

USE OF ADRENAL HORMONES IN TREATMENT

Summary of Round Table Discussion

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THE DISCUSSION of therapy with adrenal steroid hormones dealt with fundamental concepts of steroid metabolism and the application of these principles to the treatment of various important diseases of pediatric interest. This summary is limited to the basic concepts of therapy with steroids because a discussion of theory is considered likely to be of more lasting value than a temporary summing-up of clinical results.

The human adrenal cortex secretes two main types of steroid hormones, the so-called mineralocorticoids and the glucocorticoids. The first is normally represented by aldosterone, the action of which is mimicked by the synthetic steroid, desoxycorticosterone. (DOCA stands for the acetate of desoxycorticosterone.) Aldosterone secretion appears to be regulated by changes in the volume of extracellular fluid of the body via an hypothalamic-pituitary mechanism. The actions of the mineralocorticoids are widespread but mainly concern the kidney and the sweat glands, leading to retention of sodium and, with it, of water in exchange for potassium. Deficiency of mineralocorticoid, as in Addison's disease, results in loss of sodium and water, accumulation of potassium, dehydration, hypotension, and ultimately renal failure and death.

Hydrocortisone is the predominant glucocorticoid normally secreted by the adrenal cortex in response to stress or injection of adrenocorticotropin (ACTH). It appears that the concentration of hydrocortisone in the blood regulates the amount of ACTH secreted by the anterior pituitary; as it decreases, the hypothalamus stimulates the pituitary to release more ACTH in an effort to raise it; conversely, as the concentration

increases, the hypothalamus inhibits pituitary release of ACTH and the adrenal cortex becomes inactive. This "feed-back" mechanism explains why adrenocortical atrophy develops in patients treated with large amounts of hydrocortisone or cortisone. The concentration of hydrocortisone in the blood is also regulated by continuous degradation of steroids in the liver, and excretion of metabolites in the urine. It is due to this that larger and more frequent doses of steroids must be given by mouth (absorption directly into the portal system) than by intramuscular injection, to produce a sustained effect.

Hydrocortisone and cortisone have almost the same activity in the body and differ only slightly in structure. Deficient hydrocortisone production due to adrenal failure, as in Addison's disease, leads to weakness, fatigability, hypoglycemia and poor resistance to stress. When hydrocortisone or cortisone is given to man or experimental animals in excess, glycogen is deposited in the liver, hyperglycemia and glycosuria may occur, and increased amounts of protein metabolites (nitrogen and potassium) are excreted in the urine. These steroids are potent in promoting gluconeogenesis, which involves a generalized shift in cellular metabolism from synthesis of protein toward carbohydrate synthesis. Closely related to this effect is the striking anti-inflammatory activity of these compounds, which accounts for the current widespread use of the steroids in pediatric practice.

In response to medical demand the steroid chemists have produced a variety of synthetic compounds, the structures of which have been altered to increase the anti-inflammatory effect, while at the same

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time relatively diminishing the admittedly weak sodium-retaining property of hydrocortisone itself. Thus the addition of an unsaturated double-bond into the ring structure of hydrocortisone yields the synthetic analogue, prednisolone, (the analogue of cortisone is prednisone or Meticorten®) which is by weight some four or five times as active as hydrocortisone in suppressing inflammation, and no more active in causing salt retention. In the search for new steroids, other compounds have been synthesized which are more potent mineralocorticoids than DOCA itself, for example, fluorohydrocortisone. These steroids are little used except for topical application because of the great potency.

The complications of steroid therapy, as met with in practice, are an exaggerated result of the normal metabolic actions of the steroids and depend on the amounts of the compounds administered. Here an important distinction should be made between the use of corticosteroids for replacement therapy and the much commoner use for suppression of inflammation. Both the mineralocorticoids, such as DOCA, and the glucocorticoids, such as hydrocortisone, are administered in *physiologic* amounts for specific replacement therapy in adrenal insufficiency, be it in Addison's disease or in congenital adrenal hyperplasia; these amounts approximate those which the adrenal cortex would normally secrete. *Pharmacologic* doses of steroids, in contrast, greatly exceed the amount which the healthy adrenal cortex would secrete, even under stress. The mineralocorticoids are never deliberately administered in this excessive quantity; the glucocorticoids almost always are in treatment of a variety of inflammatory diseases. One may conclude on the basis of current knowledge that: (1) the favorable response of a given disease to a pharmacologic dose of hydrocortisone does *not* denote an underlying adrenal insufficiency for which physiologic amounts would suffice; (2) if pharmacologic doses of corticosteroids are necessary for treatment, the steroids are being employed to achieve a relatively non-

specific (anti-inflammatory) effect; (3) when pharmacologic doses of steroids are administered certain undesirable and even dangerous side-effects—exaggerated normal metabolic responses—are likely to develop.

Hydrocortisone and cortisone are used in pharmacologic amounts to treat a large number of diseases characterized by inflammatory changes of uncertain etiology, in which continued inflammation may lead to irreversible damage of a vital structure. This is true, for example, of rheumatic fever with active myocarditis. The steroids are useful in the treatment of rheumatic carditis by virtue of their ability to suppress inflammation, but they do not "cure" the disease or shorten the duration of an attack. It remains to be seen whether they will prove superior to time-honored therapy with salicylates in the most important clinical respect—the prevention of permanent, disabling cardiac damage.

The steroids suppress not only rheumatic inflammatory changes, whatever the etiology, but many other types and all phases of experimentally produced inflammation: the vascular permeability which leads to exudation of serum and the formed blood elements; the usual lymphocytosis; the deposition of fibrin to wall off or localize an inflammatory agent; and the prompt destruction by the reticuloendothelial system of bacteria escaping into the blood stream from a focus of infection. The steroids do not prevent phagocytosis but, rather, interfere with the ability of the phagocyte to destroy the organism once ingested. Nephrosis provides an example of one type of vascular permeability suppressed by steroid therapy; here the steroids seem to act by decreasing permeability of the glomeruli, which leads to diminished proteinuria, elevation of the oncotic pressure of the serum and finally, mobilization of edema fluid. Again, there is no evidence that steroid therapy cures nephrosis, nor that adrenal insufficiency is a feature of the disease. Steroid treatment does permit children with nephrosis, an otherwise disabling ailment, to lead an almost normal,

active life at home. From only these two examples, the use of steroids in the treatment of rheumatic carditis and in the treatment of nephrosis, one can safely conclude that if a disease undergoes a permanent remission during or following administration of steroids, this should be interpreted to mean that the steroids have permitted the survival of vital structures until such time as the body has effectively handled the underlying disease in some other unknown fashion.

When pharmacologic amounts of steroids are used to suppress inflammation, certain undesirable side-effects are to be expected; when physiologic doses are administered for replacement therapy, these rarely appear. Probably the least important side-effects are retention of salt and hypokalemia, although both may prove troublesome in the treatment of nephrosis or rheumatic myocarditis with decompensation. ACTH tends to produce edema more frequently than does hydrocortisone. The synthetic analogues, prednisone and prednisolone, have some advantage over hydrocortisone under these circumstances, but even they can produce edema when administered in large enough amount. Both natural and synthetic glucocorticoids and ACTH, administered in pharmacologic doses, can produce all the metabolic disturbances seen in Cushing's syndrome (buffalo-type obesity, moon-facies, acne and hirsutism, striae, fasting hyperglycemia and glycosuria). These are not serious and usually disappear when the dose is decreased. The "diabetes" produced by these steroids is not true diabetes mellitus because acidosis does not develop, and hence hyperglycemia and glycosuria are not necessarily contraindications to continued treatment with steroids. However, latent diabetes may become unmasked by treatment and require the use of insulin.

Another complication of treatment, seen more commonly in adults than children and perhaps even more frequently when the synthetic analogues are given, is the development of a peptic ulcer due to an in-

creased gastric secretion of hydrochloric acid and pepsin. This can usually be prevented or treated by means of antacids but it should be remembered that unsuspected, symptomless intestinal perforation may occur before treatment with antacids is started. Large doses of hydrocortisone and the synthetic steroids commonly produce a mild euphoria and sense of well-being, which may benefit the patient; but the steroids, rather rarely in children, may unleash maniacal or depressive, suicidal tendencies severe enough to prevent further use of the drugs. Continued administration of large amounts of steroids suppresses normal growth and may lead to osteoporosis and fractures, apparently the result of interference with protein synthesis by the steroids.

All these complications can develop when pharmacologic doses are used, and yet they are of less consequence than two other dangers which even the synthetic analogues cannot circumvent. The first of these is adrenal insufficiency due to adrenal atrophy, which may appear upon cessation of steroid treatment. Abrupt withdrawal of steroid therapy may precipitate an adrenal crisis which, left untreated, may prove fatal. This rarely develops if the steroids are given in large amounts for less than 10 consecutive days and very rarely if steroid treatment is withdrawn slowly, by increments of roughly 10% of the dose every 3 to 4 days. As yet no steroid has been synthesized which suppresses inflammation without suppressing adrenocortical function. In some clinics, ACTH has been used to "re-awaken" the atrophied adrenals but without proven success, for when the adrenal cortex is stimulated by ACTH it secretes increased amounts of hydrocortisone, and this in turn suppresses hypothalamic-pituitary activity. It remains to be established that pituitary inactivity is preferable to adrenocortical atrophy.

The second danger of steroid therapy is less easily handled in pediatric practice, namely, the complication of infection. The action of steroids in suppressing all types of inflammatory response may also interfere

with the patient's ability to handle an infection appearing for the first time during steroid administration, or already present but unrecognized before treatment was begun. Seemingly healed tuberculosis of the lungs or elsewhere in the body may become widely disseminated; indeed, steroids are deliberately given to experimental animals in pharmacologic amounts to increase susceptibility to tuberculosis. Fortunately there are various drugs now available to combat tuberculosis in such a situation, but it must be remembered that the steroids can prevent early recognition of an infectious complication by masking the symptoms which herald it. The situation is even more serious when the complicating infection is due to an organism, such as a virus, for which there is no specific therapy. Ordinarily the bodily defenses of the child are almost always able to overcome chicken pox effectively, but steroid therapy may render these defenses inadequate. Several deaths from chicken pox have been reported in the literature. This is a matter of prime importance to pediatricians, some of whom recommend that the steroids be given only to children who have already had varicella.

The dangers of therapy should make the clinician loathe to use steroids unless the need is great, the complaint is not trivial, and unless no other treatment will accomplish as much. If a specific drug is available it should of course be preferred to nonspe-

cific treatment with steroids. When the steroids remain the only effective treatment available they should be used with caution. They should be given only after it has been established that the patient does not have active or arrested tuberculosis (tuberculin test, roentgenogram of the chest) and with appreciation of the metabolic and infectious complications which may develop. Steroid treatment should not be initiated in patients known to have been exposed to a virus disease. Should exposure occur, or symptoms and signs of a viral or other infectious disease appear once treatment has been begun, the dose of steroids should be immediately decreased, temporarily, to what would be slightly more than a physiologic amount. In the case of hydrocortisone this would be approximately 25 to 35 mg daily by mouth in divided doses for a small child; in the case of prednisolone or prednisone roughly one fifth this amount. Such an amount is large enough to prevent adrenocortical insufficiency in patients whose adrenals have been suppressed by prior treatment, but small enough not to interfere with normal defense mechanisms. Finally, once steroid treatment is initiated, the dose should gradually be reduced to the smallest quantity which will maintain the desired response; it should be discontinued in stepwise fashion as soon as possible. Observance of these simple rules will help the pediatrician use corticosteroids and ACTH both effectively and relatively safely.

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