PURIFIED ACTH GEL

CONTROL OF THERAPY IN RHEUMATOID PATIENTS

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Brooks and Norymberski (1952) discovered that a certain group of corticosteroids could be oxidized by sodium bismuthate to 17-ketosteroids and so estimated as such. They named this group "17-ketogenic steroids" (17-KGS). The importance of this discovery lay in the fact that hydrocortisone, cortisone, and their known corticosteroid metabolites in urine are in fact 17-KGS. Norymberski

be easily undertaken by any hospital biochemical laboratory.

When hydrocortisone is given by slow intravenous transfusion, some 45 per cent. by weight is recoverable in the urine as 17-KGS. As hydrocortisone is the only known 17-KGS secreted by the adrenal, it is tentatively assumed that the increase in urinary 17-KGS that follows ACTH therapy reflects a parallel increase in hydrocortisone secreted by the adrenal. It is suggested that environmental changes may affect the percentage of hydrocortisone or cortisone metabolized to 17-KGS; so far this has not been observed in rheumatoid patients treated with cortisone, but it is a possibility that must be kept in mind. In the assay of 17-KGS we have a new research tool, which has already proved valuable in the control of ACTH therapy and in the differential diagnosis of endocrine disorders. One interesting application will lie in the differentiation between those environmental changes (? "stress") that call for an increased adrenal output of hydrocortisone and those that do not.

High purity ACTHAR gel (Armour) and purified corticotrophin gel (Wilson) were given to patients suffering from rheumatoid arthritis and ankylosing

spondylitis. The degrees of adrenal stimulation induced were measured by the assay of urinary 17-KGS. The purpose of this paper is to report some of the results of these assays in twenty patients treated continuously with ACTH gel for periods of from 1 to 18 months.

(1) *H.P. ACTHAR Gel*.—40 "Units" given every 48 hrs by intramuscular injection (Fig. 1). The output of 17-KGS remains fairly constant after the first week, but the level varies considerably from patient to patient. It has

Fig. 1.—Output of 17-KS and 17-KGS in Case 1, a man aged 47, suffering from rheumatoid arthritis, on a dosage of 40 units H.P. Acthar Gel every 48 hrs intramuscularly, for 12 days.

Fig. 2.—Output of 17-KS and 17-KGS in Case 2, a woman aged 42, suffering from rheumatoid arthritis, on a dosage of 20 units H.P. Acthar Gel every 12 hrs intramuscularly, for 9 days.

(1952) subsequently developed a method for the estimation of 17-KGS in urine. This provided a notable advance in the assay of adrenocortical steroids, in that it measured a large and precise fraction of the urinary corticosteroid output and in doing so avoided the usual destructive, and/or unreliable, procedures for hydrolizing the steroid conjugates. The method described by Norymberski, Stubbs, and West (1953) has now been further simplified (Gibson and Norymberski, 1954) and can

Fig. 3.—Output of 17-KS and 17-KGS in Case 3, a man aged 30, suffering from ankylosing spondylitis, and in Case 4, a man aged 36, suffering from rheumatoid arthritis, both on a dosage of 40 units Acthar Gel every 24 hrs intramuscularly, Case 3 for 8 days and Case 4 for 4 days.

Fig. 4.—Output of 17-KS and 17-KGS in Case 5, a man aged 47, suffering from rheumatoid arthritis, on a dosage of 40 units H.P. Acthar Gel every 48 hrs intramuscularly for 12 days, followed by 40 units Wilson's Gel every 48 hrs intramuscularly for 10 days.

been observed as low as 20 mg. and as high as 50 mg. A low output is not due to the adrenal being unable to respond, since a marked increase will occur when the injections are given more frequently. The duration of the clinical benefit varies from 30 to 45 hrs, depending, it would seem, upon the severity of the disease and the degree of adrenal stimulation achieved.

(2) *H.P. ACTHAR Gel*.—20 “Units” given 12-hrly by intramuscular injection. By the end of the first week the output of 17-KGS was equal to what one would expect from an adrenal secretion of 250 mg. hydrocortisone daily. The progressive rise suggests that the preparation

used contained an adrenal growth factor, since this rise cannot be accounted for by a simple additive effect. (Fig. 2.)

(3) *H.P. ACTHAR Gel*.—40 “Units” given every 24 hrs by intramuscular injection. The two patients were treated with the same batch of H.P. ACTHAR Gel. The assays show how greatly the adrenal stimulation achieved may vary from patient to patient in these circumstances. (Fig. 3.)

(4) *Comparison of Two “Highly Purified” ACTH Gels*.—This finding, which has been observed repeatedly, is shown because the “units” of both brands of ACTH Gel are considered to be equivalent. (Fig. 4.)

(5) *Pitfalls of Long-term Therapy*.—When ACTH is administered for a long time, its effectiveness in stimulating the adrenal cortex may diminish—though we have not seen this happen during therapy with H.P. ACTHAR Gel. On the other hand, with an increased dose, or with a change to a more potent preparation, the adrenal stimulation may increase and may do so progressively. In the case illustrated (Fig. 5), the patient was not able to return for examination

Fig. 5.—Output of 17-KS (white line) and 17-KGS (black column) in Case 3, a man aged 30, suffering from ankylosing spondylitis, in the course of 13 months, during which period he received ACTH gel in various dosages.

during the months of May and June. During this time the adrenal stimulation increased to dangerous levels. When he did return his diastolic blood pressure had risen from normal levels to 135 mm. Hg; 6 months later, at the time of the last assay, it had fallen to 115 mm. Hg.

The value of ACTH therapy to these patients has not been finally assessed, but it may be said that, at least during the initial weeks of treatment, the effectiveness is similar to what one would expect from cortisone given in corresponding amounts. For example, a daily injection of ACTH gel producing a urinary output of 40 mg. 17-KGS has the expected clinical effectiveness of 100 mg. cortisone acetate given by mouth.

Discussion

In the study of the use of ACTH it is not the amount given that matters but the level to which the secretion of corticosteroids is raised. In the first few days of treatment one can obtain a rough idea of the degree of adrenal stimulation by studying eosinophil counts and changes in electrolyte metabolism. After this time—unless steroid assays are made—one can only note the presence or absence of excessive stimulation. Various methods for assaying corticosteroids in blood and urine have been described, but to the best of our knowledge the only practicable and reliable assay of the adrenocortical function with which we are at present concerned in the treatment of rheumatic diseases, namely, the output of hydrocortisone by the adrenals, is that of the urinary 17-KGS.

Summary

17-ketogenic steroids (17-KGS) are corticosteroids that can be oxidized to 17-ketosteroids (17-KS) by sodium bismuthate. Hydrocortisone secreted by the adrenal cortex or administered hydrocortisone or cortisone are the only known sources for the 17-KGS found in urine. H.P. ACTHAR Gel and Wilson's Purified corticotrophin have been administered for prolonged periods to 20 patients suffering from rheumatoid arthritis and ankylosing spondylitis. The resulting increases in excretion of 17-KGS and 17-KS have been measured. Representative findings are recorded in graphic form. It is concluded that:

(1) The present method of describing the potency of an ACTH preparation for intramuscular injection is very unsatisfactory.

(2) The H.P. ACTHAR Gel used in these studies contained, in all probability, an adrenal growth factor.

(3) The use of a reliable method of assessing adrenocortical activity is essential for the intelligent use of ACTH.

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RÉSUMÉ

Les stéroïdes 17-cétogènes (17-KGS) sont des corticostéroïdes qui peuvent être oxydés par le bismuthate de soude pour devenir 17-cétostéroïdes (17-KS). La hydrocortisone sécrétée par l'écorce surrénale et la hydrocortisone ou la cortisone administrée sont les seules sources connues des 17-KGS de l'urine. Le Gel H.P. ACTHAR et la corticotrophine purifiée de Wilson ont été administrés pour des périodes prolongées à 20 malades atteints d'arthrite rhumatismale et de spondylarthrite ankylosante. L'augmentation de l'excrétion des 17-KGS et des 17-KS qui en a résulté, a été mesurée. Les résultats représentatifs ont été enregistrés sous forme de graphique. On conclut que:

(1) L'actuelle méthode de description de la force d'une préparation de ACTH pour injection intramusculaire est peu satisfaisante.

(2) Le Gel H.P. ACTHAR utilisé dans cette étude contenait, selon toute probabilité, un facteur surrénal de croissance.

(3) Une méthode précise d'évaluation de l'activité corticosurrénale est essentielle pour l'application intelligente de l'ACTH.

Gel de ACTH purificado Control del tratamiento de los reumáticos

SUMARIO

Los esteroides 17-cetógenos (17-KGS) son corticosteroides capaces de oxidación por el bismutato de sodio para formar 17-cetosteroides (17-KS). La hidrocortisona secretada por la corteza suprarrenal y la hidrocortisona o la cortisona administrada constituyen las únicas fuentes conocidas de los 17-KGS en la orina. El Gel H.P. ACTHAR y la corticotrofina purificada de Wilson fueron administrados durante períodos prolongados a 20 enfermos con artritis reumatoide y con espondilosis anquilosante. La resultante aumentación de la excreción de 17-KGS y de 17-KS fué medida. Los resultados representativos fueron anotados en forma diagramática. Se concluye que:

(1) El método presente de descripción de la potencia de un preparado de ACTH para inyección intramuscular no es muy satisfactorio.

(2) El Gel de H.P. ACTHAR empleado en este estudio contenía, en toda probabilidad, un factor suprarrenal de crecimiento.

(3) Un método seguro de evaluación de la actividad corticosuprarrenal es esencial para el empleo inteligente de la ACTH.