

INTRAVENOUS ACTH IN THE TREATMENT OF ALLERGIC DISEASES

STANLEY F. HAMPTON, M.D.
ST. LOUIS, MO.

THE clinical and experimental use of adrenocorticotrophic hormone (ACTH) in the treatment of allergic diseases has been rather extensive since the first clinical ACTH conference in October of 1949 and particularly since ACTH became available for general use in 1950. The majority of reports on ACTH appearing in the literature have been based upon its administration by the intramuscular route and until recently, perhaps even now, the conventional method has been intramuscularly.

The first reports of the intravenous administration of ACTH were by Gordon and his associates^{1, 2} in which it was estimated that the cortical response, measured by the increase of ketosteroid excretion and decrease in total blood eosinophils, was up to twenty times greater when ACTH was given intravenously rather than intramuscularly, dose for dose. Forsham, Renolds, and Lesh³ also reported substantial increase in the excretion of 17-ketosteroids after intravenous ACTH. Mandel and his co-workers⁴ reported on twenty-five patients, including eight cases of allergic and collagen diseases, treated intravenously with 1 to 20 mg. ACTH for 8 to 12 hours, and concluded that the therapeutic results were "as good or even better, with only $\frac{1}{10}$ to $\frac{1}{20}$ the doses previously employed intramuscularly in similar cases."

This presentation is a report of the treatment of 60 cases of asthma, urticaria, and allergic dermatitis treated with ACTH intravenously alone or by a combined intravenous and intramuscular method. The study included 35 cases of asthma, 16 cases of urticaria and angioneurotic edema and 9 cases of dermatitis, including atopic or neurodermatitis and contact dermatitis (Table I).

METHODS

1. *Route of Administration.*—All patients received intravenous ACTH (Armour) in one of the following manners: a) *Intermittent:* Daily infusions over a period of 8 to 12 hours for 2 to 10 days were administered to 14 patients. This method was used earlier in this study and was later abandoned in favor of continuous or combined therapy. b) *Continuous:* Continuous infusions from 2 to 5 days were administered to 20 patients. Occasionally the intravenous flow stopped spontaneously from extravasation or the infusion needle "plugged," in which instances the intravenous was re-started, usually at another site, with loss of only a few minutes of continuous flow. (In a few instances the patient complained of great fear of the infusion continuing throughout the first night of therapy and was therefore changed from continuous to intermittent or combined intravenous-intramuscular therapy.) c) *Combined Intravenous-Intramuscular:* Daily infusions lasting 8 to 12 hours combined with one daily intramus-

From the Department of Medicine, Washington University Medical School and Barnes Hospital, St. Louis, Missouri.

Presented at the Eighth Annual Meeting of the American Academy of Allergy, Chicago, Illinois, February 18-20, 1952.

Received for publication, June 16, 1952.

TABLE I. METHODS OF ACTH ADMINISTRATION AND NUMBER OF PATIENTS TREATED BY EACH METHOD

	INTRAVENOUS CONTINUOUS	INTRAVENOUS INTERMITTENT	INTRAVENOUS AND INTRA- MUSCULAR	TOTAL
Asthma	10	10	15	35
Urticaria	6	2	8	16
Dermatitis	4	2	3	9
Total	20	14	26	60

cular injection for 2 to 10 days were administered to 26 patients. The infusions were given from about 8 A.M. to between 4 and 8 P.M. and the intramuscular injection at midnight.

2. *Dosage*.—Each patient received 10 or 12.5 mg. ACTH per 1,000 c.c. 5 per cent glucose in water, each 1,000 c.c. of fluid requiring 8 to 12 hours for administration. The 12.5 mg. dosage was used in the earlier phase of this study when 25 mg. bottles of ACTH were employed. After 10 mg. bottles were available, 10 mg. was adopted as a routine for all dosages regardless of the method of administration. Those patients in the combined intravenous-intramuscular group received 10 to 12.5 mg. ACTH intramuscularly at midnight in addition to the daily infusion. The continuous intravenous group received a total of 20 to 30 mg. ACTH in 24 hours.

3. *Diet*.—A regular diet, permitting table salt and water as desired, was given all patients except those with other conditions such as heart disease in whom there was danger of inducing sodium and water retention. In a number of instances, however, the patient was changed from a general to a 1 or 2 Gm. salt diet after the appearance of pitting edema, excessive weight gain, or an elevated blood sodium.

4. *Potassium*.—Potassium Chloride, 3 Gm. daily, was prescribed to those patients showing low blood potassium during therapy and to those patients on low sodium diets.

5. *Observations*.—Weight, blood pressure, urinalysis for sugar, and observation for peripheral pitting edema were recorded daily. Fasting blood sugar, sedimentation rate, and blood sodium and potassium determinations were done before and just after the completion of therapy and in some cases during the course of treatment in the majority of the patients.

6. *Total Blood Eosinophil Counts*.—Fasting morning total blood eosinophil counts were performed in all patients. In most cases the counts were done daily. The technique described by Randolph⁵ was used.

7. *Ketosteroid Determinations*.—The excretion of 17-ketosteroids per 24 hours was measured in 5 patients, including the periods 24 hours prior to therapy, the first 24 hours of therapy, and the period between 72 and 96 hours of therapy. The method of analysis was a modification of the technique of Holtroff and Koch.⁶

8. *Other Drugs Used*.—Antibiotics, chiefly penicillin and streptomycin, were given to those patients showing significant evidence of active infection, regardless of the type of the allergic disease or the method of treatment with ACTH. The reports of Finland and his co-workers^{7, 8} and of Glaser, Berry, Loeb, and

Wood⁹ indicate that ACTH (or cortisone) therapy should be accompanied by appropriate antibiotic therapy in all instances where active infection is associated.

RESULTS

The therapeutic response to intravenous ACTH was, in general, excellent, although in most instances only temporary. Only one patient failed to show essentially complete clearing of the symptoms and physical signs of the particular disease before completion of the therapy. This was a case of asthma, complicated by pulmonary emphysema and arteriosclerotic heart disease. Even though there was partial clinical improvement, it appeared that cortical exhaustion may have occurred as evidence by the daily fasting eosinophil count and 17-ketosteroid excretions. Whereas this patient showed a satisfactory 17-ketosteroid excretion after 24 hours of combined intravenous and intramuscular ACTH, there was essentially no further increase in steroid excretion after 96 hours of ACTH (case C. W.).

Whereas it is difficult to evaluate clinical results of any type of therapy in different patients, it appears from this study that the best and most rapid clinical results were obtained with the continuous intravenous method of administration of ACTH. Although the combined intravenous and intramuscular method appeared not to be quite as effective as the continuous infusion, but somewhat more effective than the daily intermittent infusion, the results of this study suggest that it is probably the most practical method of administration.

Total Eosinophils.—Fasting total blood eosinophil counts, carried out on each patient, showed a significant fall in all cases, and in most instances there was a fall of 50 per cent or more after 24 hours of therapy regardless of the method employed. The daily intermittent intravenous method rarely induced a count approaching zero even after several days. The combined intravenous-intramuscular method usually induced counts approaching zero after 1 to 4 days' therapy. It was not uncommon, however, that the continuous infusion induced an eosinophil count approaching zero after one continuous infusion of 20 to 25 mg. ACTH in 24 hours. In one case, the count fell from 880 to zero after one infusion of 10 mg. in 12 hours. These observations are striking in view of findings of Shulman, Harvey, and their associates¹⁰ that the maximum satisfactory fall in total eosinophils occurred between 4.4 and 9.1 days in asthmatics receiving 100 mg. of ACTH per day intramuscularly. Table II is an example of results of eosinophil counts in patients receiving continuous intravenous and combined intravenous-intramuscular therapy.

17-Ketosteroid Excretion Studies.—There was a significant increase in the excretion of 17-ketosteroids in 24-hour urine samples after 24 hours of therapy in each of the 5 cases studied and, with one exception, a still greater increase after 96 hours of treatment. The output was greatest after continuous infusion of ACTH when the values increased from 18.6 to 44.3 after 24 hours and 66.6 mg. per 24 hours after 96 hours of therapy (Table III). With the combined intravenous-intramuscular method, the greatest values were from 13.4 to 24.7 after 24 hours and 33.7 mg. per 24 hours after 96 hours of treatment in one patient and from 16 to 32.9 after 24 hours and 44.3 mg. per 24 hours after 96

hours of therapy in another patient (Tables IV & VII). The least values were from 9.4 to 13.9 after 24 hours and 23.4 mg. per 24 hours after 96 hours of treatment (Table V). In one case (C. W.), age 67, it appeared that cortical

TABLE II. TOTAL BLOOD EOSINOPHIL COUNTS OF PATIENTS TREATED WITH ACTH

CASE	DOSE	NO. OF DAYS	BEFORE	AFTER
<i>Treatment With Continuous Intravenous ACTH</i>				
H. E.	12.5 mg. per 1000 c.c.	3	875	6
			1325	13
			2145	6
W. M.	12.5 mg. per 1000 c.c.	5	2175	1250
				0
				6
				0
				6
H. R.	10 mg. per 1000 c.c.	4	610	11
				11
				0
				0
M. F.	10 mg. per 1000 c.c.	5	642	0
				0
				0
				22
				0
<i>Treatment With Combined Intravenous and Intramuscular ACTH</i>				
H. E.	12.5 mg. per 1000 c.c.	4	286	121
				52
	12.5 mg. I.M.			22
				22
H. C.	10 mg. per 1000 c.c.	4	198	125
				56
	10 mg. I.M.			62
				0
C. M.	12.5 mg. per 1000 c.c.	5	156	19
				0
	12.5 mg. I.M.			0
				0
				0
S. W.	10 mg. per 1000 c.c.	4	131	88
				22
	10 mg. I.M.			11
				0

exhaustion occurred. Whereas, there was an increase of 17-ketosteroid excretion from 8.2 to 20.7 after 24 hours, it remained at 21.5 mg. per 24 hours after 96 hours of therapy (Table VI). One patient was treated by the combined intravenous-intramuscular method for 4 days, followed by continuous infusion for 3 days. The 17-ketosteroid excretion values increased from 16 to 32.9 mg. per 24 hours during the first 24 hours of ACTH by the combined method and to 44.3 at the end of 96 hours. The value after the subsequent three-day continuous infusion was increased to 61 mg. per 24 hours (Table VII). These values of 17-ketosteroid excretion appear to be of great magnitude, simulating those reported by Gordon, Kelsey, and Meyer.^{1, 2} Venning, Johnson, and Rose,¹¹ administering ACTH intramuscularly, reported increase in excretion of 17-ketosteroid from 7 to 44 mg. per 24 hours and 5.5 to 26 mg. per 24 hours after 11 and 9 days of ACTH, respectively, in 2 cases, but the increase after the first 24 hours of 100 mg. ACTH in divided doses was only to about 10 mg. per 24 hours in each instance.

TABLE III. CASE H. R., AGE 34, URTICARIA, TREATED BY CONTINUOUS INTRAVENOUS ACTH

DOSE (24 hr.)	TOTAL DOSE	DIET		WEIGHT		EDEMA		MOON FACIES	SODIUM		POTASSIUM		BLOOD SUGAR	
		B	A	B	A	B	A		B	A	B	A	B	A
20 mg. per 2000 c.c.	80 mg.	Gen.		162	169	0	0	+	144	145.9	3.8	3.9	98	77

URINE SUGAR	BLOOD PRESSURE		SED. RATE		EOSINOPHILS		17 KETOSTEROIDS (MG. PER 24 HR.)	
	B	A	B	A	B	A	B	A
0	120/80		10	3	410	11	18.6	44.3 (24 hr.)
	115/70					11		66.6 (96 hr.)
	140/70					0		
						0		

TABLE IV. CASE F. N., AGE 26, URTICARIA, TREATED WITH COMBINED INTRAVENOUS AND INTRAMUSCULAR ACTH

DOSE (24 hr.)	TOTAL DOSE	DIET		WEIGHT		EDEMA		MOON FACIES	SODIUM		POTASSIUM		BLOOD SUGAR	
		B	A	B	A	B	A		B	A	B	A	B	A
I.V. 10 mg. per 1,000 c.c.	40 mg.	Gen.		139	139	0	0	0	147.5	147.5	4	4.4	70	68
I.M. 10 mg.	40 mg.													

URINE SUGAR	BLOOD PRESSURE		SED. RATE		EOSINOPHILS		17 KETOSTEROIDS (MG. PER 24 HR.)	
	B	A	B	A	B	A	B	A
0	115/65		6	0	233	155	13.4	24.7 (24 hr.)
	126/70				242	122		32.7 (96 hr.)
						111		
						78		

TABLE VII. CASE M. R., AGE 29, GENERALIZED ECZEMA, TREATED BY COMBINED INTRAVENOUS AND INTRAMUSCULAR ACTH FOR 4 DAYS FOLLOWED BY CONTINUOUS INFUSIONS OF ACTH FOR 3 DAYS

DOSE 24 HR.			TOTAL DOSE		DIET	WEIGHT		EDEMA		Na		K	
I.V. & I.M.	CONT.	I.V. & I.M.	I.V. & I.M.	CONT.		B	A	B	A	B	A	B	A
10 mg. per 1,000 c.c. I.V.	25 mg. per 2,500 c.c.	40 mg. I.V.	40 mg. I.V.	75 mg. I.V.	Gen.	130	132	0	0	149/4	144.5	4.9	3.8
10 mg. I.M.		40 mg. I.M.				131	135		3.7	141.9			
							137						

BLOOD SUGAR		URINE SUGAR		BLOOD PRESSURE		SED. RATE		EOSINOPHILS		17 KETOSTEROIDS (MG. PER 24 HOURS)			
B	A	B	A	B	A	B	A	B	A	BEFORE	AFTER COMBINED I.V. & I.M.	AFTER CONTINU- OUS I.V.	
48	114	0	0	120/70	130/70	14	4	737	132	16	32.9 (24 hr.)	61 (72 hr.)	
(1 hr. after I.V.)				140/90	140/90			1166	33		44.3 (96 hr.)		
				120/60	120/60				22				
				160/70	160/70				143				
				130/70	130/70				0				
				145/60	145/60				0				
									44				

TABLE VIII. SIDE EFFECTS OF INTRAVENOUS ACTH

CASE	EDEMA	WEIGHT		SODIUM		POTASSIUM		METHOD	BLOOD PRESSURE		DIET
		B	A	B	A	B	A		B	A	
W. H.	2+	100	114	136	147	4.6	2.9	Cont.	132/90	160/100	Gen.
S. M.	1+	151	159	152	148	3.6	3.2	Comb.	100/80	140/70	Gen.
M. F.	+	151	156	143	150	4.6	3.4	Cont.	100/80	140/100	Gen.
W. M.	+	142	148	148	147	4.0	2.7	Cont.	140/90	150/90	Gen.
C. W.	+	141	142	142	152	5.2	4.7	Comb.	112/70	150/75	1 Gm. NaCl
M. P.	1+	150	155	---	---	---	---	Comb.	110/60	120/70	Gen.
S. E.	+	152	161	---	---	---	---	Comb.	120/80	120/60	Gen.
C. M.	0	113	121	151	147	5.2	4.4	Comb.	118/80	110/80	Gen.
S. W.	0	140	148	144	150	4.5	3.6	Comb.	130/70	130/60	Gen.
H. E.	0	139	150	147	146	3.8	4.9	Cont.	145/90	170/100	1 Gm. NaCl

Cont.—Continuous Intravenous.

Comb.—Combined intravenous and intramuscular.

Weight and Edema.—A gain in weight was quite common and occurred in the majority of the patients on a general diet, regardless of the change in blood sodium and potassium or demonstrable peripheral pitting edema. Furthermore, there was weight gain in some patients, such as case H. E. (Table VIII), who was on a diet of 1 or 2 Gm. of salt per day, and in whom no edema developed and no significant change occurred in the blood sodium and potassium levels. Whereas the weight gain in some cases appeared to be due to sodium and water retention, in others it seemed to be due to increased appetite and caloric intake as a result of ACTH therapy. Demonstrable pitting edema occurred in only 7 patients. Cessation of ACTH therapy resulted in diuresis and a loss of all or part of the weight gain and the edema when present (Table VIII).

Electrolytes.—An increase in blood sodium and a fall in blood potassium were not uncommon in this study but the values rarely varied beyond the extreme limits of normal even when the patient was on a general diet.

Blood Pressure.—There was a general tendency for a rise in blood pressure after intravenous ACTH but in no instance was the increase alarming, even when the patient was on a general diet.

Blood Sugar.—In no instance was there a significant rise in the fasting blood sugar value after ACTH therapy.

Urine Sugar.—In only one instance was there demonstrable glycosuria and that was minimal and occurred in only one specimen, immediately after which ACTH therapy was discontinued.

Sedimentation Rate.—There was a general tendency to a fall in the sedimentation rate values, even when the pre-treatment values were normal.

Tables III to VIII show examples of weight gain with and without pitting edema, blood sodium and potassium values, blood pressure observations, blood sugar, urine sugar, and sedimentation rate determinations before and after ACTH therapy.

COMMENT

The clinical observations and laboratory studies including total blood eosinophil counts and 17-ketosteroid excretion, carried out in this series of 60 patients with allergic diseases, treated with adrenocorticotrophic hormone administered intravenously either once daily, continuously for several days, or once daily combined with one daily intramuscular injection approximately midway (at midnight) between the daily infusions indicate the advantages of intravenous therapy over the conventional intramuscular method of administration of this hormone. The first advantage is the increased efficiency of therapy as manifested by a more rapid relief of symptoms and the clearing of the physical signs when the doses used were much smaller than usually given intramuscularly. The second advantage is the economy of its use. ACTH is relatively expensive when given in doses of 25 mg. or more intramuscularly every six hours. Whereas 10 to 12.5 mg. (most cases received 10 mg.) have been the standard dosage used in this study for sake of consistency, it is highly possible that 5 mg. or even 1 mg. intravenously may be effective as suggested by Gordon.¹²

No attempt was made in this study to gradually reduce the dosage of ACTH before cessation of therapy. Several patients, therefore, developed a post-

treatment syndrome of exhaustion, manifested chiefly by weakness and light-headedness 2 to 5 days after therapy was discontinued. These symptoms were readily controlled by cortisone orally in a gradually decreasing dosage of 25 mg. every 6 hours for 2 or 3 days, every 8 hours for 2 or 3 days, every 12 hours for 2 or 3 days and then once daily for 2 or 3 days.

Several additional patients, mostly emergencies not included in this report, in whom laboratory data before and after therapy were not recorded, have been treated by continuous infusion or by the intravenous-intramuscular method with ACTH combination technique in which the infusion was given continuously until the emergency state had subsided, followed by one infusion daily and one intramuscular injection nightly. In these cases, rather than reducing the dosage of ACTH gradually over a period of days to prevent the posttreatment exhaustion phenomenon, cortisone orally was prescribed in the gradually decreasing dosage regimen described above. Such post-ACTH oral cortisone therapy was usually carried out on an out-patient basis, thereby saving hospital days. The addition of aminophylline and sodium iodide to the intravenous fluids containing ACTH did not seem to interfere with the effectiveness of the ACTH.

The intravenous method is practical only for use in hospitalized patients, but once the patient is hospitalized, it is recommended that intravenous rather than intramuscular therapy be used. It is also recommended that an attempt be made to administer the ACTH by continuous infusion in severe or emergency cases for the period of the emergency after which the daily intermittent infusion or the combined intravenous and intramuscular method may be substituted.

It is further recommended that the sodium intake of the patient be reduced while receiving ACTH intravenously if heart or kidney disease or other diseases predisposing to electrolyte imbalance and edema are present, if edema should develop during ACTH therapy or if the patient gains an unusual amount of weight. Daily weight and blood pressure recordings should be made. Fasting blood sugar and blood sodium and potassium determinations should be carried out, if available.

Intravenous or combined intravenous-intramuscular ACTH therapy is, in general, effective in the temporary relief of the allergic state, but it is not a substitute for specific antiallergic diagnosis and therapy and the causative agent or agents must be eliminated or the patient treated accordingly such as hypersensitization as pointed out by Cooke and his associates,¹³ Feinberg and his co-worker,¹⁴ and others.

CONCLUSIONS

1. Clinical and laboratory studies on 60 patients with asthma, urticaria and allergic dermatitis treated with corticotropin (ACTH) administered intravenously or by a combined intravenous and intramuscular method have been presented.

2. The clinical response, fasting total eosinophil counts and 17-ketosteroid excretion studies indicate a great advantage of ACTH given intravenously or combined with intramuscular administration over the conventional intramuscular use of the hormone.

3. The effects of intravenous ACTH therapy upon weight and edema, blood pressure, blood sodium and potassium, blood and urine sugar values and the sedimentation rate are presented.

The author expresses sincere appreciation to Miss Ellabeth Houghton and Miss Mattie Heady of the Barnes Hospital Metabolism Laboratory (under the direction of Dr. William H. Daughaday) for the 17-ketosteroid determinations included in this report.

REFERENCES

1. Gordon, E. S.: Adrenal Stimulation by Intravenous ACTH, *J. Lab. & Clin. Med.* **36**: 827, 1950.
2. Gordon, E. S., Kelsey, C., and Meyer, E. S.: Adrenal Stimulation by Intravenous ACTH, *Proceedings of the Second Clinical ACTH Conference, Volume II—Therapeutics*, page 30, 1951, New York, Philadelphia, Toronto, The Blakiston Co.
3. Forsham, P. H., Renold, A., and Lesh, J. B.: Metabolic Effects of Small Molecular ACTH—A Preliminary Report, *Proceedings of the Second Clinical ACTH Conference Volume I—Research*, page 7, 1951, New York, Philadelphia, Toronto, The Blakiston Co.
4. Mandel, W., Singer, M. J., Gudmondson, H. R., Meister, L., and Modern, F. W. S.: Intravenous Use of Pituitary Adrenocorticotrophic Hormone (ACTH), *J. A. M. A.* **146**: 564, 1951.
5. Randolph, T. G.: Blood Studies in Allergy. I. The Direct Counting Chamber Determination of Eosinophiles in Propylene-Glycol Aqueous Stains, *J. ALLERGY* **15**: 89, 1944.
6. Holtroff, A. F., and Koch, F. S.: The Colorimetric Estimation of 17-Ketosteroids and Their Application to Urine Extracts, *J. Biol. Chem.* **135**: 377, 1940.
7. Finland, M., Kass, E. H., and Ingbar, S. H.: Further Observation on the Effect of ACTH in Acute Infections, *Proceedings of the Second Clinical ACTH Conference Volume I—Research*, page 478, 1951.
8. Kass, E. H., and Finland, M.: Role of Adrenal Steroids in Infection and Immunity, *New England J. Med.* **244**: 464, 1951.
9. Glaser, R. J., Berry, J. W., Loeb, L. H., and Wood, W. B.: The Effect of Cortisone in Streptococcal Lymphadenitis and Pneumonia, *J. Lab. & Clin. Med.* **38**: 363, 1951.
10. Shulman, L. E., Harvey, A. M., Howard, J. E., and Schoenrich, E. H.: Clinical Studies With ACTH in Bronchial Asthma, *Proceedings of the Second Clinical ACTH Conference, Volume II—Therapeutics*, page 401, 1951, New York, Philadelphia, Toronto, The Blakiston Co.
11. Venning, E. H., Johnson, L. G., and Rose, B.: Adrenal Cortical Function in Rheumatoid Arthritis and Asthma, *Proceedings of the Second Clinical ACTH Conference, Volume II—Therapeutics*, page 49, 1951, New York, Philadelphia, Toronto, The Blakiston Co.
12. Gordon, E. S.: Personal communication.
13. Cooke, R. A., Sherman, W. B., Menzie, A. E. O., Chapin, H. B., Howell, C. M., Scott, R. B., Meyer, P. A., and Downing, L. M.: ACTH and Cortisone in Allergic Disease, *J. ALLERGY* **22**: 211, 1951.
14. Feinberg, S. M., Dannenberg, T. B., and Malkiel, S.: ACTH and Cortisone in Allergic Manifestations, *J. ALLERGY* **22**: 195, 1951.