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A REVIEW ON COMMON HAZARDS OF STEROIDS USED IN HYPERTENSIVES

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Abstract:
Steroids are a wide range of molecules with varying physiological effects. Especially corticosteroids are a class of drugs encompassing both laboratory-synthesized and naturally produced hormones. [1] Glucocorticoids may lead to the development of hypertension, heart failure, myocardial ischemia and associated with the metabolic syndrome. The prolonged usage of steroids at higher doses leads to severe conditions like osteoporosis, adrenal suppression myopathy, electrolyte, and metabolic abnormalities. [2] Prednisone and Dexamethasone has the major side effects in the hypertensive patients. Prednisone may cause increase in the blood pressure and development of steroid hypertension is rapid. Dexamethasone causes the increase in sodium levels and edema which leads to rise in blood pressure. [3] On conducting studies on sheep, it has been shown that ANS and vasoactive proteinoids appear to buffer rather than cause in increase BP. The RAAS, AVP and serotonin are also unlikely to be involved. A direct involvement of CNS i.e., ACTH raises BP. There are multiple factors involved in glucocorticoid induced hypertension in human are triggering of RAAS, reduced activity of depressor systems, increased pressor responses to AG ll and norepinephrine. [4]

***KEY WORDS**: Corticosteroids, Hypertension, Dexamethasone, Prednisone*

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INTRODUCTION:

Steroids are a man-made version of chemicals, known as hormones that are made naturally in the human body. Steroids are designed to act like these hormones to reduce inflammation. They are also known as corticosteroids, and are different to anabolic steroids used by body builders & athletes. 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. Today, many of the clinical roles of steroids are related to their potent anti-inflammatory and immune-modulating properties. Clinically[i] 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. Side effects can occur at a wide range of doses and vary depending on the route of administration.

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. Steroids won't care your condition, but they are very good at reducing inflammation and will ease Symptoms such as swelling, pain and stiffness usually inflammation is the body's natural reaction to infection of bacteria. Your immune System produces extra fluid to fight infections or bacteria, which causes swelling, redness and heat in the affected area.

CLASSIFICATION:

- Male sex hormone – e.g.: testosterone
- Female sex hormone -e.g.: estradiol, progesterone
- Anti-inflammatory agent – e g: cortisone
- Cardiac Steroids – e.g.: digitoxigenin
- Diuretics - e.g.: Spironolactone
- Digestants - e.g.: dihydrochloride

PHARMACOLOGICAL EFFECTS [5]

- The pharmacologic effects and the adverse reactions of corticosteroids are closely related.
- The effects for which they are used include their anti-inflammatory action and suppression of allergic reactions.
- They also suppress the immune response. Corticosteroids are palliative rather than curative.
- The glucocorticoid effects and the mineralocorticoid effects. Many of these produce adverse reactions.

GLUCOCORTICOID AND MINERALOCORTICOID EFFECTS **[5]**

➢ **Glucocorticoid effects**

❖ Broad

- Decrease carbohydrate metabolism
- Anti-inflammatory
- Antiallergenic
- Increases enzyme action
- Negatively effects Membrane function
- Increases nucleic acid synthesis

❖ Specific

- Catabolism
- Increased gluconeogenesis
- Decreased glucose use
- Inhibition of protein synthesis
- Increased protein catabolism
- Decreased growth
- Decreased bone density
- Decreased resistance to infection

➢ **Mineralocorticoid effects [5]**
➢ Increased sodium and water retention
➢ promote potassium loss
➢ Edema and hypertension

ADVERSE REACTIONS [5]

The adverse reactions of corticosteroids are proportional to the following

- Dose frequency
- Time of administration and
- Duration of treatment
- With prolonged therapy and sufficiently high doses, the following side effects occur.

METABOLIC CHANGES:

➢ Moon face
➢ Buffalo hump (fat deposited on back of the neck)
➢ Truncal obesity
➢ Weight gain

- Muscle wasting give patients the Cushing's syndrome appearance
- Hyperglycemia (diabetes-like) may be aggravated or initiated, especially in prediabetic patients.

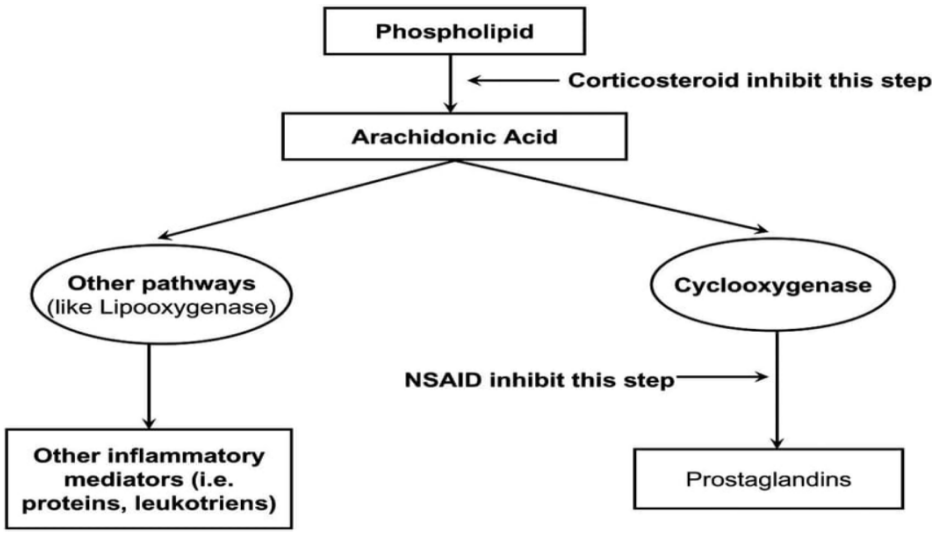
INFECTIONS:
Corticosteroids decrease resistance to infection. Because of their anti-inflammatory action, they may also mask its symptoms. Patients taking long-term glucocorticoid therapy are given isoniazid, an antituberculosis agent, to prevent tuberculosis.

CENTRAL NERVOUS SYSTEM EFFECTS: [5]
Changes in behavior and personality, including euphoria (with increasing dose), agitation, psychoses, and depression (with decreasing dose), can occur.

PEPTIC ULCER
Because corticosteroids stimulate an increase in production of stomach acid and pepsin, they may exacerbate peptic ulcers. Healing is impaired, and the ulcer may perforate.
Impaired Wound Healing and Osteoporosis

MECHANISM OF ACTION OF CORTICOSTEROIDS [6]

- Corticosteroids modify the functions of epidermal and dermal cells and of leukocytes participating in proliferative and inflammatory skin diseases.
- After passage through the cell membrane corticosteroids react with receptor proteins in the cytoplasm to form a steroid-receptor complex.
- This complex moves into the nucleus, where it binds to DNA. The binding process then changes the transcription of messenger RNA (mRNA).
- Because mRNA acts as template for protein synthesis, corticosteroids can either stimulate or inhibit the synthesis of specific proteins.
- Thus, corticosteroids are known to stimulate the production of a glycoprotein called lipocortin.
- The formed lipocortin inhibits the activity of phospholipase A2, which releases arachidonic acid, the precursor of leukotrienes, from phospholipids.
- In contrast, corticosteroids inhibit mRNA responsible for interleukin-1 formation.
- These actions of corticosteroids on arachidonic acid metabolism and interleukin-1 formation produce anti-inflammatory, immunosuppressive and anti-mitogenic effects.
- Although this theory based on protein synthesis may not explain all effects of corticosteroids, these examples illustrate that a specific action on the molecular level can explain some of the characteristic and typical pharmacological effects of topically applied corticosteroids.
- Additional studies of the mechanism of action of corticosteroids are warranted. Such studies will not only help to explain how corticosteroids work, but also create a background that is essential for the development of novel non-steroidal anti-inflammatory drugs.



HYPERTENSION

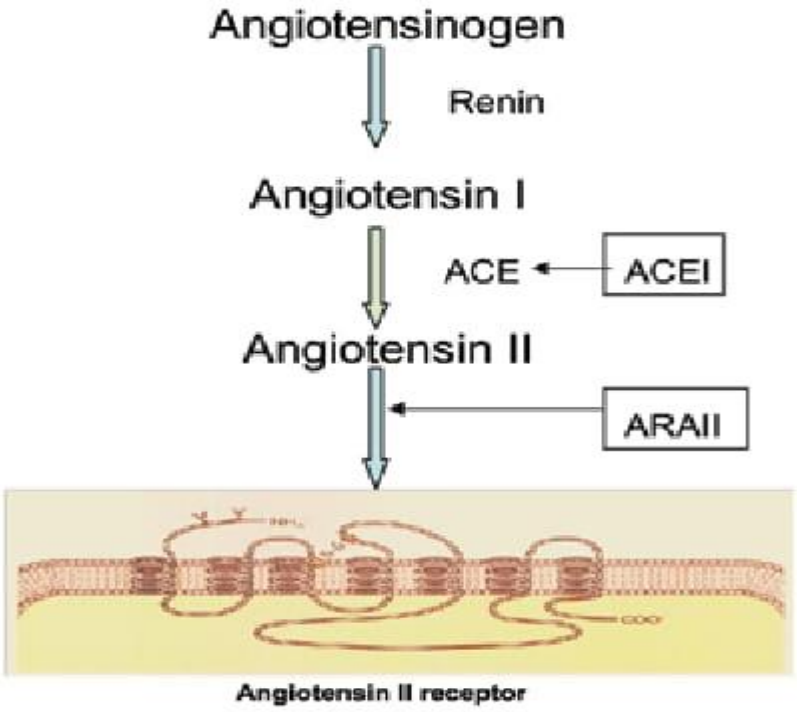
It is defined as a condition in which the force of the blood against the artery walls is too high. The blood pressure above 140/90 is considered as hypertension

A/C to JOINT NATIONAL COMMITTEE(JNC) the standard hypertension criteria is as follows

BLOOD PRESSURE CATEGORY	SYSTOLIC (mm Hg)	DIASTOLIC (mm Hg)
Healthy	< 120	< 80
Elevated	120-129	<80
Stage 1 Hypertension	130-139	80-89
Stage 2 Hypertension	140 or higher	90 or higher
Hypertension crisis	Over 180	over 120

MOA OF HYPERTENSIVES: [7]

The following describes the MOA of beta blockers, ACE inhibitors and ARB inhibitors



- Hypertension is a common preventable cause of cardiovascular morbidity and mortality and can substantially affect the quality of life and independence of older adults.
- Hypertension affects 1 in 5 of adults worldwide and is generally diagnosed and treated in primary health care services.
- The reported prevalence of hypertension among long-term users of glucocorticoids is more than 30% and it is found in 25%–93% of patients with Cushing syndrome.
- The personal and economic impact of hypertension is likely to be higher among people with chronic systemic inflammatory diseases, who already have limitations to their activity.
- These diseases are often initially treated with oral glucocorticoids for a minimum of 3months, with disease relapses and flares requiring additional glucocorticoid dose escalation in the following years.
- It is widely reported that use of oral glucocorticoids is associated with an

increased risk of hypertension and that this association is dose related.

- Evidence, however, remains inconsistent, and the pathophysiology of glucocorticoid-induced hypertension is unclear.
- Three previous population-matched case–control studies investigating glucocorticoid-related adverse events among patients with psoriasis or asthma reported conflicting results.
- These studies were of relatively small size (< 7000 patients) and had several limitations.
- For example, they excluded a substantial number of patients for different reasons (e.g., rheumatic diseases,14 < 30-day glucocorticoid exposure in 1 year15), considered only medication prescribed by specialists in outpatient or hospital services, and did not model risk in relation to changing glucocorticoid dose over time or reported unadjusted estimates.
- Moreover, none of these studies adjusted the estimates of dose–response by disease activity, which could also affect the risk of hypertension.
- The effect of oral glucocorticoid dose on incident hypertension in patients with 6 common chronic inflammatory diseases, using linked electronic health records in England.
- The study also examined whether adjustment for disease activity over time influenced the estimates.
- Hypertension is a well-recognized complication of excess glucocorticoids, both naturally-occurring and synthetic.

SIDE EFFECTS OF STEROIDS IN HYPERTENSIVES: [8]

- Glucocorticoids may play a role in hypertension development.
- Heart failure
- Myocardial ischemia
- Stroke
- Metabolic syndrome
- Osteoporosis
- Myopathy
- Electrolyte, and metabolic abnormalities

ANABOLIC STEROIDS INDUCED MYOCARDIAL INFRACTION: [9]

A Risk factors for myocardial infarction (MI) in young people are highly significant and at this age drug abuse must always be considered. Athletes use androgenic-anabolic steroids (AAS) to increase their performance (protein synthesis in skeletal muscles is increased by AAS); however, there are critical adverse effects, as follows:

- Hepatic dysfunction
- Endocrine dysfunction
- Cardiovascular and
- Behavioral changes have been reported
- An increased cardiovascular risk in those individuals who use these drugs as follows:
- ST-elevation MI (STEMI) is a life-threatening condition having 2.5-10% mortality in the first month.
- Conventional risk factors play an important role in coronary heart diseases,
- Nontraditional risk factors also need to be considered as they are present in more than 50% of coronary artery disease cases.
- In a previous study, more than 150 drugs were reported as possible causes of MI, out of which 39 drugs were thought as the main suspects that can cause MI: prednisone, betamethasone, and dexamethasone.

DEXAMETHASONE [10]

- Dexamethasone is a potent synthetic glucocorticoid, which has widespread clinical applications.
- As dexamethasone has purely glucocorticoid activity with negligible mineralocorticoid effects,
- dexamethasone-induced hypertension models have been used for studying the mechanisms of glucocorticoid-induced hypertension.
- This review examines the characteristics and mechanisms of both in the human and experimental animal models.
- The roles of hemodynamics, volume, renin-angiotensin-aldosterone system, sympathetic nervous system, vasodilators including nitric oxide, vasoconstrictors and reactive oxygen species in the pathogenesis of Dexamethasone are reviewed and differences from hypertension due to naturally occurring steroids discussed.

PREDNISOLONE [11]

- It is part of a group of medications called corticosteroids or just “steroids.” Prednisone is a human-made (synthetic) version of steroids that are naturally made in the body.
- Prednisone is commonly used to help reduce inflammation, relieve pain, and reduce discomfort.
- A major side effect of prednisone is increased blood pressure. There are two reasons leads to increase in blood pressure

- It effects on fluid balance in the body, which causes it to retain water.
- It effects on weight gain, since it can cause changes in appetite and the body's response to insulin and sugar
- One hundred and ninety-five patients undergoing low-dose prednisone or prednisolone therapy were investigated. Blood pressure, weight, serum urea, sodium and potassium were recorded before therapy and again after at least 1 year of therapy.
- The rise in both mean systolic and mean diastolic blood pressure was paralleled by an increase in the prevalence of arbitrarily defined hypertension.
- There was no relationship between change of blood pressure and either dose of corticosteroid or duration of therapy.
- Blood pressure before therapy was the main determinant of the change in blood pressure.
- Mean serum sodium levels rose slightly but serum potassium levels did not change during the follow-up period. There was no significant weight gain.
- These results indicate that treatment of asthma and rheumatoid arthritis with prednisolone or prednisolone in low dose does not cause hypertension or biochemical features suggestive of mineralocorticoid excess.

ACTH-DEPENDENT INDEPENDENT ADRENOCORTICAL STEROID HYPERTENSION [12]

ACTH dependent and independent adrenocortical steroid hypertension is thought to be due to the 'mineralocorticoid' and/or 'glucocorticoid' activity of the steroids.

- Studies in sheep examining ACTH and adrenocortical steroid hypertension have provided evidence for a hypertensive class of steroid activity.
- A hypothesis is proposed to explain how the 'hypertensive' actions of a steroid may produce hypertension.
- It is suggested that effects mediated via 'mineralocorticoid' and 'glucocorticoid' receptors may modulate or amplify the 'hypertensive' activity.
- Individual steroids may express any, all or none of these three types of steroid hormone activity.
- Hypertension as a consequence of glucocorticoid administration, soon after the introduction of pharmacologic glucocorticoid therapy, hypertension was noted as a complication of treatment with cortisone.
- Corticosteroid therapy probably contributes to the hypertension seen in renal allograft recipients and conversion from daily to alternate-day steroids reduce blood pressure in some patients
- Hypertension occurs in 20% of patients with iatrogenic Cushing's syndrome compared with 80% of patients with the naturally occurring disease.
- The lower incidence of high blood pressure with exogenous glucocorticoids reflects the use of cortisol derivatives, which have greater anti-inflammatory and lesser salt-retaining properties than does the natural hormone.
- Impaired renal function increases the incidence of hypertension during cortisone therapy

HYPERTENSION IN CUSHING'S SYNDROME [13]

- Cushing's syndrome, defined as the clinical features associated with prolonged exposure to elevated glucocorticoid blood levels, encompasses a number of clinical states. The syndrome can be divided into ACTH-dependent and adrenal forms.
- The ACTH-dependent form comprises pituitary ACTH excess (Cushing's disease), which accounts for some two-thirds of cases; production of ectopic ACTH (or pro-opiomelanocortin [POMC] or corticotropin releasing factor) by endocrine tumors (for example, medullary carcinoma of the thyroid) or nonendocrine tumors (such as oat cell tumor of the lung); and exogenous
- ACTH administration (for example, in the management of infantile spasms). The adrenal form comprises adrenal adenoma and carcinoma and exogenous glucocorticoid administration. Cushing's syndrome is the cause of hypertension in approximately one in 300 to 400 hypertensives.

GLUCOCORTICOID USE IS ASSOCIATED WITH AN INCREASED RISK OF HYPERTENSION [14]

Among patients with Cushing's syndrome, hypertension is very common, some 80% of patients Greminger and colleagues reported that 64% of patients with Cushing's disease were hypertensive (average blood pressure, 158/100 mm Hg), compared with 83% of patients with adenoma (average blood pressure, 164/100 mm Hg) and 100% with carcinoma (average blood pressure, 184/114mm Hg).

- Rosset al found hypertension in 87% of patients with hyperplasia and in all of 15 patients with adrenal tumors. Welbourn and coworkers found that 93% of patients were hypertensive but that the incidence and severity of hypertension were unrelated to gender, the nature of the underlying lesion, or the duration or severity of symptoms.
- Blood pressure was raised 43/29 mm Hg compared with age and sex-matched normal control subjects. Forty percent of the patients had cardiovascular complications . The proportion of patients with ectopic ACTH production who are hypertensive is usually lower than in other forms of Cushing's syndrome. This might reflect the relatively short duration of the disease, a different pattern of steroid production, or the underlying malignancy.
- Cushing's syndrome is an aggressive disease with a 50% 5-year mortality in untreated patients Even with a permanent biochemical remission, mortality is still 4 times that of the general population, largely because of cardiovascular disease.
- A reversible "pseudo-Cushing's syndrome" occurs in association with alcohol abuse, and these patients are usually hypertensive.
- Alcohol stimulates POMC expression, and it is possible that the well-documented association between hypertension and alcohol consumption might relate to overactivity of the hypothalamic-pituitary adrenal axis.

EXPERIMENTAL MODELS [15]

- Hypertension in experimental studies in humans' studies have shown that short-term ACTH administration increases blood pressure in normal and hypertensive adults, but not in patients with Addison's disease.
- Administration of ACTH increased cardiac index and plasma volume, but did not change peripheral resistance. Plasma renin substrate rose, plasma renin concentration fell, and urinary kallikrein activity increased.

STEROIDS INDUCED HYPERTENSION EXPERIMENTAL MODEL [15]

steroids that are responsible for the hypertensive effects of ACTH, cortisol or deoxycorticosterone was infused at rates that produced blood concentrations of steroid appropriate for conditions of ACTH stimulation. [16] Cortisol infusion reproduced the blood pressure and metabolic effects of ACTH administration, whereas deoxycorticosterone infusion did not.

It thus appears that the rise in blood pressure that occurs with short-term ACTH administration in humans is due to the increased secretion of cortisol. Whether these observations are relevant to Cushing's often have ACTH concentrations that are normal or only mildly elevated.

If cortisol is infused intravenously at a rate of 6 to 8 mg/hour for 5 days in 7 subjects and in separate studies gave oral hydrocortisone, 50 mg every 6 hours, to 6 other subjects for 5 days. In both sets of experiments daily electrolyte intake was constant: 100 mmol sodium and 100 mmol potassium for the intravenous study; 150 mmol sodium and 70 mmol potassium for the oral study. With constant infusion, plasma cortisol concentration doubled; with oral administration, plasma cortisol concentration rose to a similar extent at 0900 hours but was not maintained throughout the day, and at 2400 hours was similar to control values.

This probably reflects the variable bioavailability of the oral preparation and might explain the discrepancy in blood pressure rise, Cortisol infusion increased supine systolic blood pressure 21 mm Hg (Fig. 2). Blood pressure rose in all 7 subjects and was high in both morning and afternoon readings and with supine and standing readings. No changes were apparent in mean or diastolic pressures

Oral administration increased supine SBP only 5 mm Hg. Standing systolic pressure also was increased. No changes were detected in mean or diastolic pressure, nor were consistent changes noted in pulse rate. Cardiac output, as assessed by maximum aortic velocity determined by echocardiography, rose from 5 to 113 5ml/sec. Metabolic and hormonal effects with cortisol infusion (Fig. 2), plasma sodium increased, plasma potassium fell, and blood glucose was markedly increased as anticipated. Plasma urea and creatinine clearance increased. Body weight increased and hemoglobin and hematocrit fell, accompanied by eosinopenia and lymphocytosis.

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Cortisol withdrawal prompted increases in fluid intake and urine output as well as a diuresis. Initial urinary sodium retention was followed by a large natriuresis and a reduction in urinary when the infusion was stopped. Hypernatremia, hypokalemia, and initial sodium retention are mineralocorticoid effects and presumably reflect the binding of cortisol to the type-I mineralocorticoid) receptor.

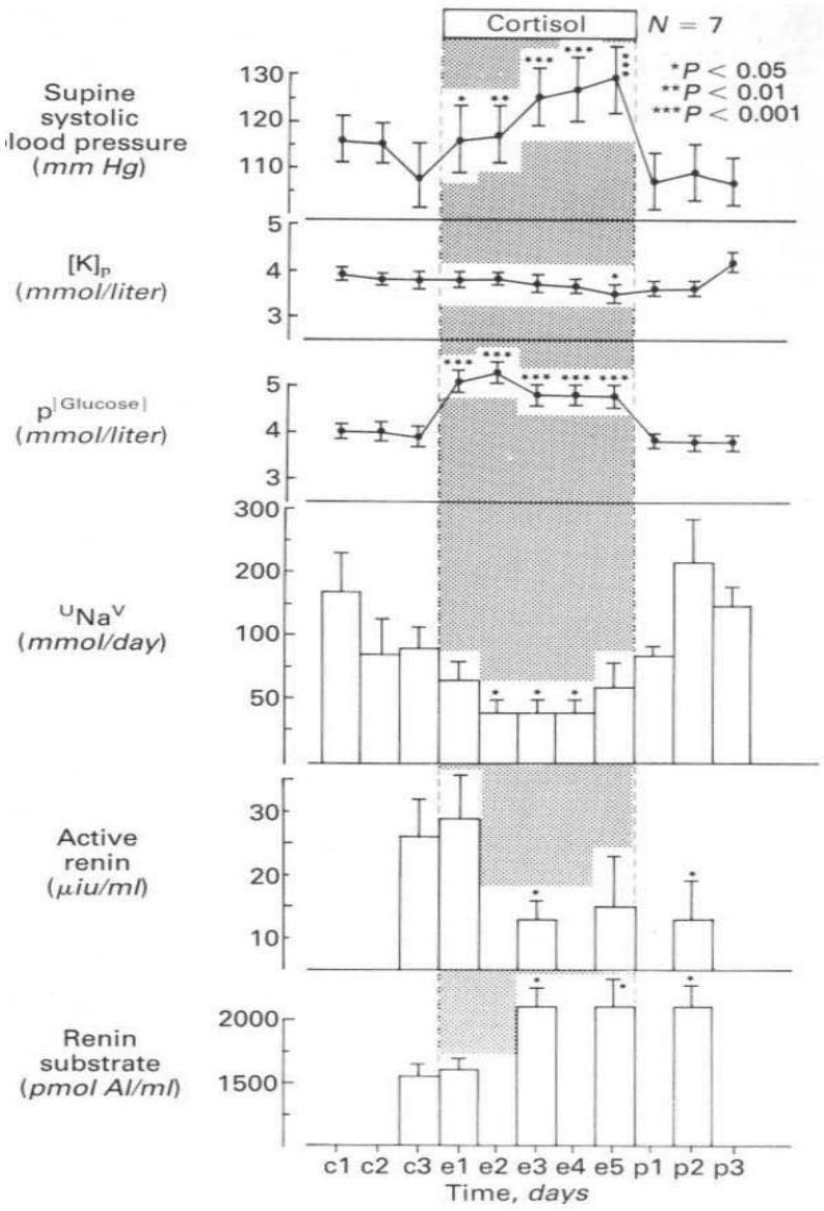

Fig. 2. Effects of cortisol infusion (6-8 mg/hr.) on systolic blood pressure, plasma glucose, urinary sodium excretion, renin concentration, and renin substrate in volunteer subjects (Reproduced from Ref. [15] , [16])

Increases in water drinking and urine output and a rise in blood glucose are typical glucocorticoid effects (binding to type (-I receptors). With oral cortisol, changes were similar to those seen in the intravenous infusion. When oral hydrocortisone was administered, plasma volume increased by approximately 800 ml, with an increase in exchangeable sodium of some 340 mmol, which was accounted for by cumulative urinary sodium retention and a 3-liter expansion of extracellular fluid volume.

Output was by the fifth day of hydrocortisone treatment, sodium equivalent to intake. With cortisol infusion, plasma renin concentration (PRC) fell; 2 days after cessation of infusion the PRC was still low. Inactive renin was unchanged and renin substrate was increased (Fig. 2). With oral steroid administration, similar changes were seen in PRC, and angiotensin II concentrations decreased. The rise in renin substrate is a classic glucocorticoid effect. Renin concentration was still suppressed 48 hours after cessation of infusion.

Thus, some other factor, apart from increases in volume and blood pressure, might be contributing to the suppression. The renin-angiotensin system does not appear to play a major role in the hypertension of Cushing's syndrome. Administration of the angiotensin II antagonist Sarala-sin had no effect on blood pressure in patients with Cushing's syndrome, and in another study, the angiotensin converting enzyme inhibitor captopril produced a reduction in pressure in some patients with high renin but had little or no effect on patients with normal or low renin.

Oral hydrocortisone, plasma adrenaline concentrations were essentially unchanged, but plasma noradrenaline fell, suggesting a decrease in sympathetic activity. Plasma vasopressin showed little change but atrial natriuretic peptide concentrations increased markedly. Renal function the role of adrenal steroid hormones in maintaining normal renal function is well recognized.

In Addison's disease, with glucocorticoid and mineralocorticoid deficiency, both glomerular filtration rate (GFR) and renal blood flow (RBF) are low. Cortisol appears to be essential for the maintenance of GFR and RBF independent of changes in volume or electrolyte status. Glucocorticoid administration increases GFR in humans, usually in association with a rise in filtration fraction.

Oral hydrocortisone administration produced substantial increases in GFR (inulin clearance) but effective renal plasma flow (PAH clearance) was unchanged (assuming constant PAH extraction) and filtration fraction rose. Renal blood flow decreased because of a fall in hematocrit (presumably a consequence of plasma volume expansion), and renal vascular resistance increased. Whether these alterations in renal function contribute to the rise in blood pressure is not known. Exaggerated natriuresis has been reported in Cushing's syndrome as in other forms of hypertension, and Birchall et al demonstrated a natriuretic response to saline loading in a normal individual given cortisone. Pressor responsiveness

STUDY REPORTS [17]

Reports of changes in vascular responsiveness in glucocorticoid-induced hypertension conflict. Some studies have reported that glucocorticoid administration increases pressor responses to noradrenaline and adrenaline in humans, but this finding is not universal.

In our studies of pressor responsiveness following oral hydrocortisone administration, we examined the effects of angiotensin II and phenylephrine. As fig 3 shows,

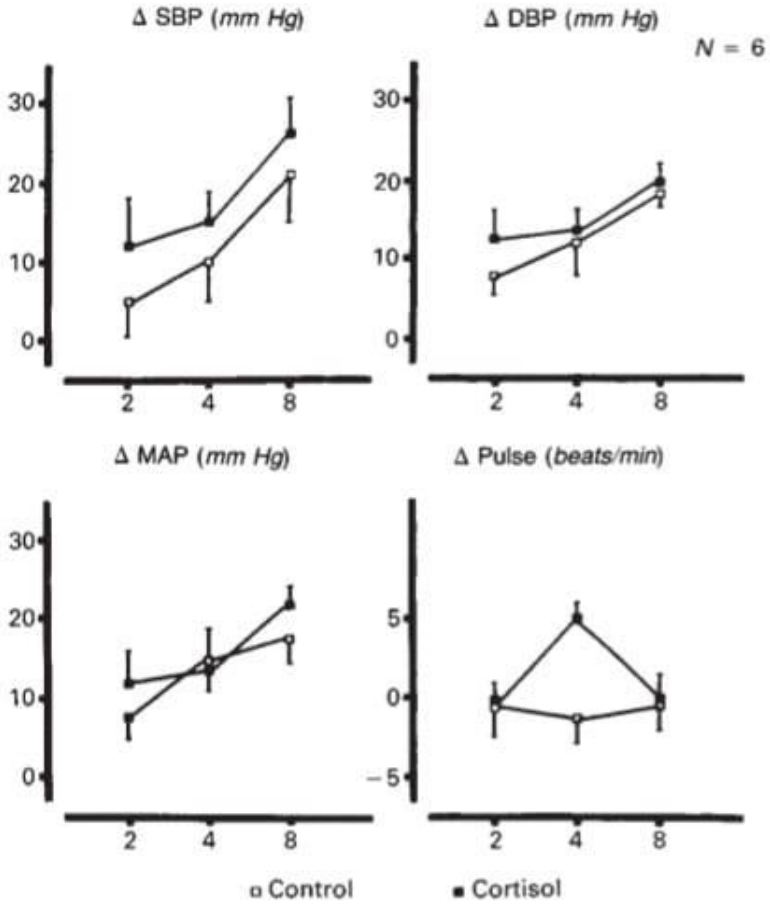

Fig.3. Pressor responsiveness to AG-II (mg/kg/min) in subjects before and during oral hydrocortisone treatment. The dose infused is shown on the horizontal axis. There are no significant differences. SBP refers to systolic blood pressure; DBP, diastolic blood pressure and MAP, mean arterial pressure. (Reproduced from Ref. [17])

There were no changes in pressor responsiveness to angiotensin II after we gave oral hydrocortisone, 200 mg daily, for 5 days. In contrast, hydrocortisone increased pressor responsiveness to phenylephrine at infusion rates from 0.6 to 2.0 min (Fig. 4), and decreased the threshold for systolic and mean arterial pressure rises.

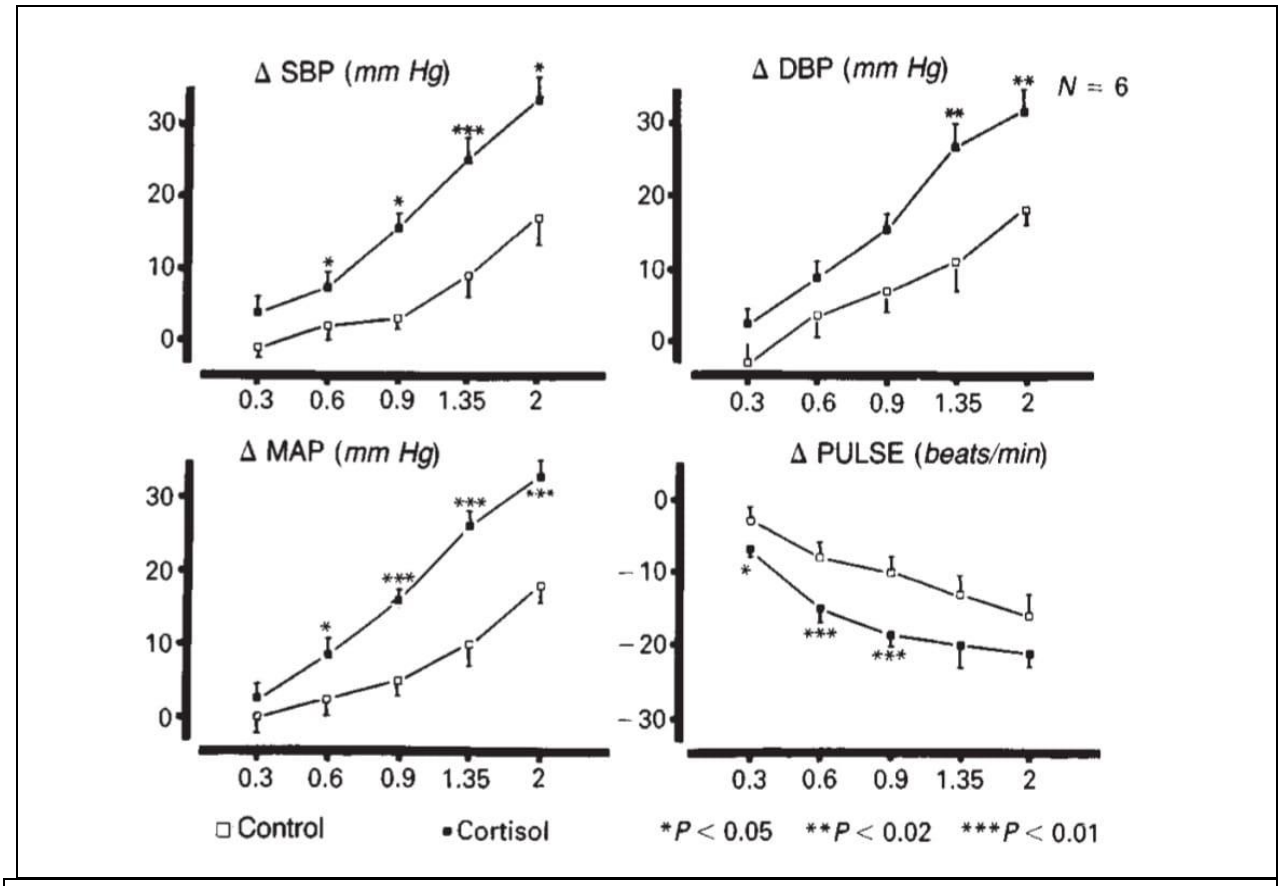

Fig. 4. Pressor responsiveness to phenylephrine (mg/kg/min) in subjects before and after oral hydrocortisone treatment, showing increased systolic, diastolic, and mean arterial pressure responses on hydrocortisone,with a greater fall in pulse rate. The dose infused is shown on the horizontal axis. (Reproduced from Ref. [17])

Whether these changes in pressor responsiveness contribute to the hydrocortisone induced rise in blood pressure is not clear. Changes in membrane ion transport Increases in sodium-potassium-ATPase activity in erythrocyte ghosts have been reported in patients with Cushing's Syndrome and in patients treated with ACTH. Increases in ouabain-sensitive uptake of rubidium also have been noted in erythrocytes of patients with Cushing's syndrome. These findings indicate an increased maximal activity of the sodium-potassium pump in patients with glucocorticoid excess. Binding sites for ouabain are increased in erythrocytes of glucocorticoid-treated patients. Wambach and coworkers speculated that generalized pump activation could contribute to the volume redistribution.

MECHANISMS [18]

The profound physiologic perturbations seen with hydrocortisone could be causal in the elevation of blood pressure, could be simply associated phenomena, or might be modulators or amplifiers of a blood pressure-raising action of the steroid. As I will discuss, we have evidence from studies in sheep that the blood pressure-raising effects of steroids cannot be explained simply in terms of their glucocorticoid or mineralocorticoid activities. These observations have led us to propose that blood pressure-raising effects of steroids might be in part separate from their classical glucocorticoid or mineralocorticoid actions, and represent a different class of steroid hormone activity, which we have termed hypertensin genic. The possibility remains that cortisol, a classic glucocorticoid with some mineralocorticoid activity, might raise blood pressure through its hypertensin genic activity. Whereas in sheep it is possible to separate hypertensin genic activity from glucocorticoid or mineralocorticoid activity, in humans the same hypertensin genic action occurs at a rate of infusion at which the classic steroid effects also are seen.

GLUCOCORTICOID INDUCED HYPERTENSION IN EXPERIMENTAL ANIMALS [19]

Cortisol, cortisone, and corticosterone Glucocorticoid hypertension was first studied in the rat given cortisone and cortisol acetate. In contrast to mineralocorticoid hypertension, which is augmented by dietary sodium supplementation prevented by dietary sodium restriction and characterized by hypokalemia, hypernatremia, and urinary sodium retention, hypertension induced by glucocorticoids is independent of dietary sodium intake, changes in plasma electrolyte concentration, and sodium retention cortisol infused intravenously in sheep in doses of 480 mg/day arterial pressure within 24 hrs. in the dog ,however, [20] cortisol lowers blood pressure corticosterone is the principal glucocorticoid secreted by the rat adrenal cortex Corticosterone possesses approximately equal mineral potent than cortisol in raising blood pressure .

In rats,9a-fluorocortisol-induced hypertension is a glucocorticoid model rather than a mineralocorticoid form of hypertension. In sheep, 9a-fluorocortisol produced hypertension at a dose without apparent mineralocorticoid or glucocorticoid effects (0.2mg/daily); this finding suggests that elevated pressure is mediated by a different mode of steroid activity, a phenomenon that has been given the designation of hypertensin genic activity.

Cortisol and corticosterone have mineralocorticoid properties, but many of the synthetic glucocorticoids, which have little sodium-retaining effect (triamcinolone, dexamethasone, prednisone, methylprednisolone) also induce hypertension in rats. There are important species differences. Although methylprednisolone induces hypertension in the rat, chronic infusion failed to raise blood pressure in the dog or sheep.

Dexamethasone causes hypertension in the rat but not sheep. We have reviewed in detail the possible mechanisms of ACTH-dependent hypertension elsewhere. Hemodynamics Whereas mineralocorticoids cause renal sodium retention, glucocorticoids produce a shift from interstitial to plasma volume compartment. It has been postulated that in consequence, there is an increase in plasma volume, and hence cardiac output, leading to vascular autoregulation, and an increase in total peripheral resistance. In turn, the increase in peripheral resistance is thought to maintain the elevation in arterial pressure. This hypothesis remains unproven.

A number of studies have demonstrated no change or only slight increases in plasma or blood volume, extracellular fluid volume, and cardiac output in steroid-induced hypertension. Hormonal changes. The renin-angiotensin system probably plays little part in the pathogenesis of glucocorticoid-induced hypertension. Krakoff Ct al reported elevated plasma renin substrate and PRA in methylprednisolone-induced hypertension in the rat, but in another study, PRA remained at normal levels despite increased plasma renin substrate in dexamethasone-induced hypertension in the rat. Infusion of Sarala sin significantly reduced arterial pressure in rats with methylprednisolone-induced hypertension, but the reduction was not sufficient to normalize arterial pressure.

The partial agonist action of Sarala sin might account for these results Subsequently, it was found that captopril failed to prevent development of glucocorticoid-induced hypertension and did not reverse it. Few data are available on central or peripheral adrenergic activity following glucocorticoid administration. In the rat, plasma catecholamines are not altered by corticosterone treatment although adrenal and brain medullary Phen ethanolamine-N-methyl transferase (PNMT) is increased by glucocorticoid administration. Methylprednisolone-induced hypertension in the rat can be partially reversed by PNMT inhibition, suggesting some role for the sympathetic nervous system in maintaining the pressure. Methylprednisolone hypertension can be produced in the ADH-deficient Brattleboro rat to the same degree as in the normal Wistar rat and is not reversed by an AVP antagonist.

Thus, vasopressin does not play a major role in this form of hypertension. In-vitro studies show that glucocorticoids affect prostaglandin biosynthesis by inhibiting the release of arachidonic acid from phospholipids. Glucocorticoids might raise blood pressure via inhibition of phospholipase A2, with reduction in vasodilator prostanoids activity. Cyclooxygenase inhibition with indomethacin increases pressor responsiveness to noradrenaline and angiotensin II in a variety of species including humans. Vascular smooth muscle responsiveness.

Cortisol potentiates the pressor effects of adrenaline but not those of noradrenaline in the cat, rabbit, and dog. In-vitro preparations of arterial smooth muscle show increased responsiveness to both adrenaline and noradrenaline several minutes after exposure to cortisone. Glucocorticoids might increase responses of vascular smooth muscle to adrenaline and noradrenaline by inhibiting catechol-o-methyl transferase (COMT). Pressor responses to

suppressor rates of adrenaline infusion have been observed in cortisol-treated dogs.

The increased vascular reactivity was abolished by indomethacin administration; these changes in reactivity might be related to altered prostaglandin synthesis. Other possible explanations include structural changes of the vascular wall, electrolyte changes, and alterations in sodium-potassium pump activity and permeability. On the other hand, a number of studies show that glucocorticoids have no effect on vascular reactivity the literature is by no means conclusive.

Changes in membrane ion transport. Glucocorticoids increase renal sodium-potassium ATPase activity and dexamethasone also increases sodium-potassium pump activity in rat arteries.[21]

Grunfeld et al found that hypertension produced in the rat by the synthetic glucocorticoid agonist was associated with increases in total and ouabain sensitive sodium efflux and rubidium efflux. Pretreatment with a glucocorticoid antagonist prevented the changes in total and ouabain-sensitive sodium efflux, largely reversed the hypertension, and partially reversed the changes in rubidium efflux. Whether these observations have any bearing on the cause of steroid-induced hypertension is unknown.

A "hypertensive" action. The concept of a "hypertensin genic" class of steroid hormone action, separate from mineralocorticoid or glucocorticoid actions of steroid hormones in raising blood pressure, is based on studies in sheep.[22] First, the hypertension produced by ACTH administration in conscious sheep could not be reproduced by infusion of the major ovine mineralocorticoid or glucocorticoid hormones (cortisol,11-deoxycortisol, deoxycorticosterone, corticosterone, and aldosterone) either alone or in combination, at rates that reproduce blood concentrations of steroid seen with [23] ACTH administration, although all the metabolic effects were seen. Following the addition to this combined steroid infusion of hydroxyprogesterone (a steroid isolated from adrenal vein blood under conditions of ACTH administration), the effects on blood pressure were identical to those seen with ACTH. This steroid showed little or no affinity for either type-I (mineralocorticoid) or type-Il (glucocorticoid) receptors. The second line of evidence came from the studies on fludrocortisone in sheep to which I have already alluded fludrocortisone raised blood pressure at an infusion rate that had no in-vivo mineralocorticoid or glucocorticoid effects.[24]

At higher rates of infusion, mineralocorticoid effects were seen, but infusion of aldosterone and cortisol (at equivalent rates based on receptor affinity) reproduced the metabolic effects of fluor cortisol without the hypertension. The third line of evidence came from extensive studies in which naturally occurring and synthetic steroids were infused, and detailed structure-activity studies undertaken. No simple relationship was found between the blood pressure-raising effects of steroids (hypertensive activity) and they're in-vivo glucocorticoid activity (assessed by changes in blood glucose and urine volume) or mineralocorticoid activity (assessed by changes in urinary sodium excretion).

Although all glucocorticoids increase plasma glucose and urine volume, some raise blood pressure with associated mineralocorticoid activity (for example, cortisol), whereas others are hypertensive without mineralocorticoid activity (such as cortivazol), or they have little effect on blood pressure (for example, dexamethasone).[25]

These and other studies have led to the hypothesis that steroid hormones raise blood pressure by a "hypertensive" action distinct from their classical mineralocorticoid or glucocorticoid actions. To produce hypertension a steroid must bind to a putative "hypertensive" receptor, probably located in the central nervous systems. Elucidation of the "hypertensive" mechanism will require separation of effects primarily responsible for the rise in blood pressure from those steroid-dependent effects that may modify or amplify the rise in pressure.

CONCLUSION:

The findings of this review indicates that effect steroids are vastly contraindicated in the hypertensives most common steroids that shows common and severe hazards in the hypertensives are prednisone, dexamethasone, hydrocortisone. The steroid induced hypertension is due to the fluid retention and causing the hypertension and also the hypotension in case of prednisone.The effect of corticosteroids and oral glucocorticoids cumulative dose on hypertension is substantial

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