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Steroids: Pharmacology, Difficulties and Practice Delivery Issues

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Abstract

Since their identification nearly 80 years ago, steroids have played a prominent role in the treatment of many disease states. Many of the clinical roles of steroids are related to their potent anti-inflammatory and immune-modulating properties. Clinically relevant side effects of steroids are common and problematic. Side effects can occur at a wide range of doses and vary depending on the route of administration. The full spectrum of side effects can be present even in patients taking low doses. Practitioners must be aware that these drugs might exacerbate a preexisting condition or present a new medical condition. Knowledge of the clinical implications of prescribing these agents is critical. Steroid withdrawal syndrome can produce a broad array of signs and symptoms, some of which are not well recognized. High fever is among these. Corticosteroids modulate immune function through various effects in the nucleus of numerous cells. When used in pharmacologic doses to suppress allergic responses or inflammation, these agents can cause numerous adverse effects associated with an excess of glucocorticoid activity. Prolonged use (>2 wk) results in suppression of the hypothalamic-pituitary-adrenal axis, which requires tapering of doses. Dosing strategies for systemic corticosteroids are designed to minimize the risk for hypothalamic pituitary-adrenal axis suppression. This review summarizes the basic pharmacology, complications, and practice delivery issues regarding steroids.

Keywords: Steroids, Corticosteroids, Adrenal cortex hormones, Glucocorticoids, Medication therapy management, Mineralocorticoids

Introduction

Since their identification in 1935, steroids have served a wide range of uses. Initially, these isolates from adrenal glands were thought to be useful only in patients suffering from Addison disease[1]. Today, many of the clinical roles of steroids are related to their potent anti-inflammatory and immune-modulating properties. Clinically relevant side effects of steroids are common and problematic, ranging from a minor case of acne to Cushing syndrome that can result in diabetes mellitus and potentially life-threatening heart disease if untreated[2]. Side effects can occur at a wide range of doses and vary depending on the route of administration[1]. The term steroid applies to a wide range of molecules with varying physiological effects. More specifically, corticosteroids are a class of chemicals encompassing both laboratory-synthesized and naturally produced hormones. Glucocorticoids, in general, regulate metabolism and inflammation; mineralocorticoids regulate sodium and water levels. Corticosteroids fall along a spectrum from exclusively glucocorticoid effects to exclusively mineralocorticoid effects and steroid compounds are selected based on their appropriateness for a given treatment. For example, although a compound may possess potent anti-inflammatory properties, it may additionally have mineralocorticoid activity that adversely affects blood pressure. Corticosteroids are important therapeutic agents used to treat allergic and inflammatory disorders or to suppress undesirable or inappropriate immune system actions. The term corticosteroid is used clinically to describe agents with glucocorticoid activity. Cortisol is the endogenous glucocorticoid, named for its effects on glucose metabolism but which also exerts the other immunological actions of corticosteroids. Cortisol is produced in the adrenal gland through cholesterol metabolism. A variety of other hormones, including mineralocorticoid, aldosterone, and male and female sex hormones, are produced through the common pathway of cholesterol metabolism. This common pathway and structural similarities among the hormones help to explain some of the side effects and adverse reactions associated with pharmacologic doses of cortisol and its synthetic analogues[3-5].

Hypothalamic-pituitary-adrenal axis physiology

Endogenous cortisol production by the adrenal gland is controlled by the hypothalamic-pituitary-adrenal axis and occurs in a diurnal and circadian pattern every 24h. Corticotrophin-releasing hormone is released from the hypothalamus and acts on the anterior pituitary to release adrenocorticotrophic hormone, which stimulates cortisol production and release from the adrenal gland[6]. Exogenously administered adrenocorticotrophic hormone results in an increase in serum cortisol and is an older therapy that has limited clinical utility today. Plasma cortisol concentrations are typically highest in the morning (eg, 10-15 µg/ml at 6:00-8:00 AM), and lowest during the night while sleeping. Circulating cortisol exerts negative feedback on adrenocorticotrophic hormone and corticotrophin releasing hormone production[7,8] Normal hypothalamic-pituitary-adrenal axis function is important for general health and well-being. Under non-stressed conditions, cortisol production is approximately 20mg daily in adults. In addition to the normal

production and control of cortisol secretion, physical or psychological stress also is associated with increased levels of cortisol. Examples of stress include infection, major trauma and diseases. There is clinical evidence that the daily production can increase to 150-200mg during physical or mental stress[6]. In serious chronic disease associated with inflammation, including sepsis, the adrenal glands ability to produce cortisol at maximal levels is impaired. This situation is described as relative adrenal insufficiency and supplementation with hydrocortisone may be warranted[9]. The adrenal gland consists of 3 functional zones. Cortisol is the product of cholesterol metabolism in the zona fasciculate[6].The primary mineralocorticoid, aldosterone, is produced in the zona glomerulosa, whereas androgens and sex hormones, including progesterone, estrogens and testosterone, are produced in the zona fasciculate and zona reticularis. A functioning and intact hypothalamic-pituitary-adrenal axis is important for maintaining health and metabolic functions. Mineralocorticoid activity through aldosterone is primarily controlled by the renin-angiotensin-aldosterone system as well as by serum potassium concentrations. Although cortisol and aldosterone control specific functions, both agents possess qualities affecting the other system due to their structural similarities and because they are derivatives of cholesterol.

Corticosteroid metabolism and clinical role

Although corticosteroid metabolism is complicated by enzyme induction, protein binding, molecular interconversion and interaction with endogenous cortisol, corticosteroids are generally metabolized by the hepatic P450 system[10]. Direct application (eg, topical, intraarticular, inhaled, or epidural) of these agents to sites of inflammation bypasses the liver and its first-pass effect. Chronic oral glucocorticoid use is common in patients with rheumatoid arthritis, chronic obstructive pulmonary disease, systemic lupus erythematosus, inflammatory bowel disease and asthma[11]. Side effects of chronic use include bruising, muscle weakness, weight gain, skin changes, sleep disturbances, cataracts and pathologic fractures[11]. Glucocorticoid administration can also have psychiatric side effects: mood disorders, anxiety, delirium, and panic disorder. Psychotropic medication may be required to treat these symptoms, but the prognosis is favorable once the glucocorticoids are reduced or discontinued[12-14]. Adverse effects occur in up to 90% of patients who take glucocorticoids for >60 days. These side effects, including the more serious fractures and cataracts, occur even in patients taking low (≤7.5mg/d) dosages[11,15]. Glucocorticoids affect bone mineralization by inhibiting calcium absorption in the gastrointestinal tract and shifting signaling-molecule production to favor bone resorption. Recommendations for preventing glucocorticoid-induced osteopenia and its subsequent complications and comorbidities include supplementing calcium with vitamin D for glucocorticoid doses ≥5 mg/d and starting bisphosphonates when indicated by densiometric evaluation[15]. Because of their effects on insulin resistance, glucocorticoids are the most common cause of drug induced diabetes mellitus[16]. Screening guidelines using a fasting glucose ≥126 mg/dl or HbA1c ≥6.5% are suitable for diagnosing steroid-induced diabetes; however, per American Diabetes Association guidelines, results should be confirmed via repeat testing[16]. Management is similar to that of type 2 diabetes mellitus; treatment options progress from single agent to double agent to insulin±another agent, based upon fasting glucose measurements and glucose control. In patients with preexisting diabetes, blood sugars should be measured more often than in patients without preexisting diabetes, and medications should be adjusted to maintain adequate control[16]. Cushing syndrome and adrenal suppression have been observed in patients taking oral, intraarticular, epidural, inhaled, nasal, ocular and topical glucocorticoid preparations. These side effects become more likely with longer durations of treatment and higher dosages[15,16]. Mineralocorticoid activity causes the retention of sodium and free water and the excretion of potassium. Derangements in mineralocorticoid production can manifest with abnormalities in any of these areas. Hyponatremia, hyperkalemia and hypotension are present to varying degrees in mineralocorticoid deficient states (eg, various congenital adrenal hyperplasias and aldosterone synthase deficiency), whereas the inverse is present in mineralocorticoid excess states (eg, Conn syndrome). Because endogenous glucocorticoids also have activity at mineralocorticoid receptors, signs and symptoms of mineralocorticoid excess can be seen in cases of excess glucocorticoid production (eg,Cushing syndrome) [2].

Structure

All steroid hormones are derived from cholesterol metabolism. The shared chemical feature of cortisol and synthetic analogues, including systemic and topical therapies, is a 17-carbon androstane structure that originates from cholesterol metabolism. There are three 6-carbon hexane rings and one 5-carbon pentane ring (Figure 1) [17]. The key characteristic of steroid molecules responsible for glucocorticoid activity is the presence of a hydroxyl group at carbon 11. Agents that have 2 carbons at position 17 on the pentane ring and methyl groups at the carbon 18 and 19 position are referred to as glucocorticoids because of their activity with glucose metabolism. Other modifications to the structure can increase potency or reduce mineralocorticoid activity. Two clinically used corticosteroid agents, cortisone and prednisone, have a ketone group at carbon 11 and require hepatic activation to active the hydroxyl compounds hydrocortisone and prednisolone, respectively. Hydrocortisone is the clinical name for cortisol. There are numerous corticosteroid agents that have been developed for topical use (eg, creams, ointments, enemas, ophthalmics, nasal and oral inhalation and intra-articular injections) and are biologically active with the carbon-11 hydroxyl group. The addition of esters at carbons 16 and 17 and of hydrophobic groups at carbons 20 and 21 improve affinity for the glucocorticoid receptor. For synthetic agents, the addition of a halogen and a 1, 2 double bond on carbons 6 and 9 results in improved potency and stability against metabolism. In general, the structural modifications result in improved specificity for the glucocorticoid receptor, a longer duration of receptor occupancy, increased lipophilicity, and reduced aqueous solubility[18]. These features are desirable pharmacologic properties to enhance efficacy and safety.

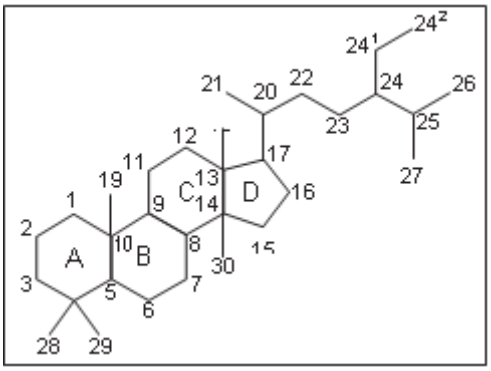

Figure 1 Corticosteroid molecule

Corticosteroid preparations

Steroid injections are associated with side effects related to dosage, duration of administration, added ingredients or

contaminates and particle size. Particulate steroids present a theoretical risk of occluding vessels depending on the size of particulate aggregates. Common additives in steroid preparations, such as benzyl alcohol and ethylene glycol, have been implicated in case reports and studies of complications following epidural steroid administration[19,20]. Dexamethasone and betamethasone sodium phosphate are pure liquids, whereas methylprednisolone, triamcinolone and betamethasone are solutions and their particle size depends upon the type of preparation and dosage. Studies have shown that transforaminal dexamethasone is just as effective at 4 mg as it is at 8 mg and 12 mg and that nonparticulate steroid preparations are just as effective as particulate preparations in treating cervical radicular pain[21,22]. Methylprednisolone and triamcinolone are the drugs most commonly used for epidural steroid injections. Common side effects of epidural steroid injections are paresthesia, pain on injection, intravascular injection, bleeding and dysesthesia[21]. The most serious complications of epidural steroid injections are related to intravascular injections. Intraarterial injections may occur even with a negative aspirate and have been shown to potentially cause paraplegia. Although the use of computed tomography guidance instead of conventional fluoroscopy provides a better image of relevant anatomy, it does not assure avoidance of these adverse events[23]. Topical corticosteroids (2.5% ointment, triamcinolone 0.1% ointment, and clobetasol propionate 0.05% foam) achieve more effective skin concentrations than oral prednisone[24]. Side effects, including skin thinning, color change, and systemic effects, can be expected with topical application of corticosteroids and increase in a dose-dependent manner[25]. Inhaled corticosteroids have evolved into a mainstay of therapy for moderate to severe asthma. Effectiveness and systemic bioavailability vary with each corticosteroid molecule and dosage, but in general, systemic effects are minimized with proper administration[26]. Common side effects of inhaled corticosteroids include gingival irritation and oral candidiasis, as well as the many systemic effects associated with corticosteroid use[26,27]. Fludrocortisone is a synthetic corticosteroid that has potent mineralocorticoid effects. It has been used clinically to achieve the mineralocorticoid effects of sodium and water retention in cases of cerebral salt wasting, orthostatic hypotension, and adrenocortical insufficiency in Addison disease[28-30]. Potassium wasting is a common side effect of fludrocortisones administration, and electrolyte levels should be monitored while a patient is undergoing fludrocortisones administration[30]. The potencies of corticosteroids vary widely, with synthetic compounds generally retaining greater anti-inflammatory potency and weaker salt-retaining properties; these potencies are summarized in the Table 1.

Table 1 Basic potency, duration of action, and equivalent dose of typical steroid preparations

Agent	Anti-inflammatory potency relative to cortisol	Mineralocorticoid potency relative to cortisol	Duration of action, hours	Equivalent dose, mg
Cortisol	1	1	8-12	20
Triamcinolone (Aristocort)	5	0	12-36	4
6-Methylprednisolone (Depo-Medrol)	5	0	12-36	4
Betamethasone (Celestone)	25	0	36-72	0.75
Fludrocortisone	10	125	-	-

Mechanistic pharmacology and physiology of steroids

The anti-inflammatory properties of steroids have been attributed to their inhibitory effects on the action of phospholipase A2, an enzyme critical to the production of inflammatory compounds[31]. Research has shown that steroids are active in affecting gene expression, translation and enzyme activity. In short, they bring about their physiologic effects through a multitude of biochemical pathways[32]. One such pathway is through their induction of the production of proteins called lipocortins. Glucocorticoids stem the production of inflammatory mediators such as leukotrienes and prostaglandins and effectively halt the inflammatory cascade[31,33]. As their wide-ranging side effects indicate, glucocorticoids can impact many systems throughout the body. Through negative feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis, exogenous glucocorticoids can directly induce hypopituitarism (Addison disease). Their actions on glucose metabolism can increase insulin resistance in tissues and increase fasting glucose levels. Glucocorticoids can act directly on osteoclasts to affect bone resorption and decrease calcium absorption in the gastrointestinal tract, resulting in osteopenia and osteoporosis[34]. Because of the wide-ranging effects that glucocorticoids can have on a patient's body and on the HPA axis in particular, a practitioner must be careful when discontinuing their administration. If steroids have been administered for less than 1 week, they can be stopped without tapering. For dosing lasting 1-3 weeks, tapering should be based upon clinical conditions and the illness for which the medication was prescribed[16]. When the patient has taken glucocorticoids for more than 3 weeks, the practitioner's goal is a quick tapering to physiologic doses and then a slow decrease in dosage while evaluating adrenal function. For patients who are taking equivalent doses of 30 mg of hydrocortisone daily or have established HPA axis dysfunction and are under stress (eg, major surgery, critical illness, trauma), an increased dosing of steroids (intravenous or intramuscular hydrocortisone) is recommended every 6 hours for 24 hours, followed by a tapering to the previous maintenance dose by 50% per day[34]. Mineralocorticoids, endogenously represented by aldosterone and deoxycorticosterone, effect physiologic changes by altering electrolyte (sodium and potassium) levels, causing volume changes to occur. Rather than being moderated by the HPA axis as glucocorticoid production is, mineralocorticoid production is mainly regulated by the renin-angiotensin-aldosterone system, although adrenocorticotrophic hormone, a product of the HPA axis, does have minimal activity in stimulating aldosterone release[2].

Tapering of corticosteroid therapy

When corticosteroids are used systemically as intensive therapy or for prolonged courses, a tapering strategy is recommended to prevent signs and symptoms of adrenal insufficiency due to hypothalamic-pituitary-adrenal axis suppression. General recommendations regarding the need to consider a tapering regimen are (1) prednisone ≥30 mg daily (or equivalent) for at least 2 weeks, (2) any dose of any systemic corticosteroid for at least 1 month, or (3) when signs and symptoms of hypothalamic-pituitary-adrenal axis suppression are already present. Some clinicians also use tapering to avoid an exacerbation or flare of the condition that is being treated. Although there may be examples among the hundreds of inflammatory and immune conditions for which corticosteroids are used, in general, an exacerbation that results from abrupt discontinuation of corticosteroid therapy (when appropriate) is rare. In clinical practice, clinicians use tapering more commonly than the situations described above. There are likely multiple reasons for this decision, including concerns about hypothalamic-pituitary-adrenal axis suppression and its consequences. It is generally unnecessary to taper doses in patients who receive corticosteroids for 5-10 d, which is among the most common regimens used for acute treatment. Unfortunately, the use of tapering in these situations can lead to longer exposure to the corticosteroid than necessary and the attendant risks associated with continued use. Tapering of corticosteroids, when appropriate, is an art rather than a science and may require frequent adjustments to the tapering schedule, depending on how the patient is tolerating the taper. Although there is no one correct strategy for tapering, general recommendations based on clinical experience are provided for consideration. First, the clinical team should determine whether a rapid or slow tapering schedule is desired. Generally, shorter use of corticosteroids can be tapered fast, whereas longer durations of treatments require slower tapering. A general observation is that the duration of a taper should be 33-100% of the treatment course. When using prednisone as an example, tapering of daily doses of >20 mg can be made in 10-mg increments, with adjustments made every few days to weeks, depending on the duration of the taper. When a daily dose of 20 mg daily is reached, it is useful for the patient to see the clinician for evaluation about how the tapering regimen is being tolerated. At this point, reducing the daily dose in 2.5- or 5-mg increments according to the schedule is often successful. At any point during a tapering regimen, if the patient develops signs of adrenal insufficiency, then the taper can be stopped or slowed until the patient is stable[35].

Adverse effects associated with long term use of corticosteroids

As discussed above corticosteroids are double edged sword, prolonged use of steroids mainly systemic steroids leads to adverse effects like osteoporosis and fractures, HPA-axis suppression, cushing syndrome and weight gain, hyperglycaemia/ diabetes, CVD and dyslipidaemia, myopathy, cataracts and glaucoma, psychiatric disturbances, immunosuppression as well as other GI and dermatologic events. Mechanisms of adverse effects during the administration of Glucocorticoids observed chronic disease (eg, prednisone or prednisolone) do not have significant mineralocorticoid, androgenic, or estrogenic activity; thus, their major adverse effects result from inhibition of hypothalamic-pituitary-adrenal function and the development of iatrogenic Cushing's syndrome. The effects of glucocorticoids are mediated by differences in bioavailability, receptor activation by phosphorylation, translocation, and repression/activation of gene expression. This leaves multiple sites where differences among glucocorticoids and/or differences among individuals can result in differences in efficacy and toxicity. It helps explain the differential resistance to therapy and toxicities among patients. Below Figure 2 is the over view of long term effects of steroids[36].

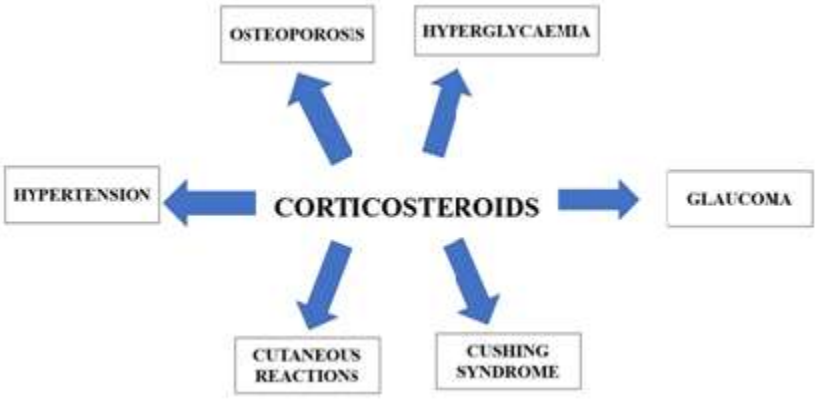

Figure 2 Effects of long term use of corticosteroids

Conclusion

Since their discovery, steroids have infiltrated nearly every branch of medicine and can be administered in nearly every route available. The effects of steroid use can vary widely, and the full spectrum of side effects can be present even in patients taking low doses. Practitioners must be aware that the drug can possibly exacerbate a preexisting condition or present a new medical condition. Knowledge of the clinical implications of prescribing these agents is critical.

References

1. Kendall, EC. Nobel lecture: The development of cortisone as a therapeutic agent. Nobelprize.org. December 11, 1950. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1950/kendall-lecture.html.

2. Stewart PM, Krone NP. The adrenal cortex. In: Melmed S, Polonsky K, Larsen PR, Kronenberg H, eds. Williams Textbook of Endocrinology. 12th ed. Philadelphia, PA: Saunders; 2011.

3. Baeck M, Marot L, Nicolas JF, Pilette C, Tennstedt D, Goossens A. Allergic hypersensitivity to topical and systemic corticosteroids: a review. Allergy. 2009; 64(7):978-94. https://doi.org/10.1111/j.1398-9995.2009.02038.x

4. Roth P, Happold C, Weller M. Corticosteroid use in neuro-oncology: an update. Neuro-oncology practice. 2015; 2(1):6-12. https://doi.org/10.1093/nop/npu029

5. Williams DM. Clinical pharmacology of corticosteroids. Respiratory care. 2018; 63(6):655-70. https://doi.org/10.4187/respcare.06314

6. Gupta P, Bhatia V. Corticosteroid physiology and principles of therapy. Indian J Pediatr. 2008; 75(10):1039-1044. https://doi.org/10.1007/s12098-008-0208-1

7. Shaikh S, Verma H, Yadav M, Jauhari M, Bullangowda J, Applications of steroid in clinical practice: a review. ISRN Anesthesiol. 2012; 985495. https://doi.org/10.5402/2012/985495

8. Becker DE. Basic and clinical pharmacology of glucocorticosteroids. Anesth Prog. 2013; 60(1):25-31. https://doi.org/10.2344/0003-3006-60.1.25

9. Annane D. Adrenal insufficiency in sepsis. Curr Pharm Des. 2008; 14(19):1882-1886. https://doi.org/10.2174/138161208784980626

10. Xu J, Winkler J, Derendorf H. A pharmacokinetic/pharmacodynamic approach to predict total prednisolone concentrations in human plasma. J Pharmacokinet Pharmacodyn. 2007; 34(3):355-372. https://doi.org/10.1007/s10928-007-9050-8

11. Curtis JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum. 2006; 55(3):420-426. https://doi.org/10.1002/art.21984

12. Kenna HA, Poon AW, de los Angeles CP, Koran LM. Psychiatric complications of treatment with corticosteroids: review with case report. Psychiatry Clin Neurosci. 2011; 65(6):549-560. https://doi.org/10.1111/j.1440-1819.2011.02260.x

13. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. Mayo Clin Proc. 2006; 81(10):1361-1367. https://doi.org/10.4065/81.10.1361

14. Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis and management. Drug Saf. 2000; 22(2):111-122. https://doi.org/10.2165/00002018-200022020-00004

15. Pereira RM, Carvalho JF, Canalis E. Glucocorticoid-induced osteoporosis in rheumatic diseases. Clinics (Sao Paulo). 2010; 65(11):1197-1205. https://doi.org/10.1590/S1807-59322010001100024

16. Lansang MC, Hustak LK. Glucocorticoid-induced diabetes and adrenal suppression: how to detect and manage them. Cleve Clin J Med. 2011; 78(11):748-756. https://doi.org/10.3949/ccjm.78a.10180

17. Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, et al. Shortterm vs conventional glucocorticoid therapy in acute exacerbations of COPD: The REDUCE randomized clinical trial. JAMA 2013; 309(21):2223-2231. https://doi.org/10.1001/jama.2013.5023

18. Jain M, Jain A, Khare B, Jain DK, Khan R, Jain D. An Update on the Recent Emergence of Candida auris. Asian Journal of Dental and Health Sciences. 2022; 2(1):14-9. https://doi.org/10.22270/ajdhs.v2i1.11

19. Benzon HT, Gissen AJ, Strichartz GR, Avram MJ, Covino BG. The effect of polyethylene glycol on mammalian nerve impulses. Anesth Analg. 1987; 66(6):553-559. https://doi.org/10.1213/00000539-198706000-00012

20. Craig DB, Habib GG. Flaccid paraparesis following obstetrical epidural anesthesia: possible role of benzyl alcohol. Anesth Analg. 1977; 56(2):219-221. https://doi.org/10.1213/00000539-197703000-00011

21. Ahadian FM, McGreevy K, Schulteis G. Lumbar transforaminal epidural dexamethasone: a prospective, randomized, doubleblind, dose-response trial. Reg Anesth Pain Med. 2011; 36(6):572-578. https://doi.org/10.1097/AAP.0b013e318232e843

22. Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. Pain Med. 2006; 7(3):237-242. https://doi.org/10.1111/j.1526-4637.2006.00162.x

23. Somayaji HS, Saifuddin A, Casey AT, Briggs TW. Spinal cord infarction following therapeutic computed tomography-guided left L2 nerve root injection. Spine (Phila Pa 1976). 2005; 30(4):E106-E108. https://doi.org/10.1097/01.brs.0000153400.67526.07

24. Aleem A, Kabir H, Review on Swertia chirata as traditional uses to its pyhtochemistry and phrmacological activity, Journal of Drug Delivery and Therapeutics 2018; 8(5-s):73-78 https://doi.org/10.22270/jddt.v8i5-s.1957

25. Morley KW, Dinulos JG. Update on topical glucocorticoid use in children. Curr Opin Pediatr. 2012; 24(1):121-128. https://doi.org/10.1097/MOP.0b013e32834ef53d

26. Jat D, Thakur N, Jain DK, Prasad S, Yadav R. Iris ensata Thunb: Review on Its Chemistry, Morphology, Ethno Medical Uses, Phytochemistry and Pharmacological Activities. Asian Journal of Dental and Health Sciences. 2022; 2(1):1-6. https://doi.org/10.22270/ajdhs.v2i1.9

27. Doherty DE, Tashkin DP, Kerwin E, et al. Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic obstructive pulmonary disease (COPD): results from a 52-week Phase III trial in subjects with moderate-to-very severe COPD. Int J Chron Obstruct Pulmon Dis. 2012; 7:57-71. https://doi.org/10.2147/COPD.S27320

28. Taplin CE, Cowell CT, Silink M, Ambler GR. Fludrocortisone therapy in cerebral salt wasting. Pediatrics. 2006; 118(6): e1904-e1908. https://doi.org/10.1542/peds.2006-0702

29. Freitas J, Santos R, Azevedo E, Costa O, Carvalho M, de Freitas AF. Clinical improvement in patients with orthostatic intolerance after treatment with bisoprolol and fludrocortisone. Clin Auton Res. 2000; 10(5):293-299. https://doi.org/10.1007/BF02281112

30. Physicians Total Care, Inc. Fludrocortisone acetate tablet. Daily Med. September 2010. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid¼bf927cd9-1891-4de4-b4be-743a26363a64.

31. Wallner BP, Mattaliano RJ, Hession C, et al. Cloning and expression of human lipocortin, a phospholipase A2 inhibitor with potential anti-inflammatory activity. Nature. 1986; 320(6057):77-81. https://doi.org/10.1038/320077a0

32. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids-new mechanisms for old drugs. N Engl J Med. 2005; 353(16):1711-1723. https://doi.org/10.1056/NEJMra050541

33. Blackwell GJ, Carnuccio R, Di Rosa M, Flower RJ, Parente L, Persico P. Macrocortin: a polypeptide causing the antiphospholipase effect of glucocorticoids. Nature. 1980; 287(5778):147-149. https://doi.org/10.1038/287147a0

34. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med. 2003; 348(8):727-734. https://doi.org/10.1056/NEJMra020529

35. Williams DM. Clinical pharmacology of corticosteroids. Respiratory care. 2018; 63(6):655-70. https://doi.org/10.4187/respcare.06314

36. Lakshmi Surekha K, Naveen Reddy P, Rasajna G. Bhavani B. A Review on Corticosteroids and Its Clinical Complications on Long Term Exposure. International Journal of Advanced Scientific Research and Management. 2020; 5(9):34-38 https://doi.org/10.36282/IJASRM/5.9.2020.1746