

STEROIDS IN THE TREATMENT OF CHRONIC DISEASES

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Received: 11 April 2019, Revised and Accepted: 24 May 2019

ABSTRACT

Since their identification, which was almost 80 years ago, steroids have played a prominent role in the treatment of many disease states such as chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, and inflammatory bowel disease. Many of the clinical roles of steroids are related to their potent anti-inflammatory and immune-modulating properties. Numerous skin diseases are successfully treated with systemic steroids. Corticosteroids, though they are lifesaving drugs, produce adverse reactions which may be mild or life threatening. Steroids have diverse effects on various systems of the body. Therefore, educational interventions among physician, patients, as well as students should be carried out to further enhance rational drug use. The purpose of this review was to identify the most commonly prescribed steroids and their side effects, basic pharmacology, complications, as well as the assessment of patient knowledge about the use of steroids in tertiary care teaching hospitals.

Keywords: Corticosteroids, Disease, Rational, Side effects, Steroids.

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INTRODUCTION

Steroids such as corticosteroids as well as androgenic steroids have a wide range of application in immunological, pulmonary, oncological, inflammatory, and dermatological diseases. Traditional teaching suggests that corticosteroids should be avoided during acute infectious episodes for fear of compromising the immune response [1].

The term steroid is relevant to a wide range of molecules showing varying physiological effects [2]. In respiratory, corticosteroids are used to treat acute exacerbations of chronic obstructive pulmonary disease (COPD) as well as uncontrolled asthma. They are also used in the treatment of hypersensitivity pneumonitis and immune-mediated vasculitis [3]. Anabolic steroids are used by athletes and bodybuilders to enhance their performance. Anabolic steroids history can be traced before the term steroid was even used as early as the 1930s. A synthetic form of testosterone (a male hormone) created by a team of scientist in the 1930s which helped to treat men who were unable to produce enough of the hormones for normal development, growth, and sexual functioning [4]. Initially, anabolic steroids were used by bodybuilders, but due to its positive effects, it became widely used in other sports also such as football, hockey, swimming, volleyball, wrestling, soccer, and cycling [5]. The misuse of anabolic steroids started in 1954 Olympics by professional athletes when Russian weightlifters were given testosterone [6].

Corticosteroids and their biologically active synthetic derivatives differ in their metabolic (glucocorticoid) and electrolyte-regulating (mineralocorticoid) activities.

Since their discovery in the 1940s, corticosteroids have become one of the most widely used and effective treatments for various inflammatory and autoimmune disorders. They are used as replacement therapy in adrenal insufficiency (at physiologic doses) as well as in suprathysiologic doses for the management of various dermatologic, ophthalmologic, rheumatologic, pulmonary, hematologic, and gastrointestinal (GI) disorders. In the field of respiratory, systemic corticosteroids are used for the treatment of acute exacerbations of COPD and severe, uncontrolled asthma, as well as for inflammatory parenchymal lung diseases such as hypersensitivity pneumonitis and immune-mediated vasculitis [7].

Inappropriate use of corticosteroids may lead to over or under treatment [8], worsening of conditions, or eventually therapy failure. Patients may refuse to take corticosteroids because they fear their unwanted, documented side effects (e.g., hyperglycemia, osteoporosis, weight gain, etc.) [9]. According to the American College of Clinical Pharmacy, the clinical pharmacist has an important role to play in patient education and promotion of patient adherence [10].

Hence, the clinical pharmacist's intervention has a positive impact in identifying and managing chronic diseases among patients.

This review focuses on the classification and functions of steroids and risks associated with their supplementation in chronic diseases. The purpose of this review was to identify the most commonly prescribed steroids in chronic diseases and their side effects, basic pharmacology, complications, as well as the assessment of patient knowledge about the use of steroids in tertiary care teaching hospitals.

CLASSIFICATION OF STEROIDS

There are two different types of steroids present in the body. The first group is corticosteroids and the second group is androgenic/anabolic steroid [11].

Adrenal cortex

Three groups of hormones are produced by adrenal cortex. These hormones are synthesized from cholesterol in the adrenal glands and gonads. Glucocorticoids, mineralocorticoids, and androgens (sex hormones) hormones are referred to as corticosteroids (adrenocorticoids) [12].

Glucocorticoids

Glucocorticoids are further classified on the basis of duration of action as follows:

- Short-acting glucocorticoids
- Intermediate-acting glucocorticoids
- Long-acting glucocorticoids.

The stimulation of adrenocorticotrophic hormone from the anterior pituitary secretes glucocorticoids and it is also secreted by stress. The main glucocorticoids include cortisol and corticosterone. Cortisol

is synthesized from cholesterol in reticularis and zona fasciculata of adrenal cortex [12]. Cortisol helps in the regulation of many metabolic processes such as synthesis of glucose from amino acids and fatty acids and in liver glycogen deposition [13].

The functions of glucocorticoids include:

- Glycogenesis promotion
- Gluconeogenesis promotion
- Decrease in protein synthesis
- In adipose tissue increased lipolysis
- Increased reabsorption of sodium and water from the renal tubules [12].

Glucocorticoids are more commonly prescribed for their anti-inflammatory and immunosuppressive properties [11].

Mineralocorticoids

Mineralocorticoids primarily act on the kidney, where they cause sodium and water retention and active excretion of potassium and protons. The primary mineralocorticoid is aldosterone, but other endogenous hormones such as progesterone and deoxycorticosterone have mineralocorticoid function. Aldosterone is synthesized exclusively in the zona glomerulosa region of the adrenal cortex. The production of aldosterone is influenced by sodium level in blood.

The main function includes:

- Control reabsorption of sodium by the renal tubules
- Potassium excretion [12].

Androgens/anabolic steroids

Anabolicsteroids are man-made or synthetic modification of testosterone which is a male sex hormone. These compounds are collectively known as anabolic/androgenic steroids. The term "Androgenic" means male sex characteristics and "Anabolic" means muscle building. Anabolic androgenic steroids (AASs) can be administered in different forms such as oral, intramuscular injection, parenteral, and transdermal [14]. Anabolic steroids are of two types, i.e., 17 alpha alkyl derivatives (e.g., oxandrolone, oxymetholone, and fluoxymesterone) and 17-beta ester derivatives (e.g., testosterone cypionate, testosterone enanthate, and nandrolone decanoate). Nandrolone phenpropionate was one of the first anabolic steroids used by professional athletes as a doping agent in 1960 [15-17].

The main function includes:

- Endogenous androgen is responsible for secondary sex characteristics
- Growth and development of male sex organs [18,19].

CORTICOSTEROIDS: SYNTHESIS, SECRETION, AND BIOAVAILABILITY

Corticosteroids consist of glucocorticoids and mineralocorticoids which are steroid hormones, synthesized, and released by the adrenal gland in response to physiological changes and stress [20]. Glucocorticoids, when released from the adrenal gland into the blood circulation, access target tissues to regulate physiologic processes such as metabolism, skeletal growth, cardiovascular function, and reproduction and immune function. Glucocorticoids play the physiological and pharmacological functions which are mediated by the intracellular glucocorticoid receptor (GR). The GR consists of three fundamental domains: An N terminal transactivation domain, a central deoxyribonucleic acid (DNA)-binding domain, and a C-terminal ligand-binding domain [21]. Mineralocorticoids such as aldosterone help in the regulation of sodium concentration in the body [22,23].

GLUCOCORTICOID: PHYSIOLOGICAL EFFECT

Metabolism

Glucocorticoid such as cortisol helps in the regulation of carbohydrate, nucleic acid, lipid, and protein metabolism. The process of gluconeogenesis by the liver is stimulated by cortisol which results in

increased concentration of blood glucose level [24-26]. In the metabolic system, cortisol is involved in the reduction of protein stores which is stored in all body cells, except for liver. The main reason for this is increased catabolism of protein already in the cell and decreased protein synthesis [24,25,27].

Anti-inflammatory effects

A large amount of cortisol shows anti-inflammatory effects. It stabilizes lysosome membrane and decreases the release of lysozymes which causes inflammation and results in a decrease in capillary permeability preventing loss of plasma proteins into tissues [24-26,28].

Bone and calcium metabolism

Glucocorticoids inhibit the function of osteoblast which results in osteopenia and osteoporosis which is the characteristic of the excess level of glucocorticoids [24,25].

Blood pressure control

Blood pressure increased by glucocorticoids involves a variety of mechanisms which includes action on kidney and vasculature. The sensitivity to pressor agents such as angiotensin-2 and catecholamines is increased in the vascular smooth muscle, while the endothelial dilation mediated by nitric oxide is reduced [24,25,28].

Central nervous system and mood

While observing the patients clinically with glucocorticoid excess and deficiency reveals that the brain is an important target for glucocorticoids with euphoria, apathy, depression, lethargy, and psychosis are being important manifestations [24,26].

Developmental changes

Plasma cortisol is required in the last trimester of pregnancy in the progression of a variety of systems that are important in extrauterine life for the survival of the fetus. These systems involve maturation of various enzymes in the liver, pulmonary surfactant production [24,25].

Gut

The risk of developing peptic ulcer disease is increased by chronic administration of glucocorticoids and in patients with glucocorticoid excess, pancreatitis with fat necrosis is observed [24-26].

MECHANISM OF ACTION OF STEROIDS

Corticosteroids after entering into the cell bind to cytosolic receptors which are responsible for transportation of steroids into the nucleus. The steroid receptor complex binds to glucocorticoid response elements or mineralocorticoid-specific elements and alters gene expression [29].

Glucocorticoids

Glucocorticoid hormones show anti-inflammatory and immunosuppressive effects. Its mechanism involves a decline in antibody production and a decrease in white blood cells count such as a number of lymphocytes, basophils, and eosinophils which ultimately decrease the number of T-lymphocytes. This results in the gradual destruction of lymphoid tissue which leads to inhibition of normal immune response. The Primary effect of glucocorticoids are mentioned in (Table 1). The major immunosuppressive effect of glucocorticoids appears to be the modulation of the production of cytokines through

Table 1: Primary effect of glucocorticoids [31]

Anti-inflammatory: Inhibits inflammation by blocking the action of inflammatory mediators or by inducing anti-inflammatory mediator
Immunosuppressive: Directly affects T-lymphocytes and suppress delayed hypersensitivity reactions
Antiproliferative: Inhibition of DNA synthesis and epidermal cell turnover
Vasoconstrictive: Inhibits histamine action and other vasoconstrictive mediators DNA deoxyribonucleic acid

DNA: Deoxyribonucleic acid

inhibition of nuclear factor B expression and nuclear translocation. The cytokines are released from immunocompetent cells which mediate both the phases of inflammation, i.e., acute and chronic and then involve in controlling the immune response. Glucocorticoids also show antiallergic properties [30].

Mineralocorticoids

Renin, an enzyme secreted by kidney cells when there occurs a reduction in renal blood flow. As a result, the angiotensinogen (produced by the liver) is converted into angiotensin which stimulates aldosterone production by the adrenal cortex. Aldosterone further leads to reabsorption of sodium and water and excretion of potassium by the kidneys. This results in increase in blood volume and blood flow through the kidneys, suppressing the production of renin and secretion of aldosterone [12].

Androgens

Androgens bind to a specific nuclear receptor in a target cell. In muscle and liver, testosterone acts as active ligand, but in other tissues, it must be metabolized to dihydrotestosterone (DHT) derivatives. Testosterone is converted to DHT by enzyme 5-alpha-reductase after diffusing into the cells of seminal vesicles, prostate, epididymis, and skin. After that, it binds to the receptor. Testosterone is biotransformed to estradiol in the brain. The synthesis of specific ribonucleic acids (RNAs) and proteins is stimulated by the hormone/receptor complex which binds to DNA [32].

STEROIDS ARE PRESCRIBED IN CHRONIC DISEASES

The commonly prescribed steroids in chronic diseases and their side effects are mentioned in (Table 2).

Chronic obstructive pulmonary disease

COPD is a multidimensional disease with a variety of intermediate and clinical phenotypes [33]. It is estimated that COPD will become the third most common cause of death worldwide by 2030 [34-36]. The Global Initiative for Chronic Obstructive Lung Disease defined COPD as "a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airway and the lung to noxious particles or gases. Exacerbations and comorbidities

contribute to the overall severity in individual patient" [37]. The pulmonary injury involves three stages, i.e., initiation (due to exposure to cigarette smoking, pollutants, and infectious agents), progression, and consolidation [33]. Symptoms including breathlessness decreased the quality of life (QOL) and loss of lung function become worst with acute exacerbations of COPD [38,39]. COPD is associated with chronic bronchitis and emphysema. The British Medical Research Council defined chronic bronchitis as "daily productive cough for at least 3 consecutive months for more than 2 successive years" [40]. The treatment of COPD includes smoking cessation and pulmonary rehabilitation. Besides, this other treatment consists of bronchodilators in the early stage and oxygen in the late stage. Short courses of systemic corticosteroids often along with antibiotics have been used since decades to treat inflammation and exacerbations. However, their side effects made them unsuitable to treat long-term stable COPD. In the early 1980s, inhaled corticosteroids were given to the patient diagnosed with asthma as well as COPD in combination with long-acting β -agonist. The inhaled form of corticosteroids proved to be highly effective in the treatment of COPD and asthma [41].

Asthma

Asthma is a respiratory condition which consists of increased airway hyperresponsiveness and increased episodes of obstruction and inflammation of airway and tissue remodeling [42]. It is observed that the prevalence of asthma has been increased rapidly over the past few decades and it is estimated that there are 334 million sufferers of asthma worldwide. The disease is expected to develop over the next 15-20 years [43,44]. Asthma is characterized by recurrent episodes of cough, wheezing, and breathlessness which can be resolved after using bronchodilator medication [45]. Corticosteroid was first used in 1956 to treat acute asthma exacerbation. Corticosteroids such as prednisone that have less mineralocorticoid activity and dexamethasone that have no mineralocorticoid activity became more attractive therapies to treat asthma. In 1972, Clark discovered the effect of inhaled beclomethasone in the treatment of asthma with fewer side effects than systemic steroids [46]. Inhaled corticosteroids are the most commonly used treatment for asthma which can suppress the characteristic inflammation in airways [47].

Table 2: Commonly prescribed steroids in chronic diseases

Generic name	Trade name	Dosage	Side effects, risks
COPD			
Prednisolone [58]	Orapred, Pediapred	30-40 mg	Acne, weight gain, increased appetite, menstrual period changes, mood changes
Prednisone [59]	Deltasone	30-40 mg	Loss of appetite, increased sweating, weakness, abdominal pain
Budesonide	Pulmicort	400-1000 μ g/day	Pneumonia, cataract, diabetes, glaucoma
Salbutamol	Proventil, Ventolin	Neb - 2.5-5 mg [60,61]	Shaking of arms and feet, irregular heartbeat, sleep disturbance, skin rash, and spotting
Ipratropium bromide	Atrovent	Neb - 0.5 mg [60,61]	Flu-like symptoms, nervousness, dry mouth, headache
Terbutaline	Terbulin	Neb - 5-10 mg	Tremor, nervousness, palpitation, dizziness, headache
Asthma			
Salbutamol [62]	Proventil, Ventolin	Neb - 2.5 mg	Shaking of arms and feet, irregular heartbeat, sleep disturbance, skin rash, and spotting
Methyl prednisolone	Medrol	80 mg/day	Upset stomach, vomiting, depression
Hydrocortisone	Enzone	400 mg/day	Redness, swelling, bruising, joint pain, itching
RA			
Prednisone	Deltasone, Sterapred	5-10 mg	Weight gain, increased blood sugar, high blood pressure
Methyl prednisolone	Depo-Medrol, Medrol	40-80 mg per ml [54,63]	High prevalence of fractures, adrenal insufficiency, lowered bone mineral density
Prednisolone	Orapred, Pediapred	2.5-15 mg	Increased susceptibility of infection, cataract formation, cutaneous atrophy, increased risk of fracture [64,65]
Breast cancer			
NPP [66]	Durabolin	25-50 mg/ml	Acne, increased hair growth, voice changes [67]
Nandrolone decanoate	Deca-Durabolin	25-50 mg	Acne, increased hair growth, voice changes, increased sexual desire

COPD: Chronic obstructive pulmonary disease, RA: Rheumatoid arthritis, NPP: Nandrolone phenylpropionate

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease which affects nearly 1% population all over the world [48]. It is characterized by inflammation of synovial and destruction of a joint which can cause severe disability if left untreated [49]. It mainly affects the small joints of hands and feet. It is a chronic inflammatory disease which causes pain, swelling, and stiffness. The disease has no cure yet. Symptomatic treatment can be given to the patients suffering from RA which can increase the QOL. Treatment includes disease-modifying anti-rheumatic drugs, nonsteroidal anti-inflammatory drugs, and low-dose steroids [50-52]. Glucocorticoids have the ability to reduce signs and symptoms in inflammatory disorders; therefore, they are widely used to treat RA [53]. Prednisone is an important drug which is used to treat different kinds of inflammatory conditions including RA [54].

Breast cancer

Breast cancer is the type of cancer that originates from breast tissues, mostly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Breast cancer is life threatening and found to be the most common cause of cancer in women. Worldwide, breast cancer is the fifth most common cause of cancer death and comprises 10.4% of all cancer incidences in women. The possibility of breast cancer is 100 times more in women than in men. Cancer cells have similar DNA and RNA (but not identical) to the cells of the organism from which they are originated [55]. AASs are commonly prescribed in the management of various pathological conditions including breast cancer, hereditary angioedema, renal insufficiency, and endometriosis [56]. The hormonal therapy for breast cancer includes tamoxifen, toremifene, and fulvestrant [57].

Adverse drug effects of steroid supplementation

Long-term effect

These effects include – osteoporosis, fractures, osteonecrosis, weight gain, hyperglycemia, cataract, glaucoma, cardiovascular disease, dyslipidemia, myopathy, psychiatric and cognitive disturbance, immunosuppression, and growth and adrenal suppression also observed in children, increased risk of infections, decrease in bone density, ulcers/GI bleeding, thin skin, bruise easily, and slower healing of wounds [68,69].

Short-term effect

These effects includes – skin rash, swelling, hot flush, abdominal discomfort, upper respiratory tract infections, spinal conditions, allergies, acne, sepsis, venous thromboembolism, insomnia and sleep disturbances, gastric irritation, sodium and fluid retention, increased appetite and weight gain, and mood changes – agitation and emotional lability [70,71].

COMMON SIDE EFFECTS OF STEROIDS

Steroids induced osteoporosis

The most common side effect with long-term use of glucocorticoid is bone loss [72]. However, the most significant effect of glucocorticoids in bone is an inhibition of bone formation [73-77]. Patient receiving high dose of glucocorticoid is at greater risk of developing bone loss as compared to patient taking lower dose of the drug. Thus, glucocorticoid-induced bone loss is dose dependent [78-81]. The treatment of glucocorticoid-induced bone loss includes decreasing the dose of glucocorticoid, calcium and Vitamin D supplementation, and pharmacologic therapy to increase bone density and prevent further bone loss [82]. The dose of glucocorticoid and duration of glucocorticoid therapy should be as low as possible because even low dose of glucocorticoid therapy can decrease bone mineral density [83].

Steroids induced hyperglycemia

Steroids are considered to be the main cause of drug-induced hyperglycemia [84]. The mechanism includes their interference with signaling cascades in muscle cells, which leads to reduction in insulin-mediated glucose uptake and synthesis of glycogen [85,86]. Due to

variations in dose of steroids and the scheme used, the hyperglycemia approach should always be individualized [87]. A complete evaluation of the degree of glucose intolerance, the patient condition, the degree of hyperglycemia, the dose, frequency, and mechanism of corticosteroid compound must be made to derive the best therapeutic outcome and determine the best treatment approach in each patient [88].

Steroids induced weight gain

Another side effect with long-term (≥ 3 months) use of corticosteroids includes weight gain [89] with prolonged use of prednisone (1.7–5.8 kg), prednisolone (1.5–4.4 kg), and cortisone (1.5–8.4 kg). These drugs are associated with significant weight gain [90-95]. There exists considerable variability in the amount of weight gain that patient will experience while taking corticosteroids [96]. However, very few alternatives are available for corticosteroids. The change in treatment regimen can be helpful in decreasing the incidence of weight gain in patients. Prednisone can be given in alternate day dosing schedule as it can also promote weight loss and reduce weight gain [97].

Gastrointestinal disease

GI side effects include candidiasis, pancreatitis, peptic ulcer disease, and GI hemorrhage. Glucocorticoid has shown to increase risk of peptic ulceration and GI bleeding, this effect could be due to concomitant use of nonsteroidal anti-inflammatory drugs [98-100]. Glucocorticoid users have shown another GI complication, i.e., acute pancreatitis [101]. However, glucocorticoid use cannot be considered as etiological agent in causing acute pancreatitis which is shown by recent study [102].

Cardiovascular disease and dyslipidemia

Glucocorticoid uses are known to cause higher cardiovascular risk, including hypertension, hyperglycemia, and obesity. Myopathy generally occurs over several weeks to months of glucocorticoid use. Proximal muscle weakness and atrophy in both the lower and upper extremities are typically present in patients [103,104].

ROLE OF PHARMACIST'S COUNSELING

The management programs of various diseases are usually fulfilled in a hospital setting and by physicians. However, community pharmacist holds their expertise on various medication and interaction with the patients regarding counseling and prescription refill. Therefore, they could also contribute their effective role in the management of diseases. They could assist asthma and COPD patients to maintain their condition and to decrease disease complications. A pharmacist could provide suitable information about medications and the proper use of inhalers. They could also ask the patients about their understanding toward disease and medications, explaining the importance of inhaled corticosteroids, provide knowledge to the patient regarding potential side effects of inhaled corticosteroids, and facilitate medication adherence [105-108]. The effect of pharmacist care on asthma patients has been investigated only by a few well-designed studies [109-114]. Community pharmacies can provide an effective platform for cost-effective treatment and health-related QOL in COPD [115-118]. The abuse of topical corticosteroid (TC) has now become a global issue [119,120]. Pharmacists are the key to address the problem of TC abuse due to a lack of patient awareness of TC use, especially in India. This problem arises because, as compared to qualified specialist, patients have easy access to the pharmacist in the pharmacy [121,122].

DISCUSSION

Corticosteroids, though they are lifesaving drugs, produce adverse reactions which may be mild or life threatening. Steroids have diverse effects on various systems of the body. Therefore, educational interventions among physician, patients, as well as students should be carried to further enhance rational drug use. Community pharmacist holds their expertise on various medication and interaction with the patients regarding counseling and prescription refill. Therefore, they could also contribute their effective role in the management of diseases.

Hence, establishing standard guidelines for prescribers for treating any acute and chronic diseases, where steroids necessary is highly warranted.

CONCLUSION

Corticosteroids are widely used in the treatment of various autoimmune and inflammatory diseases. In this article, we have focused on chronic diseases, in which steroids are commonly prescribed. Despite the benefits of these agents, their long-term use is highly associated with potentially serious adverse effects affecting the GI tract, central nervous system, endocrine, musculoskeletal, and cardiovascular system. The effects of steroid use can vary widely, and the full spectrum of side effects can be present even in patients taking low doses.

Most of the side effects can be minimized through careful patient monitoring, instructions regarding the proper use of inhalers, following preventive measures including the use of lowest effective dose and lower potency agents required to treat various disease conditions.

Strategies regarding lifestyle modification should be advised to the patient to improve their QOL.

The clinical pharmacist's intervention has a positive impact on identifying and managing chronic diseases among patients. Such intervention decreases patient's fear and increases compliance with corticosteroid treatment plan. Education of the general public through media programs and the introduction of continuing medical education programs for medical, paramedical personnel, and pharmacists are probably the most important steps to be taken to create awareness of the hazards of misuse of corticosteroids.

ACKNOWLEDGMENT

I am highly indebted to MM College of Pharmacy and Maharishi Markandeshwar (Deemed to be University) University management for the valuable guidance and constant supervision for supporting to complete this review.

CONFLICTS OF INTEREST

The author declares that we did not have the conflicts of interest for collecting the information of compiling this article and also for the paper publication.

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