

Clinical pharmacology of Corticosteroids

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The adrenal cortex releases a large number of steroids into circulation. The important ones include:

1. Glucocorticoids, mainly hydrocortisones (cortisol)
2. Mineralocorticoids, mainly aldosterone.
3. Androgen (mainly dehydroepiandrosterone, or DHEA) and estrogen.

A. Glucocorticoids

The major glucocorticoid in man is cortisol, which is synthesized from cholesterol by cells of the zona fasciculata and zona reticulata.

In the normal adult in the absence of stress, about 20 mg of cortisol (equivalent to 5 mg of prednisolone) are secreted daily. In plasma, cortisol is bound to plasma proteins. Corticosteroid-binding globulin binds 95% of the circulating hormone. The remaining 5% is the metabolically active fraction. The half-life of cortisol in the circulation is normally about 90-110 minutes.

The active form of synthetic glucocorticoids has a hydroxyl group at 11-position of the steroid. While the pro-drugs (or inactive form), including cortisone and prednisone, have a keto group at 11-position.

The glucocorticoids may stimulate glucose production (gluconeogenesis) from protein, also may stimulate fatty acid synthesis resulting in fat deposition in the trunk, face, and mesentery.

B. Adverse reactions

When the glucocorticoids are used for short periods (less than one week), it is unusual to see serious side effects even with moderately large doses.

1. Adrenal suppression

When physiologic amounts of corticosteroids are administered for long periods of time, adrenal suppression occurs and the patient should be given supplementary therapy at time of severe stress such as accidental trauma or surgery. The degree of adrenal unresponsiveness is a function of (1) the length of time the steroid is used, (2) the dose of the steroid, (3) the type of the synthesized steroid, (4) the timing of the day the steroid is given. For a patient with the adrenal gland completely suppressed,

the recovery period is about 9 months for adults and 3 months for children.

2. Iatrogenic Cushing's syndrome

Most patients who are given daily doses of 100 mg of cortisol or more (or the equivalent amount of synthetic steroid) for longer than 2 weeks undergo a series of changes which have been termed iatrogenic Cushing's syndrome or Cushingoid; the rate of development is a function of the dose.

3. Adverse effects

The patient appears as moon face, buffalo hump, and trunk obesity. There is an increased growth of fine hair (hirsutism) over the thighs and trunk. Acne may increase or appear even in the trunk. Insomnia and increased appetite are noted. In the treatment of dangerous or disabling disorders, these changes may not require cessation of therapy. The continuing breakdown of protein and diversion of amino acids to glucose increases the need for insulin and over a period of time results in weight gain, fat-deposition, muscle wasting, thinning of the skin with striae and bruising, hyperglycemia, growth retardation (in children), and eventually the development of steroid diabetes and osteoporosis.

Other serious adverse effects include the development of peptic ulcers and their complications, e.g. perforation. The symptoms and signs associated with infection, particularly bacterial and mycotic, may be masked by the corticosteroids, and patients must be carefully watched. Some patients develop a myopathy. When diabetes occurs, it is treated by diet and hypoglycemic drugs, although these patients rarely develop ketoacidosis.

When given in greater than physiologic amounts, the use of steroids such as cortisone and hydrocortisone, which have mineralocorticoid effects, cause, in addition to glucocorticoid effects, some sodium and fluid retention and loss of potassium. In patients with normal cardiovascular and renal function, this leads to a hypokalemic, hypochloremic alkalosis and eventually a rise in blood pressure. In patients with hypoproteinemia, renal disease, or liver disease, edema may occur. In patients with heart disease, even small degrees of sodium retention may lead to congestive heart failure. These effects can be minimized by sodium restriction and judicious potassium supplements. Many of the synthetic steroids (e.g. methylprednisolone) have so little mineralocorticoid effect that these problems can be avoided.

C. Contraindications & Cautions

a. Special Precautions

Patients receiving these drugs must be observed carefully for the development of hyperglycemia, sodium retention with edema or hypertension,

hypokalemia, peptic ulcer, osteoporosis, and hidden infections. A high-protein diet and adequate calcium intake are necessary. In patients with limited cardiac reserve, sodium restriction may be required.

b. Relative contraindications

These agents must be used with the greatest of caution in patients with the following disorders.

1. Peptic ulcer

In patients with previous ulceration, activation is likely.

2. Heart disease or hypertension with congestive heart failure

Measures to avoid the accumulation of extra-cellular fluid should be utilized. In patients receiving digitalis, the concomitant use of potassium-wasting diuretics may create serious problems.

3. Infections

Since symptoms and signs of infection are attenuated, great care is required when using steroids even antibiotics are concomitantly used. Ophthalmic herpes simplex is particularly dangerous in the presence of corticosteroids.

4. Psychoses

Serious behavioral disturbance may occur in patients on steroid therapy, and prior disturbances are thought to predispose patients to acute psychoses.

5. Diabetes

Since these agents increase glucose production, more insulin may be required. However, the corticosteroids do not cause acidosis or coma unless complications (such as an infection) occur.

C. Cautions

Sudden cessation of therapy should be avoided when more than physiologic amounts of steroids have been used in order to prevent an acute exacerbation of the disease process or symptoms of adrenal insufficiency. The dosage should be kept as low as possible and intermittent dosage (e.g. Alternate-day) employed when satisfactory therapeutic results can be obtained on this schedule. In patients being maintained on relatively low doses of corticosteroids, supplementary steroids may be required at times of stress such as when surgical procedures are performed or accidents occur. In general, patients treated with corticosteroids should be on high-protein and high-potassium diets.

Whether glucocorticoids are good drugs or not depends on the way the doctors used.