Ann. rheum. Dis. (1958), **17**, 376.

CLINICAL OBSERVATIONS WITH 16a-METHYL CORTICOSTEROID COMPOUNDS*

PRELIMINARY THERAPEUTIC TRIALS WITH DEXAMETHASONE (16a-METHYL 9a-FLUOROPREDNISOLONE) IN PATIENTS WITH RHEUMATOID ARTHRITIS

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During the past 3 years it has been demonstrated that the substitution of a methyl radical at one or another carbon position in the steroid nucleus may cause major changes in certain physiological activities of adrenal cortical steroids. A number of methylated analogues of hydrocortisone and cortisone have been prepared and currently these are being studied both experimentally and clinically with the hope that information may be gained which will lead ultimately to the development of therapeutically superior anti-inflammatory compounds.

Hogg, Lincoln, Jackson, and Schneider (1955) and Spero, Thompson, Magerlein, Hanze, Murray, Sebek, and Hogg (1956) synthesized several methylated steroid compounds. It was determined that when a methyl radical was substituted at the second carbon position the electrolyte metabolism of corticosteroids was augmented, but if the methyl grouping was placed at the sixth carbon position instead, sodium retention and potassium loss were not increased. During 1956 and 1957 the physiological and therapeutic effects of 6a-methylprednisolone were investigated (Boland and Liddle, 1957). Biologic screening tests in animals had suggested that the analogues might possess greater anti-inflammatory potency, and perhaps a higher therapeutic index, than prednisolone (Lyster, Barnes, Lund, Meinzinger, and Byrnes, 1957). Studies in human subjects revealed, however, that, while the sodium-retaining and potassium-losing activities of 6a-methylprednisolone might be less than those of prednisolone, the other metabolic effects of the two compounds were about the same when equal milligram amounts were administered. Dosage comparison studies in patients with rheumatoid arthritis established that the antirheumatic strength of 6a-methylprednisolone was slightly greater (about 15 to 25 per cent.) than that of prednisolone (Boland and Liddle, 1957).

During 1957 Sarett and his collaborators synthesized a new family of steroid compounds containing in common a methyl grouping at the sixteenth carbon position of the steroid nucleus (Arth, Johnston, Fried, Spooncer, Hoff, and Sarett, 1958). In May, 1957, 16a-methylprednisone was subjected to cursory clinical evaluation by the author, and the antirheumatic potency of the compound was compared with that of prednisolone in eleven patients with rheumatoid arthritis. As far as could be determined, the potencies of the two steroids were about equal; if differences did exist they were too small to calibrate clinically. Long-term treatment studies with 16a-methylprednisone were not pursued.

In December, 1957, four separate 16a-methylated derivatives of hydrocortisone were made available for clinical trial.† They were: 16a-methyl 9a-fluoroprednisolone, 16a-methyl 9a-fluorohydrocortisone, 16a-methylprednisolone, and 16a-methylhydrocortisone (Fig. 1, opposite). 16a-methyl 9a-fluoroprednisolone first received the generic name of "hexadecadrol", but this was later changed to "dexamethasone". Dexamethasone differs chemically from triamcinolone by having a methyl instead of a hydroxyl grouping at the 16-alpha carbon position. As yet, the three remaining analogues have not been given generic names.

Screening tests in animals for the biologic behaviour of these hydrocortisone derivatives conducted by Silber and his group (Arth, Fried, Johnston, Hoff, Sarett, Silber, Stoerk, and Winter,

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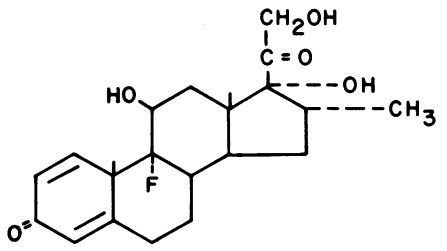
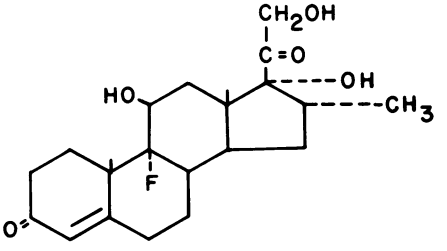
Paper presented at the scientific session honouring Dr. Philip S. Hench on the occasion of the tenth anniversary of the discovery of the antirheumatic effects of cortisone (Rochester, Minn., October 1, 1958).

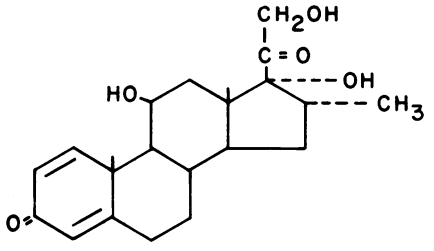
† The 16a-methyl analogues of hydrocortisone and cortisone used in this study were supplied by the Merck Sharp and Dohme Research Laboratories, Division of Merck and Co. Inc., Rahway, New Jersey.



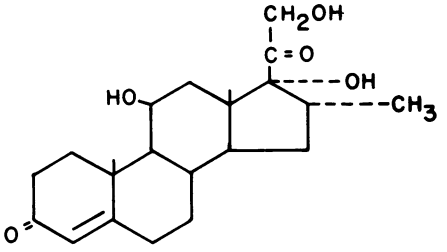
16 α - METHYL, 9 α FLUORO-PREDNISOLONE



16 α - METHYL, 9 α FLUORO-HYDROCORTISONE



16 α METHYL PREDNISOLONE



16 α METHYL HYDROCORTISONE

Fig. 1.—Structural formulae of four 16a-methyl analogues of hydrocortisone.

1958), indicated that methylation at the 16-alpha carbon position produced striking changes in several physiological properties, including a decided intensification of anti-inflammatory action and an absence of sodium retention with the experimental dosages tried (Table I). Each of the compounds displayed, in varying degrees, greater physiological potency than hydrocortisone—and in the case of 16a-methyl 9a-fluoroprednisolone and 16a-methyl 9a-fluorohydrocortisone particularly, certain properties were tremendously enhanced by methylation at the sixteenth position. Of interest and importance was the finding that the anti-inflammatory potency of dexamethasone, as gauged by granuloma inhibition, was augmented to a much greater extent than glycogen deposition—190 times as compared with 17 times—

TABLE I

RELATIVE POTENCIES OF CERTAIN BIOLOGIC ACTIVITIES OF 16-ALPHA METHYL CORTICOSTEROIDS AS DETERMINED IN ANIMALS (ADAPTED FROM ARTH AND OTHERS (1958a))

Steroid Tested	Potency Times Hydrocortisone of:			
	Thymus Involution	Granuloma Inhibition	Adrenal Atrophy	Glycogen Deposition
16a-methyl 9a-fluoroprednisolone (Dexamethasone) ..	400	190	700	17
16a-methyl 9a-fluorohydrocortisone	55	36	85	12
16a-methylprednisolone	14	12	16	5
16a-methylhydrocortisone	1·9	3	1·8	2·1
16a-methylprednisone	11	13	10	3·2

suggesting that there might be a therapeutically useful dissociation of these two effects.

Anti-rheumatic Potencies of 16a-Methyl Analogues of Hydrocortisone as compared with Prednisolone

The antirheumatic potency of each of the four new 16a-methylated analogues of hydrocortisone was compared with that of prednisolone (Table II). This was accomplished by transferring treatment in carefully selected patients back and forth from prednisolone to the test substance and ascertaining the milligram dosages required to maintain equivalent degrees of improvement (Boland, 1958).

Dosage comparison studies were made with dexamethasone in 21 patients. The dosage ratios of dexamethasone to prednisolone varied from 1 : 5 to 1 : 10, but in the majority the range was from 1 : 6 to 1 : 8. Thus, in this group of patients, the antirheumatic potency of dexamethasone was, on average, about seven times greater than prednisolone, per milligram. By calculation it could be considered to have roughly thirty times the potency of hydrocortisone.

The antirheumatic strength of 16a-methyl 9a-fluorohydrocortisone was found to be considerably more than that of prednisolone. In eleven patients the average was approximately three times greater.

16a-methylprednisolone exhibited greater antirheumatic potency than prednisolone, but the variation was fractional rather than multiple—it was roughly one-third more potent on average.

The average antirheumatic strength of 16a-methylhydrocortisone was found to be about 70 per cent. that of prednisolone. Direct comparisons with hydrocortisone yielded proportionately similar results: the doses of hydrocortisone required for equivalent improvement were approximately three times greater than for 16a-methylhydrocortisone.

Preliminary Therapeutic Trials with Dexamethasone*

Since December, 1957, the clinical effects of dexamethasone have been studied in 88 rheumatoid arthritic patients. An analysis of the improvement status was made in 55 of the patients who had received the drug uninterruptedly for 3 to 5 months, and the following results were obtained:

Eleven patients, not previously treated with steroids, were given dexamethasone as initial therapy. Dosages were varied according to disease severity and ranged from 1 to 2·5 mg. per day, an effort being made to avoid rapid and dramatic improvement with excessive doses at the beginning. The pattern of response was much the same as with other effective anti-inflammatory steroids prescribed in proportionately larger milligram amounts. At analysis, the degree of improvement was gauged as marked or very marked in nine of eleven patients (Table III, opposite). The average daily maintenance dose at the end of 3 to 5 months was 1·3 mg. (range 0·8 to 2 mg.). Unwanted side-effects developed in five of the patients: asymptomatic peptic ulcers in two, facial mooning in one, and excessive weight gain in two.

Treatment was transferred from prednisolone to dexamethasone in 44 patients. The patients were divided into two groups—those who had been adequately controlled on prednisolone, and those who had not. Each of seventeen patients that had responded satisfactorily to prednisolone retained adequate control after transfer to the new drug, and at the end of 3 to 5 months the degree of improvement had advanced from marked to very marked in five patients (Fig. 2, opposite). The average maintenance dosage for dexamethasone was 1·4 mg. per day, an amount which, by calculation, was some-

* Dexamethasone was supplied by the Merck Sharp and Dohme Research Laboratories, Division of Merck and Co. Inc., Rahway, New Jersey, under the trade name of "Decadron".

TABLE II

ANTIRHEUMATIC POTENCIES OF 16a-METHYL ANALOGUES OF HYDROCORTISONE COMPARED TO PREDNISOLONE: BASED ON CLINICAL APPRAISALS IN PATIENTS WITH RHEUMATOID ARTHRITIS (ARTH AND OTHERS, 1958a)

Steroid Tested	Number of Patients Studied	Dosage Ratios to Prednisolone		Potency Ratios to Prednisolone	
		Range	Average	Range	Average
16a-methyl 9a-fluoroprednisolone (Dexamethasone)	21	1 : 5 to 1 : 10	1 : 7·3	5 : 1 to 10 : 1	7·3 : 1
16a-methyl 9a-fluorohydrocortisone	11	1 : 2·5 to 1 : 4·2	1 : 3·2	2·5 : 1 to 4·2 : 1	3·2 : 1
16a-methylprednisolone	7	1 : 1 to 1 : 1·7	1 : 1·3	1·7 : 1 to 1 : 1	1·3 : 1
16a-methylhydrocortisone	12	1 : 0·6 to 1 : 1	1 : 0·7	1 : 1 to 0·6 : 1	0·7 : 1

TABLE III

RESPONSE TO DEXAMETHASONE AFTER 3 TO 5 MONTHS OF THERAPY IN ELEVEN PATIENTS NOT PREVIOUSLY TREATED WITH STEROIDS

Case No.	Sex	Disease Severity	Dosage (mg. per day)		Length of Treatment (wks)	Degree of Improvement			Adverse Effects at Analysis (Grading: 1 to 4)
			Initial	Maintenance		Degree	Adequate	Inadequate	
1	Female	Severe	2·0	1·0	15	Marked	x		Prepyloric ulcer (asymptomatic)
2	Male	Severe	2·5	1·4	16	Very marked	x		
3	Female	Severe	2·5	1·0	18	Marked	x		
4	Female	Moderately Severe	2·0	1·2	21	Marked	x		
5	Female	Moderately Severe	2·0	1·2	17	Marked	x		
6	Female	Moderately severe	2·0	1·0	14	Very marked	x		Weight gain (2) Abdominal girth (2)
7	Male	Moderately severe	2·0	1·8	14	Moderate		x	Weight gain (2) Diabetes not aggravated
8	Male	Moderately severe	2·0	1·6	20	Very marked	x		Prepyloric ulcer (asymptomatic)
9	Male	Moderately severe	2·0	2·0	21	Moderate		x	Facial mooning (2)
10	Female	Moderate	1·0	0·8	21	Very marked	x		
11	Male	Moderate	1·0	1·0	20	Marked	x		
Average			.. 1·9	1·3	18				

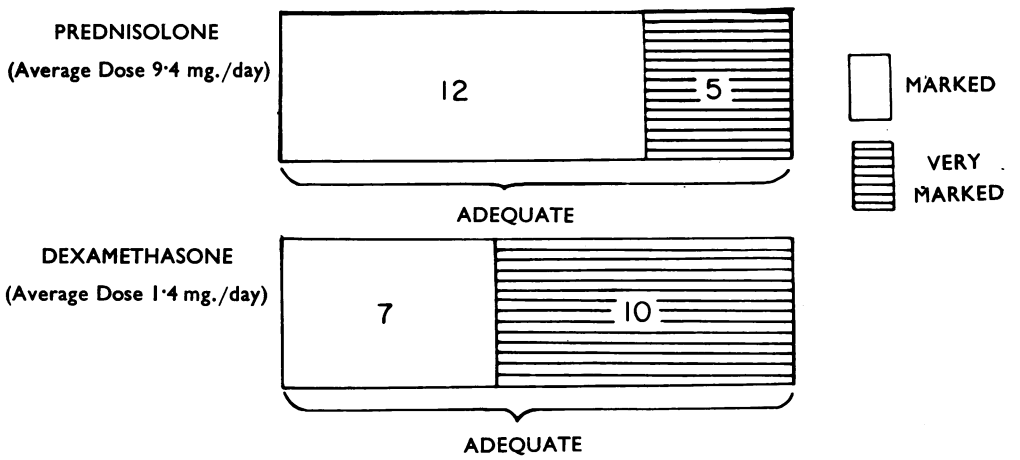


Fig. 2.—Improvement status 3 to 5 months after transfer to dexamethasone in seventeen patients adequately controlled on prednisolone.

what greater in potency than for prednisolone before transfer.

Changes in the improvement status of 27 patients who had been poorly controlled on prednisolone are shown in Fig. 3 (overleaf). This was a recalcitrant group of patients with severe or moderately severe disease, having received continuous steroid therapy for long periods. Many of them had been controlled successfully at one time or another, but with continuation of treatment they had grown worse. Attempts were made to achieve better rheumatic control by cautiously increasing the dosages of dexamethasone to amounts exceeding those used for prednisolone, in terms of antirheumatic potency. At the end of 3 to 5 months improvement had been raised to adequate levels in more than one-third

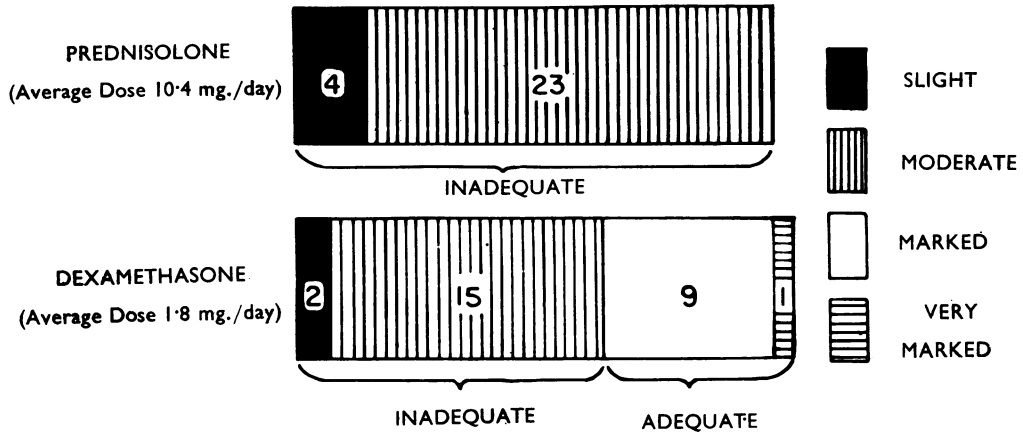


Fig. 3.—Improvement status 3 to 5 months after transfer to dexamethasone in 27 patients not adequately controlled on prednisolone.

of the group. But the total number of adverse reactions had not diminished: decreases or disappearances of such side-effects as oedema, digestive symptoms, and nervous excitation in some patients were counterbalanced by excessive weight gain, increased ecchymotic skin lesions, facial mooning, and abdominal bloating and distension in others, and by the appearance of unsuspected peptic ulcers. It may be anticipated that the overall improvement status of this obstinate group will deteriorate statistically as treatment is further prolonged.

Preliminary Observations of Adverse Effects from Dexamethasone

Certain general impressions regarding unwanted side-effects from dexamethasone as compared with those noted with prednisolone may be summarized as follows:

(1) The overall incidence of adverse reactions from dexamethasone appears to be about the same as of those from prednisolone when equally effective antirheumatic doses of the two drugs are given. However, certain differences in individual side-effects have been noted.

(2) Symptoms which are apparently peculiar to triamcinolone, such as headache, dizziness, fatigue, anorexia, weight loss, muscle weakness, and erythema, have not occurred during dexamethasone administration.

(3) Peripheral oedema (mild to moderate) was noted in five of 88 patients; but, in general, the tendency for salt and water retention appeared to be less with dexamethasone than with prednisolone, and decidedly less than with hydrocortisone.

(4) None of the patients studied so far has developed hypertension or has demonstrated aggravation of pre-existing hypertension.

(5) When dexamethasone is given in doses of comparable antirheumatic strength it appears to have about the same tendency as prednisolone to promote facial mooning, supraclavicular fat pads, and hypertrichosis.

(6) The occurrence rate and the severity of ecchymotic skin lesions are just as great, and perhaps greater, with dexamethasone as with prednisolone when similarly effective antirheumatic amounts of the drugs are taken.

(7) The most common side-effects encountered to date, and certainly those which have been most objectionable to patients, are increased appetite, excessive weight gain, and the development of abdominal girth. Preliminary observations suggest that dexamethasone may promote these reactions more readily than prednisolone when equivalently effective doses are given. In some instances excessive weight gain occurred without the quickening of appetite. A number of patients observed that the increased weight accumulated predominantly about the waist. At times such increased girth appeared without substantial weight gain and without accompanying facial mooning or supraclavicular fat pads.

(8) Approximately 10 per cent. of the patients experienced abdominal distension or bloating. In some, this complaint was persistent, but it was more often transient and recurring.

(9) It would appear that dexamethasone may be administered in effective antirheumatic doses to

patients with mild or moderate diabetes mellitus without further disrupting their carbohydrate metabolism. At least this is indicated from the experience of four patients in this series with co-existing diabetes. Three of them were well maintained with doses of 1·8, 1·5, and 1·25 mg. per day, respectively, without increasing glycosuria or insulin requirement. The fourth patient, whose disease was controlled by dietary restriction alone, has noted glycosuria more often since receiving dexamethasone in dosages of 1 mg. per day than he did without steroid therapy—but, by contrast, previous trials with prednisolone and with hydrocortisone had aggravated this patient's diabetes so greatly that it had been necessary to discontinue the drugs entirely.

(10) Nervous symptoms were rarely encountered with dexamethasone in doses up to 3 mg. per day, and it would appear that the tendency towards this reaction is less than with prednisolone given in proportionately effective antirheumatic doses. None of the patients in the present series experienced mental excitation requiring either cessation of therapy or alteration of dosage.

(11) Symptoms suggesting peptic ulcer were uncommon, *but* the incidence of peptic ulcer during dexamethasone administration appears to be comparable to that which occurs with prednisolone, and deserves comment.

Seventy patients who had taken dexamethasone for 3 months or longer were subjected to routine upper gastro-intestinal *x*-ray studies. Six active peptic ulcers were detected, five of which were prepyloric in location. Four of these were entirely asymptomatic, one was mildly symptomatic, and only one was accompanied by typical ulcer symptoms. With strict ulcer management, and without discontinuing the drug or reducing its dosage, five of the six ulcers healed roentgenographically within 6 weeks. In the sixth patient a prepyloric ulcer was smaller roentgenographically after 6 weeks of treatment, but a new ulcer was detected in the duodenum. The patient was then transferred to prednisolone treatment and rigid ulcer management was continued, but after another 8 weeks neither lesion had healed and steroid therapy was withdrawn. Since it was demonstrated that dexamethasone, like other anti-inflammatory steroids, has ulcerogenic properties, antacids have been prescribed routinely with each divided dose of the drug.

Summary

Four new synthetic analogues of hydrocortisone, containing in common a methyl grouping at the 16a-carbon position of the steroid molecule, are being studied in human subjects. The compounds are:

16a-methyl 9a-fluoroprednisolone (dexamethasone: Decadron),
16a-methyl 9a-fluorohydrocortisone,
16a-methylprednisolone,
16a-methylhydrocortisone.

Biologic tests carried out in animals demonstrated that these compounds exhibit, in varying degrees, striking alterations of several physiological properties, including enhanced anti-inflammatory activity unassociated with corresponding disturbance of electrolyte metabolism. Preliminary observations of the effects of the four new compounds in patients with rheumatoid arthritis are summarized.

Clinical estimates of the antirheumatic potency of the compounds, as compared with that of prednisolone, were accomplished by determining the milligram dosages required to maintain similar degrees of improvement of active rheumatoid manifestations. The approximate antirheumatic potencies of the compounds, on an average, were gauged as follows:

16a-methyl 9a-fluoroprednisolone (dexamethasone), about seven times greater than prednisolone;
16a-methyl 9a-fluorohydrocortisone, about three times greater;
16a-methylprednisolone, approximately one-third greater;
16a-methylhydrocortisone, about 70 per cent. that of prednisolone.

The therapeutic efficiency of dexamethasone, one of the new methylated analogues, is now being investigated in a large group of patients with rheumatoid arthritis. This compound is the most potent antirheumatic steroid which has been synthesized to date, and is highly effective in suppressing the manifestations of rheumatoid arthritis when administered in remarkably small daily doses. However, augmented antirheumatic potency alone does not denote superiority, and these clinical trials have been too brief, as yet, to allow us to judge whether dexamethasone possesses therapeutic advantages over prednisone or prednisolone in the management of those rheumatoid arthritic patients who are suitable for long-term steroid therapy.

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Observations cliniques sur des composés 16a-methyl corticostéroides: essais thérapeutiques préliminaires de la dexamethasone (16a-methyl 9a-fluoroprednisolone) chez des malades atteints d'arthrite rhumatismale

RÉSUMÉ

On est en train d'étudier chez des sujets humains quatre nouveaux analogues de l'hydrocortisone, tous ayant un groupe methyl en position 16a de la molécule stéroïde. Ces composés sont: 16a-methyl 9a-fluoroprednisolone (dexamethasone: Decadron), 16a-methyl 9a-fluorohydrocortisone, 16a-methylprednisolone et 16a-methylhydrocortisone. Des essais biologiques sur des animaux ont montré que ces composés exercent, à de différents degrés, des effets physiologiques frappants, tels que l'action antiphlogistique augmentée sans dérangement correspondant du métabolisme électrolytique. On présente ici un résumé des observations préliminaires sur les effets de ces quatre composés nouveaux sur des malades atteints d'arthrite rhumatismale.

La détermination clinique du pouvoir antirhumatismal de ces composés par rapport à la prednisolone fut effectuée en comparant la quantité en milligrammes nécessaire pour maintenir un degré similaire d'amélioration des manifestations rhumatismales actives. Approximativement, le pouvoir antirhumatismal moyen de ces composés fut jaugé comme il suit:

16a-methyl 9a-fluoroprednisolone (dexamethasone) environ sept fois plus forte que la prednisolone;
16a-methyl 9a-fluorohydrocortisone environ trois fois plus forte;
16a-methylprednisolone, environ un tiers plus forte;
16a-methylhydrocortisone, environ 70% plus forte que la prednisolone.

L'efficacité thérapeutique de la dexamethasone, un des nouveaux analogues methylés, est maintenant en train d'être étudiée dans un grand groupe de malades atteints d'arthrite rhumatismale. Ce composé est le plus puissant de tous les stéroïdes antirhumatismaux synthétisés jusqu'à présent et il supprime les manifestation de l'arthrite rhumatismale d'une manière très efficace en doses remarquablement petites. Un pouvoir antirhumatismal augmenté, cependant, n'indique pas, en soi même, de supériorité, et ces essais cliniques ne furent pas assez longs pour pouvoir juger si la dexamethasone a des avantages thérapeutiques sur la prednisone ou la prednisolone chez des malades atteints d'arthrite rhumatismale chez qui la thérapie stéroïde prolongée est indiquée.

Observaciones clinicas sobre compuestos 16a-methyl corticosteroides: ensayos terapéuticos preliminares de la dexamethasona (16a-methyl 9a-fluoroprednisolona) en enfermos con artritis reumatoide

SUMARIO

Se estudian en sujetos humanos cuatro neuvos análogos de la hidrocortisona, teniendo todos un grupo metil en posición 16a de la molécula esteroide. Estos compuestos son: 16a-metil 9a-fluoroprednisolona (dexamethasona: Decaron), 16a-metil 9a-fluorohidrocortisona, 16a-metilprednisolona y 16a-metilhidrocortisona. Ensayos biológicos sobre animales comprobaron que estos compuestos ejercen, a grados diferentes, efectos fisiológicos asombrosos, tales como una acción antiflogística aumentada sin desarreglo correspondiente del metabolismo electrolítico. Se presenta aquí un sumario de las observaciones preliminares sobre los efectos de estos cuatro compuestos nuevos sobre enfermos con artritis reumatoide.

La determinación clínica del poder antirreumático de estos compuestos en relación a la prednisolona se hizo, comparando el número de milígramos necesario para mantener un grado similar de mejoría de las manifestaciones reumáticas activas. Aproximadamente, el poder antirreumático medio de estos compuestos fué el siguiente:

16a-metil 9a-fluoroprednisolona (dexamethasona)—unas siete veces más fuerte que la prednisolona;
16a-metil 9a-fluorohidrocortisona, unas tres veces más fuerte;
16a-metilprednisolona, cerca de una tercera más fuerte;
16a-metilhidrocortisona, un 70% más fuerte que la prednisolona.

La eficacidad terapéutica de la dexamethasona, uno de los nuevos análogos metilados, está en el curso de investigación en un gran grupo de enfermos con artritis reumatoide. Este compuesto es el más potente de todos los esteroides antirreumáticos sintetizados hasta ahora y tiene el poder de suprimir las manifestaciones de la artritis reumatoide de una manera muy eficaz en dosis destacadamente pequeñas. Un poder antirreumático aumentado no indica, sin embargo por si, una superioridad; estos ensayos clínicos no fueron bastante extensos para poder decidir sobre las ventajas terapéuticas de la dexamethasona sobre la prednisona o la prednisolona en enfermos con artritis reumatoide necesitando una terapia esteroide prolongada.