Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4219 - 4229
Received 25 April 2021; Accepted 08 May 2021.

A Comprehensive Review on Corticosteroids

M Deepalakshmi[1], R Santhosh Kumar[2], Messiah Menoraj.S[3], Raghavakrishna.K. R[4], Shalini.S[5], K.P. Arun[6]

Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty-643001, The Nilgiris, TamilNadu, India.

Corresponding author mailing address: kparun@jssuni.edu.in

Contact number:9994934663

Abstract

Corticosteroids are a significant class of anti-inflammatory and immune modulators in the repertoire of a practitioner to treat a variety of scenarios. The consequences of shorter and longer-term usage are also significant, so they need to be cautiously administered. Thus, this drug is analogized as a 'double edged sword' and hence, this review explores both the positive outcomes of corticosteroids and their classic adverse effects.

Keywords: Corticosteroids, Pharmacodynamics, Pharmacokinetics.

Introduction

Steroids are a class of chemical compounds that possess a specific molecular configuration, comprising four interconnected rings. Steroids acts as signaling molecules and assist in stabilization of cell membranes which are considered to the fundamental biological functions. (Schimmer B P et.al, 2011).

Corticosteroids (CSs) are steroid hormones that are produced in cells from the sterols, these hormones are secreted by the adrenal glands in response to pituitary internal secretion that are controlled by hypothalamic corticotrophin releasing hormone. Steroids aids in chemical signaling in various organism due to their lipophilic nature. Steroids may influence many aspects of biology including osmoregulation; cellular metabolism, sexual differentiation, and reproductive physiology, Majority of steroids synthesized are secreted in ovaries, testes, adrenals, and placenta. (Hench P S et.al, 1949)

The aim of this article is to briefly provide an updated review on corticosteroids. corticosteroids are currently employed in various treatments such as neurological diseases, inflammation, pain, autoimmune disorders, and cancer. (Rhen T &cidlowski JA, 2005)

In homo sapiens the outer endocrine secretes corticosteroid hormones: i.e., glucocorticoids and mineralocorticoids, which is regulated by hypo thalamo-pituitary peptides. The hypothalamus secretes corticotrophin releasing factors (CRF), which in turn control the discharge of adreno corticotrophins (ACTH) (R FLaan et.al, 1993)

Corticosteroids alters the carbohydrates, proteins, and lipids metabolisms, affecting the majority all other endocrine secretions, salt and water balance, and an outsized number of enzymatic reactions upon administration (ConstansJ, 1992) Corticosteroids are also involved numerous physiologic functions such as stress response, retention of sodium within the kidneys, immune reaction and regulation of inflammation, bone development, blood electrolyte levels. (Jonathan R Seckl, 2004)

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4219 - 4229
Received 25 April 2021; Accepted 08 May 2021.

History

Steroid's history is a tale that has its origins in ancient endocrinology. Farmers noticed an improved capacity to domesticate animals after castration more than 6000 years ago. Years later, there emerged the scientific theories of ' humoralism '. This teaching was based on a hypothesis that sought to clarify illnesses between the four humors based on imbalances: sanguine, choleric, melancholic, and phlegmatic.

In the 1860s, a bunch of swimmers in Amsterdam were using drugs to hurry up their races. In 1935, the male hormone testosterone was first synthesized. During War II, German soldiers were reportedly given testosterone to extend their performance and aggressiveness on the battle field. By 1967 steroid use was widespread among Olympic athletes, particularly among weight lifters. Bodybuilders contracting AIDS from sharing a needle for steroid use was reported in 1984.

In 1988, the sale of anabolic-androgenic steroids for non-medical purposes was illegal under the Anti-Drug Abuse Act of 1988. In 1990, possession of anabolic- androgenic steroids without a prescription was made illegal within the U.S. Lewis Sarett of Merck & Co. was the primary to synthesize cortisone, employing a complicated 36-step process that started with deoxycholic acid, which was extracted from ox bile.

Egyptians and Romans believed that testicles and animal penises held special healing powers. Ancient Greek athletes used a wide variety of alleged performance-enhancing drugs, such as plant extracts and testicular extracts. These early theories and practices marked the beginning of future discoveries. (Dotson L J&Brown R, 2007)

Categories of steroid hormones

Corticosteroids

Glucocorticoids: These are primarily produced in zona fasciculata of the endocrine, (cortisol) which aids in immunosuppression by hindering phospholipid release and eosinophil action.

Mineralocorticoids: These are synthesized within the zona glomerulosa (Aldosterone) which helps in regulating water and electrolyte balance by promoting sodium retention within the kidney (Cooper M S
&Stewart P M, 2009).

Sex steroids

Progestogens: Progesterone regulates cyclical changes that occur in the endometrium of the uterus and maintains a pregnancy

Androgens: Testosterone, are helps to development and maintenance of male secondary sex characteristics
Estrogens: Estradiol, which is useful in development and maintenance of female secondary sex characteristics.

Additional classes of steroids

Neuro-steroids: modulates the neuronal excitability by rapid non-genomic actions.
Amino-steroids: Acts as competitive antagonists of the nicotinic acetylcholine receptor

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4219 - 4229
Received 25 April 2021; Accepted 08 May 2021.

(nAChR), and block the signaling of acetylcholine in the systema nervosum. (Cooper M S &Stewart P M, 2009)

Table-1
Physical and chemical properties:

Chemical name	Appearance	Melting point	Water solubility	Solubilities	Storage & stability
Hydrocortisone acetate	White, Crystalline powder, Odourless	222 -225 ℃	Insoluble	Slightly soluble in alcohol	Store in well closed containers
Hydrocortisone cypionate	White, Crystalline powder, Odourless	240℃	Insoluble	Soluble in alcohol	Store in tight, light resistant containers (suspension)
Hydrocortisone sodium phosphate	White to light yellow powder, odourless.	240℃	Freely soluble	Slightly soluble in alcohol	Store in room temperature & protect from light
Hydrocortisone sodium succinate	White, odourless, amorphous solid	232°C	Very easily soluble	Very easily soluble in alcohol	Store in room temperature & protect from light

Pharmacokinetics (pk) of steroids

Absorption

Administration of corticosteroid will lead to deposit of approximately 20% of dose in lungs and more or less 80% is swallowed. In new generation inhaler pulmonary deposition fraction will be 40% to 60% from the nominal dose, which is greater when compared to older devices which cause pulmonary deposition of 10-15%. Due to particle size and device used the deposition of dose may vary. In case of oropharyngeal dose, it may get rinsed incompletely and swallowed. Thus, deposition may occur in gastrointestinal tract. The dose which moves through the lungs will follow the bronchial and pulmonary level and reaches the systemic circulation to cause systemic side effects. (Wnazn g etal., 1995,Malcolm johnson, 1996, Kumar R&Thompson EB, 2005)

ICSs should be soluble in the aqueous phase of lungs and bronchitis. ICSs with lipophilicity deposits in lungs and may be dissolved in a short time and absorbed rapidly in systemic circulation. Fluticasone propionate and beclomethasone dipropionate dissolved extremely slow in time period of less than 8hrs to more than 5hrs.Whereas buclesonide and fluniconide dissolves most quickly in less than 2 mins.

However, beclomethasone dipropionate dissolves rapidly in 2-3 mins if the surface area is greater and the drug particles are less. Once the drug gets dissolved it will pass to the mucous layer and absorbed by the target tissue in order to provide the local effect. Lipophilicity takes part in pulmonary absorption as it is indirectly related to solubility in pulmonary lumen as fluid.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4219 - 4229
Received 25 April 2021; Accepted 08 May 2021.

Fluticasone fluocate takes about 20-30 hrs. for the drug to reach systemic circulation from absorption from 90% drug, which is more than fluticasone propionate 8Hrs. (Wnazn g et al., 1995, Malcolm johnson, 1996, Kumar R & Thompson EB, 2005)

When the majority of corticosteroids get absorbed through lungs or airways it distributes widely about one-fourth reaches the hepatic metabolism.

Distribution

Distribution of the ICS's due to lungs is based on the factors like type of delivery device, drugs formulation and also based on techniques used by the patient, inhalation mode and peak inspiratory flow rate.

ICS's like ciclesonide, beclomethasonedipropionate are connected to active metabolites from inactive compounds on inhalation as desiisobutyrylciclosonide and beclomethasone-17-mono propionate, due to esterase in the lung epithelium. Thus, some of the ICs are not delivered in pharmacologically active forms.

Distribution of ICS's is also affected by lipophilicity due to accumulation of drug in multiple devices, which may lead to systemic side effects. The unbound dose is now having potency to interact with GR. Newer ICS has potential binding ranges from 61.2%-99.7%. The drug absorbed by the lung /airway will get distributed widely. The drug absorbed by the stomach will get metabolized by the liver. (Wnazn g et al., 1995,Malcolm johnson, 1996, Kumar R&Thompson EB, 2005).

Metabolism

A study discusses that administration of 2 mg BDP inhaled dose, determines that plasma level of beclomethasone was not detectable and BDP were low.17-BMP which is an acetic metabolite shows plasma levels of 1.8 to 2.5mg/ml. 6- hydroxyl budesonide and 16-alpha hydroxyl budesonide are the metabolites of budesonide. 17-beta carboxylic acid is the metabolite of fluticasone propionate. Most of new ICS are metabolized in liver by cyp3a2 enzyme which is also combined by intestine. (WeberG et al., 1995)

Clearance

90L/hr is the plasma clearance rate max by the liver. The elimination of drug from the body may varies in ranges from drug to drug like betamethasone dipropionate (20l/hr) and lidesomide(228L/hr) which is high and it is due to external hepatic metabolism. For triamcinolone acetonide 37l/hr and 84L/hr for budesonide and t1/2:
If ICS have long Vd then it will have longer half-life. Elimination half-life for the inhalation is longer than the IV administration. But some drug may have similar half-life. For example, beclomethasone dipropionate & budesonide similar half-life for inhalation and IV administration. 1.6h to 14.4h is the elimination half-life for currently available ICSs. (Malcolm Johnson, 1996)

pKa of inhaled corticosteroid

Inhaled corticosteroids are the first line of drugs for all severity condition of asthma. It reduces the inflammatory condition in airways and consequently influence the hyper responsiveness. Inhaled corticosteroids act on all cell which are involved in airway inflammation. Inhaled corticosteroids do not show equilibrium with systemic drug concentration. This shows possibilities of adverse effect when it moves across some valves. This condition makes necessity for finding pka and pkd parameters for the ICS as it shows more potency in pkd than pka and vice versa.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4219 - 4229
Received 25 April 2021; Accepted 08 May 2021.

It is important to know the pka to prompt the decreased efficacy in therapeutic action of drug. Pharmacokinetics is the study time consumed by drug absorption, distribution, metabolism and excretion.
Pharmacodynamics is the relation between the drug concentration at the site of action and resulting effect or intensity of therapeutic and adverse effect. Some ICS's have been allowed for treating asthma and it includes beclomethasonedipropionate, budesonide, ciclesonide, fluocinonide, fluticasone propionate and triamcinolone acetate.

Each drug of ICs contains default pharmacokinetic properties, potency and in glucocorticoid receptor (GR) selectively. For example, ciclesonide is a pro-drug which converts to an active metabolite with the help of esterase in lung and some other tissue. 97% of the conversion takes place in the lungs. Since ICS's is influenced by various characteristics and various properties, it is a tough task to identify the influence of single property. GR binding and the concentration of drug at the site of action which happens with the help of activated GRS will determine the therapeutic effect and also the adverse effect. Corticosteroids have higher affinity in its target receptor, but it remains longer in target site after administration. In case of weak ICS, the same pharmacodynamics get induced by the higher concentration at the site of action. (Wnazn g et al., 1995,Malcolm Johnson, 1996, Kumar R&Thompson EB, 2005)

Pharmacodynamic

The pharmacodynamics can be observed by the drug binding to the receptor since GR mediates the pharmacological effect.
There are two types of GR,
 type 1- mineralocorticoid receptor
 type 2- glucocorticosteroid receptor.
The current ICS are capable of binding with type two receptor which present in cytoplasm and also in all tissue and cell. From this receptor corticosteroids are mediated through reversible binding. From the drug receptor complex move to nucleus to bind with DNA to activator repress the gene transcription. But it was found that it may also cause side effect. The nuclear factor –kB and activation protein will slow anti-inflammatory effect. Potency of the drug varies based on the receptor it binds.to show the good pharmacological action receptor affinity should be high. Receptor binding affinity for mometasone furoate (MF)-2,300, Dexamethasone-100, fluticasone propionate-(1,800), beclomethasonemonopropionate- (1.7-BMP).

The activity of ICS is induced by the affinity and efficacy. Tenacity of ICS biding with GR is described by affinity. Efficacy can be described as measuring of ICSs pharmacological effect and its capability which is activated by the factors like response to lungs, airway hyper responsiveness, asthma and density of receptor. In 4%of population N363 polymorphism will increase insensitivity for glucocorticoid. On other hand the transaction potential will increase the potential GR. Due to the pK factor and pD factor compounds may have high binding affinity. Thus, we should not understand as absolute difference in potency.(Wnazn g et al., 1995,Malcolm Johnson, 1996, Kumar R&Thompson EB, 2005)

Mechanism of action

The mechanism of action of corticosteroids differs depending on the class of corticosteroids, Glucocorticoids are used as an anti-inflammatory agent as well as an immune-suppressant.

Anti-inflammatory action

Anti-inflammatory of Glucocorticoids starts with their binding with specific receptors of the targeted cells. The receptor-steroid complex enters into the nucleus of the cell, binding to the DNA altering the

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4219 - 4229
Received 25 April 2021; Accepted 08 May 2021.

genetic synthesis of proteins. The glucocorticoid compound gets circulated in the body with an element known as 'Transcortin' (A Corticosteroid binding globulin which is a protein produced by the liver of all animals). This leads to a number of modified cellular functions which involves the synthesis of enzymes that involves some metabolic processes that regulates the synthesis of certain inflammatory autacoids and immune-related cytokines. Clinically, when glucocorticoids are administered the onset and the time required for this mechanism to occur is delayed.
These actions are said to be Anti-inflammatory when glucocorticoids inhibit the synthesis/release of inflammatory autacoids/mediators such as prostaglandins that are responsible for inflammation.

Electrolyte & water balance

The excretion of electrolyte from the kidneys is the major effect of mineralocorticoids(Maria Gabriella Matera, 2019). A cause of high sodium reabsorption and excretion of hydrogen and potassium results from Aldosterone treatment. Mineralocorticoids causes similar activities on other tissues. Alkalosis, hyperkalemia, high extracellular fluid volume is the primary feature of mineralocorticoids when given in excess. Sodium levels are modulated by activated mineralocorticoid receptors in the distal tube of the kidneys, causing high permeability of the apical membrane of the cells that lines the cortical collecting tube by Aldosterone. Hence, Sodium/potassium adenosine tri-phosphatase [ATPase] activity in the serosal membrane is increased. Probably due to volume expansion, mineralocorticoids increase the excretion of calcium and magnesium excretion. Glucocorticoid effects on the kidneys differ from the mineralocorticoid effects. well, Glucocorticoids enhance the Glomerular filtration rate, diuresis and renal plasma flow.(JuliaWinkler et al., 2004)

Endocrine system

Corticosteroids influence the action of several other hormones along with the effect of secretion of ACTH. Corticosteroids enhances the secretion of growth hormones in patients suffering from acromegaly. (Mulrow P J&Forman B H, 1972) In contrast, hypercorticism inhibits the secretion of growth hormone which results a decreased growth in children. This is due to immaturity of the epiphyseal plate and a decrease in the growth of long bones. (KobayashiO et al., 1967) Corticosteroids decreases the synthesis of thyroid-stimulating hormone in patients suffering from myxedema, thus the effectiveness of thyroxine is reduced. (Bridson W E&kohler P O, 1970) The adrenergic effect of catecholamine and the stimulation for the synthesis of epinephrine from nor-epinephrine is potentiated by Corticosteroids. (Lucky A W, 1984)

Cardio-vascular system

The major effects of corticosteroids on the cardiovascular system are a result of their influence on plasma volume, electrolyte retention, epinephrine synthesis, and angiotensin levels, which together result in the maintenance of normal blood pressure and cardiac output. Effects such as; myocardial responsiveness, arteriolar tone, and capillary permeability are resulted by corticosteroids. The ion transport in the vascular smooth muscle and in the central nervous system are affected by the mineralocorticoids causing altered sympathetic outcome influenced by periventricular area of the hypothalamus, from where information regarding cardio-vascular signs, fluid and electrolyte balance are interspersed. And when coming to Glucocorticoids, can cause hypertension by influencing many factors that can regulate blood pressure. by elevating the filtration fraction and glomerular hypertension, as well as the synthesis of angiotensinogen and atrial natriuretic peptide. They also reduce the production of prostaglandin which leads to vasoconstriction, and simultaneously elevate their responsiveness to vasopressors. They are also able to alter the vascular tone by reducing calcium-activated potassium channels expression.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4219 - 4229
Received 25 April 2021; Accepted 08 May 2021.

Musculoskeletal system

For a muscle to perform its normal function it requires an adequate level of corticosteroids, muscle abnormalities can occur with abnormal levels of corticosteroids. (Wilber J F &utiger R D. 1969) Elevated levels of mineralocorticoids causes muscle weakness by hypokalemia whereas, high levels of Glucocorticoids cause muscle wasting because of their catabolic effects on protein metabolism. Insufficiency of corticosteroids can reduce the working capacity of striated muscles resulting in weakness and fatigue. Long-time administration of Glucocorticoid results in the induction of osteoporosis which is now-a-days a considerable limiting factor in the use of steroids clinically.

Central nervous system

The nervous system is positively affected by corticosteroids in many ways such as; maintaining adequate circulation, normal plasma glucose level and electrolytes. Mood, behavior, electroencephalograph patterns, memory consolidation, and brain excitability are influenced by corticosteroids. Cell death in the hippocampal neurons occurs in chronic glucocorticoid treatment whereas; alteration in cognition, dementia, and depression can occur in aging humans because of the elevated levels of Glucocorticoids in the hippocampus. (Ellul-micallef R&fenech FF, 1975) Glucocorticoid therapy is responsible to cause symptoms like apathy, depression, irritability, and psychosis in conditions like Addison's disease, but not mineralocorticoid therapy. (Mandel S, 1982) Pseudotumor cerebri occurs primarily in children in chronic use of Glucocorticoids. (Lupien S J, nair N P,Briere S. Et al., 1999)

Hematologic effects

 Corticosteroids can increase the contents of hemoglobin and red blood cells in the blood by retarding the process called 'Erythro-phagocytosis'. Circulating white blood cells are also being affected by corticosteroids. Glucocorticoid treatment increases the polymorph nuclear leukocytes in the blood. In contrast, the levels of lymphocytes, eosinophil, monocytes, and basophils goes down after the administration of Glucocorticoids. A single dose of Glucocorticoid decreases:
 70% decrease in lymphocytes,
 90% decrease in monocytes, within a 4 to 6 hours of administration and can also persist for a day. And the probability for Glucocorticoids-induced apoptosis of T-lymphocytes than B-lymphocytes is high. (CarpenterWT jr&gruen P H., 1982)

Immuno-suppressive action

Glucocorticoids possess immune-suppressive actions by inhibiting the functions of leukocytes in certain aspects. Thus, inhibition of phagocytosis among macrophages and reduction in the number and activity of specific subsets in T-lymphocytes. The humoral immunity is at a less influence. Whereas, the B-cell response and the anti-body levels are not been inhibited and reduced respectively. They inhibit the production of interleukin-1 and other mediators that are responsible for immune response, inhibit participation of lymphocyte in delayed hypersensitivity reactions, and interfere with the rejection of immunologically incompatible graft tissue. (WeisbergL A&chutorianA M, 1977)

Other effects

Other effects of prolonged glucocorticoid therapy include ophthalmologic (posterior sub-capsular cataracts, (Pountain G D et al., 1993) increased intraocular pressure) (Gillis S et al., 1979) and dermatologic [redistribution of subcutaneous fat, hirsutism, alopecia, impaired wound healing, purpura, purple striae, and acneiform eruptions (Lubkin V L, 1977)problems. Long-term glucocorticoid treatment, leaves patients susceptible to invasive diseases such as Kaposi sarcoma

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4219 - 4229
Received 25 April 2021; Accepted 08 May 2021.

(Giles C L, 1967) and fungal infections.
(Truhan A P&Ahmed A R, 1989)

Systemic side-effects of corticosteroids

Some patients feel difficulty in taking corticosteroids due to their side-effects which are caused by oral and intra-venous administrations in common.

Infections

Since corticosteroids are immunosuppressors they can make a person taking corticosteroids more susceptible to infection by reducing the functions of immune system, where the physician can prescribe anti-infective to overcome the possible infections.

Adrenal insufficiency

Cortisol is a hormone responsible for many regulations such as blood pressure. The long-term course and high doses of corticosteroids stops the synthesis of cortisol from the adrenal glands. And when the cortisteroidal therapy is stopped suddenly, adrenal suppression and lack of cortisol synthesis both causes many symptoms, such as low blood pressure dangerously.

Side-effects of topical corticosteroids:

It occurs more commonly by topical corticosteroids mainly in pediatric and geriatric patients. The systemic side-effects are namely;

- Suppression of the hypothalamic-pituitary-adrenal axis
- Iatrogenic Cushing's syndrome
- Growth retardation in infants and youngsters
- Glaucoma and loss of vision
- Avascular necrosis of femoral head
- Severe disseminated cytomegalovirus infection leading to death in infants.

Diastolic hypertension, diabetes, buffalo hump, facio-trinocular obesity, hirsutism, striae, telangiectasia, skin fragility etc. are a number of features of Cushing Syndrome could be a result of increased levels of Glucocorticoid in blood. Hypothalamic cortisol releasing hormone and pituitary internal secretion (ACTH) are suppressed by Glucocorticoid. In long-term use of Glucocorticoids causes HPA axis suppression and adrenal insufficiency with suprarenal gland atrophy.

Infants were the majorly within the children category and also the major primary skin condition was diaper rash followed by psoriasis, burn, non-bullous ichthyosiformerythroderma and skin dryness. In adults, psoriasis was most typical indication (71%) followed by intertrigo, eczematous dermatitis, chronic skin dryness and lichen.
The use of Clobetasol propionate (0.05%) in a very dose of 2g/day can decrease morning cortisol level after some days (Trattner A, 1993) and results in features of Cushing's syndrome and symptoms of adrenal insufficiency with a use over 100g/week or 100-300 g/week. [Walsh T J et al., 1992&Kelly A et al., 1972]

Open-angle glaucoma and cataract from transpalpebraltarsa penetration are a result of utilization of topical
steroids on the eyelid for a long period of time.[StaughtonR C & august P J., 1975]

The use of Betamethasone valerate (0.1%) ointment for 3 years with 30g/week can cause growth

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 4219 - 4229
Received 25 April 2021; Accepted 08 May 2021.

deficiency in infants [Allenby C F et al., 1975]. And overuse of glucocorticoids provides a suppression effect on the synthesis of somatotropin releasing hormone from the Hypothalamus. (GuvenA et al., 2005)

CNS related adverse events:

Behavioral effects such as sleep disorders characterized by insomnia and restlessness. (Takahashi H et al., 1992) And in patients suffering from Chronic Obstructive Pulmonary Disease and treated with oral Prednisolone are more prone to develop a sense of well-being called 'Steroid euphoria'- a condition where the patient is very relaxed, free from anxiety and depression, which is a sign of the improvement of the lung function.
Behavioral effects including agitation and insomnia are due to the administration of Methylprednisolone via intra-articular injection. (TurpeinenM et al., 1988)
Psychic effects
The mechanism of prednisolone-induced psychic effects such as; mania and psychosis are unclear.(Curtis J R, 2006) Reduced levels of corticotropin, norepinephrine and beta-endorphin in the cerebro-spinal fluid is associated with prednisolone administration. (Robinson D E, 2000)

Cognitive effects

Poor memory and difficulty in concentration are in the picture representing cognitive effects.[38] Decreased hippocampal volume and brain atrophy due to decreased flow of blood to the region where the hippocampus is located are associated with the administration of corticosteroids reports neurological studies.[Benyamin R M et al., 2008]

Hepatotoxicity

Hepatotoxicity may be due to high dose than the physiologic dose and long-term administration of corticosteroids. Hepatomegaly (Liver enlargement) steatosis or glycogenesis are common with corticosteroid overdosing. They generally trigger a condition called non-alcoholic steatohepatitis. Discontinuation or withdrawal of corticosteroidal therapy may reactivate hepatitis-B which may be fatal. Acute liver injury like acute liver failure and death of the subject are largely associated with intra-venous corticosteroids like Methylprednisolone.

Corticosteroidal therapy triggers or worsens the underlying disease and rarely are responsible for drug toxicity. High doses of corticosteroids cause glycogenesis. Glycogenesis are related with hepatomegaly especially in children and they generally increase the serum amino-transferase levels with minimum or no changes in the bilirubin levels. Glycogenesis is not associated and does not progresses chronic liver injury, cirrhosis and acute liver failure.

Thus, discontinuation or avoidance of corticosteroidal therapy is a must in patients suffering from hepatitis-B and hepatitis-C. There are evidences of acute liver injury after a short and high dose of intra-venous Methylprednisolone which is severe and sometimes fatal. Hallmark symptoms of jaundice and other liver related disease can arise within 2-4 weeks after discontinuation of corticosteroidal therapy. (Wolkowitz O M, 1988).

Latest information

About 8% of the patient among who were treated with corticosteroids shows complication for cartilage breakdown (IoannouN et al., 2003). Non randomized studies on the patient shows 31% of recovery in septic shock on the 7th day after the administration of corticosteroids and some improvement in preventing organ failure (N.J.Snell, 1994). This update gives information to continue

use of a single course of antenatal corticosteroids to women at risk of preterm birth in order to accelerate fetal lung maturation. NOTE- This evidence comes from well developed countries and hospital settings; and so, the results may not be applicable for low resourced areas with increased rates of infections.

Increase in the mortality when influenza treated with corticosteroids of high doses (Peyro-saint-paulL et al., 2019). Antiviral along with corticosteroids may show some better effect than giving corticosteroid alone. Corticosteroids alone were probably more effective than antivirals alone and antivirals plus corticosteroids were more effective than placebo or no treatment. [Lansbury et al., 2020,Weber G et al., 1955]

Conclusion

About every branch of medicine has been invaded by steroids that can be delivered on almost all available routes since discovery. The consequences of steroid use can vary significantly and even in people who take small doses the entire spectrum of side effects can be present. Health professionals must be conscious that the medication can intensify or expose an underlying condition. It's critical to be aware of the health impacts of the use of these compounds.

Acknowledgements

We acknowledge the generous research infrastructure and supports from JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, The Nilgiris, Tamil Nadu, India.

References

1. Allenby C F, Main R A, Marsden R A, Sparkes C G. *Effect on adrenal function of topically applied clobetasol propionate* (dermovate) Br med j. (1975)4:619–21. [pmc free article] [pubmed] [google scholar]
2. Beta-hydroxysteroid dehydrogenase type 1 and its role in the hypothalamus-pituitary-adrenal axis, metabolic syndrome, and inflammation. Cooper M S, Stewart P M, J clin endocrinol metab. 2009 dec; 94(12):4645-54.
3. Benyamin R M, Vallejo R, Kramer J, Rafeyan R. *Corticosteroid induced psychosis in the pain management setting.* Pain physician. (2008)11:917–20. [pubmed] [google scholar]
4. Bridson W E ,kohler P O . *Cortisol stimulation of growth hormone production by human pituitary tissue in culture. J clin endocrinol metab.* (1970) 30:538–40. [pubmed] [reference list]
5. Carpenter WT jr, gruen P H. *cortisol's effects on human mental functioning.* J clin psychopharmacol.(1982) 2:91–101. [pubmed] [reference list]
6. Constans J. *Group-specific component is not only a vitamin-d-binding protein .expclinimmunogenet.* (1992) 9:161–175
7. Curtis J R, Westfall A O, Allison J, Bijlsma J W, Freeman A, George V, et al. *Population-based assessment of adverse events associated with long-term glucocorticoid use.* Arthritis rheum. (2006)55:420–6. [pubmed] [google scholar]
8. Dotson L J., & Brown R. (2007). *The history of the development of anabolic-androgenic steroids. Paediatric clinics of north america*, 54(4), 761-769. Doi: 10.1016/j.pcl.2007.04.003 (newly added)
9. Ellul-micallef R ,fenech FF. *Effect of intravenous prednisolone in asthmatics with diminished adrenergic responsiveness.* Lancet. (1975)2:1269–71. [pubmed] [reference list]
10. Gillis S ,crabtree G R , smith K A . *Glucocorticoid-induced inhibition of t cell growth factor*. J immunol. (1979)123:1632–8. [pubmed] [reference list]
11. Giles C L .*the ocular complications of steroid therapy.* Mich med. (1967) 66:298–301. [pubmed] [reference list]
12. Guven A, Karadeniz S, Aydin O, Akbalik M, Aydin M. *Ocular adverse effect of topical steroids.* Horm res. (2005);64:35–8. [pubmed] [google scholar]
13. Hench ps, kendallec, slocumbch, polley hf. *The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound e) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis.proc staff meet mayo clin* (1949)24:181-97
14. Ioannou N, Liapi C, Sekerisce, Palaiologos G. *Effects of dexamethasone on k(+)-evoked glutamate release from rat hippocampal slices.* Neurochem res. (2003)28:875–81. [pubmed] [google scholar]
15. Jonathan R Seckl,Beta-hydroxysteroid dehydrogenases: *changing glucocorticoids action.seckljrcurropinpharmaco*l. (2004) 4(6):597-602.
16. Julia Winkler, Guenther Hochhaus, Hartmut Derendorf. *How the lung handles drugs pharmacokinetics and*

pharmacodynamics of inhaled corticosteroids. Res.(2004)356-363 -1. [art journals] [google scholar]
17. Kelly A, Nelson K, Goodwin M, Mccluggage J. *Adverse effects of topical corticosteroids.* Bmj. (1972)14:114. [pmc free article] [pubmed] [google scholar]
18. Kobayashi O ,wada H , utsumi J . *Urinary lithiasis in children treated with adrenocorticosteroid hormone*. Acta med biol. (1967)15:91–105.
19. Kumar R, Thompson EB. *Gene regulation by the glucocorticoid receptor: structure:function relationship*. J Steroid biochemmol Biol. (2005)94:383–94. [pubmed] [Google Scholar]
20. Lansbury, Louise E. Mbbs, phd; Rodrigo, Chamira, phd; Leonardi-bee, Jo; phd; Nguyen-Van-Tam, jonathan DM, ffph, frcpath, frsph, frsb; shenlim, wei DM, frcp.*Corticosteroids as adjunctive therapy in the treatment of influenza: an updated cochrane systematic review and meta-analysis.* Res (2020);e98-e106:48.
21. Lubkin V L .steroid cataract—*a review and a conclusion*. J asthma res. (1977)14:55–9. [pubmed] [reference list]
22. Lucky aw. *principles of the use of glucocorticoids in the growing child. Pediatric dermatol*. (1984)1:226–35. [pubmed] [reference list]
23. Lupien S J ,nair N P , Briere S . Et al. *Increased cortisol levels and impaired cognition in human aging: implication for depression and dementia in later life. Rev neurosci.* (1999)10(2):117–39. [pubmed] [reference list]
24. Malcolm johnson, *pharmacodynamics and pharmacokinetics of inhaled glucocorticoids*. Res. L 1996; 169-176:97.
25. Mandel s. Steroid myopathy. *Insidious cause of muscle weakness. Postgrad med* (1982)72:207–10, 213–5.
26. Maria Gabriella Matera, Barbara Rinaldi, Luigino Calzetta, Paola Rogliani, Mario Cazzola. Pharmacokinetics and pharmacodynamics of inhaled corticosteroids for asthma treatment res.2019; 101828-58 [science direct] [google scholar]
27. Mulrow P J ,forman B H . *The tissue effects of mineralocorticoids.* Am j med.(1972);53:561–72.
28. N.J. Snell, *Drug interactions with anti-asthma medication.* Res. 1994; 83 – 88: 88.
29. Peyro-saint-paul L et al. *Cushing's syndrome due to interaction between ritonavir and cobicistat and corticosteroids: a case-control study in the french pharmacovigilance database*. J antimicrobchemother, online edition, https://doi:10.1093/jac/dkz324, (2019)
30. Pountain G D ,Keogan M T , Hazleman B L , Brown D L. J clinpathol. (1993) 46:1089–92. [pubmed] [reference list]
31. R F Laan, van riel P L, van de putte L B, van erning L J, van't Hof ma, lemmens J A. *Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study*. Ann intern med (1993)119:963-8.
32. Rhen T, cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N engl j med 2005;353:1711-23
33. Robinson D E, Harrison-hansley E, Spencer R F. *Steroid psychosis after an intra-articular injection.* Ann rheum dis. (2000)59:927. [pmc free article] [pubmed] [google scholar]
34. Schimmerbp, funder jw. Acth, adrenal steroids, and pharmacology of the adrenal cortex. In: bruntonll, chabnerba, knollmannbc. Goodman & gilman's the pharmacological basis of therapeutics, 12th ed. New york: mcgraw-hill.
35. Staughton R C, august P J. *Cushing's syndrome and pituitary-adrenal suppression due to clobetasol propionate.* Br med j. (1975)2:419–21. [pmc free article] [pubmed] [google scholar]
36. Takahashi H, Bando H, Zhang C, Yamasaki R, Saito S. *Mechanism of impaired growth hormone secretion in patients with cushing's disease.* Actaendocrinol (copenh) (1992)127:13–7. [pubmed] [google scholar]
37. Trattner A, Hodak E, David M, Sandbank M . *The appearance of kaposi sarcoma during corticosteroid therapy.* Cancer. (1993)72:1779–83. [pubmed] [reference list]
38. Truhan A P, Ahmed A R . *Corticosteroids: a review with emphasis on complications of prolonged systemic therapy*. Ann allergy. (1989) 62:375–91. [pubmed] [reference list]
39. Turpeinen M, Mashkilleyson N, Björkstén F, Salo OP. *Percutaneous absorption of hydrocortisone during exacerbation and remission of atopic dermatitis in adults.* Actadermvenereol. (1988);68:331–5. [pubmed] [google scholar]
Walsh T J , Lee J W , Roilides E , Pizzo P A . *Recent progress and current problems in management of invasive fungal infections in patients with neoplastic diseases.* Curropinoncol. (1992) 4:647–55. [pubmed] [reference list]
40. Weber G.; Allard C.; de lamirande,g.; and can tero, a. *Increased liver glucose-6-phosphatase activity after cortisone administration. Biochim.biophys.* Acts,(1955) 16:618-19,
41. Weisberg L A ,chutorian A M . *Pseudotumor cerebri of childhood. Am j dis child.* (1977) 131:1243–8. [pubmed] [reference list]
42. Wilber J F ,utiger R D . *The effect of glucocorticoids on thyrotropin secretion.* J clin invest.(1969)48:2096–103. [pubmed] [reference list]
43. Wolkowitz O M, Rubinow D, Doran A R, Breier A, Berrettini W H, Kling M A. *Prednisone Effects on neurochemistry and behavior. Preliminary findings.* Arch gen psychiatry. (1988) 0;47:963–8. [pubmed] [google scholar]