COMPARATIVE EFFECTS OF ACTH AND BUTAZOLIDIN IN RHEUMATOID ARTHRITIS

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The administration of 1 : 2-diphenyl-3 : 5-dioxo-4-n-butylpyrazolidine (Butazolidin, Phenylbutazone) to patients with various rheumatic disorders appears to be followed by clinical improvement in a large proportion of cases (Currie, 1951, 1953; Kuzell and others, 1952; Steinbrocker and others, 1952; Stephens and others, 1952; Davies and others, 1952). Although at present the mode of action of this drug remains unknown, it has been claimed to be an "anti-arthritis" and "anti-rheumatic" agent. The meaning of such terms would seem to be obscure in our present state of knowledge. No evidence has been produced that it acts *via* the pituitary-adrenal axis. Suggestions that Butazolidin is a more potent analgesic in rheumatic disease than in other painful conditions are not supported by more than clinical impressions: the assessment of the comparative effects of analgesics is extremely difficult. Steinbrocker and his colleagues (1952), in a blindfold clinical trial, concluded that its analgesic effect was greater than that of salicylates or amidopyrine in rheumatic conditions.

The clinical trials quoted were carried out on relatively large groups of patients and little detailed information is available as to the precise effects of Butazolidin on the various potentially reversible phenomena of rheumatoid arthritis. The present report describes a more detailed study of the effect of this drug on a small group of patients, using for comparison ACTH, a substance whose effect in reversing many of the clinical features of rheumatoid arthritis is well recognized. It would clearly be desirable to compare the effect of simple analgesics such as aspirin in the same manner, but such trials are time-consuming for the patient and this has not so far been possible. The difficulties of measuring the various features of rheumatoid arthritis are great. Clearly, no more than an approximation can be attempted in comparing the effects of two different agents.

Methods

Six patients with active rheumatoid arthritis, considered to have sufficient reversible features to enable therapeutic effects to be measured, were admitted to hospital. After a period of bed rest to allow a reasonably static state to be achieved (at least 2 weeks), they were treated with ACTH and Butazolidin. It was intended, from the long-term point of view, to treat these patients with Butazolidin, but it was felt desirable to compare the effects of ACTH and Butazolidin first, in order to obtain some assessment as to the suitability of Butazolidin for long-term treatment. In three cases ACTH was administered first, and in three cases Butazolidin first.

Dosage.—ACTH was given intramuscularly in divided doses of 100 mg./24 hrs for at least 5 days, the dose then being gradually tapered off to avoid, as far as possible, a rebound relapse. Butazolidin was given orally in doses of 600 to 800 mg./24 hrs for a minimum of 10 days. No other specific treatment was given.

Tests.—Features selected for measurement at regular intervals throughout the trial were as follows:

- Erythrocyte sedimentation rate (Westergren),
- Urinary output of 17-ketosteroids and glucocorticoids,
- Joint swelling and tenderness,
- Spontaneous pain,
- Power of grip,
- Speed of walking.

17-ketosteroids were determined by the standard Zimmerman-Callow method with correction for interfering chromogens (M.R.C. Committee on Clinical Endocrinology, 1951).

Corticosteroids were estimated as formaldehydogenic steroid with β -glucuronidase (Henly, 1952).

Joint swelling was measured by the method of Hart and Clark (1951).

Spontaneous pain and joint tenderness are impossible to measure accurately by ordinary clinical methods, but the amount of pain felt in a number of selected affected joints was roughly graded in three grades (Grade 1—slight, Grade 2—moderate, and Grade 3—severe). A total for a number of joints was thus arrived at.

Joint tenderness was divided into four grades (0—no tenderness, 1—slight tenderness, 2—wincing, 3—wincing

and withdrawal) judged by the response to firm digital pressure on the selected joints.

The grip test was carried out using a sphygmomanometer cuff inflated to 30 mm. Hg.

A second function test was carried out by the timing of a standard walk with a stopwatch.

Range of movement was excluded from this study, in view of the difficulty of obtaining accurate measurements and the absence of adequate relapses between trials.

Times of Testing.—Clinical experience has shown that in the doses used here, ACTH has a rapid effect. It was thought that Butazolidin might have a slower action, and for purposes of comparison, therefore, the response on the fourth to sixth day of ACTH therapy was compared with that on the fifth to tenth day of Butazolidin administration. When more than one assessment was carried out during these periods, the mean of the findings is taken.

Assessment.—Blindfold methods were not used, since one drug was administered by injection and the other by mouth, so that the difficulties of concealment to the patient and the observer alike were out of proportion to the need. With experienced assessors, the need for observer control is diminished; moreover, the assessments took place in a ward when other routine assessments of various drugs were being carried out, and it is doubtful whether the observers were, in fact, directly aware of the exact stage of the trial at any examination.

Placebo effects on the patient cannot be excluded, but with experienced handling these can be minimized, and both drugs had an equal chance of benefiting from such effects. The possibility that the patients were steadily improving throughout the trial, as a result of bed rest independent of the trial substances, must be borne in mind, since this might lead to misinterpretation of the results and to the assumption that both drugs had contributed equally to any improvement in the various criteria selected, whereas, in fact, both had been entirely ineffective.

If full relapse is achieved between each trial this is ruled out, but in practice only partial relapse was achieved in most cases. The degree of relapse is indicated in each analysis, and it will be seen that the amount of improvement during the first trial (independent of the drug used) exceeded the improvement indicated by comparing the assessments before treatment with those during the interval (i.e. relapse period), with the possible exception of the walking time. This trial, moreover, was not designed to establish whether Butazolidin has any effect, but to compare the effect of two different substances. The selection of ACTH for a comparison may be criticized, in view of its variable potency and the variable response of individuals to it (Kellgren and others, 1952). Cortisone was not, however, available, and the response to this is also variable. Whilst the fact that each drug was compared on the same patient does not obviate this difficulty entirely, it does exclude some variables such as the actual reversibility of the pathological changes of rheumatoid arthritis in any one case. Ansell and Bywaters (1952), using somewhat similar methods, have shown that

the activity of different batches of ACTH can be roughly assessed by clinical methods of this type. This has also been our experience of batches of ACTH of different potency provided by the Medical Research Council, and the reliability of the assessors in this trial has thus been confirmed.

Clinical Material

Particulars of the six patients with whom these experiments were carried out are shown in Table I.

TABLE I
CLINICAL MATERIAL

Case No.	Sex	Age	Duration of Disease	Erythrocyte Sedimentation Rate mm./hr (Westergren)	Order of Trial
1	F	53	7 yrs	26	ACTH/Butazolidin
2	F	54	1 yr	48	ACTH/Butazolidin
3	M	37	5 mths	36	ACTH/Butazolidin
4	F	28	3½ yrs	97	Butazolidin/ACTH
5	F	51	18 mths	100	Butazolidin/ACTH
6	F	53	6 wks	71	Butazolidin/ACTH

Case 1. Female, aged 53.—A fall in sedimentation rate occurred during ACTH administration from a pre-treatment mean of 26 to 7 mm./hr. Joint swelling was also diminished and there was slight loss of joint tenderness; spontaneous pain did not alter. The erythrocyte sedimentation rate rapidly rose on discontinuation of ACTH, and relapse occurred in 5 days. Joint swelling increased during Butazolidin administration, although spontaneous pain and joint tenderness decreased. There was no improvement in the grip test, but the walking time improved.

Case 2. Female, aged 54.—This patient showed the effect of ACTH on 17-ketosteroid excretion and glucocorticoid excretion. The 17-ketosteroid excretion increased from 9.6 to a maximum of 18.4 mg./24 hrs on the second day of treatment, with a subsequent fall. Glucocorticoid excretion rose from 14.9 and 8.4 mg./24 hrs to 44 mg./24 hrs on the second day, and again fell slowly. There was no similar change when Butazolidin was administered (Table III). The sedimentation rate also fell from 48 to 2 mm. in the first hour on the fifth day of ACTH administration. A fall also occurred during Butazolidin therapy from 28 to 8 mm. in the first hour on the fourth day of treatment. Diminution of joint tenderness and spontaneous pain occurred with both substances, and an improvement in function tests was also seen, but was more marked with ACTH.

Case 3. Male, aged 37.—This patient preferred Butazolidin to ACTH. A greater improvement occurred with Butazolidin in joint tenderness and spontaneous pain, and the grip test also showed more improvement with Butazolidin.

Case 6. Female, aged 53.—17-ketosteroid and glucocorticoid excretion were unaffected by Butazolidin, but showed a good response to ACTH (Table III). Loss of joint tenderness was greater with ACTH and spontaneous pain was reduced to a greater extent by Butazolidin. This was the only case in which a reduction in joint swelling was observed during Butazolidin treatment (Table IV).

Erythrocyte Sedimentation Rate (Table II).—The mean erythrocyte sedimentation rate before ACTH treatment was 64 mm./hr (Westergren), and before Butazolidin it was 59 mm./hr (Table II). During ACTH administration it fell to a mean of 35 mm., and during Butazolidin it fell to a mean of 52 mm./hr; the change occurring during ACTH administration is statistically significant ($t=5.373$, $P<0.01$). That occurring during Butazolidin therapy does not reach significance ($t=0.775$, $P>0.05$). This does not, of course, necessarily indicate that Butazolidin has no effect on the erythrocyte sedimentation rate. It indicates that the experiment is sufficiently sensitive in this respect to demonstrate the well-established effect of ACTH on the erythrocyte sedimentation rate in this disease, but offers no evidence that Butazolidin does as has been claimed by Currie (1952). The fall in erythrocyte sedimentation rate associated with this latter drug was much less than that produced by ACTH and within the limits which could occur by chance alone. The mean

Joint Swelling.—Four cases were suitable for measurement of joint swelling of proximal interphalangeal joints. Several joints were tested in each case and a total numerical reading was obtained. The total ring size during the trial can therefore be

Case No.	17-ketosteroid Excretion (mg./24 hrs)						Glucocorticoid Excretion (mg./24 hrs)					
	Mean of Control Values	Maximum Change						Mean of Control Values	Maximum Change			
		ACTH		Butazolidin		ACTH			Butazolidin			
		Value	±	Value	±	Value	±		Value	±		
2	9.6	18.4	+8.8	6.2	-3.4		11.2	44.0	+32.8	6.2	-5.0	
4	7.3	14.8	+7.3	4.4	-2.9		11.1	34.1	+23.0	7.0	-4.1	
5	4.5	5.4	+0.9	1.1	-3.4		—	—	—	—	—	
6	2.7	9.6	+6.9	1.2	-1.5		3.3	39.0	+35.7	5.9	+2.6	

compared. Of the four cases, two were treated with ACTH first and two with Butazolidin first. As shown in Table IV, a diminution was observed in every case during the ACTH trial, but during Butazolidin administration an increase in ring size was seen in two of the four cases. These findings should be viewed with caution however, since it is evident from a study of the total ring sizes before ACTH and before Butazolidin therapy that natural variations by this method are considerable and of the same order as the changes found during therapy. Full relapse was not achieved between trials, a mean diminution of 1.5 ring sizes occurring; these findings are therefore inconclusive.

TABLE IV
CHANGE IN TOTAL RING SIZE DURING ADMINISTRATION OF ACTH AND BUTAZOLIDIN

Case No.	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	42	39	-3	39	41	+2
3	41	38	-3	37	38	+1
5	34	32	-2	30	30	0
6	22	19	-3	25	23	-2

Mean ring size before { Trial 1 = 34.5 Difference = -1.5
 Trial 2 = 33

Subjective Changes

(1) *Spontaneous Pain*.—Table V shows the changes that occurred during ACTH and Butazolidin administration; these figures are arbitrary and too much reliance should not be placed on them. They represent no more than an attempt to estimate very roughly the amount of rest pain suffered by an individual patient, so that a comparative assessment of the "total pain" before and during treatment can be made. The "total pain" before each drug was administered was approximately the same, and this does suggest that a consistent estimate can be achieved. The reduction in pain with each substance was of the same order; the change in the figures alone is significant. (For ACTH $t=3.555$, $P<0.05$.

TABLE V
CHANGES IN SPONTANEOUS JOINT PAIN DURING ACTH AND BUTAZOLIDIN ADMINISTRATION

Case No.	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	6	6	0	6.5	5	-1.5
2	6	2	-4	4	3	-1
3	8.5	7	-1.5	8	5.5	-2.5
4	2	0	-2	3	0	-3
5	3	1.5	-1.5	4.5	2	-2.5
6	3	0	-3	7.5	1.5	-6
Mean	4.8	2.8	-2	5.6	2.8	-2.8

Mean spontaneous pain before { Trial 1 = 5.9 Difference = -1.5
 Trial 2 = 4.4
For ACTH, $t=3.555$; $0.01<P<0.05$
For Butazolidin, $t=3.914$; $0.01<P<0.05$

For Butazolidin, $t=3.914$, $P<0.05$.) Expressed as a percentage of total pain, ACTH reduced this to 58 per cent. of pre-treatment levels and Butazolidin to 50 per cent. Although only a 75 per cent. relapse was achieved between trials, these findings suggest that the effect of ACTH and Butazolidin on spontaneous pain was of much the same order.

(2) *Joint Tenderness*.—Table VI shows the changes that occurred in joint tenderness during the trial; in both cases a diminution is recorded during treatment of a comparable degree. The "total tenderness" before treatment with either substance is approximately the same, and the change in both cases is significant (for ACTH, $t=4.613$, $P<0.01$; for Butazolidin, $t=4.523$, $P<0.01$). Practically complete relapse (95 per cent.) was achieved in this test; ACTH reduced the joint tenderness to 62 per cent. of pre-treatment levels, and Butazolidin to 57 per cent.

TABLE VI
CHANGES IN JOINT TENDERNESS DURING ACTH AND BUTAZOLIDIN ADMINISTRATION

Case No.	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	5.5	4.5	-1	7.5	4	-3.5
2	10	5	-5	11	3	-8
3	11	8.5	-2.5	11	8	-3
4	4.5	2	-2.5	6	3	-3
5	11	8	-3	13.5	7.5	-6
6	8	2.5	-5.5	10	8	-2
Mean	8.3	5.1	-3.2	9.8	5.6	-4.2

Mean joint tenderness before { Trial 1 = 9.3 Difference = -0.5
 Trial 2 = 8.8
For ACTH, $t=4.613$; $P<0.01$
For Butazolidin, $t=4.523$; $P<0.01$

Function Tests

(1) *Grip Test*.—An analysis of the changes reveals essentially similar results to those found in the study of the subjective phenomena (Table VII). The increase in grip occurring during ACTH therapy does

TABLE VII
EFFECT OF ACTH AND BUTAZOLIDIN ON GRIP TEST (mm. Hg)

Case No.	Power of Grip (mm. Hg)					
	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	70	61	-9	63	63	0
2	88	185	+97	86	130	+44
3	126	141	+15	111	163	+52
4	180	208	+28	150	177	+27
5	62	66	+4	65	70	+5
6	64	73	+9	46	72	+26
Mean	98.3	122.3	+24	86.8	112.5	+25.7

Mean grip before { Trial 1 = 90.8 Difference = +3.7
 Trial 2 = 94.5
For ACTH, $t=1.555$; $P>0.05$
For Butazolidin, $t=3.058$; $0.01<P<0.05$

not, however, reach a significant level, although that during Butazolidin does. (For ACTH, $t=1.555$, $P>0.05$; for Butazolidin, $t=3.058$, $P<0.05$.) The mean change is much the same for the two substances and virtually complete relapse was achieved between trials (96 per cent.). A mean increase of 24 per cent. in the power of grip during ACTH, and of 30 per cent. during Butazolidin administration occurred.

(2) *Walking Time*.—One case was unsuitable for assessment by this test (Case 3). A constant improvement in walking time occurred during the administration of both substances (Table VIII). It is evident, however, that there was a marked failure to achieve relapse in this test between trials. The mean time before Trial 2 was 4.7 seconds better than before Trial 1 (Table VIII). This figure compares with mean improvements of only 5.5 seconds during Trial 1 and of 5 seconds during Trial 2. It would be unwise, therefore, to draw any comparison between ACTH and Butazolidin in respect of this test.

TABLE VIII
EFFECT OF ACTH AND BUTAZOLIDIN ON WALKING TIME (sec.)

Case No.	Time in Seconds					
	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	9.5	8	-1.5	11.5	8.5	-3
2	28	9	-19	12.5	9	-3.5
3	—	—	—	—	—	—
4	13.5	9	-4.5	21	13	-8
5	21.5	20	-1.5	19	14	-5
6	8	7	-1	13	7.5	-5.5
Mean	16.1	10.6	-5.5	15.4	10.4	-5

Mean walking time before { Trial 1 = 18.1 Difference = -4.7
 { Trial 2 = 13.4
Mean walking time on { Trial 1 = 10.3
 { Trial 2 = 10.7
Mean improvement during { Trial 1 = 7.8
 { Trial 2 = 2.7

Discussion

For purposes of comparison, these tests may be considered in the three groups shown above:

- (1) Erythrocyte sedimentation rate, steroid excretion, and joint swelling.
- (2) Subjective changes: spontaneous joint pain and tenderness.
- (3) Function tests: grip and walking.

(1) The response to the two drugs differs in that: ACTH produces a fall in erythrocyte sedimentation rate, a rise in 17-ketosteroid and glucocorticoid excretion, and a diminution in joint swelling, whereas Butazolidin cannot be shown to have any effect

on the erythrocyte sedimentation rate in this experiment; it has either no effect, or a depressing effect, on 17-ketosteroid and glucocorticoid excretion, and no effect on joint swelling.

(2) When subjective effects are assessed (though of necessity in an arbitrary manner), both drugs seem to have roughly the same effect.

(3) Both drugs also appear to have a comparable effect on function tests.

Although there is no evidence as to the effect of analgesics when assessed in this way, it would seem that Butazolidin has no effect which cannot be produced by an analgesic, at least over the short period in which it was administered in this trial. There is no evidence that it has a cortisone-like effect; it is impossible to judge from these tests whether it has an "anti-inflammatory" action, although the lack of evidence of diminution in joint swelling when administered for a short period does not suggest that it has. It must be emphasized that this study was in no way directly concerned with the use of either substance as practical therapy and that these observations were made simply on the short-term effects of the drugs on a few potentially reversible phenomena of rheumatoid arthritis. Nor was this study concerned with the anti-pyretic or toxic effects of either substance. No toxic reactions were, in fact, observed during the trial.

Conclusions

ACTH and Butazolidin have different effects on steroid excretion. No evidence was found that Butazolidin reduces the erythrocyte sedimentation rate when given for a short period, although ACTH given for a shorter period, produced a definite fall. No evidence was found of reduced joint swelling during Butazolidin administration. Pain and function are favourably influenced by both substances to approximately the same degree.

Summary

Six cases of rheumatoid arthritis were studied in detail to observe the comparative effects of ACTH and Butazolidin. There is no evidence that Butazolidin has a cortisone-like effect, but it appears to be roughly comparable to ACTH in its effect on the features of rheumatoid arthritis in which pain is an important element.

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Effets comparés de l'ACTH et de la butazolidine dans l'arthrite rhumatismale

RÉSUMÉ

On étudia minutieusement six cas d'arthrite rhumatismale pour y comparer les effets de l'ACTH et de la butazolidine. On n'a pas pu démontrer que l'effet de la butazolidine soit similaire à celui de la cortisone, mais il semble que cet effet est assez comparable à celui de l'ACTH quand il s'agit de manifestations arthritiques dans lesquelles la douleur constitue un élément important.

Efectos comparados de la ACTH y de la butazolidina en la artritis reumatoide

SUMARIO

Se estudió detalladamente seis casos de artritis reumatoide con el fin de comparar los efectos de la ACTH y de la butazolidina. No hubo pruebas de que el efecto de la butazolidina sea similar al de la cortisona, pero parece que este efecto asemejase bastante al de la ACTH respecto a las manifestaciones artríticas en las cuales el dolor constituye un elemento importante.