INTRA-ARTICULAR HYDROCORTISONE (COMPOUND F) ACETATE*

A PRELIMINARY REPORT

BY

C. R. STEVENSON,[†] J. ZUCKNER,[‡] and R. H. FREYBERG

*From the Hospital for Special Surgery, and Cornell University Medical College,
New York*

(RECEIVED FOR PUBLICATION FEBRUARY 25, 1952)

The suppression of inflammation in the joint structures of patients with rheumatoid arthritis by cortisone acetate administered systemically is well known. Hydrocortisone acetate, formerly known as Compound F acetate (17-hydroxy-corticosterone-21-acetate), administered orally or intramuscularly, has recently been shown to have a similar suppressive effect upon this inflammation (Ward and others, 1951; Freyberg, Stevenson, Traeger, and Zuckner, 1952). One of the most important objections to the systemic use of these steroids is that amounts adequate to produce a beneficial effect may cause undesired physiological changes of hyperadrenocorticalism.

Thorn (1951) is reported to have been the first to inject hydrocortisone acetate into an inflamed joint of a patient with rheumatoid arthritis with improvement in the inflammation. Hollander and others (1951) reported sustained local benefit and no systemic effect, after intra-articular injections of hydrocortisone into patients with various illnesses including rheumatoid arthritis. They reported no objective improvement after intra-articular injections of cortisone acetate. Other workers have demonstrated that cortisone acetate injected directly into an inflamed joint produces local improvement which is manifested clinically and by changes in the synovial fluid without producing a significant systemic effect (Freyberg and others, 1951). After repeated intra-articular injections of cortisone acetate, however, the response in most patients becomes less. In a few others this material seemed to be irritating as shown by worsening of the inflammation at the joint treated and an increase in the number of cells in the synovial fluid.

The present study deals with clinical and synovial fluid changes observed after intra-articular injections of hydrocortisone acetate in patients with rheumatoid arthritis.

Procedure

Hydrocortisone acetate was supplied for this investigation§ in two forms: the usual aqueous suspension (25 mg. per 1.0 ml.) containing Tween-80 and butyl alcohol, and also the dry crystalline state. The crystalline material was studied to determine whether any of the effects observed with the usual suspension were produced by any of its components apart from the steroid. The physical instability and uneven suspension of the

* This investigation was supported (in part) by the Fund for Research in Rheumatic Diseases, Hospital for Special Surgery, and (in part) by a grant from the Institute for Arthritis and Metabolic Diseases, Public Health Service.

[†] Schering Research Fellow in Rheumatic Diseases.

[‡] Merck Research Fellow in Rheumatic Diseases.

§ Kindly supplied by Merck and Co., Inc., Rahway, New Jersey, through the courtesy of Drs J. M. Carlisle and A. Gibson.

crystalline steroid in water made this preparation difficult to work with, and most of the studies were done with the regular suspension.

The steroid was injected into the knee joint in all patients except one in whom it was injected into the elbow. The skin was routinely prepared for injection by thorough washing with green soap, removal of the soap with ether, and application of tincture of thimerosal* which was then removed with alcohol. The needle was inserted into the knee joint by the medial sub-patellar approach, using a solution of 1 per cent. procaine for local anaesthesia. If a large quantity of fluid was to be aspirated, a 20-gauge needle was used; for steroid injection only, a 24-gauge needle was satisfactory. The first intra-articular injection of hydrocortisone acetate in each patient was to 25 mg. or less, in order to minimize undesirable effects in the event of a local intolerance to the drug. The largest amount injected at any time in these patients was 75 mg. An effort was made to maintain a decrease of at least 50 per cent. of pain and stiffness at the joint treated. The interval between injections, and, in some patients, the size of the dose, was usually determined by the patient's subjective response, especially the reduction of pain. When there was poor response injections were given more frequently or the size of the dose was increased. Objective changes were noted, but these did not influence the size of the dose or frequency of injection, since no attempt was made to effect any certain degree of objective improvement. The first two to four injections were usually given at 3- to 7-day intervals to maintain the desired effect; later the interval could be lengthened to several weeks in many cases. The average interval between injections (the number of treatment days divided by the total number of injections) varied from 3 to 29 days.

Cells in the synovial fluid were counted within 1 or 2 hours of the removal of the fluid. The differential cell count was made from smears stained with Wright's technique; whenever possible, a total of 100 cells was counted on each slide.

The patients were examined at frequent intervals after the course of injections had been begun and their clinical progress was observed for several weeks after the injections were discontinued—in two patients for as long as 100 days.

Results

Thirteen patients with rheumatoid arthritis received 96 intra-articular injections of hydrocortisone acetate into twenty different joints. All of these patients tolerated the local injections of the steroid very well, in contrast with other series of patients treated with intra-articular cortisone acetate in whom a temporary increase of joint inflammation was occasionally noted.

There was no difference between the clinical results with hydrocortisone acetate in water and those with the standard suspension. All patients reported some degree of prolonged local benefit. In some the relief of pain was apparent immediately after withdrawal of the injecting needle; in others the relief was delayed for approximately 12 to 18 hours. It is possible that the immediate pain relief noted by some patients was caused by the unintentional injection of procaine into the joint at the time of the intra-articular injection of hydrocortisone acetate.

A detailed analysis of results is presented in the Table, where the severity of synovitis at the joint injected is expressed as a composite estimate (graded 1 to 4) of the signs of inflammation, including abnormal local heat, swelling, synovial fluid, capsular thickening, tenderness, and impaired function. Subsequent objective improvement was graded by the degree of change in these same signs evaluated by the same observer. Subjective improvement represents the degree of relief from discomfort and disability compared with the pre-injection symptoms. The average

* Merthiolate.

TABLE
 INTRA-ARTICULAR INJECTION OF HYDROCORTISONE

Patient	Sex	Joint Injected	Severity of Synovitis before Treatment (Grade)	Average Improvement %		Injections					Period of Treatment (days)
				Subjective	Objective	25 mg.	50 mg.	Other Doses (mg.)	Total Amount (mg.)	Total Number	
R.C.	F	R. knee L. knee	1 to 2 2	60 65	40 60	3 7	5 1		325 225	8 8	135 124
F.S.	F	L. knee	3	85	90	4			100	4	113
I.H.	F	R. knee L. knee	2 3	70 60	50 30	3 4	6		75 400	3 10	87 101
E.R.	F	R. knee	4	80	80	2	2		150	4	102
R.J.	M	R. knee	2	70	25	3			75	3	80
M.F.	F	R. knee L. knee	2 3	50 60	50 60	2	3 4	2 of 75	350 200	7 4	80 382
E.B.	F	L. knee	2	70	70	1	6		325	7	66
T.E.	F	R. knee L. elbow	1 2	90 0	30 0	1 1	3	1 of 6·25	175 31·25	4 2	63 14
E.H.	F	R. knee L. knee	1 1	50 45	25 25	1 1	2 3		125 175	3 4	25 46
F.H.	F	L. knee	2	30	40	2	1	2 of 75	250	5	44
J.H.	M	R. knee L. knee	1 2	35 50	90 10	1 2	2		125 50	3 2	34 22
A.S.	M	R. knee	2	10	10	1	3		175	4	12
B.H.	F	R. knee L. knee	2 2	30 50	40 50	1 3	2 4		125 275	3 7	28 50

• Westergren method. † Not determined. ‡ No fluid obtainable.

improvement refers to conditions prevailing during the greater part of the period when injections were given.

Subjective improvement estimated at 70 per cent. or more was reported to occur in six of the twenty joints injected, and symptomatic improvement estimated at 50 per cent. or more was reported in fourteen joints. The clinical estimation of objective improvement of 70 per cent. or greater was observed in four joints, and of 50 per cent. or more in nine joints. Objective improvement was equal to or greater than the reported subjective improvement in half the cases. No objective change was seen until 3 to 14 days after subjective improvement was reported.

Some patients could detect no change in the injected joint until after three or four injections at close intervals; others noticed persistent partial relief from pain

ACETATE IN PATIENTS WITH RHEUMATOID ARTHRITIS

Average Interval between Injections (days)	Joint Fluid Cytology				Erythrocyte Sedimentation Rate*		Comment
	Pre-treatment		Post-treatment		Pre-treatment	Lowest Post-treatment	
	WBC	PMN ** %	WBC	PMN ** %			
16.8 15.5	10,900 19,700	73 77	4,100 3,100	25 38	53 §	15 —	
28.3	19,850	70	2,500	10	46	40	Receiving gold salt with unsatisfactory improvement of joint later injected; 96 days since last injection of hydrocortisone acetate.
29.0 10.1	8,400 15,950	86 77	2,900 550	22 12	78 §	61 —	
25.5	N.D.†	—	—	—	31	42	Receiving gold salt therapy with incomplete suppression of disease.
26.7	N.F.O.‡	—	—	—	N.D.†	—	Receiving insulin for diabetes mellitus; glycosuria unchanged.
11.4 9.5	23,350 7,500	62 40	50 2,300	18 2	§ §	— —	Treated during relapse after withdrawal of cortisone acetate given orally.
9.4	4,200	46	50	0	94	72	
15.8 7.0	N.F.O.‡ N.F.O.‡	— —	— —	— —	78 §	75 —	
8.3 11.5	N.F.O.‡ N.F.O.‡	— —	— —	— —	40 §	33 —	Receiving gold salt with unsatisfactory improvement.
8.8	22,500	68	2,400	3	91	84	
11.3 11.0	2,500 N.F.O.†	49 —	2,300 —	48 —	11 §	15 —	Receiving 75 mg. cortisone acetate daily orally with only partial improvement of injected joints.
3.0	7,800	54	3,500	11	N.D.†	—	
9.3 7.1	29,400 36,650	68 95	N.D.† 5,800	— 62	95 §	81 —	Untreated joints became worse.

§ More than one joint received treatment with hydrocortisone acetate simultaneously. ** Polymorphonuclear leucocytes.

immediately after the first injection of only 25 mg. hydrocortisone acetate. There was no apparent correlation between the measurable severity or duration of joint inflammation and the speed or degree of response to any specific dose.

In every instance in which it could be obtained for study the synovial fluid showed a decrease in the total number of cells and in the polymorphonuclear cell percentage after injection of hydrocortisone acetate. Early in the investigation, when joint fluid was present in abnormal amounts, an amount equal to the volume of hormone injected was usually aspirated. As the study progressed it was noted that joints from which *all* readily available fluid was aspirated almost always showed a better response. This then became the standard procedure. Gross blood in the synovial fluid was detected in approximately 20 per cent. of the aspirations; this was

considered to be caused by trauma from the needle. Bloody fluid was usually obtained only towards the end of the aspiration of a large volume of fluid.

In four of nine patients the erythrocyte sedimentation rate decreased by more than 10 mm. per hour.

Discussion

The available evidence indicates that the primary site of action of hydrocortisone acetate injected intra-articularly is in the structures of the injected joint. Among our patients there was no instance of improvement in uninjected joints occurring simultaneously with improvement in the treated joint. Joints that were not injected did not change in most patients; in a few patients with synovitis in two or more weight-bearing joints, the untreated joints became worse. For example, improvement in an injected knee joint was sometimes accompanied by the worsening of an ipsilateral untreated arthritic ankle or hip joint. This probably resulted from the increased weight bearing permitted by the improvement in the treated joint.

No explanation is known to us for the prolonged benefit sometimes seen after an intra-articular injection of hydrocortisone acetate.

The changes in the erythrocyte sedimentation rate which occurred during the course of intra-articular injections might have resulted from improvement in the synovitis of injected joints when this constituted the major portion of the recognizable articular inflammation. In several patients with involvement of only a few small joints in addition to the one injected, the sedimentation rate became normal when the injected joints improved.

It is fully appreciated that intra-articular use of hydrocortisone acetate in patients with rheumatoid arthritis is merely a local treatment for a systemic disease. It is not proposed as a substitute for good systemic treatment, but there are several situations in which intra-articular injection of this hormone may prove to be of considerable practical value. A patient with rheumatoid arthritis may have only a few joints affected, most of which might logically be injected. It might also be considered as an adjuvant to therapy when one joint predominates as the chief source of pain and disability. Cases F.S. and E.R. (Table) are examples of patients with rheumatoid arthritis who were practically incapacitated by severe inflammation of one knee that was slow to respond to gold therapy, and both were able to walk after hydrocortisone acetate had been injected. Another condition in which local treatment could be preferable to systemic treatment is demonstrated in the case of R.J., a patient with diabetes requiring 40 units of insulin daily. It was felt that systemic cortisone or corticotropin would be unwise because of the diabetic state; after trial of many accepted forms of treatment, without notable success, the intra-articular injection of hydrocortisone acetate produced a significant improvement in the knee that had been partially incapacitating the patient. The diabetes was not measurably affected.

In most instances the amounts of the steroid used for each injection were arbitrarily selected. Further experience may indicate more precisely the optimal dose that should be used as well as the interval at which injections should be given. In such a study extending over long periods of time, one must realize that the severity of the disease may change spontaneously by some means not related to the treatment.

The true value of intra-articular hydrocortisone acetate and the details of treatment can be determined only after extended observation of many patients.

Apart from the more obvious disadvantages of repeated injections into an inflamed joint, the possibility of accidental infection, and resultant pyarthrosis, must always be remembered. Experience has shown that cortisone acetate may considerably modify the clinical signs of infection (Ward and others, 1950). Because hydrocortisone acetate exerts a suppressive effect on inflammation very similar to that of cortisone acetate it is reasonable to consider that a high concentration of hydrocortisone acetate in the tissues might alter local tissue response so that the manifestations of infection might not be recognized at an early stage.

Summary

Altogether 96 injections of hydrocortisone acetate were made into twenty joints of thirteen patients with rheumatoid arthritis and all were well tolerated. Some degree of symptomatic improvement was reported by all patients. Objective improvement of 50 per cent. or more occurred in nine joints. The interval between injections at each joint varied from 3 to 29 days (average 13·8 days).

The following conclusions were reached:

- (1) Hydrocortisone acetate injected into an inflamed joint of a patient with rheumatoid arthritis is capable of producing local subjective and objective improvement.
- (2) This procedure is now reported as an experimental study, but may prove of significant clinical value in carefully selected cases.
- (3) Further investigation is needed to establish the practicability of the intra-articular use of hydrocortisone acetate, and to assess its long-term effect upon inflamed joint structures and upon the course of the disease.

The technical assistance of Miss Joan Kline is gratefully acknowledged.

REFERENCES

- Freyberg, R. H., Patterson, M., Adams, C. H., Durivage, J., and Traeger, C. H. (1951). *Annals of the Rheumatic Diseases*, 10, 1.
- , Stevenson, C., Traeger, C. H., and Zuckner, J. (1952). Unpublished data.
- Hollander, J. L., Brown, E. M., Jessar, R. A., and Brown, C. Y. (1951). *J. Amer. med. Ass.*, 147, 1629.
- Thorn, G. (1951). *Cited by Hollander and others* (1951).
- Ward, L. E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S. (1951). *Proc. Mayo Clin.*, 26, 361.
- Woodward, T. E., Hall, H. E., Dias-Rivera, R., Hightower, J. A., Martinez, E., and Parker, R. T. (1951). *Ann. int. Med.*, 34, 10.

Expériences avec l'acétate de hydrocortisone (Composé F) intra-articulaire Rapport préliminaire

RÉSUMÉ

On effectua en tout 96 injections d'acétate de hydrocortisone dans 20 articulations de 13 malades atteints d'arthrite rhumatismale; toutes les injections furent bien supportées. Tous les malades accusèrent une amélioration symptomatique. Une amélioration objective de 50% ou plus se produisit dans neuf articulations. L'intervalle entre les injections dans la même articulation était de 3 à 29 jours (13,8 en moyenne).

On arriva aux conclusions suivantes:

- (1) L'acétate de hydrocortisone injecté dans une articulation enflammée d'un arthritique rhumatisant est capable de produire une amélioration subjective et objective.
- (2) Ce procédé, rapporté ici à titre d'étude expérimentale, peut acquérir de l'importance clinique dans des cas soigneusement choisis.
- (3) Des recherches ultérieures sont nécessaires pour déterminer la valeur pratique des injections intra-articulaires d'acétate de hydrocortisone et pour évaluer leur effet éloigné sur les tissus articulaires enflammés et sur l'évolution de la maladie.

**Experimentos con acetato de hidrocortisona (Compuesto F) intra-articular
Informe preliminar**

SUMARIO

Acetato de hidrocortisona fué inyectado 96 veces en total en 20 articulaciones de 13 enfermos con artritis reumatoide; todas las inyecciones fueron bien toleradas. Todos los enfermos acusaron mejoría sintomática que fué, objetivamente, de 50 o más por ciento en enuve articulaciones. El intervalo entre las inyecciones en las mismas articulaciones fué de 3 a 29 días (13,8 de término medio).

Se llegó a las conclusiones siguientes:

- (1) Acetato de hidrocortisona inyectado en una articulación inflamada de enfermo con artritis reumatoide es capaz de producir mejoría subjetiva y objetiva.
- (2) Este procedimiento, referido aquí como estudio experimental, puede adquirir importancia clínica en casos cuidadosamente escogidos.
- (3) Se necesita investigaciones ulteriores para determinar el valor práctico de las inyecciones intra-articulares de acetato de hidrocortisona y para apreciar su efecto remoto sobre estructuras articulares inflamadas y sobre la evolución de la enfermedad.