Review Article

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Corticosteroids: Clinical Pharmacology and Therapeutic Use

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Summary

The widespread use of corticosteroids in clinical practice emphasises the need for a thorough understanding of their metabolic effects. In general, the actions of corticosteroids on carbohydrate, protein, and lipid metabolism result in increased hepatic capacity for gluconeogenesis and enhanced catabolic actions upon muscle, skin, lymphoid, adipose and connective tissues. Because of the morbidity associated with steroid therapy, the clinician must carefully consider in each case the gains that can reasonably be expected from corticosteroid therapy versus the inevitable undesirable side effects of prolonged therapy. Thus, it is important to remember that the enhanced anti-inflammatory activity of the various synthetic analogues of cortisol is not dissociated from the expected catabolic actions of glucocorticoid hormones.

Replacement therapy with physiological doses of cortisol in primary or secondary adrenal insufficiency is intended to simulate the normal daily secretion of cortisol. Short term, high dose suppressive glucocorticoid therapy is indicated in the treatment of medical emergencies such as necrotising vasculitis, status asthmaticus and anaphylactic shock. With improvement of the underlying disorder, the steroid dosage can be rapidly tapered and then discontinued over a 2 to 3 day period. Long term, high dose suppressive therapy is often commonly used to treat certain diseases (see sections 4.7.2 and 4.7.3). In this setting, suppression of the hypothalamic-pituitary-adrenal axis may persist for as long as 9 to 12 months following steroid withdrawal if steroid doses are administered in the supraphysiological range for longer than 2 weeks. In general, higher doses, longer duration of usage, and frequent daily administration are all correlated with the severity of pituitary ACTH suppression.

When steroid therapy is to be withdrawn, gradual tapering of the dosage is necessary; the steroid dosage should also be given as a single morning dose if possible. Rapid or total withdrawal of the steroid therapy may be associated with exacerbation of the underlying disease or with a steroid withdrawal syndrome. An additional important point to remember in any withdrawal programme is that the steroid dosage should be appropriately increased for an exacerbation of the underlying disease or for intercurrent major stress. Alternate day therapy is recommended as a steroid maintenance programme for patients requiring high dose glucocorticoid therapy over a prolonged period of time. Thus, it is usually employed to maintain a therapeutic benefit which had previously been established by daily steroid treatment.

Complications resulting from corticosteroid therapy include: (1) proximal muscle weakness; (2) osteopenia; (3) unmasking of latent diabetes mellitus; (4) sodium retention and/or elevation of mean arterial blood pressure; (5) adverse psychiatric reactions; (6) development of glaucoma; and (7) reactivation of latent infections (such as tuberculosis).

The widespread use of corticosteroids in clinical practice emphasises the need for a thorough understanding of their metabolic effects if optimum effectiveness is to be obtained with a minimum of undesirable side effects. Before instituting corticosteroid therapy, it is necessary to carefully consider the gains that can be reasonably expected versus the potentially undesirable metabolic actions of large doses of corticosteroids. The increased incidence of hypertension, chronic infectious diseases, osteoporosis and impaired glucose tolerance as metabolic sequelae of large doses of steroids must be carefully considered before embarking on a programme of steroid administration. The chemical and physiological properties of cortisol and its synthetic analogues will be reviewed in order to demonstrate how a knowledge of the clinical pharmacology of corticosteroids can aid in their rational therapeutic use.

1. Structure of Cortisol and its Synthetic Analogues

The basic chemical structure of adrenal corticosteroids consists of a 17 carbon skeleton with three 6 carbon hexane rings and a one 5 carbon pentane ring (fig. 1). Cortisol (hydrocortisone) and other anti-inflammatory steroids are referred to as C21 steroids (fig. 1) because they have a 2 carbon chain attached at position 17, and in addition, have methyl groups at C18 and C19. C21 steroids that also have a hydroxy group at position 17 are called 17-hydroxycorticosteroids, or 17-hydroxycorticoids. Those C21 steroids which have predominant actions on intermediary metabolism are referred to as glucocorticoids. For the remainder of this discussion the term 17-hydroxycorticosteroids (or corticosteroids) and glucocorticoids will be used interchangeably.

The functional integrity of the steroid molecule is dependent upon certain critical arrangements of hydrogen, carbon, hydroxyl and oxygen groups around the basic steroid nucleus. Those areas which are circled in figure 2 are essential for the preservation of the biological action of all corticosteroids, and alteration in any one of them will result in complete loss of glucocorticoid activity. This is illustrated by the observation that the administration of cortisone (with an oxygen radical at position 11) is relatively inactive in patients with severe liver disease due to impaired hepatic conversion to the active naturally occurring compound cortisol (with a hydroxyl group at position 11) (Peterson, 1971) [fig. 3]. The importance of these substituents on the molecule is also illustrated by the biological inactivation of cortisol by the liver. In this

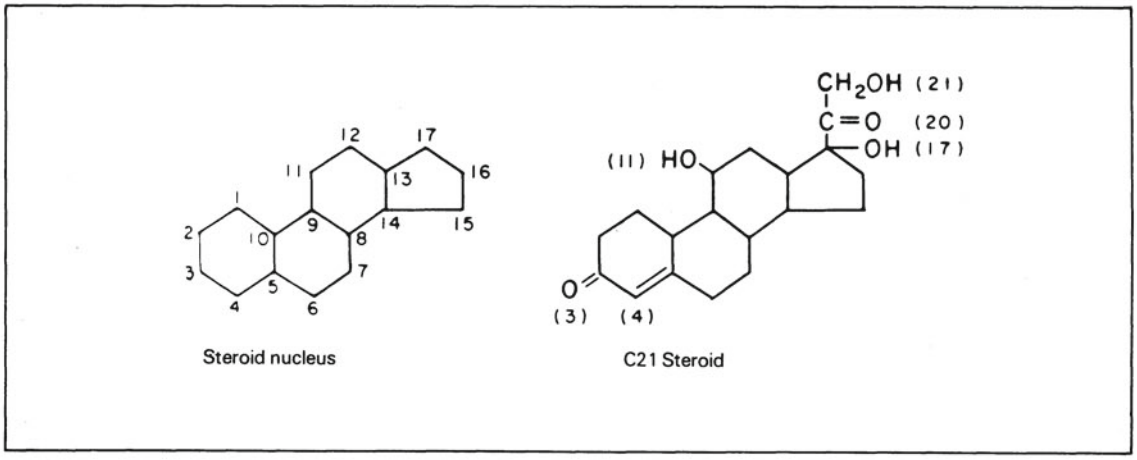

Fig. 1. Basic steroid structure.

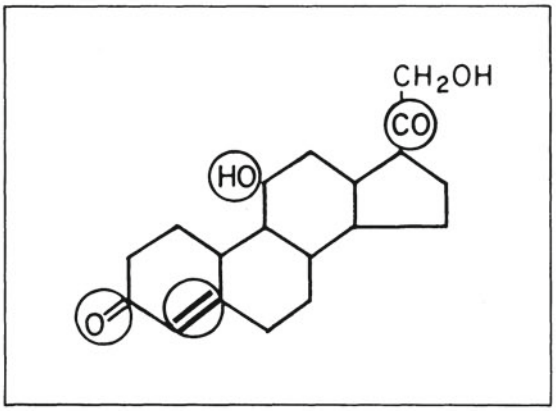

Fig. 2. Groups essential to anti-inflammatory activity.

process, reduction of the double bond at the 3-4 position renders the compound biologically inactive.

Analogues of cortisol have been synthesised which have substitutions adjacent to critical sites on the steroid nucleus. This results in enhancement of certain properties, such as anti-inflammatory activity, and diminution of other actions, such as mineralocorticoid activity. For example, introduction of a 1,2 double bond produced prednisolone which has a 4-fold enhancement of anti-inflammatory activity (fig. 4). Dexamethasone (with a methyl group at carbon 16, and a fluoride group at carbon 9) has markedly enhanced anti-inflammatory and diminished sodium retaining properties (on a mg for mg basis compared with cortisol). Fludrocortisone (9-fluorohydrocortisone) has marked enhancement of mineralocorticoid activity.

The anti-inflammatory and mineralocorticoid properties of cortisol can therefore be altered by modifying the basic steroid nucleus. It must be remembered, however, that the enhanced anti-inflammatory activities of these synthetic analogues is not dissociated from the normal catabolic actions of glucocorticoid hormones. Thus, equipotent doses of cortisol and its analogues have similar propensities for producing the undesirable actions of glucocorticoids.

2. Transport and Metabolism of Cortisol and Synthetic Analogues

Approximately 10 to 12mg of cortisol per m^2 body surface area is produced by the adrenal cortex in a normal adult each day. Although cortisol is secreted in a pulsatile or episodic fashion, the mean plasma concentration of cortisol varies predictably over a 24 hour period, with highest concentrations in the early morning and lowest levels at midnight (circadian rhythm). The normal plasma concentration at 8a.m. is 10 to 15μg/dl.

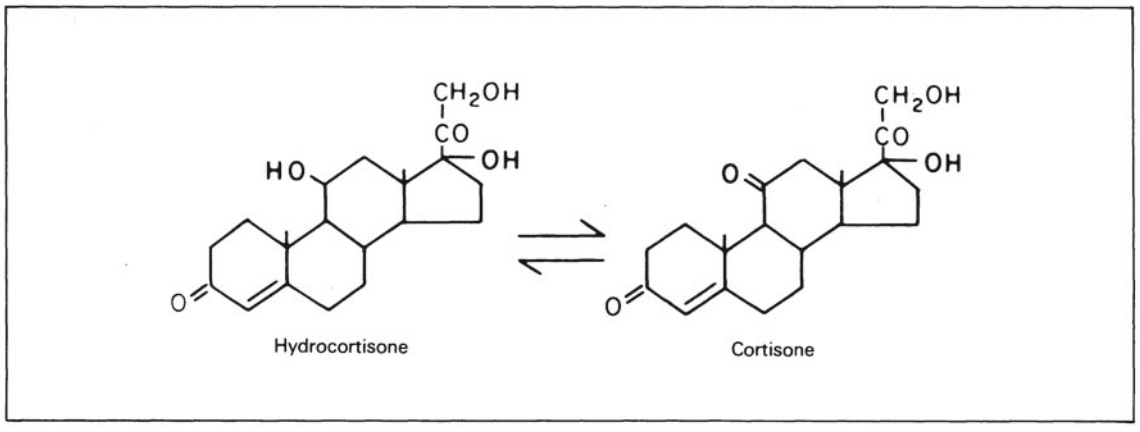

Fig. 3. Reversible oxidation-reduction reaction of cortisol (hydrocortisone) and cortisone by hepatic microsomal enzymes.

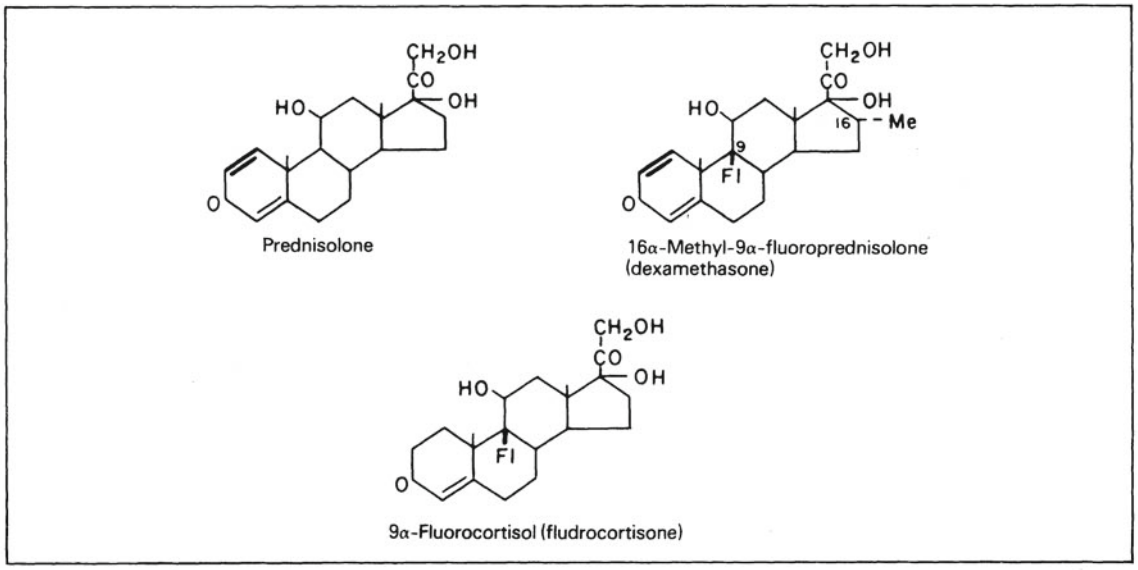

Fig. 4. Three synthetic analogues of cortisol (hydrocortisone).

2.1 Half-life and Duration of Action

The plasma half-life of cortisol, defined as the time it takes for the plasma level of the hormone to fall to 50% of its initial concentration, is approximately 90 minutes. However, the biological half-life of cortisol, defined as the time it takes for a measured metabolic activity (e.g. anti-inflammatory effect) of the hormone to fall to a half of its initial level, lasts from 8 to 12 hours. Since the anti-inflammatory potency of synthetic or natural glucocorticoids and their suppression of the hypothalamic-pituitary-adrenal axis, parallel each other in terms of degree and duration, biological half-lives are usually determined by the duration of suppression of the hypothalamic-pituitary-adrenal axis. Thus, hydrocortisone and cortisone are defined as short acting glucocorticoids on the basis of their 8 to 12 hour biological half-lives; prednisone, prednisolone, methylprednisolone and triamcinolone as intermediate acting glucocorticoids, with 18 to 36 hour biological half-lives; and paramethasone, betamethasone and dexamethasone as long acting glucocorticoids with 36 to 54 hour biological half-lives (table I).

2.2 Protein Binding

Normally, approximately 90% of the cortisol is reversibly bound to plasma proteins (10% to albumin and 80% to a high affinity, low capacity α_2-globulin, transcortin or corticosteroid binding globulin); 10% circulates free or unbound. This free fraction, estimated to range between 0.7 and 1.0μg/dl, probably determines the biological activity of the hormone, with the bound fraction serving as a reservoir. The binding capacity of transcortin is approximately 20 to 25μg of cortisol per dl plasma. With cortisol levels greater than 25μg/dl, binding sites on transcortin will be saturated, and the binding of cortisol will be largely to albumin, a low affinity, high capacity receptor (25% unbound and 75% bound). Since the unbound fraction is filtered by the glomerulus and excreted into the urine, patients with Cushing's syn-

Table I. Adrenal corticosteroid preparations

Drug	Anti-inflammatory potency[1]	Equivalent potency[1] (mg)	Sodium retaining potency	Daily dose (mg) above which HPA axis suppression possible[2]		Plasma half-life (min)	Biological half-life (h)
				males	females		
Cortisol (hydrocortisone)	1	20	2 +	20-30	15-25	90	8-12
Cortisone	0.8	25	2 +	25-35	20-30	90	8-12
Prednisone	3.5	5	1 +	7.5-10	7.5	200 or >	18-36
Prednisolone	4	5	1 +	7.5-10	7.5	200 or >	18-36
Methylprednisolone	5	4	0	7.5-10	7.5	200 or >	18-36
Triamcinolone	5	4	0	7.5-10	7.5	200 or >	18-36
Paramethasone	10	2	0	2.5-5	2.5-5	300 or >	36-54
Betamethasone	25	0.6	0	1-1.5	1-1.5	300 or >	36-54
Dexamethasone	30	0.75	0	1-1.5	1-1.5	300 or >	36-54

1 Potency is defined as a mg for mg equivalence with hydrocortisone.
2 Intended as a guide only. The dose in an individual depends on total body surface area. The figures quoted are those which apply in general.

drome (endogenous hypercorticolism) will have elevated urinary free cortisol (unmetabolised) levels. On the other hand, synthetic analogues of cortisol bind less efficiently to transcortin (approximately 70%) and diffuse more completely into the tissues, in part explaining their propensity to produce Cushingoid side effects at low doses (Dluhy et al., 1975). Similarly, serum albumin depletion, with consequent diminution in storage capacity for steroids can also, with high dose therapy, lead to unusually high levels of free drug and an enhanced susceptibility to steroid side effects (Lewis et al., 1971).

2.3 Elimination

Cortisol disappears rapidly from the circulation via hepatic metabolism. The liver converts cortisol to inactive acidic compounds by reduction and then conjugation with glucuronic acid. These water soluble polar compounds are more easily excreted by the kidney. Synthetic analogues of cortisol are metabolised in the liver more slowly than cortisol because of alterations of the steroid molecule, with the net result being a prolongation of plasma half-life. Whereas it takes approximately 90 minutes for the circulating level of cortisol to be reduced to half its initial value, methylprednisolone or dexamethasone have plasma half-lives of 200 minutes or longer.

2.4 Duration of Action and Selection of a Steroid

Since analogues with long plasma half-lives also have long biological half-lives (table I) and since the biological half-lives of the glucocorticoid hormones represent their duration of metabolic activity at the tissue level (section 2.1), long acting analogues are more likely to produce Cushingoid side effects because of their continuous stimulation of peripheral tissues. This concept is important in choosing which steroid hormone is best suited for different treatment regimens. For instance, in replacement therapy, the twice daily administration of cortisol, with an 8 to 12 hour biological half-life, simulates normal daily secretion of the endogenous hormone. In alternate day

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