Drug Treatment of Disease

PRINCIPLES OF MODERN STEROID THERAPY: PART II

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PHARMACOLOGICAL EFFECTS

The relatively simple steroid desoxycorticosterone exerts a profound effect on excretion of sodium and of potassium, especially in subjects with inadequate adrenal function. Under its influence sodium is strongly retained and potassium excreted at an increased rate. This effect is of the greatest value in the treatment of Addison's disease, but it is very much less evident in subjects with intact adrenals. Desoxycorticosterone has, however, only very slight actions in other ways. It has, for instance, little or no effect on rheumatoid arthritis. Most of the adrenal steroids possess in varying degree this tendency to cause sodium retention and potassium excretion. Although the former is often mild with cortisone or hydrocortisone, yet it may be enough to produce oedema, and is clearly an undesirable feature in some subjects—such, for instance, as those with congestive cardiac failure or a tendency to oedema from other causes.

The true adrenal hormones and their analogues have several other effects which are not shown by desoxycorticosterone. They promote powerfully the deposition of glycogen in the liver, and this so-called glycogen effect has been used for their assay. Another interesting phenomenon shown by most of these steroids is that when their concentration in the blood stream rises the eosinophil cells of the circulating blood promptly disappear. Both cortisone and hydrocortisone are especially potent in these effects. An increased activity of the adrenal cortex in producing hydrocortisone is thus to be detected by a fall nearly to zero of the eosinophils in the blood stream. This may be expected as a usual reaction resulting from a normal adrenal response to stress, and persistence of the eosinophils in any severe stressful situation such as after an operation or during shock is suggestive of failure of adrenal function. The circulating lymphocytes are also reduced by these steroids, but this effect is of much less clinical value.

Another effect which can have serious clinical import is that most of these steroids provoke a negative balance of calcium, largely owing to increased faecal excretion. With this there is also abnormal loss of phosphate. Both these are referable to a loss of mineral from the bony skeleton, and this, if prolonged, may lead to osteoporosis and collapse of one or more vertebrae. The body usually loses nitrogen also, some of the loss coming no doubt from the bones, but much from the tissues and muscles.

On carbohydrate metabolism the main effect of these steroids is a tendency to produce a diabetic type of sugar curve, but this is rarely of serious clinical import. Deposition of glycogen in the liver is strongly stimulated, an action which roughly parallels the antirheumatic activity of the hormones.

Therapeutic Actions

Though knowledge of these actions is important, since they account for many of the clinical side-effects and

complications, none of them explain the important therapeutic effects for which the adrenal steroids are now so widely given. It is indeed fair to admit that so far no adequate explanation of the mode of therapeutic action of these steroids has been offered. What is evident is that they reduce very strongly the manifestations of inflammatory reactions, the hyperaemia, the oedema, the swelling, the fibroblastic activity and proliferation, and often the pain. Many of the benefits of the steroids are directly referable to these so-called anti-inflammatory effects—in topical skin therapy, in ulcerative colitis, and in asthma, for instance. It is a curious fact that the types of inflammation most readily inhibited in this way are those usually regarded as of unknown aetiology. Allergic reactions are similarly benefited, however, in equally dramatic manner. Whether or not this inhibition of inflammation is of benefit in the individual case will depend on many complex factors. The clearly allergic cases and those of uncertain aetiology generally receive benefit. But if the cause of the disease is bacterial the inhibition of the normal inflammatory resistance to bacterial invasion can quickly have disastrous consequences. It is thus essential for a full diagnosis to be made before steroid therapy is started.

In addition to having such local effects steroids inhibit some of the general manifestations of disease. Thus fever is usually lowered considerably, often to normal; the sedimentation rate, if raised, will usually be reduced; and general malaise, so common in many diseases, may be replaced by a sense of well-being and even euphoria. It is worth bearing in mind that all these changes are non-specific effects of the adrenal steroids and by no means indicate necessarily that the disease is being favourably influenced. Indeed, their occurrence in a patient when given steroids can all too easily lull the anxious physician into a false belief that he is doing good rather than harm.

Of the many effects which these steroids are known to produce, some are undesirable and determine the complications—such, for instance, as the tendency to sodium retention and loss of calcium, and others seem to be more closely related to the beneficial therapeutic action on disease.

None of the pharmacological actions adequately explain the therapeutic benefit, and this is perhaps best measured for clinical purposes by the so-called antirheumatic effect, since selected cases of rheumatoid arthritis can permit a fairly sensitive comparison of the potency of one steroid with another. The main concern of the synthetic chemist has been to reduce the undesirable sodium-retaining action while at the same time enhancing the antirheumatic effect, so that smaller doses are needed. Reduction of dosage is particularly desirable because of a marked tendency of these steroids to cause gastric irritation and even formation of gastric ulcer when given by mouth. It is hoped that more potent steroids in smaller dose will have a less irritant effect on the stomach, and there is a little evidence to support this view.

Chemical Modifications

With these points in mind the effects of the various chemical modifications to the parent molecule may be briefly reviewed.

The slightly lower potency of cortisone compared with hydrocortisone is probably due in part to less efficient absorption and in part to the need for conversion to hydrocortisone in the body.

The introduction of the second double bond in ring A as in prednisolone increases by about four times the antirheumatic activity, but hardly influences the effect on the electrolytes. However, since the active dose is reduced to about a quarter, the effect of therapeutic dose on retention of sodium is proportionately reduced.

Attachment of fluorine to 9 carbon greatly increases the sodium-retaining action, more indeed than it increases the antirheumatic effect, so that this steroid is particularly useful for control of electrolytes in substitution therapy.

Attachment of a methyl group at carbon 2 still further increases electrolyte potency, but very curiously a methyl or hydroxyl group at carbon 16 seems to abolish almost completely the electrolyte activity of the steroid. The 16 hydroxyl group is present in triamcinolone, of recent introduction, but the 16 methyl group impairs a six times higher antirheumatic potency to the steroid, with corresponding general advantages, as in dexamethasone.

The actions of some of the clinically important steroid variants are compared roughly in the Table. Many of the figures given there are very approximate, though the relative dosages in the final column are a clinically useful comparison. At present the latest steroid to be introduced, Δ^1 -9 α -fluoro-16-methylhydrocortisone, offers the best clinical prospects in that it has very high antirheumatic activity with a negligible sodium-retaining effect, but clinical experience with it is still very small.

Steroid	Glycogen Deposition	Electrolyte Excretion	Eosinopenia	Antirheumatic	Granuloma Inhibition	Relative Dosage
Hydrocortisone (F) ..	1	1	1	1	1	100
Cortisone (E) ..	0.8	0.8	0.8	0.8	1	130
Prednisolone (Δ^1 F) ..	4	1	3	4	20	25
Prednisone (Δ^1 E) ..	3	1	3	3	16	30
Aldosterone ..	0.3	50	—	0	0	—
9 α -Fluorohydrocortisone (9 α -FF) ..	20	50	20	20	20	5
Δ^1 -9 α -Fluorohydrocortisone ..	20	50	20	20	—	3
2-Methyl-9 α -fluorohydrocortisone ..	10	200	2	—	40	—
Δ^1 -(-)-Methylhydrocortisone ..	10	—	3	4	—	20
Triamcinolone (Δ^1 -9 α -fluoro-16-hydroxy-?) ..	30	Nil	3	4	10	25
Dexamethasone (Δ^1 -9 α -fluoro-16-methyl-F) ..	17	..	15	28	190	4

REPLACEMENT THERAPY

As soon as effective steroid therapy is instituted the adrenal cortex is promptly inhibited, usually within 24 hours, so that replacement therapy is in a sense the only form of therapy which one can apply. This means in effect that, once the physician has started therapy, he alone becomes responsible for the maintenance of steroid metabolism in that patient. If the external supplies are withheld either by accident or design, the inhibited adrenal cortex may be unable for a day or two to revive sufficiently to resume its normal production of hydrocortisone. Seriously adverse effects, even including fatal adrenal crisis, can occur during this

interim period. The initiation of steroid therapy thus imposes a heavy responsibility on the physician.

Therapeutic policy can be divided in general into two types: (1) the replacement of normal adrenal cortical function, lacking because of an inactive adrenal; (2) alternatively the deliberate raising of the level of steroid concentration above normal levels in body fluids, which is the aim in most forms of systemic steroid therapy.

Adrenal Behaviour

In simple replacement, then, the aim is to imitate natural adrenal behaviour. But two aspects of activity need to be considered—the electrolyte-controlling function normally controlled by aldosterone, and the hydrocortisone-producing function. In *Addison's disease* and after *total adrenalectomy* both these are lost, but in hypopituitarism only production of hydrocortisone needs to be replaced, since formation of aldosterone is not dependent on stimulation by the pituitary.

The normal human adrenal secretes 12.5–25 mg. hydrocortisone daily, and this is found clinically to be the quantity required for minimum maintenance. The sodium-retaining effect of this small dose is often not sufficient to replace the lost aldosterone, and some steroid with a more potent salt-retaining action is usually needed. Desoxycorticosterone as trimethyl acetate injected once a month is usually sufficient, in a dosage of 37 to 50 mg., or the potent steroid 9 α -fluorohydrocortisone may be given in doses of 0.5 to 1 mg. daily by mouth. Signs of overdosage of the sodium-retaining steroid must be looked for, especially oedema, raised jugular venous pressure, and increased heart size at x-ray. While the sodium-retaining steroid can usually be maintained at a steady level, the patient's needs for hydrocortisone may vary considerably. A very active life may increase them appreciably, but any stress such as infection, trauma, or operation calls for much bigger amounts; in such circumstances the dose of cortisone acetate should be raised to 100 or 200 mg. daily temporarily.

So important is it to increase the dosage of steroid during such stresses that all patients on replacement therapy should be clearly instructed about the need; all should have steroid tablets constantly available; and all should carry on their person a statement that they are receiving steroids and an indication of the dose, so that, should an accident result in unconsciousness, their steroid intake will not be interrupted.

It is because the need for hydrocortisone and the electrolyte-controlling steroid do vary a great deal independently of one another that it is usually desirable still to administer both steroids to the patient with Addison's disease. In theory one steroid should exist with the right proportions of the two actions for normal needs, and 9 α -fluorohydrocortisone probably approaches closest to this. But this steroid, on which the patient with quiescent Addison's disease can be maintained, is insufficient by itself to meet the demands of stress without also causing retention of sodium.

Resistance to Infection

The view that steroid therapy tends to reduce the body's resistance to bacterial invasion is well founded, and the problem frequently arises of patients with bacterial disease who need replacement therapy. In Addison's disease with active tubercle

of adrenal glands is perhaps the best example. In such circumstances maintenance therapy, which aims at merely replacing normal adrenal production, is likely to improve rather than reduce the patient's resistance. It is excessive dosages such as may be needed for therapy of some diseases which reduce bacterial resistance.

Pregnancy occasionally occurs in patients with Addison's disease; it constitutes a mild stress. During most of its course the patient can usually receive a daily dose of 25 to 37.5 mg. cortisone acetate daily. Labour, either natural or by caesarean section, is a more severe stress, and daily doses of 100 to 200 mg. of cortisone acetate are needed to cover this period.

In *hypopituitarism* the problem is usually simpler. Production of hydrocortisone is lost, but in contrast to Addison's disease the production of aldosterone is not appreciably impaired. The need is for the replacement of the former, but additional control of electrolytes is not needed. Oral cortisone acetate in a dosage of 12.5 to 25 mg. daily is all the adrenal steroid replacement needed. In practice, however, it is frequently found that testosterone gives the patient more subjective benefit than does cortisone. It is important and sometimes difficult to persuade such subjects that they need the additional cortisone.

In *total adrenalectomy* the conditions are essentially those of Addison's disease but aggravated by the persistence of the disease—carcinoma or severe hypertension—for which the operation was performed. Although many patients with adrenalectomy have been maintained on cortisone alone without recourse to electrolyte-controlling steroids, this is an essentially precarious regime, and it is desirable to include in the therapy a small quantity of either desoxycorticosterone trimethyl acetate as a once-monthly injection or a small daily supplement of the very potent electrolyte-controlling steroid 9 α -fluorohydrocortisone. This should go far to ward off the risks of adrenal crises developing in such subjects.

Medical Emergencies

The condition of acute *adrenal crisis* is one of the important medical emergencies calling for prompt action. Such crises may be divided usefully into several types. Sudden shock-like collapse occurring in subjects with known adrenal inadequacy, whether due to disease of the glands, to their surgical excision, or to recent steroid therapy, is not especially difficult to suspect, since such subjects are known to be at risk. A further group comprises cases of acute adrenal failure in a previously normal gland. The Friderichsen-Waterhouse syndrome is the best-known example of this, but it may occur occasionally under a wide variety of other clinical situations. In both these types the urgent need is for large volumes of saline and for prompt supplies of hydrocortisone. In such circumstances the oral route is often uncertain and impracticable, and absorption from intramuscular sites too slow owing to the poor circulation, so that the only safe route is the intravenous. A dose of 100 mg. of any of the intravenous preparations of hydrocortisone added to the saline drip is usually sufficient to correct the deficiency. The third group consists of those problem cases of shock, often post-operative, in which, though adrenal failure has not previously been suspected, it may be a factor in the crisis, yet there is no time to make tests to find out. Such problematic situations are not infrequent; many

hypotensive crises which fail to respond to noradrenaline will fall in this category. When one is suspected, intravenous hydrocortisone should be promptly given. It may be life-saving, but if no benefit results it will have done no harm, and adrenal failure as a major factor in the collapse will have been excluded.

There remains one other type of steroid replacement therapy to consider, that of *congenital adrenal hyperplasia*. In this disorder there is a primary inability of the adrenal cortex to synthesize hydrocortisone and sometimes also there are defects of electrolyte control. The steroid metabolism of such patients, whether children or adults, can be restored almost to normal by supplying cortisone. Though this is fairly effective when given orally, it is more so when given as an intramuscular injection, for such a depot provides a more regular supply of the hormone. When the balance of electrolytes is disturbed small doses of desoxycorticosterone or of 9 α -fluorohydrocortisone may be needed in addition.

In conclusion, it is worth emphasizing that the initiation of systemic steroid therapy makes the physician completely responsible for the patient's hydrocortisone metabolism. Consequently, failure to follow the basic principles or to recognize small warning signs of impending complications may seriously harm the patient. For these are potent drugs having an action on fundamental processes in the body's reaction to disease which are as yet little understood. Therapy, to be successful, must be preceded by accurate clinical diagnosis and accompanied by close attention to the diverse clinical effects on the individual patient.

Any Questions?

Gout and Disk Lesions

Q.—Is there any relationship between gout and disk lesions?

A.—There is no relationship between gout and disk lesions. Gout is a metabolic abnormality characterized by acute attacks of pain in peripheral joints, usually starting in the big toe, and by a high level of uric acid in the serum. A disk lesion is a mechanical condition in which a prolapsed intervertebral cartilage, usually in the lumbar or cervical region, presses either on the posterior ligament or a posterior nerve root causing pain which may radiate down the sciatic or a lower cervical root distribution. The treatment of each condition is quite different.

Sewage Purification

Q.—To what extent are pathogenic organisms in sewage rendered innocuous by treatment in settlement tanks, percolating filters, humus tanks, etc.?

A.—Pathogenic organisms are not affected to any significant extent by the ordinary processes of sewage purification. Such purification aims only at providing an effluent of a satisfactory chemical standard, and any reduction which has taken place in the pathogenic bacteria is due almost entirely to the passage of time and not to any factor in the so-called purification system. It is becoming increasingly the custom to chlorinate effluent from sewage-disposal plants, and, of course, when this is done the bacterial standard is greatly improved, but such effluent should never be considered as fit for drinking purposes.