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ANTIRHEUMATIC EFFECTS OF HYDROCORTISONE (FREE ALCOHOL), HYDROCORTISONE ACETATE, AND CORTISONE (FREE ALCOHOL) AS COMPARED WITH CORTISONE ACETATE

RESULTS FROM ORAL ADMINISTRATION IN PATIENTS WITH RHEUMATOID ARTHRITIS

BY

EDWARD W. BOLAND, M.D., M.S.Med., F.A.C.P.

Los Angeles, California

The results of prolonged uninterrupted cortisone acetate therapy given orally to patients with rheumatoid arthritis were recently reported.[1] By using initial suppressive amounts of the hormone, then gradually reducing the dosage in step-like manner, and finally employing smaller maintenance doses, it was possible to sustain satisfactory, though not complete, rheumatic control in approximately two-thirds of the patients. Adequate degrees of improvement were maintained in 47% of severe cases, in 70% of moderately severe cases, and in 92% of moderate and mild cases. Results were poorer in those patients whose disease was severe, because they required continued large or relatively large maintenance amounts of the hormone which often could not be tolerated, as they incited objectionable hormonal complications; large but efficient doses frequently had to be reduced, with sacrifice to clinical improvement.

The limitations of cortisone acetate as a therapeutic agent, together with its cost, and, until recently, its restricted supply, have led investigators to search for steroidal substitutes which might possess similar anti-inflammatory and anti-allergic properties. Many substances, some closely allied chemically to cortisone, have been tested by critical observers and have been found devoid of significant antirheumatic activity in the dosage ranges explored. Among these may be listed: substance S of Reichstein (11-desoxycorticosterone),[2 3] compound A of Kendall (11-dehydrocorticosterone),[4 5] 21-desoxycortisone,[5] 21-desoxy-11-dehydrocorticosterone,[5] desoxycorticosterone acetate (alone or with ascorbic acid),[6 7 8 9 10] 17-hydroxyprogesterone,[11 12] pregnenethiolone acetate, [3 7] delta-5-pregnenolone,[5 12 13] and 21-acetoxypregnenolone.[2 5 12] An exception has been Kendall's compound F (17-hydroxycorticosterone : "substance M" of Reichstein), recently named "hydrocortisone," which has shown physiological activity at least comparable to that of cortisone. Weak antirheumatic action has been demonstrated also by certain adrenal cortical extracts, their strength apparently depending upon the amounts of cortisone or hydrocortisone they contain.[5]

In April, 1951, small quantities of hydrocortisone acetate were made available to us, and two patients with rheumatoid arthritis were given the drug orally. The doses needed to suppress the rheumatic manifestations were substantially greater than those ordinarily required for cortisone acetate.[14] Conversely, pilot trials made later with hydrocortisone (free alcohol) indicated that this substance was highly effective and perhaps even more potent than cortisone acetate. Subsequently, when supplies of materials permitted, a systematic study designed to compare the antirheumatic potencies of cortisone acetate, hydrocortisone (free alcohol), hydrocortisone acetate, and cortisone (free alcohol) was undertaken. Appraisals of the relative clinical effectiveness of these compounds were made by: (1) estimating differences in initial clinical response to large suppressive doses, and (2) comparing the maintenance doses required to uphold equivalent degrees of clinical improvement in the same patient. The results of this investigation are reported here.

In comparing the maintenance-dosage requirements of other compounds with those already established for cortisone acetate, care was taken to select only those patients whose maintenance doses of cortisone acetate had remained quite stable over periods of weeks or months. Transfers from one substance to another were not made in rapid sequence and patients were usually kept on the test preparation for at least two or three weeks. They were then transferred back to the original compound in order to cross-check differences. During the study attempts were made to compare the amounts of the compounds needed to sustain marked (70 to 85%) improvement, but not complete suppression of the disease. Thus sufficient subjective and objective manifestations remained to allow changes in rheumatic response to be measured.

Cortisone Acetate

The favourable influence of cortisone acetate therapy on rheumatoid arthritis has been repeatedly documented. In more than 150 patients treated with the compound by oral administration we have followed a fairly uniform plan of dosage, which has consisted of three stages: (1) a period of initial suppressive doses; (2) a period of gradual dose reduction; and (3) a period of smaller maintenance-dose administration.[1 15 16 17]

Initial suppressive therapy usually has been given as follows: for severe and moderately severe cases, 200 or 150 mg. for the first one or two days, followed by 100 mg.

daily; for moderate and mild cases, 100 mg. on the first and subsequent days. The drug has been prescribed in four divided doses daily, at meal-times and at bedtime. Amounts of 100 mg. have been continued until the clinical manifestations were suppressed satisfactorily; the number of days required for this has varied, more or less, with the initial activity of the disease, averaging, for example, about 21 days for severe cases and about 14 days for moderate cases. The dosage then has been gradually reduced in steplike fashion, by 12.5 mg. (half a tablet) at a time at intervals of every five to seven days. The smallest daily amount which would sustain adequate suppression of rheumatic symptoms, not necessarily full symptomatic relief, has been regarded as the patient's maintenance dose. This dose has been continued uninterruptedly, adjustments being made from time to time to counteract fluctuations in disease activity.

With large suppressive amounts of cortisone acetate given by mouth, symptoms generally begin to subside within the first 24 hours of treatment, and almost invariably some response is noted within the first 48 hours. Early benefits consist in reduction of aching and stiffness, lessening of articular tenderness and pain, increase in range of joint motion, lessening of fatigue, and increased appetite. Joint swelling and other reversible objective changes recede more gradually, but with continued administration the overall improvement progresses. Elevated erythrocyte sedimentation rates are corrected more slowly than are the joint manifestations, and their reductions usually lag several days behind clinical improvement. In spite of continued large daily doses of the hormone, however, sedimentation rates may at times fail to decrease to levels commensurate with the rheumatic response.

After the manifestations have been brought under initial control and the dose has been gradually reduced, the daily amount of cortisone acetate needed to maintain satisfactory symptomatic suppression varies, but it depends to a large extent on the initial activity of the rheumatoid arthritis—the more severe the disease, the more cortisone acetate required. Usual ranges for maintenance doses have been: 62.5 to 125 mg. a day for severe cases; 50 to 75 mg. a day for moderately severe cases; 37.5 to 62.5 mg. for moderate cases; and 25 to 50 mg. a day for mild cases. In nearly two-thirds of patients the dosage has remained fairly constant for months, with only minor adjustments being needed periodically. In about one-third of patients the amounts of hormone required have fluctuated considerably from time to time, and major manipulations of dosage have been necessary to offset changes in disease activity.

Hydrocortisone (Free Alcohol)

Hydrocortisone (Kendall's compound F, free alcohol: 17-hydroxycorticosterone) differs from cortisone (Kendall's compound E, free alcohol: 17-hydroxy-11-dehydrocorticosterone) in that a hydroxy radical instead of a ketone group is present at the eleventh carbon position of the steroid nucleus. From facts now available it seems probable that hydrocortisone rather than cortisone is the chief glycogenically active corticoid secreted by the adrenal gland, at least under conditions of stress.[18 19] A number of laboratory procedures indicate that hydrocortisone is more active physiologically than cortisone. Comparisons made from muscle-work tests, assays of liver glycogen, and ability to incite regressive changes in the thymus and adrenals have shown that when the non-esterified forms of the two hormones are given intravenously or subcutaneously hydrocortisone is approximately twice as potent as cortisone.[20 21 22 23] It also appears that one-half as much hydrocortisone as cortisone will promote an equivalent eosinopenic response.[24]

Meagre quantities of hydrocortisone (free alcohol) have been available for laboratory and clinical research because production of the hormone has depended upon complicated processes of biosynthesis. These have involved the transformation of 11-desoxy-17-hydrocorticosterone (Reichstein's compound S)—a steroid which may be derived from soy beans and which is devoid of anti-inflammatory activity—to hydrocortisone through the action of adrenal cortical enzymes. By enriching the substrate with 11-desoxy-17-hydrocorticosterone and perfusing it through intact isolated bovine adrenal glands or by adding it to and incubating it with slices of adrenal cortex, this steroid is converted (by placing a hydroxy radical at the eleventh carbon atom) to hydrocortisone. Very recently small amounts of the hormone produced by partial chemical synthesis have been made available for trial.

In 1949 Hench and colleagues demonstrated that hydrocortisone (free alcohol), like cortisone and corticotropin (A.C.T.H.), possessed antirheumatic activity when administered systemically.[5 25 26] They gave a total of 900 mg. of the hormone intramuscularly to one patient with rheumatoid arthritis over a 12-day period and noted that the articular manifestations subsided rapidly; overall relief was estimated as 60% and the erythrocyte sedimentation rate was reduced from 85 to 24 mm. in one hour. No other accounts of the effects of hydrocortisone (free alcohol) given systemically to patients with rheumatoid arthritis have been recorded.

Experience with Suppressive Doses of Hydrocortisone (Free Alcohol) Given Orally

Five patients with rheumatoid arthritis of the peripheral type who had not previously received hormonal therapy for arthritis were given large initial doses of hydrocortisone (free alcohol) by mouth.* The disease was graded as severe in one patient, moderately severe in three, and moderate in one; erythrocyte sedimentation rates before treatment were 119, 61, 60, 53, and 48 mm. in one hour (Westergren method) in the respective patients. Four of the subjects were women and one was a man. Their ages ranged from 42 to 56 years.

The one patient with severe disease received 150 mg. of the hormone daily for two days and then 100 mg. each day for 13 days. The three patients with moderately severe and the one patient with moderate rheumatoid arthritis received 100 mg. on the first day and for several days thereafter. Because supplies of hydrocortisone were limited, the doses given on the first day of treatment were smaller than those customarily employed for cortisone acetate in cases of similar severity.

The results from suppressive doses of hydrocortisone (free alcohol) will be reported elsewhere in greater detail.[27] The initial response was strikingly prompt in each patient, and symptoms such as aching and stiffness began to subside within three, four, six, seven, and ten hours respectively after the first dose of the hormone. In four patients (three with moderately severe and one with moderate rheumatoid arthritis) subsequent progress was extremely rapid, and very marked degrees of overall improvement (more than 85%), as gauged by both objective and subjective criteria, resulted after four, six, six, and eight days. In these the improvement progressed at a more rapid rate and was more complete than that which usually follows oral cortisone acetate therapy within such periods, even when larger doses are given on the first day. The fifth patient (with severe disease) responded less dramatically, and the improvement was graded as marked after 15 days; the rate of improvement was considered to be about the same as might have resulted from cortisone acetate given in identical doses.

Erythrocyte sedimentation rates were lowered with remarkable speed and, in contrast to the lag which is often noted during cortisone acetate therapy, reductions kept pace closely behind clinical improvement. Elevated rates in the five patients were reduced as follows: 53 to 10 mm. in 7 days, 60 to 20 mm. in 7 days, 61 to 11 mm. in 10 days, 48 to 16 mm. in 6 days, and 119 to 39 mm. in 15 days.

*Gratitude is expressed to G. D. Searle & Co., who supplied most of the hydrocortisone (free alcohol); to Merck & Co., Inc., who supplied the cortisone acetate; and to the Upjohn Company, who supplied part of the hydrocortisone (free alcohol).

Comparisons of Maintenance-dosage Requirements of Cortisone Acetate and Hydrocortisone (Free Alcohol)

By directly comparing the maintenance doses required in the same patient to provide similar antirheumatic control, appraisals of the relative potencies of cortisone acetate and hydrocortisone (free alcohol) could be made more accurately than by estimating differences in the immediate response to suppressive doses. Ten patients with rheumatoid arthritis who had been treated uninterruptedly with cortisone acetate orally for long periods (3 to 16 months), and whose maintenance requirements were stable and well established, were transferred directly to hydrocortisone (free alcohol). Uniformly the patients needed smaller amounts of hydrocortisone (free alcohol) for equivalent degrees of clinical improvement. Dosage differences were clearly defined and, milligram for milligram, hydrocortisone (free alcohol) was found to be approximately 50% more potent than cortisone acetate. Dosage ratios of cortisone acetate to hydrocortisone (free alcohol) ranged from 1.43:1 to 1.7:1 among the ten patients, and the average ratio for the group was 1.56:1 (Table I).

In three of the five patients the initial response was definitely less than would ordinarily be experienced with corresponding large suppressive doses of cortisone acetate, but in two patients (both with moderately severe disease) the progress of improvement was similar. In the five patients some degree of symptomatic relief was noted within 8, 15, 24, 24, and 30 hours after the first dose of hydrocortisone acetate, but in three of them the immediate reaction was not striking, and at the end of several days of treatment the overall improvement was considered to be distinctly less than should have resulted from similar amounts of cortisone acetate.

Response to suppressive therapy varied among the five patients as follows. The first patient, with moderately severe rheumatoid arthritis, exhibited moderate symptomatic relief after the first day's treatment with 200 mg. of hydrocortisone acetate, and after 48 hours some improvement in the objective joint findings was recorded. Two days after the dose was reduced to 100 mg. a day, however, regression ensued and very little additional improvement resulted from continued administration. After 15 days, improvement was

TABLE I.—*Maintenance-dosage Requirements for Cortisone Acetate and Hydrocortisone (Free Alcohol) Given Orally in Rheumatoid Arthritis*

Case	Severity of Disease	Degree of Overall Improvement	Maintenance Doses needed for Equivalent Degrees of Clinical Improvement						Average Dosage Ratios Cortisone Acetate to Hydrocortisone (Free Alcohol)
			First Comparison		Second Comparison		Averages		
			Cortisone Acetate (mg.)	Hydrocortisone (Free Alcohol) (mg.)	Cortisone Acetate (mg.)	Hydrocortisone (Free Alcohol) (mg.)	Cortisone Acetate (mg.)	Hydrocortisone (Free Alcohol) (mg.)	
1	Mod. severe	Marked (85%)	62·5	40	62·5	50	62·5	40·0	1·56 to 1
2	,, ,,	,, (85%)	62·5	40	62·5	40	62·5	40·0	1·56 ,, 1
3	,, ,,	,, (75%)	75·0	50	75·0	55	75·0	52·5	1·43 ,, 1
4	,, ,,	,, (85%)	62·5	40	—	—	62·5	40·0	1·56 ,, 1
5	Severe	,, (75%)	75·0	50	75·0	50	75·0	50·0	1·50 ,, 1
6	,,	,, (80%)	125·0	80	125·0	70	125·0	75·0	1·67 ,, 1
7	,,	,, (75%)	68·8	40	62·5	40	65·7	40·0	1·64 ,, 1
8	Mod. severe	,, (85%)	62·5	40	—	—	62·5	40·0	1·56 ,, 1
9	,, ,,	,, (85%)	62·5	40	75·0	40	68·8	40·0	1·72 ,, 1
10	Mod.	Very marked (90%)	50·0	35	—	—	50·0	35·0	1·43 ,, 1
								Average	1·56 ,, 1

Hydrocortisone Acetate

Hydrocortisone acetate (17-hydroxycorticosterone-21-acetate: compound F acetate) is produced by partial chemical synthesis from desoxycholic acid, through a similar but more complex process than that used in the manufacture of cortisone acetate. Reports of systemic administration of this compound to patients with rheumatoid arthritis have been few. Perera and associates[28] gave the drug intramuscularly to two patients with the disease; one received 100 mg. a day for 24 days and the other 12.5 mg. a day for 11 days. They concluded that the clinical and metabolic effects may have been somewhat less than would have occurred with cortisone acetate. Ward and co-workers[29] judged that the improvement which resulted in two patients who received the compound orally was comparable to that expected from cortisone acetate in corresponding doses.

Experience with Suppressive Doses of Hydrocortisone Acetate*

The acetate ester of hydrocortisone was administered orally as initial treatment to five women, one with severe and four with moderately severe rheumatoid arthritis. Erythrocyte sedimentation rates before treatment were recorded as 103, 67, 58, 53, and 50 mm. in one hour (Westergren method). Dosages used were identical to those customarily employed with cortisone acetate in cases of like severity: 200 mg. in divided doses was given on the first and second days of treatment and 100 mg. daily thereafter to the patient with severe arthritis; 200 mg. was administered on the first day and 100 mg. on subsequent days to the four patients with moderately severe disease.

*The hydrocortisone acetate used in this investigation was supplied by Merck & Co., Inc.

graded as slight (less than 30%) and the erythrocyte sedimentation rate had not changed significantly (58 to 56 mm. in one hour). The dose of hydrocortisone acetate was then raised to 200 mg. a day for 10 days; further suppression of the disease manifestations promptly ensued, but endocrine side-reactions, consisting of pronounced mooning of the face, nervousness, insomnia, and oedema of the lower legs, also developed.

The second patient suffered from severe rheumatoid arthritis, and previously, for a period of 11 months, she had responded well to uninterrupted cortisone acetate administration. The immediate improvement from cortisone acetate had been dramatic, and satisfactory control was held with daily amounts ranging from 50 to 75 mg. Cortisone acetate therapy had been discontinued five months beforehand in order to ascertain the rate of return of adrenal cortical function following long-term therapy; functional recovery, as indicated by the eosinopenic response to corticotropin and urinary 17-ketosteroid determinations, had returned to normal within 45 days after withdrawal. The improvement resulting from hydrocortisone acetate in amounts of 200 mg. daily for two days and then 100 mg. a day was graded as slight. After 19 days of treatment overall improvement was estimated as between 20 and 30% and the sedimentation rate had not decreased greatly, from 103 to 87 mm. in one hour. The preparation was then given in amounts of 150 mg. a day for a period of nine days; this afforded somewhat greater relief, and improvement was finally graded as moderate (about 50%). At this point transfer to cortisone acetate in amounts of 100 mg. a day was accomplished. Within 18 hours there was striking acceleration of improvement, and continued administration resulted in rapid sup-

TABLE II.—*Maintenance Requirements for Cortisone Acetate and Hydrocortisone Acetate Given Orally in Rheumatoid Arthritis*

Case	Severity of Disease	Degree of Overall Improvement	Maintenance Doses needed for Equivalent Degrees of Clinical Improvement						Average Dosage Ratios Cortisone Acetate to Hydrocortisone Acetate
			First Comparison		Second Comparison		Averages		
			Cortisone Acetate (mg.)	Hydrocortisone Acetate (mg.)	Cortisone Acetate (mg.)	Hydrocortisone Acetate (mg.)	Cortisone Acetate (mg.)	Hydrocortisone Acetate (mg.)	
1	Mod. severe	Marked (85%)	62·5	87·5	—	—	62·5	87·5	1 to 1·40
2	Severe	,, (75%)	62·5	100·0	62·5	75·0	62·5	87·5	1 ,, 1·40
3	Mod. severe	,, (85%)	50·0	75·0	62·5	100·0	56·3	87·5	1 ,, 1·55
4	,, ,,	,, (85%)	62·5	87·5	62·5	100·0	62·5	93·8	1 ,, 1·50
5	,, ,,	,, (85%)	62·5	87·5	62·5	75·0	62·5	81·3	1 ,, 1·30
6	,, ,,	,, (75%)	75·0	100·0	—	—	75·0	100·0	1 ,, 1·33
7	,, ,,	,, (85%)	62·5	62·5	62·5	62·5	62·5	62·5	1 ,, 1·00
8	Severe	,, (75%)	75·0	125·0	62·5	100·0	68·8	112·5	1 ,, 1·64
9	Mod.	,, (80%)	50·0	75·0	50·0	50·0	50·0	62·5	1 ,, 1·25
								Average	1 ,, 1·37

pression of the rheumatic manifestations, comparable to that which had been experienced from previous treatment with cortisone acetate.

The third patient, with moderately severe disease, experienced rapid and progressive improvement from suppressive doses of hydrocortisone acetate, which at the end of 16 days was graded as marked (80%). Thereafter the dosage was gradually reduced to a maintenance level of 62.5 mg. a day, which was sufficient to uphold satisfactory suppression of the clinical manifestations. The erythrocyte sedimentation rate failed to reflect the good rheumatic response, however, and at the end of 22 days of treatment had decreased only from 67 to 46 mm. in one hour. Transfer to cortisone acetate was subsequently made, and the same maintenance dose was required to provide equivalent clinical control.

The fourth patient, with moderately severe rheumatoid arthritis, responded slowly and undramatically to initial suppressive doses of hydrocortisone acetate, and after 20 days of treatment the overall improvement was graded as moderate or about 50%. The erythrocyte sedimentation rate decreased during the period from 53 to 40 mm. in one hour.

The fifth patient, with moderately severe disease, responded well to 200 mg. of hydrocortisone acetate on the first day, noting subjective improvement within 24 hours after the initial divided dose. Subsequent progress on total daily amounts of 100 mg. was steady, and after 19 days of treatment the improvement was graded as marked (about 80%). The erythrocyte sedimentation rate during this period was reduced from 50 to 20 mm. in one hour.

Comparisons of Maintenance-dosage Requirements of Cortisone Acetate and Hydrocortisone Acetate

In contrast to hydrocortisone (free alcohol), which was found to be more potent than cortisone acetate when the maintenance requirements of the two substances were tested on the same patients, hydrocortisone acetate was less effective, milligram for milligram, than cortisone acetate in eight of nine patients studied. Dosage ratios of cortisone acetate to hydrocortisone acetate ranged from 1:1 to 1.64:1 among the nine patients, with an average for the group of 1.37:1 (Table II).

Comparisons of Maintenance-dosage Requirements of Hydrocortisone (Free Alcohol) and Hydrocortisone Acetate

Direct comparisons of these two compounds in the same patients clearly demonstrated that hydrocortisone (free alcohol) was distinctly superior to hydrocortisone acetate in controlling the manifestations of rheumatoid arthritis. Results were fairly uniform in nine patients tested, and indicated that hydrocortisone (free alcohol) was nearly twice as potent, milligram for milligram, when the two substances were given by mouth (Table III).

TABLE III.—*Maintenance Requirements for Hydrocortisone (Free Alcohol) and Hydrocortisone Acetate Given Orally in Rheumatoid Arthritis*

Case	Severity of Disease	Degree of Overall Improvement	Maintenance Doses Needed for Equivalent Degrees of Clinical Improvement		Average Dosage Ratios: Hydrocortisone (Free Alcohol) to Hydrocortisone Acetate
			Hydrocortisone (Free Alcohol) (mg.)	Hydrocortisone Acetate (mg.)	
1	Severe	Marked (75%)	40	87·5	1 to 2·19
2	Mod. severe	,, (80%)	40	75·0	1 ,, 1·88
3	,, ,,	,, (80%)	60	125·0	1 ,, 2·08
4	,, ,,	,, (80%)	40	75·0	1 ,, 1·88
5	,, ,,	,, (75%)	50	100·0	1 ,, 2·00
6	,, ,,	,, (80%)	40	87·5	1 ,, 2·19
7	Severe	,, (75%)	50	87·5	1 ,, 1·75
8	Mod. severe	,, (80%)	40	75·0	1 ,, 1·88
9	Mod.	,, (80%)	40	75·0	1 ,, 1·88
				Average	1 ,, 1·97

Cortisone (Free Alcohol)

Of the 21 rheumatoid arthritis patients with whom Hench, Kendall, Slocumb, and Polley[25 26] originally demonstrated that cortisone exerted an inhibiting influence on the disease, 9 received the free hormone and 12 were given the acetate ester as initial treatment. The relative therapeutic potencies of the two preparations were not compared directly by them.

When our studies revealed that hydrocortisone (free alcohol) was distinctly superior in antirheumatic activity to hydrocortisone acetate when they were administered orally, the question arose whether a similar discrepancy might exist between the free and acetated forms of cortisone. Cortisone (free alcohol)* was made available to us in small quantities, and maintenance-dosage requirements for the hormone were compared with those for cortisone acetate in seven patients, and with those for hydrocortisone (free alcohol) in six patients. The data evolved from these comparisons are given in Table IV. Supplies were not sufficient to test the effects of initial suppressive doses in previously untreated patients.

Cortisone (free alcohol) and cortisone acetate were found to be approximately equal in their antirheumatic potencies when administered by mouth. Except for minor variations in three of the seven patients, the maintenance dosages required for the two compounds were interchangeable.

Hydrocortisone (free alcohol) proved to be more effective, milligram for milligram, than cortisone (free alcohol). Although dosage differences among the individual patients showed less uniformity, the average calculated dosage ratio was much the same as with cortisone acetate. The dosage ratio of cortisone (free alcohol) to hydrocortisone (free alcohol) ranged in the six patients from 1.25 : 1 to 2.08 : 1, with an average ratio for the group of 1.6 : 1—against 1.56 : 1 for cortisone acetate to hydrocortisone (free alcohol).

*The cortisone (free alcohol) used in this investigation, produced by partial chemical synthesis, was supplied by the Upjohn Company.

TABLE IV.—*Maintenance Requirements for Cortisone (Free Alcohol), Cortisone Acetate, and Hydrocortisone (Free Alcohol) Given Orally in Rheumatoid Arthritis*

Case	Severity of Disease	Degree of Overall Improvement	Maintenance Doses Needed for Equivalent Degrees of Clinical Improvement				Calculated Dosage Ratios.	
			Cortisone Acetate (mg.)	Cortisone (Free Alcohol) (mg.)	Hydrocortisone (Free Alcohol) (mg.)	Cortisone (Free Alcohol) (mg.)	Cortisone Acetate to Cortisone (Free Alcohol)	Cortisone (Free Alcohol) to Hydrocortisone (Free Alcohol)
1	Mod. severe	Marked	62·5	62·5	40	62·5	1·0 to 1·0	1·56 to 1
2	,, ,,	,,	62·5	62·5	40	62·5	1·0 ,, 1·0	1·56 ,, 1
3	,, ,,	,,	62·5	62·5	30	62·5	1·0 ,, 1·0	2·08 ,, 1
4	,, ,,	,,	62·5	50·0	40	50·0	1·0 ,, 0·8	1·25 ,, 1
5	,, ,,	,,	62·5	75·0	40	75·0	1·0 ,, 1·2	1·88 ,, 1
6	,, ,,	,,	75·0	62·5	50	62·5	1·0 ,, 0·83	1·25 ,, 1
7	Mod.	,,	50·0	50·0	—	—	1·0 ,, 1·0	—
						Averages	1·0 ,, 0·98	1·6 to 1

Comment

Data derived from the present study indicate that when administered orally hydrocortisone (free alcohol) is, milligram for milligram, approximately 50% more potent than either cortisone acetate or cortisone (free alcohol), and nearly twice as effective as hydrocortisone acetate. These observations suggest that hydrocortisone (free alcohol) may prove to be superior to cortisone acetate as a therapeutic agent. Although the hormone used in the present study was produced by expensive and complicated procedures of biosynthesis, it has been made recently by partial chemical synthesis from a precursor of cortisone. If future investigations prove that the hormone has distinct therapeutic advantages, it is probable that practical methods for its commercial manufacture will be found.

The number of cases studied were too few and the periods of observation were too short to allow the incidence of the adverse hormonal effects from hydrocortisone (free alcohol), hydrocortisone acetate, or cortisone (free alcohol) to be compared with those already known for cortisone acetate. However, it seems that the greater antirheumatic activity of hydrocortisone (free alcohol) is not accompanied by a correspondingly greater tendency to produce adverse reactions. Endocrine complications were present in several patients during the administration of maintenance doses of cortisone acetate, and these disappeared or diminished when the patients were transferred to smaller but equally effective amounts of hydrocortisone (free alcohol). Five of the ten patients transferred from cortisone acetate to hydrocortisone (free alcohol) had signs of hormonal excess prior to transfer. Slight to moderate oedema, which was present beforehand in four patients, disappeared entirely after hydrocortisone (free alcohol) therapy was instituted. Facial mooning, which was present in two patients, became less noticeable in one and receded completely in the other. In no patient did new hormonal complications develop after transfer to hydrocortisone (free alcohol). We believe that this lessening of adverse effects may be accounted for by the fact that smaller doses of hydrocortisone (free alcohol) were employed to control the rheumatoid arthritis.

The reasons for the marked disparity in therapeutic effectiveness between hydrocortisone (free alcohol) and hydrocortisone acetate when administered orally are not entirely clear, but the relatively low solubility of hydrocortisone acetate may provide at least part of the explanation. Recent studies made at the Merck Laboratories have demonstrated that hydrocortisone (free alcohol), when compared with hydrocortisone acetate, is approximately 28 times more soluble in water, six times more soluble in synovial fluid, 35 times more soluble in plasma, and 36 times more soluble in serum albumin.[30] The lower solubility of hydrocortisone acetate could substantially lessen the rate and degree of its alimentary absorption.

Recently Hollander and co-workers,[31 32] and others[33 34] have observed that intra-articular injections of small quantities (25 to 50 mg.) of hydrocortisone acetate are highly effective in temporarily suppressing the inflammatory reaction in individual joints treated, but that similar injections of cortisone acetate are not so successful. These findings are in contrast to our results from oral administration, in which cortisone acetate exhibited the greater potency. Again this could be explained, but possibly only in part, on the basis of differences in solubility and absorption of the two compounds. Solubility data have revealed that cortisone acetate is approximately twice as soluble in water as hydrocortisone acetate, nine times as soluble in synovial fluid, eight times as soluble in plasma, and 18 times as soluble in serum albumin.[30] Whereas the low solubility of hydrocortisone acetate may lessen its therapeutic effectiveness with oral administration, it may, by delaying absorption from the joint and allowing more prolonged local action, serve as an advantage with intra-articular application.

Summary

Comparisons of the antirheumatic effects of hydrocortisone (free alcohol), hydrocortisone acetate, cortisone (free alcohol), and cortisone acetate given orally for short periods were made in patients with rheumatoid arthritis. The relative potencies of the preparations were appraised by estimating the differences in clinical response to initial suppressive doses, and by comparing directly in the same patient the maintenance doses required to uphold similar degrees of clinical improvement.

Hydrocortisone (free alcohol) was found to possess greater antirheumatic activity, milligram for milligram, than any of the other three preparations when given by mouth. This substance, administered in large initial doses, was highly efficient in suppressing the disease manifestations of rheumatoid arthritis, and its action appeared to be more rapid than that regularly encountered with cortisone acetate. By comparing the maintenance doses required for equivalent clinical control, hydrocortisone (free alcohol) was found to be approximately 50% more potent than either cortisone (free alcohol) or cortisone acetate, and nearly twice as effective as hydrocortisone acetate.

In a small number of patients tested by comparing maintenance-dosage requirements the effectiveness of cortisone (free alcohol) and cortisone acetate appeared to be about equal.

The relative incidence of endocrine complications from the various preparations could not be determined from the short-term studies involved. However, the greater antirheumatic activity of hydrocortisone (free alcohol) did not seem to be accompanied by a correspondingly greater tendency to produce adverse physiological effects. In several patients signs of hormonal excess present while on maintenance doses of cortisone acetate actually diminished or disappeared after transfers were made to smaller, but equally effective, doses of hydrocortisone (free alcohol).

The marked disparity in therapeutic effectiveness between hydrocortisone (free alcohol) and hydrocortisone acetate when given by mouth may be accounted for, at least in part, by differences in solubility of the compounds. The low solubility of hydrocortisone acetate may substantially lessen its alimentary absorption.

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According to a report from the Informacion Medica Española the Spanish Government has allotted money for the provision of homes for doctors; the municipality provides the ground and a large amount of the manpower for the building. The administration of these houses, which include facilities for primary health centres, is under the control of provincial councils. They are placed at the disposal of the medical officer of health of the district, who has two or three rooms for his medical work and five or six for his personal use; he pays a monthly rent not exceeding 2% of the cost of the house, and this is set aside for repairs and upkeep. Each is equipped with examination facilities and everything necessary for emergency operations; all medicaments are supplied by the municipality. So far 200 of these houses have been built, and by the end of this year there should be over 500.

PROGUANIL-RESISTANCE IN MALAYAN STRAINS OF PLASMODIUM VIVAX

BY

T. WILSON, M.B., D.P.H.
Institute for Medical Research, Federation of Malaya

D. S. MUNRO, M.B., M.R.C.P.
Captain, R.A.M.C.; Physician, Military Hospital, Kinrara, Kuala Lumpur

AND

D. R. RICHARD, B.M., B.Ch.
Captain, R.A.M.C.

Proguanil (" paludrine ") has been widely used throughout the Federation of Malaya for the prevention of malaria since it first became generally available in 1947. Controlled experiments showed that proguanil in doses of 100–300 mg. once a week was an effective suppressive, and reduced parasite and spleen rates in the semi-immune populations on estates. Overt malaria was usually associated with irregular dosage; transmission, however, was light during the period of these experiments (Institute for Medical Research, 1950).

Proguanil was first used by the Army in Malaya in place of suppressive mepacrine early in 1949, with no apparent change in the malaria sickness rate. The present investigation started as an inquiry into an outbreak of malaria which occurred late in 1950 in a British Army unit engaged in operations against bandits in the Tampin district of the State of Negri Sembilan.

Malaria in the Tampin District

Parts of the Tampin district, and of the surrounding districts, have long been regarded as highly malarious. The Army unit concerned arrived in Malaya in the middle of 1947. The unit headquarters were established in Tampin from then until March, 1950, but detached parties were scattered over a wide area of perhaps 100 miles radius, working in the neighbouring States of Selangor, Pahang, Johore, and Malacca. The incidence of malaria during this period seems to have been low. In March, 1950, the unit was moved to Singapore for about six weeks, returning to Tampin in April, and remaining there until April, 1951, when it left for the Middle East.

The main operational differences between the early period and this later period of twelve months were that the detachments were now all working within a more restricted area, inside a radius of some 30 miles from Tampin, and that the malaria rate for several months was high.

The total strength of the unit was about 600 men, and at any one time perhaps 350 men might be engaged in jungle operations. These figures are merely totals; there was a continual interchange of individuals to and from the unit, and between its various sections. As was the standard Army practice in Malaya, the official suppressive dose was one 100-mg. tablet of proguanil daily.

Four malaria infections occurred between the return from Singapore in mid-April and the end of July, 1950; the sequence of events from then on is shown in Table I.

TABLE I.—*Primary Attacks of Malaria (British Troops Only)*

Parasite Species	1950					1951				Total
	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr. 1–9	
P. falciparum	2	1	3	9	9	4	1	3	3	35
P. vivax ..	4	2	1	7	7	2	3	3	0	29
Total ..	6	3	4	16	16	6	4	6	3	