biobehavioral model regarding pain perception and motor behavior for the diagnosis and treatment of patients with painful TMD.

Keywords: biobehavioral, review, temporomandibular disorders, biobehavioral orofacial pain, multimodal approach, motor behavior, disability

Introduction

According to health sciences definitions, temporomandibular disorder (TMD) comprises a variety of conditions affecting the anatomy and functional characteristics of the TM joint (TMJ). Factors contributing to TMD complexity are related to dentition, clenching, and other related systems that frequently provoke symptoms of muscular, articular, and periarticular pain.[1]

Orofacial pain is defined as a pain manifested in the face or oral cavity, including such disorders as TMD, which are a major cause of nonodontogenic orofacial pain.[2,3] TMD has considerable prevalence, with significant impact on physical and psychosocial factors.[2] Its prevalence has been reported to be between 3.7% and 12%, and is three to five times more frequent in women.[4] TMD also contributes to a high proportion of socioeconomic costs, which are usually associated with comorbidities, such as depression and other psychological factors.[5–7] Also, the loss of work and work productivity is a major issue to consider in TMD patients being treated early on, and it requires significant public education.

Before 2000

Although before the 1980s, malocclusion and other related factors were considered fundamental and key causes of TMD, during this decade authors began to publish critical articles on these subjects.[8] In current clinical practice, orthodontic treatments are still used to treat TMD; however, it was established in the 1990s that the role of

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ESSENTIAL DENTAL KNOWLEDGE

Pharmacotherapy in Temporomandibular Disorders: A Review

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ABSTRACT

Temporomandibular disorder (TMD) is a collective term that includes disorders of the temporomandibular joint (TMJ) and of the masticatory muscles and their associated structures. TMDs are characterized by pain, joint sounds and restricted mandibular movement, and drugs are widely used in the management of that pain. Pharmacological agents commonly used for the treatment of TMDs include non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, muscle relaxants, antidepressants, anticonvulsants and benzodiazepines. In this paper, we discuss these agents and the potential adverse drug reactions and interactions associated with their use.

Temporomandibular disorder (TMD) is a collective term used for a number of clinical problems that involve the masticatory muscle complex, the temporomandibular joint (TMJ) and associated structures. TMD is one of the most common disorders in the maxillofacial region. Signs and symptoms of TMD may include pain, impaired jaw function, malocclusion, deviation from the midline on opening or closing the jaw, limited range of motion, joint noises and locking.[1] Among other signs and symptoms, headaches and sleep disturbances can appear concomitantly.[2] This disorder is most prevalent in people aged 20–40 years.[3] Approximately 33% of the population have at least 1 TMD symptom, and 3.6–7.0% of the population have TMD with sufficient severity to seek treatment.[3] There is some evidence to suggest that anxiety, stress and other emotional disturbances exacerbate TMD.[4] As many as 75% of patients with TMD have a significant psychological abnormality.[5]

Most TMD symptoms resolve over time, but, for a significant number of patients, this may take a year or more.[3] Treatment is directed toward reducing pain and improving function. Many non-invasive therapies, such as self-care, physical therapy and appliance therapy, are commonly used for the treatment of TMD.[3] Pharmacological intervention has been used for many years, and the most effective pharmacological agents for the treatment of TMD include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, anxiolytics, muscle relaxants, antidepressants, anticonvulsants and benzodiazepines. However, we found only 1 relevant Cochrane study, which included 11 randomized controlled trials of pharmacotherapy for TMD.[6] In this article, we review the pharmacology and research supporting the use of a host of pharmacologic agents that have been prescribed for patients who have TMD. The decision to select any of

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REVIEW ARTICLE Open Access

Reported concepts for the treatment modalities and pain management of temporomandibular disorders

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Abstract

Background: Pain related to temporomandibular disorders (TMD) is a common problem in modern societies. The aim of the article is to present the concepts of TMD pain clinical management.

Methods: A survey was performed using the PubMed, SCOPUS and CINAHL databases for documents published between 1994 and 2014. The following search keywords were selected using MeSH terms of the National Library of Medicine in combination: TMD pain, TMD, TMJ, TMJ disorders, occlusal splint, TMD physiotherapy, TMJ rheumatoid disorders and TMJ surgery. Original articles and review papers which presented the clinical relevance and practical validity regarding the possibility of application in TMD management have been included. Authors have excluded articles without outstanding practical aspect and evidence-based background. A first selection was carried out by reviewing titles and abstracts of all articles found according to the criteria. After that the full texts of potentially suitable articles were assessed. In line with these criteria, among 11467 results the writers have included 66 papers.

Results: The most commonly reported conservative treatments are massage therapy and individually fabricated occlusal splints. In addition to massage, other popular methods include manual therapy and taping, warming/cooling of aching joints, and light and laser therapy. Drugs are also commonly used. In the most severe cases of the temporomandibular joint degeneration, surgical restoration of the joint is sometimes applied.

Conclusions: The authors concluded that conservative treatment including counselling, exercises, occlusal splint therapy, massage, manual therapy and others should be considered as a first choice therapy for TMD pain because of their low risk of side effects. In the case of severe acute pain or chronic pain resulting from serious disorders, inflammation and/or degeneration pharmacotherapy, minimally invasive and invasive procedures should be considered.

Keywords: Temporomandibular disorders, Temporomandibular joint disorders, Facial pain, Masticatory muscle pain

Introduction

Currently, temporomandibular disorders (TMD) refer to the causes responsible for the impaired function of the temporomandibular joints (TMJ) and the associated neuro-muscular system, which may provoke TMD-related pain [1]. The term TMD is not a diagnosis but rather a broad term that contains a number of disease entities, such as pain in masticatory muscles and temporomandibular joints, headache, disturbances in jaw movements and sounds in joints while opening and closing the mouth. The causes of these diseases/symptoms are numerous and include trauma, systemic, iatrogenic, occlusal and mental health disorders [2–7]. Today, mental health plays a dominating role in the pathogenesis of TMD [8, 9]. The neuromuscular system responsible for chewing function has a high potential to adapt to changing conditions. Only when the compensatory capabilities of the masticatory- and the neuromuscular system are overstretched dysfunction occurs resulting in clinical symptoms and manifests as pain, severe clicking, or limited mobility of the mandible, forcing the patient to seek help.

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Pharmacologic Management of Temporomandibular Disorders

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The pharmacologic management of pain related to temporomandibular disorders (TMDs) should ideally be driven by therapeutic efficacy and safety established in one or more well-controlled randomized clinical trials [1]. For the US Food and Drug Administration (FDA) approval of new analgesic agents, this typically implies the use of a double-blind, placebo-controlled design in which medication is randomly allocated to study patients. Evidence supporting the analgesic efficacy and tolerability of nonsteroidal anti-inflammatory drugs (NSAIDs) and combinations of aspirin, acetaminophen, or ibuprofen with opiates for relieving acute postsurgical dental pain is abundant throughout the scientific literature and these studies have often been significant parts of successful new drug applications submitted to the FDA in obtaining general acute pain indications for these agents [2–10].

As illustrated in Fig. 1 [11], although there are theoretically numerous targets for relieving TMD-associated pains, evidence-based literature clearly establishing the efficacy and safety of any of these drugs in the TMD population is limited at best [12]. Often decisions regarding the use, type, and dose of medication to use in these patients are made from uncontrolled clinical reports claiming efficacy, poorly controlled clinical trials, and well-controlled clinical trials in a completely different pain population, such as those having acute postsurgical dental pain, arthritic pain, chronic lower back pain, and neuropathic pain.

The goal of prescribing drugs in the management of chronic TMD pain is not to cure the disorder but is aimed at helping patients manage their discomfort or dysfunction for extended periods of time often in concert with other therapies (ie, physical therapy, appliance therapy) or until a more definitive treatment (ie, surgery), or simply time itself, either eliminates the pain or reduces it to a level at which it is not overly burdensome to the patient [13]. The remainder of this article is devoted to pharmacologic agents that have been used in the treatment of TMD with a special emphasis on clinical trials that either support or refute their efficacy.

Nonsteroidal anti-inflammatory drugs

NSAIDs can be grouped as being nonselective COX inhibitors (that is, they inhibit cyclooxygenase-1 [COX-1] at least as readily if not more so than they inhibit COX-2), semiselective COX-2 inhibitors (meaning they are two- to threefold more selective in blocking COX-2 over COX-1), or highly selective COX-2 inhibitors (meaning they are sevenfold or more selective in their COX-2 blocking activity) (Box 1) [14]. Although chronic use of highly selective COX-2 inhibitors (because they spare COX-1 cytoprotective prostaglandins) have been associated with a significantly lower incidence of serious gastrointestinal (GI) events, including ulcerations, perforations, and

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Review Article

The use of pharmacologic agents in the management of temporomandibular joint disorder

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Abstract: Temporomandibular joint disorders (TMD) are oro-facial pain conditions that originate from either intraarticular or extraarticular related pathology. Following an accurate diagnosis, there are a variety of non-surgical and surgical management options available. The aim of this article is to review the available pharmacologic agents for the management of extraarticular and intraarticular TMD. These medical options are often first line and are combined with other non-surgical modalities. There are multiple pharmacologic options utilized to treat TMD, from non-steroidal anti-inflammatory drugs (NSAIDs) to muscle relaxants and steroids. Many of these medications are used synergistically to provide symptom improvement and prevention of persistent disease. This paper will discuss the use of the following classes of medications used to manage TMD: NSAIDs, corticosteroids, narcotics, muscle relaxants, anticonvulsants, anxiolytics, and topical therapy. Despite their extensive clinical use, there remains insufficient evidence to recommend one therapy over another. This is due to the lack of systematic reviews and meta-analyses in the current literature. For this reason, there remains a need for a randomized control trial with clear pre-pharmacotherapy diagnoses, blinding, and research objectives. NSAIDs have been recommended as first line therapy for intraarticular disorders with the addition of muscle relaxants if there is a muscle component. Several of the other medications discussed are often patient specific or given secondarily when previous therapy has failed. It is critical to recognize systemic patient factors when prescribing any of these medications to avoid side effects and drug-drug interactions.

Keywords: Temporomandibular joint disorder (TMD); medical therapy; non-surgical management

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Introduction

Temporomandibular joint disorders (TMD) encompass a wide variety of diseases that affect the temporomandibular joint itself (intraarticular) and/or the surrounding musculature (extraarticular) (1-3). Some of the studied etiologic factors associated with TMD include a history of trauma, systemic related inflammatory conditions, and psychosocial issues (4). Symptoms consist of pain, joint sounds, limited mouth opening, and/or tenderness in the preauricular region (5). These conditions affect females more frequently than males and are most common between the ages of 20–40 (5). TMD has been estimated to affect between 3–12% of the general population (6).

As with any disease, an accurate diagnosis must be made prior to treatment. The Diagnostic Criteria for TMD

Original Article

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Use of etoricoxib and dexamethasone for postoperative pain prevention and control in mucogingival surgery - A randomized parallel double-blind clinical trial

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Abstract

Aim: To compare the use of etoricoxib and dexamethasone for postoperative pain prevention and control after mucogingival surgery. **Methods:** Fifty-eight patients with indication for mucogingival surgery took part in this randomized parallel double-blind clinical trial. They were divided into three groups (G): G1 – placebo 1 h before surgery; G2 – 8 mg dexamethasone 1 h before surgery; G3 – 90 mg etoricoxib 1 h before surgery. Pain intensity was assessed in donor and recipient sites separately using the 101-point numerical rating scale NRS – 101, every hour for the first 8 h after surgery and three times a day on the following 3 days. **Results:** there was a statistically significant difference in the postoperative pain intensity in the donor site between G1 and G3 after 1 h, 2 h, 3 h, 7 h, 8 h and on the second day – in the evening after 32 h; between G1 and G2 after 2 h and 3 h, and between G2 and G3 only after the first hour. Pain intensity in the recipient site was statistically significant between G1 and G3 after 1 and 2 h ($p<0.05$). In addition, there was a lower ingestion of rescue medication in G2 and in G3 than in G1 ($p=0.002$). **Conclusions:** the use of a pre-emptive single dose of etoricoxib or dexamethasone may be considered an effective protocol for postoperative pain prevention and control after mucogingival surgery.

Keywords: analgesia; pain, postoperative; surgery, oral.

Introduction

Periodontal surgical procedures, such as soft tissue grafts (mucogingival surgeries) or those involving bone resection may have a significant expectation of pain and edema for patients after surgery [1,2].

Soft tissue grafts are autogenous grafts from masticatory mucosa completely detached from their original site and placed in a prepared recipient bed[3]. The so called "free gingival graft" has been widely used to increase the width of the keratinised tissue and to treat gingival recessions[4,5]. The predictability of root coverage procedures was dramatically increased by the use of subepithelial connective tissue graft techniques[6].

Pain following periodontal surgery results from a cascade of events during the inflammatory response triggered by a surgical tissue trauma. To prevent or minimize these effects preemptive analgesia has been used, which consists in the

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Comparison Between Dexamethasone and Ibuprofen for Postoperative Pain Prevention and Control After Surgical Implant Placement: A Double-Masked, Parallel-Group, Placebo-Controlled Randomized Clinical Trial

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Background: Postoperative pain is a potential adverse side effect of oral surgeries, and attempts should be made to prevent or minimize it. This study compares efficacy of preemptive ibuprofen and dexamethasone protocols for pain prevention or control after surgical implant placement.

Methods: This prospective, double-masked, parallel-group, placebo-controlled, randomized clinical trial included 117 patients with planned dental implant placement. Patients were assigned to receive one of three different protocols: 1) 600 mg ibuprofen 1 hour before surgery and another 600 mg 6 hours after the first dose; 2) 4 mg dexamethasone 1 hour before surgery and another 4 mg 6 hours after the first dose; or 3) placebo. Rescue medication (1,000 mg acetaminophen) was made available to each patient, and they were instructed to take it as necessary. Pain intensity was evaluated via a 101-point numeric rating scale and a visual analog scale, and discomfort was evaluated using a four-point verbal rating scale hourly for the first 8 hours after surgery and three times daily for the following 3 days.

Results: Ibuprofen and dexamethasone significantly reduced pain (Kruskal–Wallis; $P < 0.05$) up to 3 days after surgery and discomfort ($P < 0.05$) up to 2 days after surgery compared with placebo treatment. Both treatments reduced the number of painkillers taken and increased time before the first painkiller was taken ($P < 0.01$).

Conclusion: Steroidal dexamethasone is as effective as non-steroidal ibuprofen for preventing or controlling postoperative pain and discomfort after surgical implant placement. *J Periodontol 2017;88:69-77.*

KEY WORDS

Dental implants; dexamethasone; double-blind method; ibuprofen; pain; pain measurement.

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The use of topical corticosteroides in the treatment of oral lichen planus in Spain: A national survey

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Abstract

Background: Explore the treatment of oral lichen planus with topical corticosteroids by the healthcare professionals in Spain.

Material and Methods: A questionnaire targeted health professionals who treat OLP, in particular maxillofacial surgeons, dermatologist and dentist. The dissemination of the questionnaires was conducted through professional associations and dental and medical societies. The questionnaire was previously evaluated by means of a cognitive pre-test procedure to ensure that the questions were opportune and appropriate, understandable and acceptable among the professionals.

Results: Of the 890 questionnaires sent a total of 190 questionnaires were answered by 90 dentists, 60 dermatol gists and 40 by maxillofacial surgeons. The most frequent treatment was 0.1%triamcinolone acetonide in orobase 3 times a day. The effectiveness of the topical corticosteroid treatment was 6.68 (SD= 2.26) in a scale of 1 to 10. The 30% of the dentists and 10.49% of maxillofacial surgeons combined treatment with other drugs. The most frequent one (80%) was nystatin (100,000 IU per millimetre). Dermatologists did not use other treatments in co bination with corticosteroids

Conclusions: There is a need for national guidelines in treatment for oral lichen planus (treatment criteria, drug, dose, treatment time and method of application of corticosteroid) that can be applied by all professionals who treat this disease.

***Key words:** Oral lichen planus, topical corticosteroids, triamcinolone acetonide, questionnaire.*

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Original article

Evaluation of efficacy of peri-operative administration of hydrocortisone and dexamethasone in prevention of post-operative complications in oral and maxillofacial surgeries

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ABSTRACT

Objective: To evaluate the role of intra-operative hydrocortisone and post-operative dexamethasone on reducing post-operative complications following major surgeries involving oral cavity as in oral and maxillofacial surgeries performed under general anesthesia.
Methodology: The post-surgical stress induces changes in metabolic and endocrinal pathways and also results in activation of inflammatory pathways. Post-operative administration of steroids helps in blocking all the stages of inflammatory process. This study was conducted on a group of 20 patients undergoing major surgical procedures. These patients were administered a combination of intra-operative hydrocortisone and post-operative dexamethasone therapy. Efficacy of these drugs in reducing post-operative complications was evaluated, using parameters like post-operative pain, number of analgesic injections, edema, sore throat, nausea and vomiting.
Results: A 70% mean reduction in pain was seen on 2nd post-operative day and a drastic 97% pain reduction was noted on 4th post-operative day. An overall 12 mm reduction in swelling was noted over the span of 4 days of hospital stay. Post-operative administration of dexamethasone helped in reduction of sore throat up to 95% on 2nd post-operative day. A remarkable finding noted was, that, none of the patients developed nausea and vomiting post-operatively.

Abbreviations: ASA, american Society of Anesthesiologists; Hr, hour; PO, post-operative; P, pain; S, swelling; ST, sore throat; DI, number of diclofenac injections administered; STDEV, standard deviation; F, f-factor; P value, probability; df, degree of freedom; mm, millimeters; mg, milligrams.

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ORIGINAL ARTICLE
ASTHMA

Oral corticosteroid prescription patterns for asthma in France, Germany, Italy and the UK

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This study gives a real-world snapshot of oral corticosteroid (OCS) use in western Europe, by highlighting an opportunity to shift towards corticosteroid-sparing therapies or safer alternatives that mitigate the risk of OCS-associated adverse effects http://bit.ly/3cB8kk8

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ABSTRACT Oral corticosteroids (OCS) are used to manage asthma exacerbations and severe, uncontrolled asthma, but OCS use is associated with adverse effects. We aimed to describe the patterns of OCS use in the real-world management of patients with asthma in western Europe.

We used electronic medical records from databases in France, Germany, Italy and the United Kingdom from July 2011 through February 2018. Patients aged ⩾12 years with an asthma diagnosis, at least one non-OCS asthma medication within ±6 months of diagnosis, and available data ⩾6 months prior to and ⩾90 days after cohort entry were included. High OCS use was defined as OCS ⩾450 mg prescribed in a 90-day window during follow-up. Baseline characteristics and OCS use during follow-up were described overall and by OCS use status.

Of 702 685 patients with asthma, 14–44% were OCS users and 6–9% were high OCS users at some point during follow-up. Annual prevalence of high OCS use across all countries was ~3%. High OCS users had a mean of between one and three annual OCS prescriptions, with an average daily OCS dosage of 1.3–2.2 mg. For patients who continued to meet the high-use definition, daily OCS exposure was generally stable at 5.5–7.5 mg for ⩾2 years, increasing the risk of adverse effects.

Our study demonstrates that OCS use is relatively common across the four studied European countries. Data from this study may provide decisive clinical insights to inform primary care physicians and specialists involved in the management of severe, uncontrolled asthma.

Data underlying the findings described in this manuscript may be requested in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagroup-dt.pharmacm.com/DT/Home

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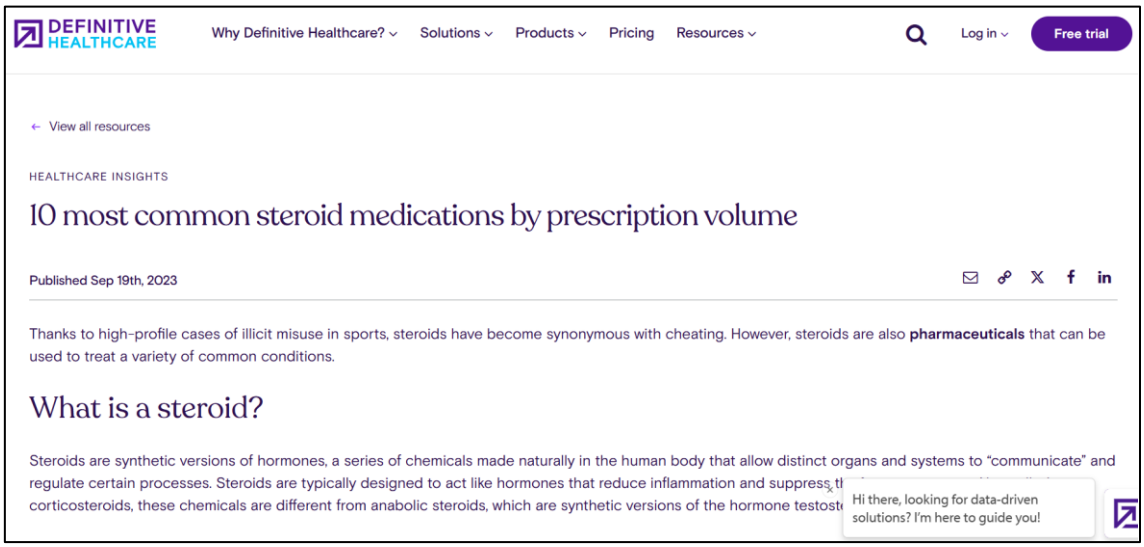
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HEALTHCARE INSIGHTS
10 most common steroid medications by prescription volume
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Thanks to high-profile cases of illicit misuse in sports, steroids have become synonymous with cheating. However, steroids are also pharmaceuticals that can be used to treat a variety of common conditions.
What is a steroid?
Steroids are synthetic versions of hormones, a series of chemicals made naturally in the human body that allow distinct organs and systems to "communicate" and regulate certain processes. Steroids are typically designed to act like hormones that reduce inflammation and suppress
corticosteroids, these chemicals are different from anabolic steroids, which are synthetic versions of the hormone testost
Hi there, looking for data-driven solutions? I'm here to guide you!

Review Article

Application of Corticosteroids in Dentistry: A Review

Souptik Satpathi[1], Yogesh V. Rathod[2], Kamil N. Rajpari[3], Rohit Kandlikar[4], Y. Rajiv Kumar[5], Arti Gachake[6], Pratik Surana[7]

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ABSTRACT

Corticosteroids are crucial in dentistry for their anti-inflammatory and immunosuppressive properties, aiding in managing conditions such as oral lichen planus, recurrent aphthous stomatitis, and post-operative inflammation. By inhibiting pro-inflammatory mediators and immune cell activity, they offer significant symptomatic relief and promote healing. However, potential systemic and local side effects necessitate cautious application. This article explores the use of corticosteroids in routine dental practice.

Keywords: *Corticosteroids, dental application, dentistry*

Introduction

Steroids are endogenous substances synthesized by the human body and are among the most frequently prescribed pharmaceuticals in both medical and dental practices. Commonly utilized steroids include hydrocortisone, dexamethasone, methylprednisolone, and prednisolone. It is imperative to consider the history of corticosteroid use in dental patients before initiating any dental procedures. The prevalent issue with steroids

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Review Article

Corticosteroids in Dentistry

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Abstract

Steroids are one of the widely used drugs in dentistry. These are immunosuppressive agents. The reason for its use is its anti-inflammatory as well as immunosuppressive properties. Corticosteroids have revolutionized the management of several disabling conditions, but its use in term of dosage is inappropriate. The current review highlights its uses, contraindications, side-effects as well as a guideline for its use in dentistry.

Key words: Adrenal insufficiency, anti-inflammatory, corticosteroid, immunosuppressive

Steroids are the substances that are naturally produced in our body. These are one of the widely prescribed drugs in both medical and dental sciences. Commonly used steroids are hydrocortisone, dexamethasone, methyl prednisolone, prednisolone, etc. Dental patients with a history of corticosteroid use may require special consideration before receiving any dental treatment. Currently, the misuse of steroids is its overdosage as it is prescribed even before minor dental procedures. The risks associated with excess glucocorticoid administration are relatively small.[1] These includes impaired electrolyte balance and hypertension.[2] The current review emphasizes on the uses and guidelines of use of corticosteroid in dentistry.

Uses and Effects of Steroid in Dentistry

Endodontics

Steroids have shown its effects on root resorption.[3] In intracanal medicaments such as ledermix paste which reduces pulpal inflammation as well as root resorption. Further, zinc oxide eugenol along with steroids is also used as root canal sealer. In cavity liners, when steroid is mixed with chloramphenicol and gum caphor to reduce mainly postoperative thermal sensitivity.

Orthodontics

It is reported that the upon treatment with hydrocortisone at a dose of 10 mg/kg/day for 7 days on rats followed by observed for 20 h; the teeth showed a lower amount of tooth movement. Hence, it is essential that the patients are reviewed of their prior history of corticosteroids use.[4]

Oral surgery

Steroids are used after oral surgical procedures to limit postoperative inflammation. In 1974, Hooley and Hohl elaborated the use of steroid in the prevention of postoperative edema. He further concluded that topical use of steroid helps to prevent ulceration and excoriation which results during retraction during surgery over the lips and corners of the mouth.[1]

Oral medicine

In the treatment of various diseases as summarized.

Oral submucous fibrosis

Topical application of steroid applied over ulcerative or painful mucosa. The anti-inflammatory property of steroid shows a direct healing action on the mucosal patch.[5]

Oral lichen planus

A gingival tray can also be used to deliver 0.05% clobetasol propionate with 100,000 IU/ml of nystatin in orabase. Around 3–5 min application of this mixture daily appears to be effective in controlling erosive lichen planus.[6]

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Review Article

Systemic and Topical Steroids in the Management of Oral Mucosal Lesions

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Abstract

From the time of its introduction in the 1040s, glucocorticoids have provided a panacea for many diseases. The therapeutic benefit of corticosteroids lies in their anti-inflammatory and immunosuppressive properties which makes them highly effective in the management of oral mucosal lesions. This article aims to present to the clinician, the plethora of options available as steroid therapy and enables one to choose based on the underlying disease and the properties of the drug.

Keywords: *Glucocorticoids, oral mucosal lesions, topical steroids*

Introduction

Glucocorticoids have revolutionized the management of several diseases since they were introduced more than half a century ago. Corticosteroids include the endogenous steroid hormones produced from the adrenal cortex as well as those synthetically produced for pharmacotherapeutics.[1] While the therapeutic benefits of steroids are many, their adverse reactions, as well as long-term effects, must be noted while treating a patient. Topical and systemic steroids find use in the management of various mucosal diseases such as lichen planus, pemphigus, oral submucous fibrosis, and so on. Conversely, the dental clinician might on occasions, be confronted with a patient who is on long-term steroid therapy for systemic diseases such as arthritis or lupus. The management of the dental condition of such patients should be planned keeping in mind, the effect of long-term steroid therapy and its bearing on the dental treatment.

Pharmacology of Steroids

The adrenal cortex secretes glucocorticoids, mineralocorticoids (collectively referred to as corticosteroids), and sex hormones. The first two are synthesized from cholesterol.

Corticosteroids are classified as hydrocortisone, prednisone, triamcinolone, dexamethasone, clobetasol, and mometasone.

Glucocorticoids influence the metabolism of lipids, carbohydrates, proteins, calcium, and electrolytes. While the physiologic and metabolic effects of corticosteroids are many, the pharmacological utility mainly lies in its anti-inflammatory and immunosuppressive effects. Glucocorticoids suppress all types of inflammation and allergic reactions. Glucocorticoids bring about these effects by inhibition of white blood cell function, stabilization of lysozyme membrane, inhibit plasminogen activation, and reduce the synthesis of inflammatory mediators such as prostaglandins and leukotrienes.

Glucocorticoids may be administered systemically (oral and parenteral) as well as topically. They are metabolized in the liver and following conjugation are excreted through the urine. The metabolism of synthetic steroids is slower and hence their action is prolonged.

Systemic and topical steroids find application in a number of inflammatory and immune mediated mucosal conditions. We have discussed the role of them in some of the commonly encountered mucosal conditions.

Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis (RAS) is perhaps one of the most commonly encountered painful mucosal conditions. RAS is usually preceded by localized burning sensation in the area of concern a day or two before ulceration. The ulcers themselves are painful, superficial,

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