16a-Methyl Corticosteroids

A New Series of Anti-Inflammatory Compounds; Clinical Appraisal of Their Antirheumatic Potencies

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• Four new derivatives of hydrocortisone, each containing in common a methyl grouping at the 16a-carbon position of the steroid molecule, have been synthesized and are being studied in human subjects. The compounds are 16a-methyl 9a-fluoroprednisolone (MK-125: hexadecadrol), 16a-methyl 9a-fluorohydrocortisone (MK-126), 16a-methylprednisolone (MK-110), and 16a-methylhydrocortisone (MK-117). Biologic tests in animals have indicated that these analogues exhibit, in varying degrees, striking alterations of several physiologic properties, including enhanced anti-inflammatory activity unassociated with corresponding disturbance of electrolyte metabolism.

In the present study preliminary observations of the effects of the four new compounds were made in patients with rheumatoid arthritis. Clinical estimates of the antirheumatic potencies of the compounds, as compared with 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: for 16a-methyl 9a-fluoroprednisolone, about seven times greater than prednisolone; for 16a-methyl 9a-fluorohydrocortisone, about three times greater; for 16a-methylprednisolone, approximately one-third greater; and for 16a-methylhydrocortisone, about 70 per cent that of prednisolone. In the dosage used, none of the compounds promoted discernible salt and water retention.

These observations would indicate that 16a-methyl 9a-fluoroprednisolone (hexadecadrol) possesses greater anti-inflammatory potency per milligram than any steroid yet produced. The therapeutic efficiency of the compound on long-term administration is being studied.

IT IS NOW ESTABLISHED that the biologic properties of hydrocortisone and cortisone may be altered quantitatively, sometimes selectively, by substituting certain chemical groupings and by making minor configurational changes in molecular structure. During the past five years chemists have worked diligently to design synthetic steroid compounds that could be applied as treatment agents more successfully than the naturally occurring hormones—steroids which ideally would retain powerful anti-inflammatory action but be free of the physiologic properties which induce deleterious effects. Hundreds of synthetic compounds have been prepared and tested in animals; many of these have been investigated clinically and a few have been introduced commercially as suppressive drugs for rheumatoid arthritis and other responsive conditions. Of the modified compounds that have been made available, some possess advantages in one respect or another, but as yet none is divested of the major deterrent features of corticosteroid therapy, and some produce peculiar objectionable reactions of their own. Hence the search for more efficient derivatives has continued.

The development of synthetically modified steroid compounds has proceeded in step-by-step fashion. The first important discovery was that the anti-inflammatory potency of hydrocortisone and cortisone could be enhanced and that some of their other physiologic effects could be changed by substituting halogen atoms at the ninth carbon position of the steroid nucleus.[12,13] As an example, one such derivative—9a-fluorohydrocortisone—was found to be about ten times as powerful as hydrocortisone, per milligram, in respect to antirheumatic and certain other properties.[4,5] However, its sodium-retaining and potassium-losing effects were so excessive that it could not be applied systemically as an anti-inflammatory drug. A second major chemical innovation was the introduction of a double bond between the first and second carbon atoms in the steroid ring, resulting in the production of prednisolone and prednisone.[14] These analogues of hydrocortisone and cortisone have approximately four times the anti-inflammatory potency of their parent compounds—yet their electrolyte activity is not intensified correspondingly.[9,10] The relative dissociation of these two properties has made prednisolone and prednisone useful therapeutically, but the compounds have greater proclivity to promote certain undesirable reactions, notably digestive symptoms, peptic ulcers and cutaneous ecchymoses.[6,8]

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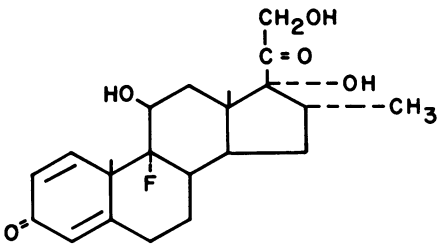
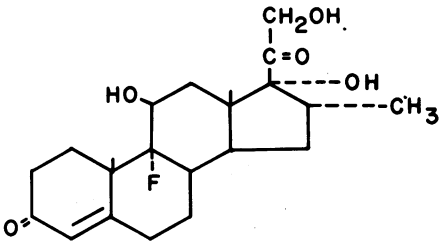
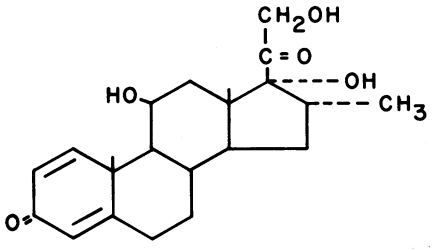


16 α - METHYL, 9 α FLUORO-PREDNISOLONE



16 α - METHYL, 9 α FLUORO-HYDROCORTISONE



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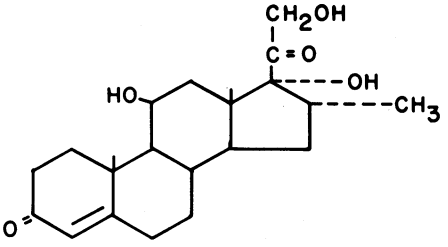

16 α METHYL HYDROCORTISONE

Chart 1.—Structural formulas of a new series of corticosteroid compounds: 16a-methyl analogues of hydrocortisone.

Another significant discovery was that the addition of a hydroxyl grouping at the 16-carbon position eliminated the excessive electrolyte activity of 9a-fluorination.[3] Triamcinolone (9a-fluoro-16a-hydroxyprednisolone), for example, contains a fluorine atom at the ninth carbon position and is relatively free of salt and water retention when ordinary doses are prescribed. The compound has about the same milligram antirheumatic potency as prednisolone[11] and appears to have little or no additional merit as a treatment agent for rheumatoid arthritis. In 1955 several methylated corticosteroid derivatives were synthesized[15,16] and the effects of one of them—6a-methylprednisolone—have been studied in human subjects. Metabolic and clinical investigations have shown that the sodium-retaining and potassium-losing activities of the drug may be slightly less than those of prednisolone, but the other biologic properties of the two compounds, including antirheumatic effect, are about the same when equal milligram amounts are administered.[7]

16α-METHYL CORTICOSTEROID COMPOUNDS

Recently Sarett and co-workers[1] synthesized a new family of hydrocortisone analogues containing, in common, a methyl grouping at the 16a carbon position of the steroid nucleus. Screening tests for the biologic behavior of these compounds in animals, conducted at the Merck Sharp and Dohme Research Laboratories, indicated that methylation at the 16-carbon position produced striking changes in several physiologic properties, including a decided intensification of anti-inflammatory action and an absence of sodium retention with the experimental dosages tried. The following new steroids were prepared and made available for clinical trial:* 16a-methyl 9a-fluoroprednisolone (MK-125: hexadecadrol), 16a-methyl 9a-fluorohydrocortisone (MK-126), 16a-methylprednisolone (MK-110), and 16a-methylhydrocortisone (MK-117) (Chart 1).

Preliminary assessments of the potencies of various biologic effects of the four compounds, as compared with those of hydrocortisone, were made in laboratory animals.[2] Some of the pertinent results of those studies may be summarized as follows: As to anti-inflammatory activity, as gauged by the inhibition of granuloma formation in rats, the four compounds compared with hydrocortisone as follows: 16a-methyl 9a-fluoroprednisolone, 190 times greater; 16a-methyl 9a-fluorohydrocortisone, 36 times greater; 16a-

*Supplied by the Merck Sharp and Dohme Research Laboratories, Division of Merck and Co., Inc., Rahway, N. J.

TABLE 1.—*Comparisons of Milligram Dosages of 16a-Methyl 9a-Fluoroprednisolone (MK-125: Hexadecadrol) and Prednisolone Required for Equivalent Degrees of Rheumatic Control*

Patient	Dosages (Mg./Day) for Equivalent Rheumatic Control		Dosage Ratios: 16a-Methyl 9a-Fluoroprednisolone to Prednisolone	Potency Ratios: 16a-Methyl 9a-Fluoroprednisolone to Prednisolone
	Prednisolone	16a-Methyl 9a-Fluoroprednisolone		
1	15.0	1.75	1 to 8.6	8.6 to 1
2	8.75	1.0	1 to 8.8	8.8 to 1
3	20.0	3.5	1 to 5.7	5.7 to 1
4	10.0	1.0	1 to 10	10 to 1
5	12.5	2.0	1 to 6.3	6.3 to 1
6	12.5	1.5	1 to 8.3	8.3 to 1
7	10.0	1.25	1 to 8	8 to 1
8	15.0	2.0	1 to 7.5	7.5 to 1
9	17.5	1.75	1 to 10	10 to 1
10	7.5	1.0	1 to 7.5	7.5 to 1
11	12.5	2.0	1 to 6.3	6.3 to 1
12	7.5	1.0	1 to 7.5	7.5 to 1
13	8.75	1.25	1 to 7	7 to 1
14	15.0	2.5	1 to 6	6 to 1
15	7.5	0.75	1 to 10	10 to 1
16	12.5	2.0	1 to 6.3	6.3 to 1
17	7.5	1.0	1 to 7.5	7.5 to 1
18	10.0	1.25	1 to 8	8 to 1
19	10.0	1.25	1 to 8	8 to 1
20	10.0	2.0	1 to 5	5 to 1
21	10.0	1.25	1 to 8	8 to 1
Average	11.43	1.57	1 to 7.3	7.3 to 1

methylprednisolone, 12 times greater; 16a-methylhydrocortisone, 3 times greater. Each of the 16-methylated steroids showed enhanced capacity to promote the deposition of glycogen in the livers of fasting mice. Of considerable interest was the finding that the enormous increase in anti-inflammatory activity of 16a-methyl 9a-fluoroprednisolone (hexadecadrol) was not accompanied by a proportionate increase in glycogenic activity (190 times compared with 17 times). In the experimental doses used, none of the four new analogues induced sodium retention in rats that had had adrenalectomy.

Although animal studies cannot be translated directly into terms of the effect of a steroid in human subjects, the powerful biologic activity of 16a-methyl 9a-fluoroprednisolone indicated that this analogue might prove to be the most potent steroid with adrenocortical function yet prepared. The laboratory findings were sufficiently arresting to invite investigations with each of the new analogues in human subjects.

PRESENT STUDY

Clinical evaluations of the effects of 16-methylated derivatives of hydrocortisone in patients with rheumatoid arthritis were begun in December, 1957. The four new steroids have been studied separately and concurrently. The first stage of investigation consisted of an appraisal of the relative antirheumatic potencies of the compounds and the results of this portion of the investigation will be presented herein. Long-term observations of the therapeutic efficiency of two compounds, 16a-methyl 9a-fluoroprednisolone (MK-125: hexadecadrol) and 16a-methylhydrocortisone (MK-117), with continuous administration are being made and will be the subject of a future report.

Determinations of the antirheumatic potencies of the new steroids as compared with prednisolone were accomplished by establishing the total daily milligram amounts of the compounds required to uphold approximately the same control of rheumatoid manifestations. The method consisted of transferring the treatment of patients from one drug to another and determining the number of milligrams of each substance needed to maintain equivalent clinical improvement. Care was taken to select patients whose maintenance doses of the initial preparation were well established and stable and who had sufficient residual evidences of active joint inflammation to permit objective measurement of changes. The improvement status was recorded at intervals of every three to seven days and appraisal of status was based on an overall estimate of rheumatic control as reflected by the degree of subjective complaints (pain, aching, stiffness, limited functional capacity, and the severity of constitutional reaction), by objective measurements of involved joints (swelling, local tenderness, pain on motion, and range of joint movement), and by changes in the erythrocyte sedimentation rate. Medication was transferred back and forth from the original and test substances in deliberate fashion to allow adjustment and stabilization of dosage in relation to clinical response. In each instance at least two cross-comparisons of dosage were made.

TABLE 2.—*Comparisons of Milligram Dosages of 16a-Methyl 9a-Fluorohydrocortisone (MK-126) and Prednisolone Required for Equivalent Degrees of Rheumatic Control*

Patient	Dosages (Mg./Day) for Equivalent Rheumatic Control		Dosage Ratios: 16a-Methyl 9a-Fluorohydrocortisone to Prednisolone	Potency Ratios: 16a-Methyl 9a-Fluorohydrocortisone to Prednisolone
	Prednisolone	16a-Methyl 9a-Fluorohydrocortisone		
1	20.0	6.0	1 to 3.3	3.3 to 1
2	10.0	3.0	1 to 3.3	3.3 to 1
3	12.5	4.5	1 to 2.8	2.8 to 1
4	12.5	4.0	1 to 3.1	3.1 to 1
5	12.5	5.0	1 to 2.5	2.5 to 1
6	10.0	3.0	1 to 3.3	3.3 to 1
7	12.5	3.0	1 to 4.2	4.2 to 1
8	17.5	5.0	1 to 3.5	3.5 to 1
9	12.5	4.0	1 to 3.1	3.1 to 1
10	7.5	2.0	1 to 3.8	3.8 to 1
11	12.5	4.5	1 to 2.8	2.8 to 1
Average	12.73	4.0	1 to 3.2	3.2 to 1

TABLE 3.—*Comparisons of Milligram Dosages of 16a-Methylprednisolone (MK-110) and Prednisolone Required for Equivalent Degrees of Rheumatic Control*

Patient	Dosages (Mg./Day) for Equivalent Rheumatic Control		Dosage Ratios: 16a-Methylprednisolone to Prednisolone	Potency Ratios: 16a-Methylprednisolone to Prednisolone
	Prednisolone	16a-Methyl-prednisolone		
1	15.0	10.0	1 to 1.5	1.5 to 1
2	7.5	6.0	1 to 1.3	1.3 to 1
3	7.5	6.0	1 to 1.3	1.3 to 1
4	10.0	6.0	1 to 1.7	1.7 to 1
5	10.0	7.0	1 to 1.4	1.4 to 1
6	10.0	7.0	1 to 1.4	1.4 to 1
7	10.0	10.0	1 to 1	1 to 1
Average	10.0	7.43	1 to 1.3	1.3 to 1

RESULTS

16a-methyl 9a-fluoroprednisolone (MK-125: hexadecadrol): The doses of prednisolone and 16a-methyl 9a-fluoroprednisolone needed to maintain equivalent degrees of clinical improvement were compared in 21 patients. Strikingly smaller amounts of the new steroid were required in each instance. Dosage ratios of 16a-methyl 9a-fluoroprednisolone to prednisolone varied from 1:5 to 1:10.0, and averaged 1:7.3 for the group (Table 1). Thus, from clinical appraisal alone, the antirheumatic potency, per milligram, of the compound averaged about seven times that of prednisolone. By calculation it could be considered to have roughly 30 times the potency of hydrocortisone.

16a-methyl 9a-fluorohydrocortisone (MK-126): The anti-inflammatory strength of this compound was also found to be considerably greater than that of prednisolone. Dosage comparison studies made in 11 patients indicated that the analogue was approximately three times as powerful as prednisolone (average, 3.2—range, 2.5 to 4.2) (Table 2).

16a-methylprednisolone (MK-110): This derivative exhibited greater antirheumatic potency than prednisolone, but the variation was fractional rather than multiple. From comparisons made in seven patients, the dosage ratios of 16a-methylprednisolone to prednisolone varied from 1:1 to 1:1.7, and averaged 1:1.3 (Table 3). The findings suggest that the anti-inflammatory strength of the analogue is roughly one-third greater, on an average, than that of prednisolone.

16a-methylhydrocortisone (MK-117): The antirheumatic activity of this relatively simple analogue of hydrocortisone was studied in sixteen patients. The dosage requirements were compared to prednisolone in 12 patients, and to hydrocortisone in four patients. Surprisingly, its anti-inflammatory power, per milligram, was found, on an average, to be nearly as great as that of prednisolone. Dosage ratios of 16a-methylhydrocortisone to prednisolone ranged from 1:0.6 to 1:1 (average: 1:0.7) (Table 4). Direct comparisons with hydrocortisone yielded proportionately similar results; the milligram dosages of hydrocortisone required to maintain similar degrees of clinical control in four patients were three to three and one-half times greater than for 16a-methylhydrocortisone.

TABLE 4.—*Comparisons of Milligram Dosages of 16a-Methylhydrocortisone (MK-117) and Prednisolone Required for Equivalent Degrees of Rheumatic Control*

Patient	Dosages (Mg./Day) for Equivalent Rheumatic Control		Dosage Ratios: 16a-Methylhydrocortisone to Prednisolone	Potency Ratios: 16a-Methylhydrocortisone to Prednisolone
	Prednisolone	16a-Methyl-hydrocortisone		
1	7.5	10.0	1 to 0.8	0.8 to 1
2	10.0	12.5	1 to 0.8	0.8 to 1
3	10.0	10.0	1 to 1	1 to 1
4	5.0	7.5	1 to 0.7	0.7 to 1
5	17.5	25.0	1 to 0.7	0.7 to 1
6	7.5	10.0	1 to 0.8	0.8 to 1
7	10.0	15.0	1 to 0.7	0.7 to 1
8	10.0	12.5	1 to 0.8	0.8 to 1
9	10.0	10.0	1 to 1	1 to 1
10	12.5	17.5	1 to 0.7	0.7 to 1
11	10.0	12.5	1 to 0.8	0.8 to 1
12	7.5	12.5	1 to 0.6	0.6 to 1
Average	9.8	13.0	1 to 0.7	0.7 to 1

COMMENT

From these clinical appraisals of potency it is evident that the substitution of a methyl radical at the 16a-carbon position intensifies greatly the antirheumatic strength of certain 11-hydroxy corticosteroids. None of the four compounds studied produced signs of salt and water retention with the dosages employed during the investigation. The observations conform, in general, with those made in laboratory animals which indicated that the 16a-methyl derivatives of hydrocortisone possessed strikingly augmented anti-inflammatory potency without corresponding disturbance of electrolyte metabolism. It would appear that the discovery of these new analogues represents another important step toward the future invention of ideal suppressive drugs for rheumatoid arthritis and other conditions amenable to adrenocortical steroid therapy. Undoubtedly other compounds containing a 16-methyl substituent will be devised.

It is fully recognized that increased anti-inflammatory potency alone does not imply therapeutic superiority. Rather, the superiority of a steroid depends on its ability to achieve and maintain higher levels of improvement without producing unwanted reactions in greater number or intensity—or, preferably, its capacity to promote better control with fewer or no side effects. Critical clinical observations over periods of many months in large numbers of patients, together with extensive metabolic studies in human subjects, are necessary before the virtues and potential hazards of a drug can be assessed. To date clinical trials with the 16a-methyl steroids now available have been limited and brief, and the results of metabolic studies, designed to ascertain whether they do or do not possess significant and useful dissociations of impedient physiologic properties, are incomplete. Thus it is too early to speculate as to their future therapeutic possibilities.

Nonetheless, preliminary observations with 16a-methyl 9a-fluoroprednisolone (MK-125: hexadecadrol), administered uninterruptedly for periods up to four months, have been interesting. Satisfactory control of rheumatoid manifestations has been maintained with total daily dosages ranging from 0.6 to 2.8 mg. The maintenance dose, as with other steroids, has varied with the severity or activity of the disease, but in a group of 86 patients with rheumatoid arthritis now being treated with the compound, the average dose has been 1.6 mg. a day. The degree of clinical improvement has been elevated in a number of patients following change from prednisolone or prednisone to the new analogue. This has been made possible by the application of relatively higher antirheumatic (but lower milligram) doses of 16a-methyl 9a-fluoroprednisolone. Whether these more effective doses will eventually be accompanied by more or less undesirable effects remains to be seen. So far edema has not been observed with dosages of 4.0 mg. a day or less, and the drug, as yet, has not provoked significant gastrointestinal symptoms.

It would appear that other 16-methylated analogues are deserving of thorough clinical appraisal. This is particularly true of 16a-methylhydrocortisone, a relatively simple derivative of hydrocortisone with an antirheumatic potency approaching that of prednisolone and prednisone. In the author's experience, furthermore, it has not induced edema with trial doses as large as 40 mg. a day.

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