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EVALUATION OF NEWLY SYNTHESISED HUMAN CORTICOTROPHIN

By

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INTRODUCTION

Although the preparations of natural corticotrophin (ACTH) are highly purified, these are extracts of bovine or porcine pituitary glands capable of inducing, in a proportion of patients, either immediate or delayed allergic reactions (*Thorn et al.* 1953). Reports on the incidence, type and severity of allergic reactions to commercially available ACTH were reviewed in a previous study (*El-Shaboury* 1965). A recent finding in this unit was the occurrence of immediate generalised hypersensitivity reactions following an intravenous infusion of porcine ACTH in 10 of 200 (5 per cent) steroid treated patients who had received previous therapy with animal ACTH.

A polypeptide containing the first 24 of the 39 aminoacids of natural corticotrophin has been synthesised by Ciba (B¹⁻²⁴, tetracosactrin, "Synacthen"). This polypeptide, and its depot preparation (*El-Shaboury* 1965 and 1968) was shown to be safe when given to patients with proven hypersensitivity reactions to animal corticotrophin. In 1967, Gideon Richter Limited synthesised the 1-39 aminoacids of human corticotrophin and injections of this material were found by *Kovács et al.* (1968) to be a potent adrenocortical stimulant and safe in three patients allergic to other ACTH prepara-

tions. Unlike tetracosactrin, this synthetic material, however, has not been available commercially. Recently Armour Pharmaceutical Company synthesised, by a different process, the polypeptide chain of 39 aminoacids in correct sequence for human corticotrophin. This synthetic human corticotrophin has not been tried previously in man and this communication reports its effect on adrenal function in normal volunteers.

MATERIAL AND METHODS

Four healthy female volunteers were given over a period of exactly four hours an intravenous infusion of 500 ml. normal saline containing 45 units of animal ACTH (Aethar), and another containing 1 mg. of the synthetic human ACTH (Lot DEV 27109, Armour). One week was allowed to elapse between the two infusions which were started in every case between 9 and 10 a.m. In cases 1 and 2 the first infusion was the human synthetic ACTH and in the other two cases, animal ACTH. The pulse and blood pressure were recorded before and at the end of the infusion. Plasma 17-hydroxycorticosteroids (17-OHCS, "cortisol") were measured immediately before and at every hour during the infusion. Twenty-four hour urinary 17-OH-CS were also measured before and on the day of ACTH infusion.

Plasma 17-OH-CS were determined by a modification (*Hatfield & Shuster 1959*) of the method of *Peterson et al. (1957)*; a method which was shown by *Peterson et al.* to be highly specific for cortisol in blood. Urinary 17-OH-CS were measured after complete B-glucuronidase hydrolysis by a modification of the method of *Silber & Porter (1954)* described by *Liddle et al. (1955)*.

RESULTS

Results for urinary 17-OH-CS and plasma 17-OH-CS are shown in *Tables 1 and 2 respectively*. Basal urinary 17-OH-CS excretion in the 4 subjects was within the normal range, and the values in each case were similar before either type of ACTH was given. In all subjects human synthetic ACTH produced a marked rise in urinary 17-OH-CS. The 17-OH-CS output was comparable to that of animal ACTH although in cases 3 and 4 it was slightly higher.

Table 2 shows that with both types of ACTH infusion, plasma 17-OH-CS at the first hour increased markedly over the basal values and this increase continued throughout the

period of infusion. The degree of response was similar with the two types of ACTH.

The pulse and systolic blood pressure rose at the end of either infusion but this did not exceed 12 beats/min. and 15 mm. Hg respectively. No rise in diastolic pressure was recorded and none of the subjects complained of side effects.

TABLE 1

Urinary 17-OH-CS in four normal volunteers at rest (basal) and during intravenous infusions of 1 mg. human synthetic ACTH and 45 units animal ACTH given over four hours.

Case	Age (in yrs) and sex	Urinary 17-OH-CS mg/day			
		Basal	Human synthetic ACTH	Basal	Animal ACTH
1	20 F	5.8	14.8	7.0	15.0
2	24 F	9.2	15.7	9.0	15.6
3	20 F	7.9	27.1	8.5	25.6
4	16 F	6.1	18.8	7.1	14.8

TABLE 2

Plasma 17-OHCS at basal (0) and during intravenous infusions of 1 mg. Human synthetic ACTH and 45 units of animal ACTH given over 4 hours.

Case	Plasma 17-OH-CS U μ /100 ml.									
	Human synthetic ACTH (Time in hours)					Animal ACTH (Time in hours)				
	0	1	2	3	4	0	1	2	3	4
1	17	28	35	38	39	16	33	37	35	46
2	21	28	36	41	42	20	30	33	34	39
3	20	34	38	44	47	29	36	38	43	45
4	17	43	43	47	45	16	39	39	38	39

DISCUSSION

The results show that this newly synthesised human ACTH is a potent stimulant of adrenocortical function when given as

an intravenous infusion. Since the dose given of both human and animal ACTH was in excess of that required for "maximal" adrenal stimulation the results of plasma 17-OH-CS were similar during both infusions. Also, the urinary 17-OH-CS output in response to both types of ACTH infusion was comparable. *Upton et al.* (1970) found that an infusion of purified human ACTH had a longer duration of action than that of porcine origin. This may explain the finding in the present study of slightly higher urinary steroid output after synthetic human ACTH in 2 of 4 subjects.

The synthetic human ACTH was not given to patients hypersensitive to animal corticotrophin since only a limited amount was available for clinical trial. A synthetic part of the ACTH chain, tetracosactrin, is known to be well tolerated by patients who are hypersensitive to animal ACTH (El-Shaboury, 1965 and 1968), though allergic reactions to depot tetracosactrin have been reported recently (*Binns* 1969). However, these reactions were not clearly defined, and hypersensitivity to pure tetracosactrin has not been proven except in one case (*Jensen & Sneddon* 1969). Such proven cases of hypersensitivity to a synthetic part of the ACTH chain, rather than the vehicle for depot preparation, must remain rare (*Lancet* 1956). *Brombacher et al.* (1969) found that a gelatin preparation of a synthetic ACTH 1-39 peptide had more activity and longer duration of action than that of 1-24 ACTH peptide. Since the synthetic polypeptide assessed in the present study had the exact sequence of the 39 aminoacids found in human corticotrophin, it would seem reasonable to assume that a depot preparation, when it becomes available, should contribute a further advance in ACTH therapy.

SUMMARY

The activity of a recently synthesised polypeptide chain of 39 aminoacids of human corticotrophin (Lot DEV 27109, Armour) was evaluated in four normal volunteers. It was found to be a potent stimulant of adrenocortical function when

given as an intravenous infusion. Results of plasma and urinary 17-hydroxycorticosteroids are compared with those obtained in response to animal ACTH infusion.

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