An attempt at combining corticotrophin with long-term corticosteroid therapy

With a view to preserving hypothalamic-pituitary-adrenal function

MARY E. CARTER AND V. H. T. JAMES

From St. Mary's Hospital and the Department of Chemical Pathology, St. Mary's Hospital Medical School, London

It is generally accepted that the majority of patients treated with corticosteroids develop pituitary-adrenal suppression within a few days of starting treatment with daily doses equivalent to 7.5 mg. or more of prednisolone, but it is recognised that various patients show individual susceptibility.

In contrast, it has been shown by others, for example (Bacon, Daly, Myles, and Savage, 1968), as well as ourselves (Carter and James, 1970a) that patients treated with long-term daily doses of corticotrophin invariably retain their hypothalamic-pituitary-adrenal (HPA) responsiveness to stress as judged by tests employing insulin hypoglycaemia as the stressor. We showed that patients receiving therapeutically effective doses of corticotrophin (ACTH) equivalent to 7.5 mg. to 15 mg. prednisolone daily maintained stress responsiveness even when therapy extended well over 2 years.

In patients with rheumatoid and other similar chronic diseases, where steroids or ACTH are reserved for those in whom all other forms of treatment have been tried and have failed to control symptoms, it is nearly always necessary to administer those drugs daily. In the case of ACTH, a daily injection is involved which is disadvantageous from the points of view both of discomfort and of difficulty of self-administration due to physical disability in some cases; dependence on a daily visit from a District Nurse may also be an inconvenience, especially for those who go out to work.

This study was therefore planned to see whether a therapeutically effective regime combining oral corticosteroids with injections of ACTH could be devised which would reduce the number of injections of ACTH per week to the minimum necessary to maintain HPA responsiveness, in the presence of corticosteroids. As in the previous study of patients on ACTH (Carter and James, 1970a), responsiveness to stress has been tested over extended periods of

treatment in order to detect any changes which might develop with prolonged treatment, and to eliminate as far as possible individual patient variability.

Material

A series of eighteen patients was studied, twelve women and six men. Some of them took part in two or even three treatment regimes. Their ages ranged from 13 to 66 years at the start of the trial (mean 53 years). Fifteen have classical rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) and three psoriatic arthropathy. The mean duration since the onset of disease is 6 years (range 1 to 16).

Method

Six different combinations of ACTH and steroids were planned and patients were maintained on one of these regimes for as long as it proved therapeutically effective. Doses were chosen to suit individual needs, and were adjusted if necessary without changing the proportion of ACTH to prednisolone.

GROUP 1 (Cases 1 to 5)

ACTH in one large dose of 80 units once a week.
Prednisolone daily, mean dose 12 mg./day.

GROUP 2 (Cases 2, 5, 6 to 8)

ACTH in one large dose of 80 units twice weekly.
Prednisolone daily, mean dose 12 mg./day.

GROUP 3 (Cases 9 to 11)

ACTH 1 day in 3, mean dose 30 units/day.
Prednisolone on the 2 remaining days out of 3, mean dose 10 mg./day.

GROUP 4 (Cases 5, 11, 12)

ACTH on alternate days, mean dose 25 units/day.
Prednisolone on alternate days, mean dose 6 mg./day.

GROUP 5 (Cases 13 and 14)

ACTH 2 days in 3, mean dose 35 units/day.

Prednisolone on the 1 remaining day out of 3, mean dose 7.5 mg./day.

GROUP 6 (Cases 6 to 8, 15 to 17)

ACTH every day, mean dose 15 units/day.

Prednisolone every day, mean dose 10 mg./day.

All patients had received previous treatment with salicylates and one or more additional anti-inflammatory drugs, and in most cases these were continued when steroids or ACTH or both were introduced in order to restrict the dosage of the two latter drugs to the minimum. Some patients had already been receiving steroid therapy when they entered the trial of combined therapy. The patients were all admitted to hospital for the first few weeks of combined treatment in order to assess their responses to treatment, to balance the doses of both drugs, and to make sure that they learned their own drug routine and that they could be relied upon to continue it at home correctly. Tests of pituitary-adrenal function were carried out in hospital, and were repeated regularly on patients who returned to the ward for half-day visits.

The corticosteroid used was enteric-coated prednisolone, 'Delta Cortril' (Pfizer). Various types of corticotrophin were given: 'Acthar Gel' (Armour), 'ACTH/cmc' (Crookes), 'Cortrophin ZN' (Organon), and 'Cortrosyn' (Organon). In every case the intramuscular route was used for the injection of ACTH.

The following tests were performed as described elsewhere:

Insulin stress test (Greenwood, Landon, and Stamp 1966).

Lysine-8-vasopressin test (Brostoff, James, and Landon, 1968).

Plasma cortisol: This was estimated by an automated fluorimetric technique (Townsend and James, 1968).

Results**INSULIN HYPOGLYCAEMIA**

Figures 1 to 6 show the results of serial insulin stress tests carried out in the six different treatment

groups. The graphs for each individual patient show the resting level of plasma cortisol and the maximum level attained during hypoglycaemia connected by a line. The doses of ACTH and prednisolone and the variations in combinations of the drugs are given at the foot of each graph. The duration of treatment when the tests were performed is shown above each graph in weeks. The criteria for a normal test were a resting plasma cortisol level of at least 5 $\mu\text{g./100 ml.}$, an increment of at least 7 $\mu\text{g./100 ml.}$, and a maximum stimulated level of at least 20 $\mu\text{g./100 ml.}$

Since one of our objectives was to reduce the frequency of ACTH injections to the minimum compatible with preservation of HPA function, our first patients were started on a regime which required only one injection of ACTH per week. Fig. 1 shows the results in five patients treated in this group for a mean period of 7 months. There is considerable variation in individual response from one patient to another, and from time to time in each patient, but none produced a normal test except Case 2, that of a man aged 56 whose test at 6 months fulfilled all normal criteria. The last recorded tests of the other patients at the same stage as the normal test of Case 2 or later, were all considerably subnormal.

As some of the tests were subnormal but showed by no means total suppression, the next logical step seemed to be to increase the proportion of ACTH to steroids by giving ACTH in two large doses per week, while daily steroids were continued (Fig. 2). These patients have been followed for shorter periods, but none showed a normal response. The patient whose last test in Group 1 was normal (Case 2) showed a slightly poorer response with two injections per week of ACTH instead of one.

Treatment Groups 3, 4, and 5 were next designed.

FIG. 1 Group I. Serial plasma cortisol responses to insulin hypoglycaemia in five patients receiving intramuscular ACTH once a week and oral prednisolone daily. Doses in u./day and m./day respectively shown at foot of each graph.

Oblique lines show maximum increment in plasma cortisol for each test, measured in $\mu\text{g./100 ml.}$ (ordinate). Tests were carried out at intervals, shown above the graph in weeks.

Treatment with daily ACTH/prednisolone before this study is shown in the left-hand column.

Case 5 had transferred from ACTH and prednisolone on alternate days after 42 weeks.

FIG. 2 Group II. Serial plasma cortisol responses to insulin hypoglycaemia in five patients receiving intramuscular ACTH twice a week and oral prednisolone daily.

Case 6 had transferred from ACTH and prednisolone daily. Cases 2 and 5 had transferred from ACTH once a week and prednisolone daily.

ACTH was given more frequently than in Groups 1 and 2, but in doses approximately equivalent to the steroid dose, as a replacement for the steroid on certain days rather than in addition to it.

Fig. 3 shows results in three patients given ACTH 30 units/day on 1 day out of 3, and prednisolone 10 mg. on each of the remaining 2 days out of 3. Case 10 and Case 11 showed subnormal responses, which in Case 11 (surprisingly) were depressed below the response he had given previously when he was taking 5 mg./day only. Case 10 showed further diminution of response when the dose of ACTH was increased from 30 to 40 units.

The effect of giving ACTH and steroids on alter-

nate days (Fig. 4) eventually produced subnormal results in all three patients tested after what seemed a more promising maintenance of an intact HPA system in the first few weeks of treatment.

In two patients (Fig. 5, overleaf), the amount of ACTH compared with steroids was increased, ACTH being given on 2 days out of 3, with steroid on the within a few weeks.

In the final group (Fig. 6, overleaf), in which ACTH was given daily with steroids (a system which would in any case defeat one of the objects of the study, viz. the sparing of the patients from daily injections), none of the patients tested produced a normal response.

FIG. 3 Group III. Serial plasma cortisol responses to insulin hypoglycaemia in three patients receiving intramuscular ACTH one day in every three, and oral prednisolone on the remaining two days in every three.

FIG. 4 Group IV. Serial plasma cortisol responses to insulin hypoglycaemia in three patients receiving intramuscular ACTH and oral prednisolone on alternate days.

Case 11 had transferred from ACTH one day in 3 and prednisolone 2 days in 3.

FIG. 5 Group V. Serial plasma cortisol responses to insulin hypoglycaemia in two patients receiving intramuscular ACTH two days in every three and oral prednisolone on the third day.

FIG. 6 Group VI. Serial plasma cortisol responses to insulin hypoglycaemia in six patients receiving both intramuscular ACTH and oral prednisolone daily. Cases 7 and 8 had transferred from ACTH twice a week and prednisolone daily.

Table Comparison of plasma cortisol response to insulin stress test and to lysine vasopressin in patients receiving combined corticotrophin and corticosteroid therapy.

Resting level and mean stimulation level shown in parentheses together with increment achieved during test.

Patient no.	Age (yrs)	Sex	Group	Test	Period on steroids (wks)	Periods on ACTH (wks)									
5	38	F	IV		203/4	8	15	19	27	30	36	42	57		
				IST		+23 (3-26)	+9 (11-20)	+11 (9-20)	+12 (3-15)	+6 (20-26)	+3 (9-12)	+6 (9-15)	+3 (8-11)	+9 (3-12)	
				LVP		-1 (5-4)	-1 (5-4)	-1 (5-4)	-3 (12-9)	-1 (5-4)	+1 (6-7)	+2 (5-7)	0 (4-4)		
9	48	F	III		78	2	11	16	21	39	93				
				IST		+8 (4-12)	+13 (6-19)	+22 (8-30)	+13 (4-17)	+20 (9-29)	+18 (3-21)	+14 (10-24)			
				LVP						+6 (10-16)	-4 (13-9)				
12	54	F	IV		156/3	7	12	16	25	39	58				
				IST		+6 (7-13)	+20 (9-29)	+14 (22-36)	+4 (16-20)	+4 (3-7)	0 (13-13)	+1 (2-3)			
				LVP				-3 (19-16)	-1 (9-8)	+7 (4-11)	+3 (7-10)	+3 (2-5)			
11	48	M	III		78	3	6	10	16	} same case					
				IST		+14 (3-17)	+12 (3-15)	+2 (10-12)	+4 (6-10)						
				LVP					+6 (6-12)						
			IV			8									
				IST											
				LVP											
						+4 (10-14)									
						+1 (16-17)									

Group IV ACTH/steroid on alternate days Group III ACTH 1 day, steroid 2 days IST = Insulin stress test LVP = Lysine vasopressin test

have been expected to offer certain advantages. Thus, when steroid therapy is terminated, the limiting step in the rate of recovery of HPA-function may be the reversal of adrenocortical atrophy; if such atrophy can be avoided (by ACTH administration), faster restoration of normal HPA function might be expected. Secondly, although apparently uncommon, it appears that prolonged treatment with corticosteroids may produce a state of permanent or prolonged adrenocortical dysfunction in which the gland fails to respond even to massive stimulation with ACTH (El-Shaboury, 1966); maintenance of adrenocortical function may be advantageous in avoiding the development of this situation. Thirdly, since patients receiving prolonged ACTH therapy appear to enjoy relatively undisturbed HPA function (Bacon and others 1968; Carter and James, 1970a), it is theoretically possible that combined therapy might confer similar advantages.

In earlier studies, Young, De Filippis, Meyer, and Wolfson (1957) had concluded that, when ACTH was given once a week to steroid-treated patients, at least 200 units were needed to maintain adrenal responsiveness. Nevertheless, our initial investigations, although limited in number, showed that combined treatment with ACTH and corticosteroids appeared to maintain adrenocortical responsiveness when as little as 100 units ACTH per week were given in divided doses through the week. Moreover, Young and others (1957) made no attempt to investigate their patients' ability to produce endogenous ACTH in response to stress, so that HPA function in these patients cannot be defined. In the study presented here, our objective has been to attempt to preserve function by combined treatment, and the response to hypoglycaemia has been used as an index of the integrity of the HPA axis.

The results are disappointing in that this objective could not apparently be achieved by any combination of ACTH and steroids which would be an improvement over giving ACTH alone. The only exception was one 50-year-old woman, Case 9 (Fig. 3), who has been successfully treated with ACTH 1 day in 3 and steroids 2 days in 3 for well over 3 years. Apart from one marginally subnormal test, she has shown excellent responses over a prolonged period, all of which were an improvement on her response when receiving daily prednisolone before the introduction of ACTH into her regime. This patient, who is now 53 years old, has severe active rheumatoid arthritis, with L.E.-cells present from time to time and evidence of vasculitis, who has nevertheless managed exceptionally well. She has had no alteration in dosage and has not once missed her 3-day routine since she started in January, 1967, continuing on holidays abroad and visits from home

in this country. This one patient has demonstrated the ideal result, but unfortunately she is the exception, and it is not at all obvious why combined therapy has failed in all the others.

Attempts to combine ACTH and corticosteroid therapy in most patients rapidly produce loss of pituitary-adrenal reserve, even when steroids are given on only 1 day in 3 (Fig. 3). Moreover, the impression soon developed during this study that the combination of ACTH with steroids causes an even greater degree of pituitary-adrenal suppression than steroids given alone; that is, there appears to exist some type of synergism. Case 13 (Fig. 5), a woman aged 33, who produced an excellent stress response after she had received ACTH 50 units/day for 3 months, rapidly lost her ability to respond to stress when only 7.5 mg. prednisolone were substituted for ACTH every third day. Although her adrenal glands would undoubtedly be hypertrophied, a circumstance which would lead one to suppose that she would be in a good position to withstand the effect of a small intermittent dose of steroids, a total of 100 units of ACTH over 2 days was unable to counteract the effect of 7.5 mg. prednisolone every third day.

Although, from the point of view of achieving a better therapeutic deal for patients, the scheme has failed, some unexpected facts have emerged which may eventually contribute towards unravelling the basic problem why patients on ACTH retain HPA responsiveness, at least to the stress of insulin-induced hypoglycaemia, and to surgery (Carter and James, 1970b). Our results suggest that the practice adopted by many physicians of giving occasional doses of ACTH to patients on steroids to improve adrenocortical function and to protect them from adrenal suppression may cause more marked HPA suppression than do steroids alone. Thus, there no longer seems to be any point in adding ACTH while weaning patients off steroids, —although, in our experience, one can quickly obtain excellent plasma cortisol responses by converting completely to ACTH. As pointed out above, the results of El Shaboury (1966) suggest that steroid-treated patients may sometimes fail to respond subsequently to ACTH, and biochemical control of such situations would seem to be highly desirable.

The clinical experience of treating patients on these mixed schedules was not unduly difficult, because they all started this treatment in hospital, where the reasoning behind the scheme was explained to each of them and they were supervised in handling their drugs and learning the routine until it was certain they could cope at home. Those who could do so injected the ACTH themselves, and the District Nurse attended the few others. By

using approximately equivalent doses of steroids and ACTH, calculated from our own data on urinary excretion of 17-hydroxycorticosteroids measured over prolonged periods and correlated with clinical efficacy, it was found that patients usually noticed little symptomatic difference between the ACTH days and the steroid days; there was a tendency towards a preference for the ACTH days in some, although few wanted to continue the ACTH injections once it had been explained to them that they did not offer the advantage we anticipated. Most patients, even on the moderate doses of ACTH given to Groups 3, 4, 5, and 6, suffered from oedema, requiring diuretics and large potassium supplements, and most, though tolerating the injections, disliked them however frequently or infrequently they were given.

We hope to discuss more fully elsewhere our clinical experience in the management of chronic rheumatic diseases with ACTH.

In conclusion, therefore, it seems as if we have eliminated all practical therapeutic combinations of ACTH and corticosteroids as a means of treating patients with corticosteroids without loss of pituitary-adrenal reserve.

Contrary to previous unsubstantiated supposition,

ACTH in conjunction with corticosteroids seems to increase rather than diminish the suppressive effect on the HPA system. We suggest, therefore, that the practice of giving 'booster' doses of ACTH to patients on steroids should be discontinued.

Summary

In the expectation that corticotrophin (ACTH) given in conjunction with corticosteroids would protect hypothalamic-pituitary-adrenal responsiveness to stress, which would otherwise be lost in patients receiving corticosteroids alone, a series of rheumatoid patients was treated with six different combinations of the two drugs. None of these combinations produced the desired results; in fact, it seems as if ACTH in conjunction with corticosteroids increases the suppressive effect on the hypothalamic-pituitary-adrenal system.

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References

- BACON, P. A., DALY, J. R., MYLES, A. B., AND SAVAGE, O. (1968) *Ann. rheum. Dis.*, **27**, 7 (Hypothalamo-pituitary-adrenal function in patients on long-term adrenocorticotrophin therapy).
- BROSTOFF, J., JAMES, V. H. T., AND LANDON, J. (1968) *J. clin. Endocr.*, **28**, 511 (Plasma corticosteroid and growth hormone response to lysine-vasopressin in man).
- CARTER, M. E., AND JAMES, V. H. T. (1970a) *Ann. rheum. Dis.*, **29**, 73 (Effect of corticotrophin therapy on pituitary-adrenal function).
- , — (1970b) *Lancet*, **1**, 328 (Pituitary-adrenal response to surgical stress in patients receiving corticotrophin treatment).
- EL-SHABOURY, A. H. (1966) *Brit. med. J.*, **2**, 1478 (Adrenal failure complicating status asthmaticus in steroid-treated patients).
- GREENWOOD, F. C., LANDON, J., AND STAMP, T. C. B. (1966) *J. clin. Invest.*, **45**, 429 (The plasma sugar, free fatty acid, cortisol and growth hormone response to insulin: I. In control subjects).
- ROPES, M. W., BENNETT, G. A., COBB, S., JACOX, R., AND JESSAR, R. A. (1959) *Ann. rheum. Dis.*, **18**, 49 (Diagnostic criteria for rheumatoid arthritis. 1958 revision).
- TOWNSEND, J., AND JAMES, V. H. T. (1968) *Steroids*, **11**, 497 (A semi-automated fluorimetric procedure for the determination of plasma corticosteroids).
- YOUNG, I. I., DE FILIPPIS, V., MEYER, F. L., AND WOLFSON, W. Q. (1957) *Arch. intern. Med.*, **100**, 1 (Maintenance of adrenal cortical responsiveness during prolonged corticoid therapy).