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# Similarities Between Corticosteroids

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## Abstract

Corticosteroids are a class of potent drugs with important physiological effects on the body. Regular use is linked with common and serious side effects. This paper uses studies to analyze the similarities between various corticosteroids. All drugs in this class are molecules that contain the same steroid backbone and are therefore associated with the same cellular receptor. This results in a comparable mechanism and parallel overall effect in the body. Side effects of corticosteroids are analogous as well. Using the knowledge of physiological changes in the body due to corticosteroids will allow healthcare providers to determine the most effective corticosteroid least likely to cause adverse effects, and treat and monitor the patient accordingly.

## Introduction

Corticosteroids are a class of commonly prescribed drugs containing a backbone of four fused cycloalkanes. These drugs are prescribed to treat a wide variety of ailments including: autoimmune disorders, arthritis, asthma, dermatitis, cancer treatment, pain management and others. Corticosteroid drug therapy is currently used in the treatment of over 175 diseases. Additionally, these drugs are commonly used by patients, as seen by the fact that Advair diskus, a corticosteroid inhaler, was sixth in retail sales during the year 2013. The drug can be administered and absorbed by the body in a variety of different forms: topically applied creams, inhaled sprays, injected systemically, drops for the eyes or ears, and orally. What are the common physiological effects of the different corticosteroids? The medications in this class share a common molecular backbone and cause analogous effects on a cellular level. Much research has been done trying to determine an exact mechanism of steroidal function. Mechanisms have been proposed, but as of today, they are hypotheses that explain some, but not all, effects. Though corticosteroid drugs are used for seemingly disparate pathologies, there are many similarities in physiological effects of corticosteroids, both medicinal as well as detrimental.

## Methods

The similarities between the corticosteroid class of drugs, as well as the differences between specific corticosteroids, were analyzed using original studies and critiques obtained by typing corticosteroid along with other associated keywords, such as inflammation, into databases, such as Ebsco, Medline, ProQuest, and other similar databases.

## Similarity in Structure

Steroids are molecules with a backbone consisting of three bonded cyclohexane rings fused with a cyclopentane. The backbone can vary in oxidation state as well as in functional groups, producing numerous different steroid molecules. The body produces cholesterol and steroid hormones as part of normal function, most importantly: aldosterone, and the sex hormones. Synthetic steroids can be introduced into the body.

Corticosteroids are a class of drugs similar to the hormone cortisol, and they contain this steroid backbone. Different corticosteroids vary somewhat in shape due to the differing functional groups and oxidation state. Though all steroid molecules are quite similar in structure, slight changes between each molecule's backbone results in differing affinity between the molecule and the corresponding glucocorticoid receptor . Structural changes also affect the bioavailability of a corticosteroid. Inhaled corticosteroids with a hydroxyl group on carbon 21 have been shown both in vitro and in vivo to undergo esterification inside lung cells and therefore take a longer period of time to eliminate from the body (Kelly, 2009).

## Mechanism of Action

The physiological effects of corticosteroids are well

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documented, and medical practitioners administer these drugs because the effects are beneficial to the patients. Corticosteroids are sometimes referred to as a "miracle drug" because of the diverse pathologies that are alleviated or managed by these drugs. The precise mechanism of action, nevertheless, is as of yet unknown. Much research has been done to discover this mechanism, and varying hypotheses have been suggested. There is a strong possibility that corticosteroids have numerous effects on a cellular level, resulting in what seems to be several valid mechanisms.

Corticosteroids function by diffusing into a cell and binding to glucocorticoid receptors in the cytoplasm (Barnes, 2005). The receptor corticosteroid complex stimulates changes in the cell by influencing transcription. Research testing cardiovascular effects of the corticosteroid dexamethasone, found that treatment of cells with dexamethasone and the glucocorticoid antagonist mifepristone (RU 486) blocked the known effects of the corticosteroid (Hafezi-Moghdam et al., 2002). When cells are treated with mifepristone, the glucocorticoid receptor is inactivated. When the cell with the inactivated receptor is treated with corticosteroid, no corticosteroid effect takes place. This demonstrated that a corticosteroid must bind to the receptor for an effect to occur in the cell.

This theory was replicated in a study showing that dexamethasone inhibits vasculogenesis in a tumor through suppressing vascular endothelial growth factor A. Treatment of steroid along with mifepristone prevented this suppressive effect (Greenberger et al., 2010). A limit of the conclusion, however, is that both studies were done using the same corticosteroid dexamethasone, and therefore, does not prove that other corticosteroids need to bind to the glucocorticoid receptor to have an effect.

Further proof of this theory lies in the clinically seen observation that different topical corticosteroids have different potencies. Corticosteroids are therefore separated into classes. In the United States, corticosteroids are divided in classes from one, the extremely potent, to seven, the least potent. In Europe, classes are numbered differently with class one, the mild corticosteroids, to class four, the strongest of the corticosteroids. Percentage of active ingredient in corticosteroid creams, lotions, or ointments fluctuates depending on the strength of the corticosteroid.

In a double blind study testing the bioavailability of different corticosteroids, desoximetasone 0.25%, clobetasol-17-propionate .05%, hydrocortisone 1.0%, and betamethasone dipropionate .064% were applied on the volar forearm of 30 healthy volunteers. After six hours, skin color changes were noted. The degree of skin blanching is associated with the efficacy of the corticosteroid. Though the corticosteroid concentration in each cream was different, the vasoconstrictive effect of the corticosteroid, as seen by blanching of the skin was quite similar between three of the four corticosteroids tested. Hydrocortisone caused milder skin blanching and in fewer individuals, but is known to be a weak corticosteroid so the results were not atypical (Borelli et al., 2008). The clinical observation that three of the four creams caused similar blanching despite differing concentrations, clearly demonstrated that corticosteroids differ in potency.

Research has shown that each corticosteroid has a different binding affinity to the glucocorticoid receptor because of structural differences (Kelly, 2009). Clinical trials show that the change in binding affinity from one corticosteroid to another is associated with the potency of the corticosteroid (Kelly, 2009). This correlation that greater the affinity of the corticosteroid to the receptor the more powerful its effects, bolsters the theory that corticosteroids need to bind to the glucocorticoid receptor to have physiological effects. The corticosteroid receptor complex causes numerous changes in the cell, both in the short term as well as long term.

After binding to the corticosteroid, the activated glucocorticoid receptor complex is transported from the cytoplasm into the nucleus and binds to the promoter of specific genes containing the glucocorticoid response elements. This induces transcription of glucocorticoid response elements mRNA (Barnes, 2005). In endothelial cells, dexamethasone induced promoter activity for the glucocorticoid response elements and caused transcription of these genes beginning four hours after treatment of cells. Actinomycin D, which inhibits transcription, and 5, 6-dichlorobenzimidazole riboside, which inhibits RNA polymerase, given in conjunction with the corticosteroid

blocked the promoter activity (Hafezi-Moghdam et al., 2002). These results indicate the influence of corticosteroids on transcription, which will subsequently affect proteins produced by the cell.

Some of the genes contained within the glucocorticoid response elements code for proteins with anti-inflammatory effects, such as interleukin 10. Leucine zipper protein and I kappa beta alpha (IkBα) are proteins synthesized in a cell exposed to corticosteroid. They suppress an important proinflammatory transcription factor called nuclear factor kappa B (Barnes, 2006). Some genes are indirectly inhibited by corticosteroids through the suppression of nuclear factor kappa B (Maneechotesuwan et al., 2009). There are also genes directly inhibited by corticosteroids, and these genes are considered to be negative glucocorticoid response elements. Examples of these directly suppressed genes include genes that regulate osteocalcin and keratin (Barnes, 2006). The suppression of these proteins results in common side effects of corticosteroids, such as epidermal, and to a lesser extent, dermal thinning and increased risk of fractures.

Corticosteroids inhibit proteins that have deleterious effects on specific pathologies. As a result corticosteroid therapies are beneficial for these diseases. A study seeking to explain the function of corticosteroid therapy in the treatment of infantile hemangioma found that the medicinal property was due to a negative glucocorticoid response elements and a decrease in amount of a corresponding protein. Corticosteroids suppressed the expression of vascular endothelial growth factor A mRNA and protein in hemangioma stem cells in a dose dependent manner, suggesting that corticosteroids may slow the growth of cancer cells. . Untreated infantile hemangioma cells express larger quantities of vascular growth factor than normal endothelial cells, but use of corticosteroids inhibited growth factor mRNA and protein. This effect was replicated using different corticosteroids including dexamethasone, prednisone, prednisolone, methylprednisolone, and hydrocortisone (Greenberger et al., 2010) leading to a conclusion that this effect is common to all corticosteroids. Other proangiogenic factors were suppressed in the hemangioma stem cells, in addition to vascular endothelial growth factor A. These factors included matrix metalloproteinase 1, interleukin-6, and monocyte chemoattractant protein 1. The latter two molecules are both involved with the immune system (Greenberger et al., 2010). Inhibition of metalloproteinase is also seen in corticosteroid treatment of arthritic diseases (Fubini et al., 2001). Steroidal medications induce changes in gene expression. The expressed genes, as well as the repressed genes, have physiological effects on the cell, which are attributed to the corticosteroid.

Numerous studies demonstrate that corticosteroids affect transcription, but this does not explain all of the physiological effects of corticosteroids. Corticosteroids inhibit cytokine production in T helper 2 cells, specifically interleukin 4, 5, and 13. The genes coding these interleukins are not fully regulated by nuclear factor kappa B and are not known to be part of the glucocorticoid response element (Maneechotesuwan et al., 2009). Additionally, effects of dexamethasone were seen in cells after only ten minutes , quite a short time for the transcription of glucocorticoid response element genes and translation of corresponding proteins. Furthermore, although the inhibitor of transcription actinomycin D blocked the promoter of the glucocorticoid response elements, overall the molecule did not inhibit the physiological changes of a cell exposed to dexamethasone (Hafezi-Moghdam et al., 2002). Based on these observations, the theory that corticosteroids binding to a receptor cause a cell to express certain genes and repress others is insufficient.

T cells exposed to anti CD3 antibodies and anti CD 28 antibodies cause GATA-3, a transcription factor, to be imported into the nucleus and stimulate the expression of interleukin 4 and 5. T lymphocytes that were exposed to the corticosteroid, known as fluticasone propionate, were found to have inhibited GATA-3, which affected interleukin gene expression. Interleukin 4 expression, which is regulated by GATA-3, was inhibited, and GATA-3 did not bind to the promoter of interleukin 5. Research on this phenomena found that GATA-3 uses importin alpha for protein to enter the nuclear membrane. Activated glucocorticoid receptors use importin alpha for nuclear translocation as well, leading to competition between GATA-3 and the glucocorticoid receptor for importin alpha. This decreased quantity of importin alpha available to GATA-3 results in

less nuclear translocation, less transcription, and less translation of interleukins 4,5, and 13 (Maneechotesuwan et al., 2009).

Corticosteroids were found to have non-transcriptional effects as well. Treating endothelial cells with dexamethasone stimulated endothelial nitric oxide synthase, an enzyme that has physiological effects on the cells. Activating the enzyme begins with the corticosteroid binding to the glucocorticoid receptor. The complex stimulates protein kinase B (also known as Akt) either directly or indirectly through the phosphoinositide 3-kinase/Akt pathway. Protein kinase B phosphorylates endothelial nitric oxide synthase thereby activating this enzyme (Hafezi-Moghdam et al., 2002). Researchers carried out this experiment with only one corticosteroid, dexamethasone, and the cells were evaluated for the function of only one enzyme. This raises an important question whether a corresponding mechanism applies to other corticosteroids and the phosphorylation and activation of other enzymes.

## General Effects of Corticosteroid Drugs

Based on proteins produced or inhibited, as well as the enzymes activated in a cell exposed to corticosteroids, these drugs have predictable physiological effects. One of the most important effects of corticosteroid drugs is the suppression of inflammation. This effect is so significant that other drugs that also have anti-inflammatory properties are separated into a class titled nonsteroidal anti-inflammatory drugs (NSAIDs). Healthcare practitioners therefore often prescribe corticosteroids in the treatment of pathologies involving an inflammatory reaction. Inflammation is associated with the immune system, and corticosteroids influence cytokine production, increasing some cytokines while decreasing others, resulting in an immunosuppressant effect. Repressing the immune system is beneficial for the treatment of pathologies caused by an overactive immune system, but detrimental to a patient on long-term corticosteroid therapy. Immune system suppression increases patient susceptibility to infections, which can become quite serious. This effect is especially deleterious to patients with compromised immune system due to other medical issues. Corticosteroids affect mRNA transcription and proteins produced in the cell. Researchers are studying the effects of proteins produced or repressed by cells exposed to corticosteroids and the physiological effects these proteins have on the cell.

## Therapeutic Usage of Corticosteroids

The properties listed above are what cause corticosteroids to have a therapeutic influence on a wide variety of diseases. One of the most common uses of corticosteroids is in the treatment and management of asthma (Eurich et. al, 2013) and other diseases characterized by an obstructed airway (Sibila et al, 2013). Corticosteroids are used to treat inflammation in other areas of the body as well. Therefore, corticosteroid drug therapy is commonly used to treat inflammatory skin disease,s such as eczema and psoriasis. Injections of corticosteroids are used in the controlling of inflammation and the suppression of matrix metalloproteinase activity in arthritic diseases (Fubini et al.,2001). Corticosteroids are beneficial for autoimmune disorders because of the immunosuppressive effect. Some pathologies, such as allergies, are aided by both the anti-inflammatory and immunosuppressive effects of corticosteroids.

The proteins produced in cells exposed to corticosteroids are beneficial to some diseases. Cardiovascular disease can be treated using corticosteroids, though a high dose is needed to achieve results (Hafezi-Moghdam et al., 2002). Dexamethasone increased the activity of the enzyme endothelial nitric oxide synthase (eNOS) and the production of nitric oxide. This radical protects muscle microvessels in mice after ischemia. Under normal conditions, leukocytes are present in the blood and do not adhere to venule walls. Following ischemia and reperfusion, leukocytes' velocity in the bloodstream decreases and they begin to stick to the venule walls. Mice given dexamethasone, directly following the ischemia and reperfusion, did not have the decrease in leukocyte velocity and the increase in adhesion normally seen after ischemia and reperfusion (Hafezi-Moghdam et al., 2002). This effect was studied in the cremaster muscle, but corticosteroids were found to have beneficial effects on myocardium as well. Dexamethasone treated mice were found to have myocardial infarctions affecting a smaller percentage of their region at risk for infarction, while mice in the control group

had a larger percentage of their region at risk affected by a myocardial infarction. Other studies have demonstrated that corticosteroids given to cardiovascular patients improved short-term survival following a myocardial infarction. In the experiments using mice, only very high doses caused physiological effects, and an established clinical dose offered no cardiovascular protection (Hafezi-Moghdam et al., 2002).

Corticosteroids are effective in reducing pain, as evidenced by a study comparing the effectiveness of intravenous hydrocortisone plus conventional treatment versus a placebo and conventional methods at reducing a severe postdural puncture headache. The results clearly showed the effectiveness of corticosteroids at reducing intense pain. Dural puncture is thought to cause a headache by causing cerebral spinal fluid leakage and a lessening of the fluid cushioning around the brain. The mechanism for the resolution of the headache is unknown, but possibilities include the anti-inflammatory properties of corticosteroids at the puncture site, the suppression of interleukins and prostaglandins, and causing the reabsorption of cerebrospinal fluid (Alam et al., 2012). Similarly, corticosteroids, in addition to antibiotics, relieved the pain and symptoms of patients suffering strong discomfort from pharyngitis sooner than than antibiotics and a placebo did (Bergeson et. al., 2013).

Topical corticosteroids have the benefit of maintaining a localized concentration of corticosteroids. Patients with bullous pemphigoid, a potentially fatal autoimmune disease of the skin, were divided into one group receiving treatment of 40 grams of the topical corticosteroid 0.5% clobetasol propionate twice daily, and the other group was treated with one milligram per kilogram of oral prednisone. The topical corticosteroid was found to be more effective at controlling the disease and caused a lower incidence of side effects than the oral corticosteroid (Joly et al., 2002). Similarly, topical steroids were found to be effective at reducing inflammation and ear discharge in otitis media. Clinicians commonly prescribe ear drops, containing a combination of an antibiotic, such as Augmentin®, and a corticosteroid, to treat otitis media with discharge (Florea et al., 2006).

Corticosteroids are used in oncology treatment of infantile hemangioma. They suppress vascular endothelial growth factor A, thereby inhibiting tumor vasculogenesis and limiting tumor growth (Greenberger et al., 2010). Additional research is needed to determine whether this effect extends to other forms of cancer and can be used accordingly, as a part of treatment. Furthermore, the safety of corticosteroid therapy in cancer patients must be evaluated as well.

## Side Effects Common to Corticosteroids

The change in proteins produced by a cell exposed to corticosteroids has numerous effects on the cell, both positive and negative. Side effects of a corticosteroid depend on the binding affinity, which is the potency of the given corticosteroid; the length of time for which it is taken; and the method of introduction in the body. Side effects of topically applied corticosteroids generally affect the location of application.

Skin atrophy is a common effect of corticosteroids (Cobman and Wezel, 2006). In a double blind study, twenty healthy volunteers applied four different topical corticosteroids with differing potencies to their volar arm for four weeks. Researchers quantified skin atrophy, using optical coherence tomography to measure epidermal thickness, and using high frequency ultrasound to measure dermal thickness. Additionally, they used a profilometer, an instrument that measures the profile of a given surface, to quantify epidermal roughness. All of the volunteers experienced epidermal thinning, demonstrating the frequency of this side effect. The epidermis thickened considerably after treatment was completed, but three weeks after finishing treatment, the epidermis was still measurably thinner than it had been before treatment. The subjects were followed for only three weeks following steroid use, so the length of time for which this effect persisted and the time needed for the epidermis to return to its original thickness was not determined in the study. The dermis of volunteers thinned as well. The dermal thinning, however, was less than that of the epidermal thinning. Additionally, three weeks post-treatment the dermis had almost returned to its original thickness. Using the profilometer, areas of corticosteroid use had a decreased roughness. The effect of the corticosteroid on the skin corresponded with its known potency; the more potent corticosteroids caused more significant

thinning. Hydrocortisone, a mild corticosteroid, did not cause significant atrophy.

It is evident from this study that in many cases, the skin, particularly the epidermis, is affected by corticosteroid use (Cobman and Wezel, 2006). This effect is likely because corticosteroids directly inhibit genes coding the protein keratin; these genes are part of the negative GRE. Healthcare providers should treat a patient using the least potent corticosteroid found to be effective and should monitor skin changes in the patient (Cobman and Wezel, 2006). Similar results were obtained in a study testing the effects of corticosteroids on different skin phototypes. An additional side effect of corticosteroids was seen in the study: changed skin pigmentation (Shlivko et al., 2013).

The method used to introduce corticosteroids into the body influences the side effects experienced by the patient. The effects of topical corticosteroids are concentrated and limited to the location of application. Therefore, topical corticosteroids may be more effective for treatment of the skin and are known to have a lower toxicity as compared to oral corticosteroids (Joly et al., 2002).

Based on numerous studies, adverse effects of oral corticosteroids are not detected at low and infrequent doses. Patients treated with oral corticosteroids were evaluated for risk of bone fractures. Those on medium to high doses of prednisone or prednisolone were found to have increased risk of fracture. Significantly, the fracture risk remained elevated for up to a year after the last dose, indicating that effects of corticosteroids linger even after discontinuing drug therapy . Budesonide has a low systemic availability, as it is designed for release in the intestine. Due to the low systemic concentration, budesonide was not associated with increased risk of fracture. Methylprednisolone is generally not used regularly, and as a result, did not cause an increased risk of fractures. Likewise, low doses of corticosteroids and doses taken intermittently were not associated with increased risk (Vestergaard et al., 2008). Similarly, short-term use of corticosteroids in treating the intense pain of a postdural headache did not cause short-term negative effects (Alam et al., 2012). Additionally, in the study using corticosteroids to treat severe sore throat, the corticosteroids did not exacerbate illness. Likewise, the use of corticosteroids in croup and mononucleosis did not worsen the infection (Bergeson et al., 2013). These studies did not follow up with the patients to see if any long-term effect or non-immediate reaction to the corticosteroid occurred. Additionally, it is possible that corticosteroids cause subtle effects that are not detected by laboratory means currently available.

A low to medium dose of inhaled corticosteroid is not likely to cause adverse effects (Kelly, 2009). As an immunosuppressant, regular corticosteroid use may negatively impact the immune system's ability to fight infection. Eighty nine patients, with a diagnosis of community-acquired pneumonia and had previously taken inhaled corticosteroids, were compared with a control group of 575 patients, with the same diagnosis who had not taken any inhaled corticosteroids. Inhaled corticosteroids are used in the control of disorders involving lung inflammation, such as asthma and COPD. The corticosteroid inhaler is generally used daily or on a regular basis. The patients, who had previously used inhaled corticosteroids, were more likely to have an illness caused by an antibacterial resistant microbe and presented a more critical case of pneumonia upon admission. Clinicians measure pneumonia by using the Pneumonia Severity Index and Curb-65 scores, which measures the likelihood of the pneumonia patient to die from their disease within 30 days (Sibila et al., 2013). Similarly, a study of 6874 patients, who had community-acquired pneumonia, found that inhaled corticosteroid use in high-risk patients increased the risk of a repeat incident of pneumonia by ninety percent (Eurich et al., 2013). Healthcare providers should relay this risk to asthmatic patients and instruct the patient, or the patient's caregiver, to seek medical care as soon as they feel symptoms of pneumonia. Earlier diagnosis will lead to treatment and a better prognosis.

Treatment of arthritis using corticosteroids has been proven effective. There are negative effects, however, and a healthcare provider should perform a benefit versus risk assessment and treat the patient accordingly. Corticosteroid injections into joints negatively affected chondrocytes, in addition to the cartilage damaged by the arthritis. A single dose of methylprednisolone succinate suppressed the expression of type 2 procollagen mRNA and decreased the relative percentage of the fibronectin form

unique to cartilage. Researchers found that injecting the recommended dose of methylprednisolone acetate into synovial fluid resulted in a high corticosteroid concentration, that was maintained for a longer period of time, because the half-life of corticosteroid in synovial fluid is found to be 10.3 hours (Fubini et al., 2001).

## Conclusion

Corticosteroids are a class of drugs with similarities in structure, and they have immunosuppressant and anti-inflammatory properties with comparable mechanisms. Gene expression is affected by corticosteroids, with genes coding the glucocorticoid response elements expressed more than normal, while other genes coding interleukins are inhibited. Various corticosteroids are used in a wide variety of disparate pathologies, because of their immunosuppressant and anti-inflammatory properties. These properties are responsible for the side effects of corticosteroids, including a decreased immune function and changes in cells exposed to high concentrations of corticosteroids. Differences in corticosteroid structure influence bioavailability and affinity to glucocorticoid receptor; both of which are directly related to potency. Additionally, the method of introduction of corticosteroid into the body, as well as the place of introduction, are major determinants of corticosteroid effects.

Overall, corticosteroids are an important method of treatment for illnesses involving an overactive immune system and/or inflammation. However, their use should be limited, as much as possible, due to their side effects. Before prescribing corticosteroids, physicians and other healthcare providers should evaluate the patient's overall immune function and assess the need for corticosteroid therapy. Healthcare providers should experiment with the patient to determine the least potent, lowest dose of corticosteroid found to be effective, particularly in patients requiring long-term use. Patients or the primary caregiver, in the case of children or the elderly, need to be informed of the possible side effects such as increased risk of infection and thinning of the skin. Awareness of corticosteroid risk, along with monitoring by medical professionals, will likely diminish many of the adverse side effects accompanying corticosteroid use.

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