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1st INTERNATIONAL COLLOQUIUM ON GLUCOCORTICOID EFFECTS

Abstracts

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GLUCOCORTICOIDS (GCS): PAST and PRESENT.
L.V. Avioli.

Since compound E (cortisone) was administered to the first patient with rheumatoid arthritis on September 21, 1948, the anti-inflammatory and immuno-suppressive effects of GC medications have proven both therapeutic, and in many instances, life-saving. An analysis of the results obtained after 34 years of experience with pharmaceutical preparations of GCS reveals beneficial responses in a variety of connective tissues and immunoproliferative disorders.
In each instance, the primary arm of therapy has been to control the disease, alleviate the symptoms, and reduce the morbidity. Because of the undesirable side-effects of cortisol which result from sodium retention, a variety of synthetic derivatives of cortisol have been produced. Despite the decreased capacity for sodium retention which characterizes the synthetic GC analogues, it should be stressed that the other adverse multisystem effects of these compounds are proportional to their anti-inflammatory effects which conditions the overall clinical response.
Physicians must respect that, despite the continued appearance of "newer and more potent" synthetic analogues of the cortisol molecule with less salt retaining effects, the other undesirable side effects of these potent drugs still confront the unsuspecting patient. A detailed understanding of the clinical pharmacology and the nature and extent of the potential complications that occur with each of the synthetic analogues is essential before any therapeutic regimen is either initiated or continued for prolonged periods.

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IMPACT OF STRUCTURAL MODIFICATIONS ON THE HYDROCORTISONE MOLECULE.

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The first period 1952-1962 of research involving modification of the hydrocortisone molecule was characterized by the introduction of new substituents, addition of double bonds and other relatively simple chemical modifications. The positive outcome of this period was the discovery of highly potent antiinflammatory agents and the success in eliminating electrolyte retention. In the second period (1962-75) more profound modifications of the steroidal nucleous (replacement of one or more carbons of the skeleton with nitrogen or oxygen) were intensely pursued. Other studies involved attachment of the heterocyclic pyrazole ring to position C_2 and C_3 or of the oxazoline ring to position C_{16} and C_{17}. This last modification has proven to have an effect on Calcium balance and possibly a reduction of the risk of osteoporosis. The third period is characterized by involvment of new screening techniques at the receptor level which will hopefully allow the selection of drugs with higher specificity of action and consequently fewer side effects.

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GLUCOCORTICOIDS AND INTERMEDIATE METABOLISM
D. KIPNIS

The tendency of glucocorticoids to induce hyperglycemia, glycosuria, increased hepatic gluconeogenesis, increased hepatic glycogen deposition and antagonism to insulin action has been well established. Enhancement of protein catabolism, inhibition of protein synthesis and a negative nitrogen balance have also been demonstrated in glucocorticoid excess states. These as well as the effect of glucocorticoids on fatty acid synthesis, hepatic enzyme activity and amino acid metabolism will all be reviewed and discussed with reference to specific glucocorticoids and reported effects of new synthetic glucocorticoid analogues.

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GLUCOCORTICOIDS (GCs) GLUCOSE METABOLISM and HPA AXIS.
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Exogenous and endogenously given GCs impair glucose tolerance with increased insulin levels-characteristic of an insulin-resistant state with a tendency to amelioration on continued GC use. Evidence exists that GCs increase hepatic glucose production secondary to increased availability of gluconeogenic substrates, however not always demonstrated under prolonged treatment. Besides, there is a decrease in peripheral glucose utilization with a temporary alteration of insulin binding to its receptors(IR)--increase(prednisone and deflazacort) or decrease(dexamethasone)binding to the IR in cells such as RBC, their number and affinity being normal in Cushing's syndrome--associated with post-receptor defects of insulin action, heterogeneously distributed in body tissues. GCs will block HPA which is proportional to size of dose and duration of treatment. Recovery of HPA function occurs when basal cortisol(F)becomes normal, preceeded by elevated ACTH, indicating recovery of adrenal responsivess to exogenous ACTH, such test predicting the integrated response to stress in GC-treated patients. The entire process may require up to 1 year for completion. The rise of F after insulin-hypoglycemia is the most sensitive test for HPA function being its impairment already observed after short-term GC administration and also on alternate-day therapy and may not indicate significant depression of the axis, as suggested by the presence of F circadian rhythm and LVP responsiveness after 14-day prednisone or deflazacort. Steroid withdrawal syndrome and depression of HPA can be avoided by either gradual reduction of dosage, the adrenals beginning to regain its ability to ACTH stimulation at daily doses of 5-7.5 mg prednisone equivalent given in the morning or by alternate - day therapy.

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