Steroidal & Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Steroids: Since their identification in 1935, have played a prominent role in the treatment of many disease states. clinical roles of steroids are related to their potent anti-inflammatory and immune-modulating properties.

Steroids initially, isolates from adrenal glands were thought to be useful only in patients suffering from Addison disease.

Applications of Steroid in Clinical Practice:

Corticosteroids and their biologically active synthetic derivatives differ in their metabolic (**glucocorticoid**) and electrolyte-regulating (**mineralocorticoid**) activities. These agents are employed at physiological doses for replacement therapy when endogenous production is impaired. In addition, glucocorticoids potently suppress inflammation, and their use in a variety of inflammatory and autoimmune diseases makes them among the most frequently prescribed classes of drugs.

Regulation of Cortisol Secretion

The following three major mechanisms control ACTH release and the Cortisol secretion.

(a)**Negative feedback mechanism**: the most important stimulus for secretion of cortisol is the release of ACTH from anterior pituitary. The secretion of ACTH in anterior pituitary is determined by hypothalamic neurohormones & Circulating cortisol also exerts a direct negative feedback on the hypothalamus and anterior pituitary to decrease the release of CRF and ACTH from respective sites. (b)**Diurnal variation**: cortisol is secreted from adrenal gland in an episodic manner and frequency of pulses follows a circadian rhythm that is dependent on both day-night and sleep-wake patterns and is disrupted by alternating day-night shift working patterns and by long distance travel across time zones. It may take up to 2 weeks for circadian rhythm to reset to an

altered day-night cycle. Levels are the highest in the morning on waking and the lowest in the middle of evening.

(c)**Stress:** Stress such as physical (trauma, surgery, exercise); psychological (pain, anxiety, apprehension); physiological (nausea, fever and hypoglycemia) can over ride the negative feedback mechanism and diurnal variation. Cortisol rises immediately (within minutes) and dramatically during stress.

Physiological Effect of Glucocorticoids:

1-Effect Cortisol on Metabolism:

- Stimulates liver resulting in increased blood glucose concentrations.
- Reduction of protein stores essential in all body cells, except those of liver.
- Cortisol promotes mobilization of fatty acids from adipose tissue; excess cortisol causes deposition of fat in neck and chest regions, giving a "buffalo like" torso.

2- Anti-Inflammatory Effects

- Cortisol in large amounts has anti-inflammatory effects, decrease the release of inflammation causing lysozymes, and decrease capillary permeability which prevents loss of plasma protein in to tissues .
- It interferes with complement pathway activation and formation of chemical mediator.

3. Bone and Calcium Metabolism: Osteoblast function is inhibited by glucocorticoids and this is thought to be the explanation for osteopenia and osteoporosis that characterize excess glucocorticoid.

4. Blood Pressure Control: Glucocorticoids increase blood pressure. In the vascular smooth muscle they increase sensitivity to catecholamines(dopamine, epinephrine (adrenaline), and norepinephrine (noradrenaline) and angiotensin II.

5. CNS and Mood: Clinical observation of patients with glucocorticoid excess and deficiency reveals that brain is an important target for glucocorticoids with depression, euphoria, psychosis, & lethargy.

6. Developmental Changes: Plasma cortisol in last trimester of pregnancy is necessary for maturing of number of systems that are critical for survival of fetus in extrauterine life. These systems include production of pulmonary surfactant, maturation of various enzyme systems in the liver, the enzyme necessary for synthesis of epinephrine from norepinephrine.

7. Eye: In the eye, glucocorticoids act to raise intraocular pressure through an increase in aqueous humor production .

8. Gut: Chronic but not acute administration of glucocorticoid increases the risk of developing peptic ulcer disease. Pancreatitis & fat necrosis.

9. Endocrine Effects:

suppress thyroid axis through a direct action on thyroid stimulating hormone secretion.

It acts centrally to inhibit gonodotrophin-releasing hormone & then inhibit release of lutenizing hormone and follicular stimulating hormone.

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.

CLINICAL uses:

- 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.

- **Side effects** of chronic use include bruising, muscle weakness, weight gain, skin changes, sleep disturbances, cataracts, and pathologic fractures. 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.
- Adverse effects occur in up to 90% of patients who take glucocorticoids for >60 days.
- the more serious fractures and cataracts, occur even in patients taking low (≤7.5 mg/d) dosages.
- Glucocorticoids affect bone mineralization by inhibiting calcium absorption in the gastrointestinal tract and shifting signaling-molecule production to favor bone resorption.
- glucocorticoid-induced osteopenia.
- glucocorticoids are the most common cause of drug-induced diabetes mellitus.
- Cushing syndrome and adrenal suppression have been observed in patients taking oral, intra articular, epidural, inhaled, nasal, ocular, and topical glucocorticoid preparations.

CORTICOSTEROID PREPARATIONS

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. Methylprednisolone and triamcinolone are the drugs most commonly used for epidural steroid injections.

Topical corticosteroids (2.5% ointment, triamcinolone 0.1% ointment, and clobetasol propionate 0.05% foam) achieve more effective skin concentrations than oral prednisone.

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.

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.

NONSTEROIDAL ANTIINFLAMATORY DRUGS: NSAIDs are a class of medications used to treat pain, fever, and other inflammatory processes.

Indications

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a drug class FDA-approved for use as antipyretic, anti-inflammatory, and analgesic agent. These effects make NSAIDs useful for treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, migraines, and used as opioid-sparing agents in certain acute trauma cases.

NSAIDs are typically divided into groups based on their chemical structure and selectivity:

Non-selective NSAIDs: acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen, acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam) anthranilic acids (meclofenamate, mefenamic acid), naphthylalanine (nabumetone), and

COX-2 Selective NSAIDs : (celecoxib, etoricoxib).

Topical NSAIDs (diclofenac gel) are also available for use in acute tenosynovitis, ankle sprains, and soft tissue injuries.

Mechanism of Action

The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). Cyclooxygenase is required to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins.

Thromboxanes play a role in platelet adhesion, prostaglandins cause vasodilation, increase the temperature set-point in the hypothalamus. There are two cyclooxygenase isoenzymes, COX-1 and COX-2. COX-1 gets constitutively expressed in the body, and it plays a role in maintaining gastrointestinal mucosa lining, kidney function, and platelet aggregation. COX-2 is not constitutively expressed in the body; and instead, it inducibly expresses during an inflammatory response.

Administration

Most commonly, NSAIDs are available as oral tablets. According to the package insert, the dosage for the most common over-the-counter NSAIDs are as follows:

- Ibuprofen: for 200 mg tablets, 1 to 2 tablets every 4 to 6 hours while symptoms persist. The daily limit for ibuprofen is 1200 mg.
- Aspirin regular strength: for 325 mg tablets, 1 to 2 tablets every 4 hours, or 3 tablets every 6 hours. The daily limit for aspirin is 4000 mg.
- Naproxen sodium: for 220 mg tablets, 1 to 2 tablets every 8 to 12 hours. The daily limit for naproxen sodium is 660 mg.

Topical NSAIDs are also available (diclofenac sodium 1.5% topical solution, diclofenac hydroxyethyl pyrrolidine 1.3% patch, and diclofenac sodium gel 1%). They are most useful for treating pain due to soft-tissue injuries and osteoarthritis.

Specific NSAIDs can also be administered parenterally; for example, intravenous ibuprofen is available, given as a 30-minute infusion; this can be used as a non-opioid analgesic to manage pain and can also reduce fever. Trials have shown that using intravenous ibuprofen and morphine in postoperative adult patients can lower the total use of morphine. For treating pyrexia, an initial 400mg dose then 400 or 100 to 200 mg every 4 to 6 hours as needed. For the treatment of pain, 400 to 800 mg, every 6 hours as needed, is the recommended dose regimen.

Adverse Effects

NSAIDs have well-known adverse effects affecting the gastric mucosa, renal system, cardiovascular system, hepatic system, and hematologic system.

Gastric adverse effects are likely due to the inhibition of COX-1, preventing the creation of prostaglandins that protect the gastric mucosa. The damage is more likely in a patient that has a prior history of peptic ulcers. Since it is COX-1 specific, the use of COX-2 selective NSAIDs is a lower-risk alternative.

Renal adverse effects: are because COX-1 and COX-2 facilitate the production of prostaglandins that play a role in renal hemodynamics. In a patient with normal renal function, in a patient with renal dysfunction, these prostaglandins play a greater role and can be the source of problems when reduced via NSAIDs. Complications that can occur include acute renal dysfunction, fluid and electrolyte disorders, renal papillary necrosis, and nephrotic syndrome.

Cardiovascular adverse effects can also be increased with NSAID use; these include MI, and atrial fibrillation. Diclofenac seems to be the NSAID with the highest reported increase in adverse cardiovascular events.

Hepatic adverse effects are less common; NSAID-associated risk of hepatotoxicity Among the various NSAIDs, Diclofenac has a higher rate of hepatotoxic effects.

Hematologic adverse effects are possible, particularly with nonselective NSAIDs due to their antiplatelet activity. This antiplatelet effect typically only poses a problem if the patient has a history of GI ulcers, diseases that impair platelet activity (hemophilia, thrombocytopenia and in some perioperative cases.

Other minor adverse effects include anaphylactoid reactions that involve the skin and pulmonary systems, like urticaria and aspirin-exacerbated respiratory disease.

Contraindications

NSAIDs are contraindicated in patients:

- With NSAID hypersensitivity or salicylate hypersensitivity, as well as in patients who have experienced an allergic reaction (urticaria, asthma, etc.) after taking NSAIDs
- Who have undergone coronary artery bypass graft surgery
- During the third trimester of pregnancy

Monitoring

Recommended monitoring includes a CBC, renal tests, and hepatic panel.