

CLINICAL AND METABOLIC EFFECTS OF Δ^1 -DEHYDRO-9-ALPHA-FLUORO HYDROCORTISONE ACETATE

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The discovery of the therapeutic properties of certain steroids has recently given rise to interesting chemical and pharmacological problems. The remarkable antiphlogistic activities of halogenated derivatives of hydrocortisone, and the disappearance of secondary effects obtained by the Δ^1 -diene derivatives of cortisone, have suggested the synthesis of a steroid which joins the two chemical characteristics (Hirschmann, Miller, Beyler, Sarett, and Tishler, 1955; Stafford, Barnes, Bowman, and Meinzing, 1955; Fried, Florey, Sabo, Herz, Restivo, Borman, and Singer, 1955; Hogg, Lincoln, Nathan, Hanze, Schneider, Beal, and Korman, 1955).

Preliminary experiments have been carried out with the following derivative: Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate, the structural formula of which is shown in Fig. 1.

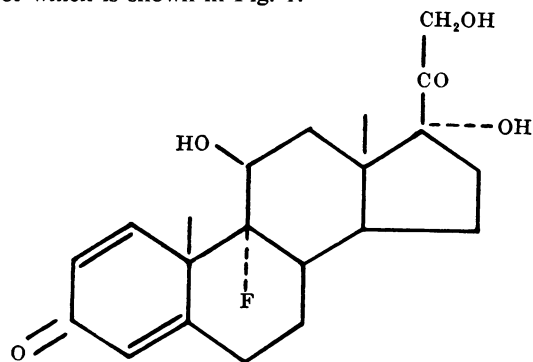


Fig. 1.—Chemical structure of Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate.

The first biological researches show that in the liver glycogen deposition test the new steroid is 25 to 50 times as potent as hydrocortisone acetate; in the reduction of sodium excretion in the adrenalectomized rat it is two to five times stronger than desoxycorticosterone acetate (DCA).

In the clinical field the work of Thorn, Renold,

Morse, Goldfien, and Reddy (1955) makes evident that, in one normal subject and in three patients suffering from Addison's disease, Δ^1 -9- α -fluoro hydrocortisone acetate has 50 and 20 times more effect than hydrocortisone on electrolyte and organic metabolism respectively.

Methods

The new steroid was tested in three subjects with rheumatoid arthritis, in one with chronic gout, and in two with Addison's disease. Daily 4- to 10-mg. doses were administered orally for 10 days in the rheumatic diseases and 0.5 to 1 mg. for 7 days in Addison's disease.

The therapeutic properties of Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate (Δ^1 -9- α -FFa) were estimated qualitatively and quantitatively, with particular reference to the comparison of activity with cortisone acetate (Ea), prednisolone (Δ^1 F), and 9- α -fluoro hydrocortisone acetate (9- α -FFa).

The metabolic study was carried out according to the methods described in previous papers (Villa, Ballabio, and Sala, 1955; Sala, D'Amico, Pasargiklian, Amira, and Ballabio, 1955) using the tests set out in the Table.

TABLE
LABORATORY TESTS

Investigation	Authors	Date
Sedimentation rate	Westergren	1924
Serum mucoproteins	Winzler, Devor, Mehl, and Smyth	1948
Plasma and urinary Na and K (by flame photometry)	Mosher, Boyle, Bird, Jacobson, Batchelor, Iseri, and Myers	1949
Plasma chloride	Van Slyke and Hiller	1947
Urinary chloride	Harvey	1910
Serum carbon dioxide	Van Slyke and Cullen	1917
Plasma and urinary endogenous creatinine	Bonsnes and Taussky	1945
Blood glucose	Hagedorn and Jensen	1923
Blood pyruvic acid	Friedemann, Haugen, and Kmiecik	1945
Plasma cholesterol	Bloor	1916

Results

Antirheumatic Activity.—Three patients affected by rheumatoid arthritis showed marked subjective and objective improvement within the first 48 hrs

of treatment, with relief of pain and aching on motion, reduction of stiffness and swelling, and lessening of tenderness, the improvement in function being clearly evident. The subject suffering from gout showed a subjective and objective improvement; the local improvement was accompanied with a general one, with a corresponding euphoria.

Two cases presented sleeplessness and restlessness.

Relapses occurred on discontinuing treatment in all the cases observed up to the present.

A definite decrease was observed in the sedimentation rate and in serum mucoproteins.

Δ^1 -9- α -fluoro hydrocortisone acetate possesses all the anti-inflammatory and antirheumatic properties of cortisone and prednisone.

Comparing it with other steroids, maintenance therapy produces similar effects with doses two or three times lower than those required with prednisolone and practically equivalent to those required with 9- α -fluoro hydrocortisone acetate, so that its antirheumatic activity may be considered ten-fifteen times higher than that of cortisone acetate.

Metabolic Activity

Salt and Water Balance.—A marked difference between the effects of prednisolone and Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate was observed at doses clinically equivalent.

In fact prednisolone (or prednisone) increases urine volume and sodium excretion without greatly

affecting potassium loss; serum electrolytes not being consistently modified. On the contrary Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate causes initial decrease of urine volume, strong sodium retention, and potassium loss*; successively, after 3 to 4 days of treatment, a diuresis occurs with sodium and chloride loss up to values higher than the basal ones (Fig. 2).

It is worth mention that a similar pattern in the sodium balance was observed in the same cases, treated with equivalent doses of 9- α -fluoro hydrocortisone acetate.

In the serum a sharp fall in potassium to 2.5 to 2 mEq/l., and a slight increase in sodium concentration are observed; haematocrit values (per cent. cells) are constantly decreased, as an expression of hemodilution (Fig. 3).

The marked activity of Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate on water and electrolyte metabolism causes an increase in body weight, blood pressure, and heart size, to a decrease of heart rate, and alterations in the electrocardiogram (lengthening of QT-space, displacing of ST-segment, depression of T-wave).

In adrenal insufficiency, daily doses of 0.5 to 1 mg. Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate are able to normalize electrolyte metabolism or even to cause sodium retention and potassium loss.

In these preliminary experiments we have not

* In one case the total sodium daily urinary excretion fell from 172 to 5 mEq. (Fig. 2).

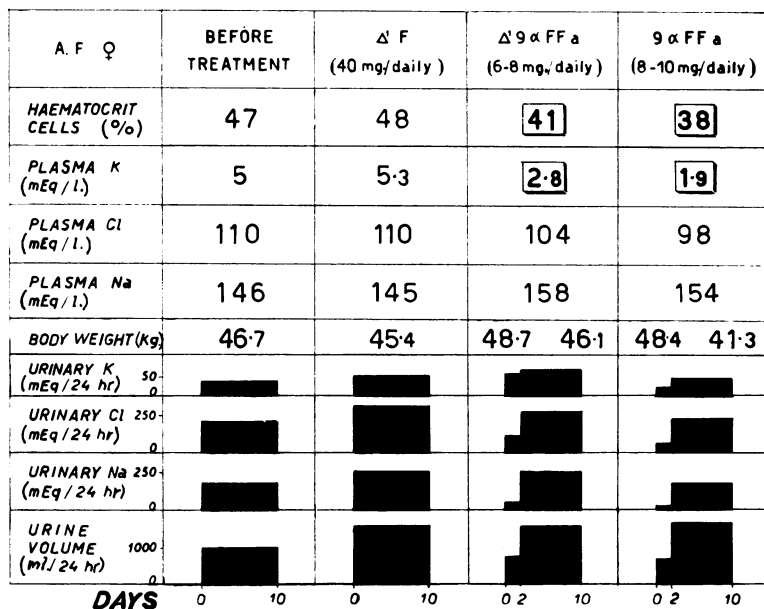


Fig. 2.—Metabolic balance in a woman aged 43 with rheumatoid arthritis treated with various steroids.

PLASMA VALUES	BEFORE TREATMENT	Δ^1 E or Δ^1 F 10-40 mg/day	9 α FF a 1-10 mg/day	Δ^1 9 α FF a 0.5 α -8 mg/day
HAEMATOCRIT CELLS(%)	50 45 40	50 45 40	45 40	45 40
Na(mEq/l.)	150 140	150 140	150 140	150 140
Cl(mEq/l.)	110 100 90	110 100 90	110 100 90	110 100 90
K(mEq/l.)	5 4 3 2	5 4 3 2	5 4 3 2	5 4 3 2

● R. A. and GOUT ○ ADDISON'S DISEASE

Fig. 3.—Effect of various steroids on plasma electrolytes in three patients with rheumatoid arthritis, one with gout, and two with Addison's disease.

gone below a daily 500 γ dose, but the intensity of the obtained effect suggests the use of reduced doses (100–200 γ).

In plasma a loss of potassium and a moderate increase in sodium and CO_2 may occur, while the chlorides remain almost unchanged (Fig. 3).

A fall in the ratio Na/K (from 0.41 to 0.24) in the non-stimulated saliva was noticed in one case after a 3-days treatment with 500 γ of the new steroid, administered daily.

As far as the diuretic activity of corticoids is concerned, Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate is even more efficient than prednisolone in increasing the urine output after a water load in Addison's disease, at doses 10–20 times smaller.

Carbohydrate Metabolism.—In three out of the four rheumatic patients treated up to date, who presented a normal glucose tolerance test before the treatment, Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate did not modify glucose tolerance and did not cause glycosuria.

It is to be noticed that a decrease in glucose tolerance had previously been caused in two out of these cases by treatment with prednisolone (30–40 mg. administered daily).

In one patient, a woman aged 43, 8-mg. doses of the new steroid daily for 10 days caused diabetes with fasting blood glucose of 160 mg. per cent., pyruvic acid of 2.45 mg. per cent., daily glycosuria

of 15–20 g., and a decrease in glucose tolerance (Fig. 4). It must be noted that this patient showed a slight decrease in carbohydrate tolerance before treatment.

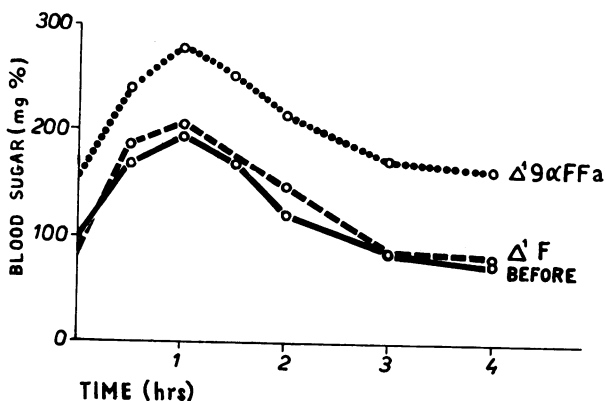


Fig. 4.—Influence of Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate (Δ^1 -9- α -FFa) and of prednisolone (Δ^1 F) on results of oral glucose tolerance tests in a woman aged 43 (0.75 g. glucose per kg.).

Comment

Practical considerations prevented us from studying a large series of patients, but our results allow us to define the clinical and metabolic activity of Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate.

From the clinical point of view this steroid shows a strong antirheumatic action when administered in

doses remarkably inferior to those needed with cortisone and prednisone or prednisolone. According to our experiments, the new steroid is two to three times more active than prednisone and 10 to 25 times more active than cortisone acetate.

However, the introduction of a double bond in C₁-C₂ is not able to avoid the strong mineralcorticoid activity of 9- α -fluoro hydrocortisone acetate, so that the high activity against electrolyte metabolism prevents the practical use of Δ^1 -9- α -fluoro hydrocortisone acetate, at least in rheumatic diseases.

Sodium retention, although temporary and reversible, may be dangerous in the presence of abnormal cardiocirculatory conditions.

The constant and lasting decrease of plasma potassium causes a depletion in intracellular potassium and may cause serious functional changes in the nervous and circulatory systems, as demonstrated by the electrocardiogram.

On the other hand, the high mineralcorticoid activity of Δ^1 -dehydro-9- α -fluoro hydrocortisone suggests that it should be used in Addison's disease to normalize the metabolism; efficient doses of this new steroid in Addison's disease seem about the same size as with aldosterone.

Δ^1 -9- α -fluoro hydrocortisone acetate appeared to have a diabetogenic effect, but the small number of patients treated prevents us from establishing the importance of this side-effect as compared with cortisone, prednisone, and prednisolone.

Summary

(1) The clinical and metabolic effects of Δ^1 -dehydro-9- α -fluoro hydrocortisone acetate were determined in four patients affected by rheumatic diseases, and in two patients with adrenal insufficiency.

(2) In rheumatic disease the compound is two to three times more potent than prednisone, and 10-25 times more active than cortisone acetate. In Addison's disease daily doses of 0.5 to 1 mg. are able to reduce most of the metabolic alterations to normal.

(3) The marked effect on electrolyte metabolism (sodium retention and potassium loss) prevents the practical use of this drug in rheumatic diseases; but it may be usefully employed to treat adrenal insufficiency.

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Effets cliniques et métaboliques de l'acétate de Δ^1 -dehydro-9- α -fluoro hydrocortisone

RÉSUMÉ

(1) Les effets cliniques et métaboliques de l'acétate de Δ^1 -dehydro-9- α -fluoro-hydrocortisone furent déterminés chez quatre sujets atteints de maladie rhumatismale et chez deux sujets atteints d'insuffisance surrénale.

(2) Pour les cas de rhumatisme, le produit est deux ou trois fois plus puissant que la prednisone et 10 à 25 fois plus actif que l'acétate de cortisone. Dans la maladie d'Addison des doses quotidiennes de 0,5 à 1 mg. sont capables de ramener la plupart des altérations métaboliques à la normale.

(3) L'effet marqué sur le métabolisme électrolyte (rétention du sodium et perte du potassium) empêche l'utilisation pratique de ce médicament dans les maladies rhumatismales, mais il peut être utilement employé pour traiter l'insuffisance surrénale.

Efectos clínicos y metabólicos del acetato de Δ^1 -dehidro-9- α -fluoro hidro cortisona

SUMARIO

(1) Se determinaron los efectos clínicos y metabólicos del acetato de Δ^1 -dehidro-9- α -fluoro hidro cortisona en cuatro enfermos afectos de enfermedades reumáticas y en dos con insuficiencia suprarrenal.

(2) En la enfermedad reumática este compuesto es dos o tres veces más poderoso que prednisone y 10 a 25 veces más activo que el acetato de cortisona. En la enfermedad de Addison dosis diarias de 0,5 a 1 mg. pueden normalizar la mayoría de las alteraciones metabólicas.

(3) El efecto marcado sobre el metabolismo electrolítico (retención de sodio y pérdida de potasio) previene el uso práctico de este medicamento en las enfermedades reumáticas; se puede, sin embargo, emplearle útilmente para tratar insuficiencia suprarrenal.