PRELIMINARY CLINICAL TRIALS WITH 9-ALPHA-FLUORO HYDROCORTISONE ACETATE IN RHEUMATOID ARTHRITIS*

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That the properties of adrenal cortical hormones may be modified by relatively minor alterations in their structural formulae is well known. Addition or removal of various chemical radicals and groupings at one or another carbon position in the steroid nucleus may enhance or lessen one or more of the physiological activities of the parent compound. The imagination of chemists has been so stimulated by this fact that literally hundreds of synthetic steroid preparations have been made, and at a rate more rapid than they can be tested therapeutically or experimentally in animals.

Because hydrocortisone and cortisone have definite limitations as treatment agents for rheumatoid arthritis, investigators have continued to search for substitutes which might be applied with greater success. We have screened a number of esterified preparations of hydrocortisone and have made clinical comparisons of their anti-rheumatic activity. Recently our attention was attracted to a halogen derivative, 9-alpha-fluoro hydrocortisone acetate, which, though probably not destined as a practical agent for systemic therapy in rheumatoid arthritis, is of interest because it exhibits far greater anti-rheumatic potency, milligram for milligram, than any steroid we have tested heretofore.

Clinical interest in the halogenated derivatives of hydrocortisone was stimulated by results of animal studies which indicated that these compounds possess unusually high glycogenic activity as measured by rat liver glycogen assays for 11-oxygenated corticoids. Fried and Sabo (1953, 1954), Borman and Singer (1954), and Borman, Singer, and Numerof (1954) determined that the 9-alpha-halo derivatives (chloro, fluoro, iodo, and bromo) manifest both

glucocorticoid and mineralocorticoid properties, and each in differing degrees. With the fluoro compound, glycogen deposition activity was twice as great while its sodium-retaining effect was only one-fifth of that of the chloro derivative. Compared with cortisone acetate, 9-alpha-fluoro hydrocortisone acetate was much more potent in glycogenic activity (about 10 times), in producing thymus involution (four times), and in sodium retention.

Data concerning clinical trials with 9-alpha-fluoro hydrocortisone acetate are meagre. Goldfien and others (1954) found that the substance, administered orally as sole treatment and in extremely low dosage, was highly efficient in maintaining patients with Addison's disease; dosages as small as 0.25 to 1 mg. a day were sufficient to hold patients in a near optimal state. Metabolic studies conducted by these workers in Addisonian or bilaterally adrenalectomized patients demonstrated that the preparation caused marked retention of sodium and diuresis of potassium, and a striking and prolonged eosinopenic response. Comparative studies in a patient with Addison's disease disclosed that the compound's effect on electrolyte excretion was at least as powerful as that of aldosterone (electrocortin) and was considerably more prolonged. In female patients with adrenogenital syndrome 9-alpha-fluoro hydrocortisone acetate in total daily doses as low as 5 mg. caused marked reduction in urinary 17-ketosteroid excretion.

The immediate results of pilot trials with 9-alpha-fluoro hydrocortisone acetate in rheumatoid arthritis have recently been described (Boland, 1954; Bayles, 1954; Bunim, 1954). Incomplete and extremely brief observations made in a total of six patients suggested that the compound exerted a suppressive influence on the disease when taken orally in very small

* Based on material presented in a discussion at the annual meeting of the American Rheumatism Association, June, 1954. See p. 348.

daily amounts, but data were not sufficient to appraise adverse reactions or therapeutic practicability.

Present Investigation

The clinical response to orally administered 9-alpha-fluoro hydrocortisone acetate* was determined in thirteen patients with active peripheral rheumatoid arthritis. The drug was given as initial investigative treatment to seven patients who had received no therapy, other than conservative measures, for at least 3 months beforehand; in three of these medication was later transferred to hydrocortisone (free alcohol) in order to make dosage comparisons. Six patients, who had been maintained on established daily amounts of hydrocortisone (free alcohol) with satisfactory and stable clinical improvement, were transferred directly to the fluoro compound, and differences in dosage requirements for approximately equivalent degrees of rheumatic control were estimated.

* Supplies of 9-alpha-fluoro hydrocortisone acetate were made available to us by The Squibb Institute for Medical Research, New Brunswick, New Jersey, U.S.A. Hydrocortisone (free alcohol) was supplied by Merck and Co., Rahway, New Jersey, U.S.A.

9-alpha-fluoro hydrocortisone acetate was administered in divided doses four times a day, after meals and at bedtime. Changes in dosage were made by increases and decreases of 0.5 or 1.0 mg. each. No supplemental medication was prescribed, but the patients were kept on sodium-poor (not quantitatively measured) diets. Three patients were observed under hospital conditions at the beginning and the others were followed as ambulatory outpatients throughout the period of study. The decision to employ small total daily dosages was based on reported animal and clinical data which indicated that the derivative possessed extraordinary metabolic potency.

Results in Patients receiving 9-Alpha-Fluoro Hydrocortisone Acetate as Initial Suppressive Therapy

With total initial suppressive dosages ranging from 4 to 8 mg. a day, subjective and objective improvement in the articular manifestations resulted in five of the seven patients (Table I). Improvement was slight or questionable in one patient (Case 6), and another (Case 7) experienced an acute articular

CLINICAL RESPONSE OF PATIENTS WITH RHEUMATOID ARTHRITIS TO INITIAL DOSE

Case No.	Age (yrs)	Sex	Duration of Disease (yrs)	Activity of Disease	Initial Dosage (mg./day)	Onset of Improvement (hrs after first divided dose)	Degree of Improvement
1	55	F	4	Severe	4 × 2; 6 × 2; 8 × 4; 7 as maintenance dose	17 (after total of 3 mg.)	Marked in 6 days
2	48	F	7	Moderately severe	6 × 7; 5 × 3; 4 as maintenance dose	6 (after total of 2 mg.)	Marked in 13 days
3	59	F	8	Moderate	6 × 5; 5 × 3; 4 × 5; 3 × 8; transfer to hydrocortisone	7 (after total of 3 mg.)	Very marked in 3 days
4	55	F	5	Moderately severe	4 × 21; transfer to hydrocortisone	30	Marked in 14 days
5	65	M	1	Moderate	4 × 14; transfer to hydrocortisone	24	Marked in 14 days
6	58	F	1	Moderately severe	4 × 4; 6 × 4; 7 × 5; transfer to hydrocortisone	? (Improvement too little and gradual to estimate)	Slight in 13 days
7	53	M	4	Moderate	4 × 7; discontinuance	Worse after 72 hrs	Worse

exacerbation involving multiple joints 72 hrs after initiation of the drug. In the five patients who demonstrated definite benefits, the onset and subsequent rate of improvement were rapid. The erythrocyte sedimentation rate was reduced promptly and strikingly in four of the seven patients. The degree and speed of overall improvement in five of the seven patients compared favourably with that which would have been expected from hydrocortisone or cortisone administered in much larger initial suppressive doses. These observations indicated to us that 9-alpha-fluoro hydrocortisone acetate exerts potent anti-rheumatic action when administered in relatively very small total daily doses.

Comparisons of Maintenance Dosage Requirements for 9-Alpha-Fluoro Hydrocortisone Acetate and Hydrocortisone (Free Alcohol)

Attempts were made in nine patients to estimate differences in dosage requirements for the maintenance of similar degrees of rheumatic control (Table II, overleaf). One patient (Case 16), who had been held under satisfactory clinical control with 50 mg.

hydrocortisone (free alcohol) per day, was transferred to 9-alpha-fluoro hydrocortisone acetate in doses of 5 mg. a day, and 4 days later experienced a severe articular relapse. Dosage comparisons were not permitted in this case because marked fluid retention and moderate hypertension also developed and these prohibited trials with larger doses of the fluoro compound. From comparisons made in the remaining eight patients, the calculated dosage ratios of hydrocortisone (free alcohol) to 9-alpha-fluoro hydrocortisone acetate ranged from 8.3:1 to 12.5:1. Thus it appeared from clinical appraisals alone that the milligram anti-rheumatic potency of 9-alpha-fluoro hydrocortisone acetate was roughly ten times greater than that of hydrocortisone (free alcohol).

Adverse Reactions

During the short periods of observation embraced by this study, and with the dosage range explored, two adverse reactions to 9-alpha-fluoro hydrocortisone acetate were prominent: fluid retention and blood pressure elevation.

Retention of fluid, as manifested by oedema and/or sudden gains in weight, was observed in twelve of

DOSES OF 9-ALPHA-FLUORO HYDROCORTISONE ACETATE ADMINISTERED ORALLY

Erythrocyte Sedimentation Rate (Westergren) (mm./hr)		Duration of Administration (days)	Fluid Retention		Other Effects; Miscellaneous Comments
Before Administration	Rapidity of Change with Administration		Objective Oedema	Sudden Weight Gain	
96	29 after 8 days	81	Moderate to slight (variable)	None	Slight elevation of blood pressure
58	25 after 10 days	77	Slight	10 lb. during first 10 days on doses of 6 and 5 mg./day; no further gain on 4 mg./day	Moderate elevation of blood pressure; moderate insomnia on 6 mg./day, slight on 4 mg./day; slight facial mooning after 4 weeks administration; irregular nausea after 8 weeks
49	16 after 10 days	21	Marked on doses of 6 and 5 mg./day; moderate on doses of 3 mg./day	13 lb. during first 13 days on doses of 6, 5, and 4 mg./day	Moderate elevation of blood pressure. After transfer to hydrocortisone (free alcohol) evidences of fluid retention disappeared within 5 days and blood pressure returned to pre-treatment level in 14 days
44	16 after 10 days	21	Moderate	4½ lb. during first 5 days; then no further gain	Slight elevation of blood pressure. After transfer to hydrocortisone (free alcohol) evidences of fluid retention disappeared and blood pressure returned to normal in 5 days
47	34 after 14 days	14	Moderate	10 lb. in 14 days	Evidences of fluid retention disappeared 4 days after transfer to hydrocortisone (free alcohol)
65	48 after 13 days	13	None	None	Improvement only slight, even questionable; definite improvement later, after transfer to hydrocortisone (free alcohol)
33	23 after 7 days	7	Moderate	5 lb. in 7 days	Acute articular flare-up after 72 hrs of administration; subsidence followed withdrawal. History of similar exacerbation after 1 week of cortisone therapy 2 years previously. Refused trial on hydrocortisone

MAINTENANCE DOSAGE REQUIREMENTS FOR 9-ALPHA-FLUORO HYDROCORTISONE

Case No.	Activity of Disease	Improvement maintained with Both Compounds	Daily Dosages required for Equivalent Rheumatic Control (mg.)		Calculated Dosage Ratios (Hydrocortisone (free alcohol) : 9-alpha-fluoro Hydrocortisone Acetate)	Fluid Retention on Maintenance Doses	
			Hydrocortisone (free alcohol)	9-alpha-fluoro Hydrocortisone Acetate		Hydrocortisone (free alcohol)	9-alpha-fluoro Hydrocortisone Acetate
8	Moderate	Very marked	25	3	8.3 to 1	None	Moderate
9	Moderately severe	Marked	40	4	10.0 to 1	None	Moderate
10	Moderate	Marked	40	4.5	8.9 to 1	None	Moderate
11	Moderately severe	Very marked	30	3	10.0 to 1	None	Slight
12	Moderately severe	Marked	50	5	10.0 to 1	None	Moderate
13	Moderately severe	Marked	35	4	8.8 to 1	None	Marked
14	Moderately severe	Marked	50	4	12.5 to 1	None	Marked
15	Moderate	Marked	35	3.5	10.0 to 1	None	Slight
16	Moderately severe	Marked on hydrocortisone. Relapse on fluoro hydrocortisone	50	? (greater than 5)	—	Slight	Marked

the thirteen patients, marked in four, moderate in five, and slight in three. Signs of fluid retention usually began after 2 to 6 days of administration, and, when pronounced, it was accompanied by weight increases as great as 1 to 2 lb. per day. In order that this effect could be observed uninfluenced by countermeasures, diuretics were not employed. In each instance where the patient was transferred to hydrocortisone (free alcohol) in larger but equally efficient amounts, signs of fluid retention disappeared quite promptly, ordinarily within 2 to 5 days. These observations suggested that the substitution of a fluorine atom at the ninth carbon position of hydrocortisone enhanced not only the anti-inflammatory activity of the steroid but also its salt and water retaining property to an even greater degree.

Blood pressure elevations were recorded in six of the thirteen patients; these were regarded as slight in three and moderate in three. In each instance where transfer to hydrocortisone (free alcohol) was made the blood pressure returned to its former level within 4 to 14 days.

The treatment periods with 9-alpha-fluoro hydrocortisone acetate were too brief to permit assessment of other possible endocrine side-effects. One patient (Case 2), who received the preparation in maintenance dosages of 4 mg. a day for a total of 77 days, exhibited slight, questionable, facial mooning after 4 weeks of administration.

Two unusual reactions were observed. One patient (Case 12) suddenly experienced dryness of the mouth, a "toxic" feeling, and low-grade fever after the fluoro compound had been taken for 14 days; the symptoms disappeared 2 days after resumption of hydrocortisone (free alcohol) therapy. Another patient (Case 13) developed abdominal bloating, moderate facial oedema, and Grade II albuminuria with cylindruria but without azotaemia after 13 days of medication; the manifestations were corrected within 5 days of transfer to hydrocortisone (free alcohol). Two other patients complained of intermittent nausea.

Comment

The number of cases studied were too few and the periods of observation too short to allow more than limited and provisional deductions. However, it was obvious to us that the powerful salt and water retaining properties of 9-alpha-fluoro hydrocortisone, and perhaps other metabolic effects which may ensue with prolonged administration, would probably prohibit its employment as systemic medication for rheumatoid arthritis. Dosages of the order of 3 to 8 milligrams a day seemed to be necessary to provide adequate suppression of rheumatic manifestations when the disease was of moderate or greater activity. Even with these relatively small total daily amounts, most of the patients developed evidences of fluid

ISONE ACETATE AND HYDROCORTISONE (FREE ALCOHOL) COMPARED

Blood Pressure Elevations on Maintenance Doses		Miscellaneous Comments
Hydrocortisone (free alcohol)	9-alpha-fluoro Hydrocortisone Acetate	
Slight	Moderate	
None	None	
None	None	
None	Slight	Nausea with 9-alpha-fluoro hydrocortisone acetate; none with hydrocortisone (free alcohol)
None	Moderate	After 2 weeks 9-alpha-fluoro hydrocortisone acetate developed sudden dryness of mouth, "toxic feeling", and low-grade fever. Symptoms disappeared 2 days after transfer to hydrocortisone (free alcohol)
None	None	After 13 days 9-alpha-fluoro hydrocortisone acetate developed abdominal bloating, moderate facial oedema, gr. 2 albuminuria without azotaemia. Symptoms disappeared 4 days after transfer to hydrocortisone (free alcohol)
None	None	
None	Slight	
Slight	Moderate	Pronounced articular relapse 4 days after transfer to 9-alpha-fluoro hydrocortisone acetate. Fluid retention and blood pressure elevation disallowed trial of larger doses

retention which in some were pronounced and intolerable. The fact that this complication disappeared promptly when treatment was changed to hydrocortisone (free alcohol) in larger but equally efficient doses signified that the substitution of a fluorine atom at the ninth carbon position of hydrocortisone enhances its salt-retaining effect more than its anti-phlogistic action.

These observations are of interest chiefly because they demonstrate that it is possible to enhance the anti-inflammatory activity of hydrocortisone, as well as to modify other of its properties, by altering its chemical structure. This implies that it is not beyond the realm of hope that, through other substitutions or changes in chemical configuration, a derivative of hydrocortisone may be prepared which, in effective anti-rheumatic doses, may be devoid of significant complications.

Summary

A halogenated derivative of hydrocortisone—9-alpha-fluoro hydrocortisone acetate—was administered as investigative therapy to thirteen patients with active rheumatoid arthritis. Seven patients received the preparation as initial medication; three were transferred later to hydrocortisone (free alcohol) for comparison of dosage requirements. Six patients who were being maintained on estab-

lished daily amounts of hydrocortisone (free alcohol) were transferred directly to the fluoro compound and the doses needed for similar degrees of rheumatic control were compared.

The following conclusions were drawn:

(1) Weight for weight, the anti-rheumatic potency of 9-alpha-fluoro hydrocortisone acetate was found to be much greater than that of the parent compound, hydrocortisone. This was indicated by the following:

- Initial suppressive doses of the fluoro derivative ranging from 3 to 8 mg. a day were sufficient, in five of seven patients, to promote rapid improvement in the rheumatic manifestations;
- Comparisons of maintenance dosage requirements for approximately equivalent degrees of clinical control revealed that, in eight of nine patients, the anti-rheumatic power of 9-alpha-fluoro hydrocortisone acetate, milligram for milligram, was roughly ten times that of hydrocortisone (free alcohol).

(2) With the small total daily amounts of the fluoro compound employed, fluid retention developed in twelve of the thirteen patients, and became pronounced in some. This suggested that the substitution of a fluorine atom at the ninth carbon position increased the electrolytic activity of hydrocortisone more than it enhanced its anti-phlogistic property. The excessive salt and water retaining

effect of the fluoro derivative would seem to preclude its use as practical systemic therapy in rheumatoid arthritis.

(3) These observations demonstrate that the anti-inflammatory potency of hydrocortisone may be enhanced, and other of its properties modified, by altering its formula. This raises a hope that, through changes in structure or other chemical substitutions, a more successful therapeutic agent for rheumatoid arthritis may be produced in the future.

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Essais cliniques préalables de l'acétate de 9-alpha-fluoro hydrocortisone dans l'arthrite rhumatismale

RÉSUMÉ

Un dérivé halogène d'hydrocortisone—acétate de 9-alpha-fluoro hydrocortisone—fut administré, à titre d'enquête thérapeutique, à treize malades atteints d'arthrite rhumatismale active. A sept malades on donna cette préparation comme médication initiale; on soumit ensuite trois d'entre eux à l'hydrocortisone (alcool libre), pour comparer les doses requises. Six malades recevant jusqu'alors des doses quotidiennes fixes d'hydrocortisone (alcool libre) furent assignés au dérivé fluoré. On compara les doses nécessaires pour obtenir la même mesure d'amélioration de leur rhumatisme. On a tiré des conclusions suivantes:

(1) A poids égal, le pouvoir antirhumatismal de l'acétate de 9-alpha-fluoro hydrocortisone fut très supérieur à celui du composé parent, hydrocortisone, pour des raisons suivantes:

- Pour le traitement d'attaque, des doses quotidiennes de 3 à 8 mg. de dérivé fluoré furent suffisantes chez cinq malades sur sept pour améliorer rapidement leurs manifestations rhumatismales.
- En comparant les quantités requises pour maintenir une mesure similaire d'amélioration clinique, on trouva que chez huit malades sur neuf le pouvoir antirhumatismal de l'acétate de 9-alpha-fluoro hydrocortisone, milligramme pour milligramme, fut à peu près dix fois supérieur à celui de l'hydrocortisone (alcool libre).

(2) Malgré les doses quotidiennes totales faibles de composé fluoré, on observa chez douze sur treize malades une rétention aqueuse qui chez certains d'eux devint prononcée. Cela suggère que la substitution d'un atome

de fluor à la neuvième position du carbone augmente l'action électrolytique plus que l'antiphlogistique de l'hydrocortisone. Cette propriété de retenir un excès de sel et d'eau semble anéantir l'application pratique du dérivé fluoré dans l'arthrite rhumatismale.

(3) Ces observations montrent qu'en changeant la formule on peut augmenter le pouvoir anti-inflammatoire de la cortisone et modifier ses autres propriétés. Cela permet d'espérer qu'on créera un jour un agent thérapeutique plus efficace contre l'arthrite rhumatismale par un changement de la structure ou par une autre substitution chimique.

Ensayos clínicos preliminares del acetato de 9-alfa-fluoro hidrocortisona en la artritis reumatoide

SUMARIO

Un derivado halógeno de hidrocortisona—acetato de 9-alfa-fluoro hidrocortisona—fué administrado, como terapia investigadora, a trece enfermos con artritis reumatoide activa. Siete enfermos recibieron esta preparación como medicación inicial; tres de ellos fueron luego trasladados a hidrocortisona (alcohol libre) para comparar las dosis requeridas. Seis enfermos tratados anteriormente con dosis diarias fijas de hidrocortisona (alcohol libre) fueron sometidos directamente al tratamiento con el compuesto de fluor, comparándose las dosis requeridas para el grado similar de control del reumatismo.

Se concluyó lo siguiente:

(1) A peso igual, el poder antirreumático del acetato de 9-alfa-fluoro hidrocortisona fué mucho mayor que el del compuesto pariente, la hidrocortisona, lo que fué indicado por lo siguiente:

- Dosis iniciales supresoras de 3 a 8 mg. por día del derivado de fluor fueron suficientes, en cinco de los siete enfermos, para motivar una mejoría rápida de las manifestaciones reumáticas.
- Al comparar las dosis requeridas para mantener un control clínico de grado aproximadamente equivalente, se halló que la potencia antirreumática del acetato de 9-alfa-fluoro hidrocortisona, miligramo por miligramo, fué cerca de diez veces mayor que la de la hidrocortisona (alcohol libre).

(2) A pesar de la pequeñez de las dosis diarias totales del compuesto de fluor, sobre trece enfermos doce acusaron una retención hídrica que en algunos llegó a ser pronunciada. Esto sugiere que la sustitución de un átomo de fluor en la novena posición del carbón aumenta mas la acción electrolítica que la antiflogística de la hidrocortisona. Esta acción retentiva de sal y de agua en exceso impediría la aplicación práctica del compuesto de fluor en la artritis reumática.

(3) Estas observaciones muestran que cambiando la formula se puede aumentar el poder anti-inflamatorio y modificar otras propiedades de la cortisona. Esto permite esperar que se llegará a producir por un cambio de la estructura o por otra sustitución química un mejor agente terapéutico contra la artritis reumatoide.