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Comparison of Depot Tetracosactrin and Corticotrophin Gel

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Summary: Depot tetracosactrin has been compared with corticotrophin gel in 12 inpatients of a rheumatic diseases unit. Every patient received one subcutaneous injection each of the synthetic and the animal preparation, with serial measurements of plasma 11-hydroxycorticosteroids, 12-hourly urinary 11-hydroxycorticosteroids, and 17-oxogenic steroids. The duration of action of the depot tetracosactrin was virtually twice that of corticotrophin gel, the dose relationship being about 0.25 mg. of depot tetracosactrin to 50 units of gel. Local reaction to the injection of depot tetracosactrin was relatively frequent.

Introduction

The first report of synthetic polypeptides with corticotrophin-releasing activity came from Kappeler and Schwyzer (1960). Subsequently these authors (1961) described the preparation of a synthetic polypeptide (Synacthen) in crystalline form which was highly soluble in water and rapidly absorbed after intramuscular injection. Landon *et al.* (1964) showed that infused Synacthen (tetracosactrin) increased both plasma cortisol levels and urinary 17-ketosteroids and 17-hydroxycorticosteroids (17-OHCS). The synthetic preparation caused no sensitivity reaction in two patients sensitive to animal corticotrophin. Tetracosactrin consists of the first 24 amino-acids found in the 39 amino-acid chain of animal corticotrophin. It has a high degree of activity lasting one and a half to three hours by intramuscular injection. Since 1967 a long-acting preparation of

tetracosactrin adsorbed on to an inorganic zinc complex has been on trial. Besser *et al.* (1967) and Nelson *et al.* (1968) reported the effect of depot tetracosactrin on plasma 11-hydroxycorticosteroids (11-OHCS). We describe here our experience of this substance with both plasma and urinary steroids as criteria, our aim being to assess biochemical and clinical effects in comparison with corticotrophin gel.

Patients and Methods

There were 12 subjects, 11 with rheumatoid disease and 1 with gout. All were hospital inpatients with clinical disease activity, so that therapeutic observations were possible. No patient had ever previously been treated with corticosteroids or corticotrophin. In every case the proposed investigation was fully explained to the patients, their approval to proceed being obtained. Administration of depot tetracosactrin and corticotrophin gel was subcutaneously, as this is the only feasible route for self-administration should long-term therapy be required.

Studies in each case covered six days with 12-hourly urine collections from 9 a.m. to 9 p.m. and from 9 p.m. to 9 a.m. throughout. Corticotrophin was administered at 9 a.m. on Day 2 and Day 5, every patient receiving one dose of depot tetracosactrin and one dose of corticotrophin gel. During the course of the trial three dose levels of tetracosactrin were used: 1, 0.5, and 0.25 mg. Corticotrophin gel was assessed at two-dose levels: 50 and 25 units. Half the patients received tetracosactrin on Day 2 and corticotrophin gel on Day 5. The remaining patients received their injections in the reverse order. Plasma 11-OHCS (Mattingly, 1962) were determined in each

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TABLE I.—Plasma 11-OHCS Expressed as $\mu\text{g./100 ml.}$ Related to Time of Day. Corticotrophin (A.C.T.H.) was Administered at 9 a.m. on Day 2 and Day 5

Case No.	Age	Sex	Day 1 9 a.m.	Day 2					Day 3 9 a.m.	Day 4 9 a.m.	Day 5					Day 6 9 a.m.		
				A.C.T.H.		9 a.m.	1 p.m.	5 p.m.			9 p.m.	A.C.T.H.		9 a.m.	1 p.m.		5 p.m.	9 p.m.
				Type	Dose							Type	Dose					
1	56	M	16	TCA	1 mg.	18	76.8	36	32.5	64	53.3	Gel	25 units	16	57	66.5	35.5	59.5
2	68	F	19	TCA	1 mg	20	72	95	—	64	9	Gel	50 units	14	41.3	44.5	28	—
3	45	M	17.5	TCA	0.5 mg.	18	38.5	59.5	51	47	15	Gel	25 units	19	44.5	34	12	20.5
4	54	M	6.5	TCA	0.5 mg.	6	78	87	89	90	24	Gel	50 units	35	71	55	53	10
5	50	F	9.5	TCA	0.25 mg.	31	59	62	44.5	41	33	Gel	25 units	37	45	47	32	25
6	52	F	15	TCA	0.25 mg.	19.5	55	56	65	54	20	Gel	50 units	35	52.5	48	20	2
7	61	F	7	Gel	25 units	17.5	77.5	85	67	16	20	TCA	1 mg.	26	96	93	133	120
8	68	F	2	Gel	50 units	2	55.5	71	44.5	2	8	TCA	1 mg.	20	36	64	52	55
9	54	F	7	Gel	25 units	9	70	40.5	21.5	2	2	TCA	0.5 mg.	2	43	45	54	49
10	60	F	17.5	Gel	50 units	23.5	63	79	47	14	26.5	TCA	0.5 mg.	18.5	62	75	67	68.5
11	76	M	21.5	Gel	25 units	13	50	49	32	7.5	24	TCA	0.25 mg.	14	70	81	69	34
12	50	M	21	Gel	50 units	27	66.5	40	33.5	20	37	TCA	0.25 mg.	31	55	48	81	49

TCA = Depot tetracosactrin. Gel = Corticotrophin gel.

case at 9 a.m. on Days 1, 3, 4, and 6, and at 9 a.m., 1 p.m., 5 p.m., and 9 p.m. on Days 2 and 5. The 12-hour urinary excretion of 11-OHCS (Mattingly *et al.*, 1964) and 17-oxo- and 17-oxogenic steroids (17-OGS) (Appleby *et al.*, 1955) was also measured.

Results

Biochemical Observations

The findings in Case 6 are depicted (Fig. 1) illustrating the form of each case study. Neither plasma nor urinary steroid measurements showed any significant or consistent advantage attached to the order of administration, whether it be the first or the second injection. It is not proposed, therefore, to consider this aspect further.

FIG. 1.—Case 6. Findings illustrating the time relationship between corticotrophin (A.C.T.H.) injections, blood samples, and urine collections. Each day starts at 9 a.m. TCA=tetracosactrin depot.

As three dose levels of depot tetracosactrin and two dose levels of corticotrophin gel were used it is apparent that four patients had the same dose of the synthetic preparation and six patients the same dose of corticotrophin gel. Table I records the details of plasma 11-OHCS in each case studied, together with the age and sex, and the type and dosage of corticotrophin. Individual 12-hour urinary 11-OHCS findings are given in Table II. When the mean plasma 11-OHCS levels for each dose are calculated (Fig. 2), it can be seen that following corticotrophin gel the levels of these steroids fall rapidly towards the baseline after 12 hours, reaching basal values in

24 hours after 25 units, and have almost reached baseline in 24 hours after 50 units. Plasma 11-OHCS levels, however, remain high 24 hours after the injection of the synthetic preparation in a dose as low as 0.25 mg., and may still be a little raised after 48 hours, at least with a dose of 1 mg.

FIG. 2.—Mean plasma 11-OHCS at each dose level of depot tetracosactrin (TCA) and corticotrophin gel (GEL) on a time scale of 72 hours.

It is apparent from the mean urinary 11-OHCS (Fig. 3) that following 1 mg. of depot tetracosactrin the 11-OHCS response increases to a maximum at 24 to 36 hours, during which period the output is nine times that following 50 units of corticotrophin gel. If no allowance is made for individual baseline variation, the output of 11-OHCS following 0.25 mg. of depot tetracosactrin is similar to that following the injection

FIG. 3.—Mean urinary 11-OHCS ($\mu\text{g./12 hours}$) following depot tetracosactrin (TCA) at three dose levels, and corticotrophin gel (GEL) at two dose levels.

TABLE II.—Urinary 11-OHCS Expressed as $\mu\text{g./12 Hours}$ for Both Collection Periods of All Six Days in Every Patient Assessed. Corticotrophin was Administered at 9 a.m. on Day 2 and Day 5

Case No.	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6	
	9 a.m.—9 p.m.	9 p.m.—9 a.m.	9 a.m.—9 p.m.	9 p.m.—9 a.m.	9 a.m.—9 p.m.	9 p.m.—9 a.m.	9 a.m.—9 p.m.	9 p.m.—9 a.m.	9 a.m.—9 p.m.	9 p.m.—9 a.m.	9 a.m.—9 p.m.	9 p.m.—9 a.m.
1	1,345	742	3,290	3,090	3,500	1,028	1,420	1,100	4,650	1,140	1,162	960
2	275	625	1,170	3,000	2,400	1,190	432	705	1,380	870	370	450
3	385	335	2,210	2,580	1,270	415	370	285	1,860	235	164	56
4	1,960	2,850	3,900	5,370	602	1,780	440	273	6,000	2,760	201	405
5	388	380	2,150	1,315	608	502	398	755	2,030	2,130	3,220	1,745
6	258	258	2,400	1,620	905	387	538	224	2,670	1,360	326	368
7	77	124	1,320	780	110	140	312	109	3,070	4,090	4,580	1,390
8	198	198	147	445	449	448	130	56	1,340	2,040	830	1,560
9	354	285	1,335	111	283	336	569	440	2,580	2,620	1,180	580
10	173	101	910	480	560	112	90	99	865	1,030	634	236
11	100	41	450	227	114	152	435	260	560	633	230	221
12	280	372	1,840	800	500	221	482	304	3,200	2,540	1,000	210

of 50 units of corticotrophin gel. It is noted that the mean baseline urinary 11-OHCS were raised in the subjects receiving 0.5 and 0.25 mg. of tetracosactrin. This occurred in the

FIG. 4.—Mean urinary 11-OHCS ($\mu\text{g./12 hours}$) with allowance for individual baseline variation (TCA=tetracosactrin depot; GEL=corticotrophin gel).

FIG. 5.—Mean urinary 17-OGS (mg./12 hours) following depot tetracosactrin (TCA) at three dose levels, and corticotrophin gel (GEL) at two dose levels.

presence of normal values for plasma 11-OHCS. Possible reasons for these raised urinary steroid values are spurious background fluorescence due to bacteria and the undisclosed presence of certain drugs—for example, dibenzanthracene in laxatives. The normal urinary 17-OGS levels in these subjects would suggest interference with the urinary 11-OHCS determinations.

When individual baseline levels are subtracted before the urinary 11-OHCS are averaged, the resulting histogram (Fig 4) discloses the differences between the two preparations in a more obvious way, though 1 mg. of depot tetracosactrin produces an appreciably greater response than 50 units of corticotrophin gel, lasting a full 48 hours.

FIG. 6.—Mean urinary 17-OGS (mg./12 hours) with allowance for individual baseline variation (TCA=tetracosactrin depot; GEL=corticotrophin gel).

The major part of the urinary 17-OGS response following corticotrophin gel occurs within the first 24 hours (Fig. 5), the levels at 24 to 36 hours approaching the baseline after 25 or 50 units. After all three strengths of depot tetracosactrin the 24- to 36-hour levels of 17-OGS are still raised, and after 1 mg. the 36- to 48-hour level is still four times that of the baseline. Individual values for each collection are recorded in Table III.

TABLE III.—Urinary 17-OGS Expressed as mg./12 Hours for Both Collection Periods of All 6 Days in Every Patient Assessed. Corticotrophin was Administered on Day 2 and Day 5

Case No.	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6	
	9 a.m.—9 p.m.	9 p.m.—9 a.m.	9 a.m.—9 p.m.	9 p.m.—9 a.m.	9 a.m.—9 p.m.	9 p.m.—9 a.m.	9 a.m.—9 p.m.	9 p.m.—9 a.m.	9 a.m.—9 p.m.	9 p.m.—9 a.m.	9 a.m.—9 p.m.	9 p.m.—9 a.m.
1	11.5	7.3	32.5	21.8	38.5	23.6	16.8	8.5	27.5	29.5	12.0	20.0
2	8.5	7.5	9.9	45.0	35.0	38.2	12.2	12.5	19.4	25.6	7.6	7.5
3	11.3	11.2	35.7	19.5	39.0	16.4	20.9	7.3	14.7	12.0	20.8	5.5
4	21.8	5.9	92.5	75.5	107.0	22.9	23.1	13.9	78.0	60.0	11.2	18.8
5	10.1	15.1	53.0	36.6	14.8	10.8	18.8	15.2	48.3	24.5	8.5	11.7
6	18.5	10.3	37.0	50.5	33.0	12.7	14.2	12.1	43.5	29.0	10.4	8.5
7	3.5	4.5	31.0	30.5	13.1	7.6	9.0	4.3	53.7	103.0	94.0	68.5
8	10.6	7.9	19.4	24.2	34.6	9.6	12.6	10.8	32.4	27.1	26.2	6.6
9	7.9	6.9	19.0	11.6	11.4	9.2	9.4	8.7	19.8	39.2	20.5	11.3
10	7.1	6.9	17.2	10.6	11.9	12.4	7.9	28.4	41.8	30.8	16.5	12.0
11	7.7	9.3	14.7	13.7	8.9	10.8	10.8	11.2	18.2	47.0	27.5	14.5
12	14.6	17.6	36.8	28.3	19.6	15.0	23.5	13.4	41.1			

After subtraction of individual baseline levels the data on urinary 17-OCS (Fig. 6) show a similar response after 0.25 mg. of depot tetracosactrin to that after 50 units of corticotrophin gel, the higher doses of the synthetic preparation again producing a more sustained effect.

Clinical Observations

Reactions with subcutaneous administration of both preparations were not infrequent, occurring in 5 of the 12 cases following depot tetracosactrin and in 2 of 12 cases after corticotrophin gel. In every case reactions took the form of local erythema and pruritus lasting from a few hours to about two days. None was severe. In one instance corticotrophin gel was subsequently continued long-term without difficulty.

The effect of both preparations on disease manifestations did not appear to differ one from the other, apart from duration of response. There is a wide variability of dose-response among individuals to long-acting corticotrophin, so that the numbers in this series are too few to draw significant conclusions regarding the clinical dose relationship between the two preparations. Nevertheless, in every instance in which a significant clinical response to both injections occurred, that following depot tetracosactrin was sustained longer than that following corticotrophin gel.

Discussion

In terms of maximum plasma cortisol concentration Besser *et al.* (1967) concluded that 1 mg. of the synthetic preparation is equivalent to about 80 units of corticotrophin gel, both doses stimulating the adrenal glands maximally, but that the gel must be given twice daily and depot tetracosactrin once daily to maintain stimulation. There can be little doubt that the latter substance has a distinctly greater duration of action. In a dose of 1 mg. adrenal stimulation lasts 48 hours, implying that, in this dosage at least, injections every two days should suffice. In regard to the relative degree of adrenal stimulation, our results suggest that 0.25 mg. of depot tetracosactrin is equivalent to about 50 units of corticotrophin gel by the subcutaneous route.

It is open to question whether the prolonged action of depot tetracosactrin will prove to be an advantage in long-term corticotrophin therapy. Nichols *et al.* (1965) have shown that

corticosteroids administered at night cause a significantly longer suppression of pituitary-adrenal response than administration earlier in the day. There is some evidence (Jasani *et al.*, 1968) that maintenance of the diurnal rhythm of plasma corticosteroid levels is an important factor in retaining normal pituitary-adrenal response.

Clinically, local reactions to depot synthetic corticotrophin may be a problem. Within the very limited experience of this trial erythema and skin irritation were appreciably more frequent with depot tetracosactrin than with gel. No doubt local reactions would be less frequent with intramuscular injection. Such reactions are not to be confused with inactivation of the hormone by antibody formation, which is most unlikely to tetracosactrin (Felber *et al.*, 1966).

In conclusion, it seems fair to state that depot tetracosactrin has a very real place in medical investigation and therapeutics in view of its potency and the convenience of its prolonged action. From these aspects it could replace the use of animal corticotrophin gel. The incidence of local reactions, however, may prove troublesome, and its obliterative effect on the diurnal rhythm of cortisol production is a theoretical disadvantage in long-term therapy.

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Preliminary Communications

Effect on Airways Resistance of Prostaglandin E₁ Given by Aerosol to Healthy and Asthmatic Volunteers

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Summary: The forced expiratory volume in one second (F.E.V.₁) was measured in healthy and asthmatic volunteers and the inhalation of prostaglandin E₁ (PGE₁) was compared with that of isoprenaline, using metered aerosols.

In healthy volunteers PGE₁, either as the free acid or the neutral triethanolamine salt, did not affect the F.E.V.₁; the free acid was irritant to the upper respiratory tract. In five out of six asthmatic volunteers with reversible airways obstruction, inhalation of 55 µg of

PGE₁ (triethanolamine salt) produced an increase in F.E.V.₁ comparable in both degree and duration to that produced by an inhalation of 550 µg. of isoprenaline sulphate.

Though the triethanolamine salt was well tolerated in most of the asthmatic subjects studied, in one asthmatic subject this preparation caused coughing and there was a progressive reduction in the F.E.V.₁ associated with bronchospasm.

INTRODUCTION

The prostaglandins have been intensely studied since 1962, when the chemical structure of the first member of this group of naturally occurring fatty acids was determined (Bergström, Ryhage, Samuelsson, and Sjöwall, 1962). Of their pharmaco-