Review Article

Usage of Corticosteroids as Therapeutic Agents in Diseases

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Abstract

Corticosteroids are class of human-made or synthetic drugs used in almost every medical specialty. They lower inflammation in the body by reducing the production of certain chemicals. At higher doses, corticosteroids also reduce immune system activity. Corticosteroids are commonly prescribed for a variety of indications due to the wide range of effects on the human body. Although they exhibit many therapeutic uses, corticosteroids are, unfortunately, known for their many dose—and duration—dependent toxicities. The purpose of this review is to explore indications for corticosteroid use, mechanism of action, review the toxicity of corticosteroids, and adverse effects and their management.

Keywords: Corticosteroids, immune system, inflammation

Introduction

Corticosteroids are class of steroid hormones that are produced in the adrenal cortex of vertebrates, as well as the synthetic analogues of these hormones. Two main classes of corticosteroids, glucocorticoids and mineralocorticoids, are involved in a wide range of physiological processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.[1]

Some common naturally occurring steroid hormones are cortisol (C21H30O5), corticosterone (C21H30O4), cortisone (C21H28O5), and aldosterone (C21H28O5). (Note that cortisone and aldosterone are isomers.) The main corticosteroids produced by the adrenal cortex are cortisol and aldosterone.[2] 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, are 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. 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.[3] 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.[4]

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Anti-inflammatory Action of Corticosteroids

The anti-inflammatory action of corticosteroids is complex. At a cellular level, they cause redistribution of granulocytes, resulting in increased circulating granulocytes and reduced tissue pools. They also cause lymphopenia. The significance of these phenomena in relation to the anti-inflammatory activity of steroids is unknown. The most obvious pharmacological effects of corticosteroids are seen on blood vessels. They cause adrenergically mediated vasoconstriction and non-competitive antagonism of vasodilation due to prostaglandin E and bradykinin.[5]

Prostaglandin formation is inhibited by corticosteroids but whether this is due to effect on enzymic synthesis or release is uncertain. Corticosteroids stabilize the lysosomal membrane preventing release of lysosomal enzymes *in vitro* but the significance of this invidious debatable. Corticosteroids differ from almost all other anti-inflammatory drugs in that they are capable of inhibiting virtually all components of inflammation. It is proposed to deal with the anti-inflammatory action of corticosteroids on three interrelated components of the inflammatory response: (1) inflammatory cells; (2) blood vessels; (3) release or formation of mediators.[6] Before embarking on this scheme, it is worth considering some general features common to most inflammatory responses.

The response to injury is bimodal. There is an initial transitory increase in vasoactivity which soon dwindles. It is soon followed by gradual rise to a sustained plateau vasodilation or increased permeability. The delayed phase of reaction finally dwindles after about 24 h or more. The biphasic reaction can be identified clinically although it is often overlooked. In the skin an immediate transitory erythematous phase occurs after short wavelength UV irradiation to be followed by characteristic delayed "sunburn" erythema.[7] Much effort has gone into the identification of mediators which bring about this dual response. However, the natural history of most inflammatory responses to injury leads to spontaneous remission. It may well be that the pharmacological and cellular mechanisms involved in the natural termination of inflammation are just as important in terms of understanding the pathology and therapy of inflammation as the mechanisms involved in the production.[8]

The initial phase of inflammatory response is due to release histamine from tissue mast cell. Experiments with cytotoxic polymorphonuclear depleting agent (Spector and Willoughby, 1968) suggest that polymorphs, if involved, may you play only a minor part in the delayed response because granulopenic animals show a normal delayed response.[9] The interactions of the mediators of the delayed reaction are probably very complex. The E prostaglandins (PGE) and the F prostaglandins (PGF), both of which are present in the delayed inflammatory response, act in opposition to each other, PGE causing vasodilatation and PGF causing vasoconstriction. The spontaneous resolution of inflammation could well be a result of an increase in the proportion of F relative to E.[9]

At the same time PGE enhances the inflammation-producing potentiation of pharmacological actions of histamine and bradykinin. Thus PGE, in doses which alone do not cause wealing, will amplify wealing due to histamine or bradykinin.[10] Synergism seems to be an important factor in the pharmacology of delayed inflammation. PGE has a further action on secretion of histamine. PGE causes inhibition of histamine secretion by mast cells via a negative feedback mechanism. The feedback inhibition is probably dependent upon activation of the adenyl cyclase cyclic adenosine monophosphate mechanism of the mast cell via prostaglandin-specific adenylcyclase receptors. It seems clear that inflammation is the result of complex interaction among several different mediators.[11]

The Relationship of the Anti-inflammatory Action of Corticosteroids to Cellular Changes in Inflammation

In man, neutrophilia occurs 24 h after a systemic dose of prednisolone. This seems to be related to a diminution of the marginal pool of neutrophils, especially in the lungs, which in turn is related to reduced granulocyte or possibly endothelial stickiness.[12] Whether the anti- inflammatory action of prednisone may be related, at least in part, to diminution of the local population of polymorphs in an inflammatory lesion seems to be uncertain. It has been suggested that at least in some laboratory animal models, neutrophils had no more than a minor role in delayed inflammation. There is also evidence listed by Ward and Engel (1966) that steroids in therapeutic concentrations can inhibit neutrophil chemotaxis.[13] Lymphopenia occurs after a single dose of prednisolone and this involves both B and T lymphocytes. The response of the remaining T lymphocytes to antigen and concanavalin A is impaired but both numbers and reactivity return to normal within 24 h. The mechanism for steroid-induced lymphopenia is uncertain. Lymphocyto lysis seems unlikely in the view of the rapid return of the peripheral blood lymphocyte count to normal levels. Alternatively the lowered counts may be a result of redistribution of lymphocytes between blood and bone marrow. There is also some *in vitro* and *in vivo* evidence suggesting that corticosteroids in high dosage interfere with phagocytosis by macrophages.[14] Most of the anti-inflammatory and immunosuppressive actions of glucocorticoids are attributable either directly or indirectly to the transcriptional effects of glucocorticoid receptor agonism which alters transcription of numerous genes in leukocytes, both up and down. Although expression of mineralocorticoid receptor, which binds glucocorticoids with high affinity in the absence of 11β-hydroxysteroid

dehydrogenase type 2 (11β-HSD2), has been reported in immune cells which do not normally express 11β-HSD2, it appears of little consequence to the anti-inflammatory effects of glucocorticoids, and may even have pro-inflammatory effects.[15,16] It should also be noted that some anti-inflammatory effects of glucocorticoids are apparent within minutes and a number are independent of the transcriptional effects of glucocorticoid receptor. Notably, glucocorticoids repress transcription of many genes-encoding pro-inflammatory cytokines and chemokines, cell adhesion molecules and key enzymes involved in the initiation and/or maintenance of the host inflammatory response.[17] Many of these genes are commonly over-expressed during chronic non-resolving inflammation. Intriguingly, recent data have shown that whereas glucocorticoid administration 1 h following endotoxin (lipopolysaccharide, LPS) challenge is immunosuppressive, administration of the same glucocorticoid dose before LPS challenge augments immune responses. This was true in both the brain and the liver, raising the possibility that chronic hypothalamic–pituitary–adrenal axis activation (as may occur during chronic inflammation for example) exacerbates inflammation in the brain and elsewhere.[18]

Until recently, it was widely believed that the repressive, anti-inflammatory effects of glucocorticoids were dependent on the ability of glucocorticoid receptor to inhibit the activity of crucial transcriptional regulators of pro-inflammatory genes, including NF-κB and AP-1, by a mechanism termed "transrepression." This contrasted with the metabolic actions of glucocorticoids which require gene activation by glucocorticoid receptor. This view has recently been revised, with the discovery that key anti-inflammatory actions of glucocorticoids are brought about through gene activation.[19]

What Are Corticosteroids Therapeutic Indications?

As a replacement therapy

- Adrenocortical insufficiency (Addison disease)
- Congenital adrenal hyperplasia

Systemic symptomatic treatment

Acute

- Allergic reactions and anaphylactic shock (vasoconstrictive effects)
- Asthma (bronchodilatory effects)
- Antiemetic treatment (for example, nausea due to chemotherapy)
- Toxic pulmonary edema
- Acute exacerbation of autoimmune diseases such as multiple sclerosis, vitiligo, uveitis, rheumatoid arthritis and systemic lupus erythematosus.
- Acute exacerbation of chronic obstructive pulmonary disease
- Cerebral edema: Recommended only in specific conditions such as elevated intracranial pressure due to the neoplasm or central nervous system infection; generally avoided in moderate to severe brain injury

Long-term

- Chronic inflammatory diseases (asthma, chronic obstructive pulmonary disease, inflammatory bowel disease)
- Rheumatic diseases (sarcoidosis, Sjogren syndrome, systemic lupus erythematosus)
- Graves' ophthalmopathy
- Local symptomatic treatment: anterior uveitis, steroid-responsive dermatoses, tenosynovitis, and osteoarthritis or juvenile idiopathic arthritis

Prophylactic

- Organ transplant (to prevent rejection due to their immunosuppressive action)
- Preterm delivery (to allow fetal lung maturity)

Mineralocorticoids are primarily involved in the regulation of electrolyte and water balance by modulating ion transport in the epithelial cells of the collecting ducts of the kidney. The use of mineralocorticoid drugs is limited to their replacement therapy in acute adrenal crisis and Addison disease.[20]

Because of several roles played by corticosteroids in the human body, they see extensive use in medical practice to treat various diseases. As a result, their side effects have, in turn, become another significant medical issue requiring special attention. Corticosteroids can also be used to replace certain hormones that are not naturally produced by the body. This is the case in people with Addison's disease.[21] Systemic corticosteroids have been used in the treatment of numerous medical conditions for approximately 50 years. Short-acting products such as hydrocortisone are the least potent. Prednisone and methylprednisolone, which are intermediate-acting products, are four to five times more potent than hydrocortisone. Dexamethasone is a long-acting, systemic corticosteroid; its potency is about 25 times greater than the short-acting products. Corticosteroids reduce the need for hospitalization in patients with croup and decrease morbidity and the incidence of respiratory failure in the treatment of patients with AIDS who have Pneumocystis carinii pneumonia. Other often overlooked indications for corticosteroids are the treatment of hyperthyroid states, including thyroid storm, subacute thyroiditis, and ophthalmopathy of Graves' disease. Systemic steroids can be used as adjuvant analgesics in the treatment of neuropathic and cancer-related pain. They may also decrease mortality in patients with severe alcoholic hepatitis and concomitant encephalopathy. Corticosteroids can reduce complications in patients with meningitis caused by Hemophilus influenzae or *Mycobacterium*

tuberculosis.[21] Corticosteroids were first used in clinical practice in 1949 for the treatment of rheumatoid arthritis. Indications since then have spanned multiple specialties and organ systems, including dermatology, rheumatology, immunology and oncology.[21]

Major Side Effects of Corticosteroids[20]

- skin and muscle atrophy
- increased risk of infections
- high blood pressure
- mood or behavioral changes
- osteoporosis
- glaucoma
- diabetes

Long-term use is associated with:

- weight gain
- facial swelling or puffiness (fluid retention)
- depression
- nausea and vomiting
- other types of stomach irritation
- bone fractures

Side effects from inhaled corticosteroids trusted source may include:

- cough
- difficulty speaking (dysphonia)
- oral thrush

Side effects from topical corticosteroids trusted source may include:

- acne
- rosacea
- atrophy
- stretch marks
- perioral dermatitis
- delayed wound healing (rare)

Side effects from injected corticosteroids may include:

- temporary pain and soreness
- loss of skin color at injection site
- high blood sugar
- facial flushing
- insomnia
- infection

Conclusions

Corticosteroids are used to provide relief for inflammatory conditions. Corticosteroids are very strong medicines and play important role in some life-threatening conditions. In addition to their helpful effects in treating medical problem, they have side effects that can be very serious. From my point of view, the doctor must compare advantage rate and damage rate and decide whether use it or not. I think we will get more benefits from corticosteroids in autoimmune disease if we combine it with other drugs to reduce side effect.

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Conflicts of interest

There are no conflicts of interest.

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