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A COMPARISON OF PREDNISOLONE WITH ASPIRIN OR OTHER ANALGESICS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

A SECOND REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, ACTH, AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES*

In 1955 the Joint Committee initiated a controlled therapeutic trial designed to compare the value of prednisolone with that of aspirin or other analgesics in the treatment of defined cases of rheumatoid arthritis. Eight centres participated and 84 patients entered the trial, a detailed description of which was published in a previous report (1959). During the first 2 years of treatment the patients receiving prednisolone showed an early significant improvement in both clinical and laboratory indices of inflammatory polyarthritis, and less progression of radiological signs of erosive joint disease, but in many patients treated with prednisolone a rise in agglutinating titre in the sheep cell agglutination test was noted and five patients had major complications (two psychoses, three peptic ulcers). In this report we are concerned only with the changes which occurred during the third year of treatment in the 76 patients who remained in the trial at the end of its second year.

Towards the end of the third year one male patient in the prednisolone group died from carcinoma of the colon. His arthritis remitted at the end of the second year and he developed psoriasis of skin and nails, but he was fully assessed 2½ years after entry into the trial and these assessments have been included in the analysis of the third year's results. All the remaining 75 patients were reassessed at approximately 3 years from the date of their entry into the trial.

Of the total 76 patients, 41 were originally allocated to prednisolone and 35 to analgesics, but towards the end of the second year the treatment was changed in a number of patients, so that during the third year nine of the 35 patients in the analgesics group were receiving prednisolone in addition to analgesics, and seven of the 41 patients in the prednisolone group were no longer receiving this drug. During the third year one of these seven patients was being treated with dexamethazone, one with corticotrophin, one with aspirin, and four (including the man who died) were recorded as taking no tablets of any kind. Many of the patients treated with prednisolone, however, also took a varying number of analgesic tablets of which the main constituent was aspirin.

Since the results of the first 2 years showed a significant difference between patients treated with prednisolone and those being treated with analgesics, the nine patients who received prednisolone in addition to analgesics during the third year have been analysed separately from the 26 patients who continued on analgesics throughout the 3 years. The mean daily dose of prednisolone at the end of

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the second year was 10 mg., and at the end of the third year it was 10·5 mg.; there was little change in dosage during the third year.

Results

The general condition of the patients in the two treatment groups (as judged by the physician's opinion about disease activity, functional capacity, joint pain and tenderness, and joint swelling) are shown in Tables I to IV, in which the findings on entry into the trial and after 2 and 3 years of treatment are shown. At the start the prednisolone group contained rather more severely disabled patients with a high grade of disease activity than the analgesics group, but at the third year assessment this difference was reversed, the prednisolone group containing more patients judged to have no disease activity or a normal (Grade 1) functional status. The records of joint pain and swelling, however, showed only minor differences.

The changes in the strength of grip and body

TABLE I

NUMBER OF PATIENTS WITH GIVEN GRADE* OF DISEASE ACTIVITY

Time of Assessment	Treatment Group	Grade				Total
		0	1	2	3	
Week 0	Analgesics throughout trial	—	9	16	1	26
	Changed to prednisolone in 2nd or 3rd year	—	4	4	1	9
	All analgesics patients	—	13	20	2	35
	Prednisolone	—	9	27	5	41
Year 2	Analgesics throughout trial	4	15	7	—	26
	Changed to prednisolone in 2nd or 3rd year	—	7	2	—	9
	All analgesics patients	4	22	9	—	35
	Prednisolone	5	30	6	—	41
Year 3	Analgesics throughout trial	3	17	6	—	26
	Changed to prednisolone in 2nd or 3rd year	—	6	3	—	9
	All analgesics patients	3	23	9	—	35
	Prednisolone	10	20	9	2	41

* Grade: 0 = None 1 = Slight 2 = Moderate 3 = Severe.

TABLE II

NUMBER OF PATIENTS WITH GIVEN GRADE* OF FUNCTIONAL CAPACITY

Time of Assessment	Treatment Group	Grade					Total
		1	2	3	4	5	
Week 0	Analgesics throughout trial	—	5	19	2	—	26
	Changed to prednisolone in 2nd or 3rd year	—	2	5	1	1	9
	All analgesics patients	—	7	24	3	1	35
	Prednisolone	—	11	16	9	5	41
Year 2	Analgesics throughout trial	8	14	3	—	1	26
	Changed to prednisolone in 2nd or 3rd year	1	4	4	—	—	9
	All analgesics patients	9	18	7	—	1	35
	Prednisolone	19	18	3	1	—	41
Year 3	Analgesics throughout trial	9	15	2	—	—	26
	Changed to prednisolone in 2nd or 3rd year	1	6	1	1	—	9
	All analgesics patients	10	21	3	1	—	35
	Prednisolone	23	13	3	2	—	41

* Grade: 1 = Fully employed or employable in normal work and able to undertake normal physical recreations for their type.
2 = Fully employed in special work after vocational training, or doing light or part-time work in normal occupation. Limitation in the amount of physical recreation. Housewives, all except the heaviest housework. In-patients, in hospital for investigation only.
3 = Not employed or employable. Very limited physical activity and little or no capacity for physical recreation. Housewives, light housework and/or limited shopping only. In-patients in hospital for treatment, but up and about in ward.
4 = Confined to hospital, house, or wheelchair, but able to look after themselves in the essentials of life. In-patients in hospital for treatment, sitting up but not getting about.
5 = Confined to bed and unable to look after themselves. In-patients on complete rest in bed.

TABLE III

NUMBER OF PATIENTS WITH GIVEN GRADE* OF JOINT PAIN OR TENDERNESS

Time of Assessment	Treatment Group	Grade				Total
		0	1	2	3	
Week 0	Analgesics throughout trial	—	8	14	4	26
	Changed to prednisolone in 2nd or 3rd year	—	3	6	—	9
	All analgesics patients	—	11	20	4	35
	Prednisolone	—	13	19	9	41
Year 2	Analgesics throughout trial	3	17	6	—	26
	Changed to prednisolone in 2nd or 3rd year	—	6	2	1	9
	All analgesics patients	3	23	8	1	35
	Prednisolone	9	22	10	—	114
Year 3	Analgesics throughout trial	5	16	5	—	26
	Changed to prednisolone in 2nd or 3rd year	2	6	1	—	9
	All analgesics patients	7	22	6	—	35
	Prednisolone	13	17	8	3	41

* Grade: 0 = None 1 = Slight 2 = Moderate 3 = Severe.

TABLE IV

NUMBER OF PATIENTS WITH GIVEN GRADE* OF JOINT SWELLING

Time of Assessment	Treatment Group	Grade				Total
		0	1	2	3	
Week 0	Analgesics throughout trial	1	11	13	1	26
	Changed to prednisolone in 2nd or 3rd year	—	3	6	—	9
	All analgesics patients	1	14	19	1	35
	Prednisolone	1	20	18	2	41
Year 2	Analgesics throughout trial	5	13	8	—	26
	Changed to prednisolone in 2nd or 3rd year	—	5	4	—	9
	All analgesics patients	5	18	12	—	35
	Prednisolone	16	18	7	—	41
Year 3	Analgesics throughout trial	6	15	4	1	26
	Changed to prednisolone in 2nd or 3rd year	1	7	1	—	9
	All analgesics patients	7	22	5	1	35
	Prednisolone	14	20	7	—	41

* Grade: 0 = None 1 = Slight 2 = Moderate 3 = Severe.

weight, and the results of laboratory tests such as the erythrocyte sedimentation rate, haemoglobin concentration, and white cell count, are shown in Table V (overleaf).

The strength of grip in the prednisolone group showed a slight fall during the third year, but the difference between the initial and third-year grip for both hands remained significant ($p < 0{\cdot}01$), whereas the improvement in grip in the analgesics group failed to reach conventional levels of significance.

The erythrocyte sedimentation rate (recorded by the Westergren technique) showed a rise of 2 mm./hr in the mean of the prednisolone group and a fall of 1 mm./hr in the group of 26 patients who received analgesics throughout the trial. At both the 2nd and 3rd year assessments the average erythrocyte sedimentation rate for both treatment groups was almost the same and still below the level at the start of the trial.

The haemoglobin concentration showed little change during the third year, the mean value in the prednisolone group being still slightly higher than that of the analgesics group at the end of the third year. The mean white cell counts showed no significant change.

The mean body weight of the patients who received analgesics throughout the trial increased by 2 lb. during the third year, whereas the patients in the prednisolone group showed a fall of ½ lb. Since

TABLE V

AVERAGE MEASUREMENTS OF VARIOUS CHARACTERISTICS

Time of Assessment	Treatment Group	Strength of Grip (mm. Hg)		Erythrocyte Sedimentation Rate (mm./1 hr, Westergren)	Hb (g. per cent.)	White Cell Count	Body Weight (lb.)
		Left hand	Right hand				
Week 0	Analgesics throughout trial	148	142	33	13·3	8,900	135·2
	Changed to prednisolone in 2nd or 3rd year	93	99	45	12·6	9,200	137·2
	All analgesics patients	133	131	36	13·1	8,900	135·7
	Prednisolone	119	110	41	12·7	8,300	141·4
Year 2	Analgesics throughout trial	162	178	27	13·3	8,000	136·0
	Changed to prednisolone in 2nd or 3rd year	123	119	35	12·7	10,000	143·3
	All analgesics patients	152	163	29	13·2	8,500	137·7
	Prednisolone	195	199	25	13·7	9,500	145·8
Year 3	Analgesics throughout trial	160	183	26	13·3	8,100	138·6
	Changed to prednisolone in 2nd or 3rd year	120	117	23	12·9	9,100	142·2
	All analgesics patients	150	166	25	13·2	8,400	139·5
	Prednisolone	191	195	27	13·6	8,900	145·3

the prednisolone group had shown a greater rise in body weight earlier in the trial when a higher dosage was given, the findings at the third-year assessment are the same, the mean body weight in both treatment groups at 3 years being 4 lb. greater than it was initially.

The results shown in Tables I to V demonstrate a small but definite advantage to prednisolone therapy compared with treatment with aspirin or other analgesics, and this advantage was still present at the end of the third year of treatment. The records of the nine patients who were originally allocated to analgesics and later changed to prednisolone suggest that these patients had a more serious disease and did less well than the average patient in the analgesics group, so that if these nine patients had continued on analgesics only throughout the trial the difference between the original treatment groups at the third year assessment might have been more pronounced.

X-Ray Changes

The *x* rays of the hands and feet taken at 2 and 3 years after entry into the trial were read by one observer (J.H.K.) who was unaware of the treatment given. As in the previous report, each film was given a grading for rheumatoid changes (0 = None, 1 = Doubtful, 2 = Definite but Slight, 3 = Moderate, 4 = Severe). In computing these grades, changes such as articular erosion, joint narrowing or subluxation, and osteoporosis were all taken into account. In addition, an opinion was expressed about improvement, deterioration, or no change between the second and third-year films, since such changes were not always of sufficient magnitude to alter the rather coarse grading employed.

The number of patients showing changes in grade between the second and third year films* are shown in Table VI, and the numbers showing improvement or deterioration in Table VII. Slight radiological improvement was noted in only a few patients, whereas over one-third of the patients in both treatment groups show some radiological deterioration; this was perhaps slightly greater in the prednisolone group, but the overall picture is one of little change during the third year.

Table VIII shows the actual gradings of rheumatoid change seen in the films of hands and feet taken at the start of the trial and after 2 and 3 years of treatment. There was much more progression of radiologically demonstrable joint change amongst the patients allocated to analgesics than amongst those allocated to prednisolone, although both groups were comparable at the start. In the analgesics group the differences between the rheumatoid gradings of the initial and the 3-year films of the hands and feet show $p < 0{\cdot}0001$ and $p < 0{\cdot}02$ respectively. These differences are even greater than those between the initial and the 2-year films previously reported. In the prednisolone group p has now reached $< 0{\cdot}05$ for the differences in grading between the initial and the 3-year films of the hands, but remains not formally significant with regard to the feet films.

* Films of one patient in the analgesic group who was Grade 4 at 2 years were not available at 3 years.

TABLE VI

CHANGES IN RHEUMATOID GRADING OF *X*-RAY FILMS OF HANDS AND FEET DURING THE 3RD YEAR

Films	Treatment Group	Change in Grade (3-yr minus 2-yr)					Total
		+2	+1	0	−1	−2	
Hands	Analgesics throughout trial	—	5	21	—	—	26
	Changed to prednisolone in 2nd or 3rd year	—	—	8	—	—	8
	All analgesics patients	—	5	29	—	—	34
	Prednisolone	—	4	36	1	—	41
Feet	Analgesics throughout trial	—	1	24	1	—	26
	Changed to prednisolone in 2nd or 3rd year	—	1	7	—	—	8
	All analgesics patients	—	2	31	1	—	34
	Prednisolone	1	3	36	1	—	41

TABLE VII

IMPROVEMENT OR DETERIORATION IN *X*-RAY FILMS OF HANDS AND FEET DURING THE 3RD YEAR

Films	Treatment Group	3-year Compared with 2-year Films			Total
		Deterioration	No Change	Improvement	
Hands	Analgesics throughout trial	13	12	1	26
	Changed to prednisolone in 2nd or 3rd year	2	6	—	8
	All analgesics patients	15	18	1	34
	Prednisolone	16	24	1	41
Feet	Analgesics throughout trial	4	20	2	26
	Changed to prednisolone in 2nd or 3rd year	1	6	1	8
	All analgesics patients	5	26	3	34
	Prednisolone	11	29	1	41

TABLE VIII

ACTUAL GRADING OF RADIOLOGICAL CHANGES OF RHEUMATOID ARTHRITIS IN FILMS OF HANDS AND FEET AT VARIOUS PERIODS

Films	Time of Assessment	Treatment Group	Grade					Total
			0	1	2	3	4	
Hands	Initial	Analgesics	13	5	11	5	1	35
		Prednisolone	15	8	13	4	1	41
	Year 2	Analgesics	3	2	13	11	6	35
		Prednisolone	9	8	16	4	4	41
	Year 3	Analgesics	3	2	8	16	5	34
		Prednisolone	9	7	14	7	4	41
Feet	Initial	Analgesics	10	6	9	8	1	34
		Prednisolone	10	7	14	9	1	41
	Year 2	Analgesics	5	2	10	14	4	35
		Prednisolone	12	3	14	9	3	41
	Year 3	Analgesics	4	3	11	12	4	34
		Prednisolone	11	3	13	11	3	41

Grade: 0 = None 1 = Doubtful 2 = Slight 3 = Moderate 4 = Severe.

Sheep Cell Agglutination Test

Details of the techniques used by the participating centres were given in the previous report. Since these were not uniform the minimal positive titre used by each centre has been taken as zero, and dilutions above and below this have been scored as +1, +2, etc., and −1, −2, etc.; the results* so

* Agglutination test results of the patient in the prednisolone group who died (negative at 2 years), and of one patient in the analgesics group (low positive at 2 years) were not available at the 3-year assessment.

obtained are set out in Table IX. The distribution of agglutinating titres within the two treatment groups was very similar at the start of the trial. After 2 years' treatment there were more patients in the prednisolone group with high titres, whereas the distribution of titres in the analgesics group remained unchanged. This tendency for the titre to rise in the prednisolone group did not continue in the third year and indeed there were slightly fewer patients with high titres in the prednisolone group at the 3-year assessment than there had been at the 2-year assessment.

Complications

During the third year of the trial no major complications were reported and the records of minor complications (Table X) show that moon face, hirsuties, euphoria, and depression were still noted in some patients receiving prednisolone in spite of the lower mean dosage employed during the second and third years of the trial. The barium meals and spinal *x* rays which were done at the 2-year assessment were not repeated at the 3-year assessment.

TABLE IX

RESULTS OF SHEEP CELL AGGLUTINATION TESTS*

Time of Assessment	Treatment Group	Results of Tests							Total Positive and Negative
		Negative			Positive				
		−5 to −3	−2 to −1	Total	0 to +1	+2 to +3	+4 to +7	Total	
Initial	Analgesics throughout trial	4	4	8	7	8	3	18	26
	Changed to prednisolone in 2nd or 3rd year	2	2	4	1	2	2	5	9
	All analgesics patients	6	6	12	8	10	5	23	35
	Prednisolone	5	8	13	14	11	3	28	41
Year 2	Analgesics throughout trial	3	8	11	7	5	3	15	26
	Changed to prednisolone in 2nd or 3rd year	2	1	3	2	2	2	6	9
	All analgesics patients	5	9	14	9	7	5	21	35
	Prednisolone	6	6	12	5	12	12	29	41
Year 3	Analgesics throughout trial	3	8	11	7	3	5	15	26
	Changed to prednisolone in 2nd or 3rd year	2	1	3	1	2	2	5	8
	All analgesics patients	5	9	14	8	5	7	20	34
	Prednisolone	3	11	14	8	9	9	26	40

* Based on minimal positive titre = 0, with deviations above and below in numbers of tubes showing agglutination.

TABLE X

NUMBER OF PATIENTS WITH GIVEN SIDE-EFFECTS

Time of Assessment	Treatment Group	Tinnitus or Deafness	Dyspepsia	Moonface	Acne	Hirsuties	Oedema	Euphoria	Depression
Week 0	Analgesics throughout trial	—	1	—	—	1	—	—	2
	Changed to prednisolone in 2nd or 3rd year	1	1	—	—	—	1	—	2
	All analgesics patients	1	2	—	—	1	1	—	4
	Prednisolone	2	3	—	—	—	2	1	4
Year 2	Analgesics throughout trial	1	4	—	—	—	2	—	—
	Changed to prednisolone in 2nd or 3rd year	—	3	4	—	1	—	—	—
	All analgesics patients	1	7	4	—	1	2	—	—
	Prednisolone	2	8	14	3	2	2	3	2
Year 3	Analgesics throughout trial	1	3	—	—	—	—	—	—
	Changed to prednisolone in 2nd or 3rd year	—	2	4	—	—	—	—	—
	All analgesics patients	1	5	4	—	—	—	—	—
	Prednisolone	—	5	15	—	2	—	1	4

Discussion

During the third year of observation there was remarkably little change. Many patients in both treatment groups deteriorated slightly and a few improved a little. The difference between the two treatment groups previously noted was still significant at the end of 3 years, though it was less than it had been earlier. The results are, however, complicated by the fact that nine of the patients in the analgesics group who were not doing well at the end of the second year received prednisolone during the third year.

During the first 2 years of the trial the sheep cell agglutinating titre rose to high levels in many patients treated with prednisolone, but this tendency to rising titres did not continue and at the 3-year assessment there were in fact fewer patients with very high titres than had been at the end of the second year. The suppression of articular erosion obtained with prednisolone during the earlier part of the trial when a higher dosage was given was less evident during the third year, during which the mean dosage was between 10 and 10·5 mg. daily, since at this lower dosage there was roughly equal deterioration of the radiological appearances in the films of hands and feet in both treatment groups, and it may be that the striking advantage to prednisolone as compared with analgesics described in the first report of this trial was largely due to the profound suppressive effects of the higher dosage used in the first year, which unfortunately proved to be unacceptable because of serious side-effects such as psychosis and bleeding peptic ulceration. Alternatively, the effectiveness of prednisolone in suppressing erosions may diminish after years of administration. The long-term complications of corticosteroid therapy (such as osteoporosis, thinning of the skin and blood vessels, senile purpura, etc.) may still develop, so that many more years of observation will be required before the true long-term balance sheet comparing the advantages and disadvantages of corticosteroid therapy can be drawn up.

Summary

In 1955 a controlled trial comparing prednisolone with analgesics in the treatment of certain defined cases of rheumatoid arthritis was initiated, and the results of the first 2 years of the trial have already been reported.

During the third year many of the patients in both treatment groups deteriorated slightly and one or two improved, but the overall picture was one of little change. The advantage to prednisolone demonstrated at the 2-year assessment was still present to a significant but slightly lower degree at the 3-year assessment.

The tendency for the sheep cell agglutinating titre to rise during the first 2 years in some patients treated with prednisolone did not continue during the third year.

REFERENCE

Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, ACTH and Other Therapeutic Measures in Chronic Rheumatic Diseases (1959). *Ann. rheum. Dis.*, **18**, 173.

Comparaison de la prednisolone avec l'aspirine ou d'autres analgésiques dans le traitement de l'arthrite rheumatismale

RÉSUMÉ

En 1955 on a entrepris un essai contrôlé, comparant la prednisolone avec d'autres analgésiques dans le traitement de certains cas définis d'arthrite rhumatismale et on a déjà publié les résultats des premiers deux ans de cet essai.

Pendant la troisième année on a noté une légère détérioration chez beaucoup de malades des deux groupes de traitement et une amélioration chez un ou deux d'entre eux, mais le tableau général était peu changé. L'avantage de la prednisolone, démontré à l'évaluation des résultats de deux ans, demeurait appréciable mais un peu inferieur à l'évaluation de la troisième année.

La tendance à monter du titre d'agglutination des globules sensibilisés de mouton chez certains malades traités par la prednisolone pendant les premiers deux ans n'a pas continué pendant la troisième année.

Comparación de la prednisolona con la aspirina u otros analgésicos en el tratamiento de la artritir reumatoide

SUMARIO

En 1955 se inició una prueba controlada comparando la prednisolona con los analgésicos en el tratamiento de ciertos definidos casos de artritis reumatoide, y los resultados de los dos promeros años de la prueba han sido ya publicados.

Durante el tercer año muchos de los enfermos de ambos grupos de tratamiento empeoraron ligeramente y uno o dos mejoraron, pero el cuadro predominante fué de escasa variación. La ventaja de la prednisolona, demostrada en las investigaciones de dos años estaba presente todavía de una forma significativa, pero en un grado ligeramente inferior, en las comprobaciones del tercer año.

La tendencia a la elevación del título de aglutinación de los eritrocitos sensibilizados de carnero en algunos pacientes tratados con prednisolona durante los dos primeros años, no continuó durante el tercer año.