

ABSORPTION OF HYDROCORTISONE FROM THE JOINT CAVITY INTO THE CIRCULATION

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Intra-articular hydrocortisone therapy has been in extensive use for approximately 5 years. It has been stated that this therapy is strictly for local palliation and has no systemic effects (Hollander, 1953). Local hydrocortisone therapy is especially recommended in cases in which the systemic use of cortisone is contra-indicated on general medical grounds (Kersley, 1953).

On the other hand, Young, Ward, and Henderson (1952) noted clinically systemic as well as local effects after intra-articular injections of hydrocortisone acetate in 31 (21 per cent.) of their 148 patients. There was clinical improvement in involved but uninjected joints in this group, the effect being similar in nature, both subjectively and objectively, to that which results from the oral or intramuscular administration of cortisone. Its occurrence indicates that at least part of the hydrocortisone acetate injected into the synovial cavity is absorbed into the blood stream and reaches the general circulation.

In a study of the intra-articular metabolism of hydrocortisone and cortisone (Wilson, Fairbanks, McEwen, and Ziff, 1955), it was found that hydrocortisone acetate disappeared rapidly from the synovial fluid after intra-articular injection. After 1 hour and 3 hours, 86 and 97 per cent. respectively had disappeared. Appreciable amounts of what was most probably hydrocortisone was found by paper chromatography 30 minutes after the intra-articular injection in the contralateral uninjected knee, indicating that a large proportion of the injected hormone entered the circulation unchanged and also escaped metabolism in the liver during the first 30 minutes after injection.

The aim of the present investigation has been to study the absorption of hydrocortisone acetate from the joint cavity into the blood by measuring the free

plasma 17-hydroxycorticosteroids under experimental conditions in which the endogenous output of hydrocortisone had been eliminated. The suppression of the endogenous hydrocortisone was made possible by administering Δ^1 -9- α -fluoro hydrocortisone (Δ FF). Liddle (1956) has shown that Δ FF is so effective in suppressing the secretion of corticotropin that relatively minute doses of this steroid will reduce the blood 17-hydroxycorticosteroid level almost to zero. Subsequently, for as long as this suppressive dose is maintained, one may consider any appreciable rise in the 17-hydroxycorticosteroid level to be the result of some additional treatment, *e.g.* the administration of either steroids or corticotropin.

Material and Methods

The free plasma 17-hydroxycorticosteroids were determined by the method of Silber and Porter (1954) as modified by Peterson, Wyngaarden, Guerra, Brodie, and Bunim (1955). In this laboratory the average plasma 17-hydroxycorticosteroid level of normal adults was 13 μ g./100 ml. with a range of from 7 to 21 μ g./100 ml.

In this study 0.5 mg. Δ FF* was administered orally every 6 hours for 2 days before the intra-articular or oral administration of hydrocortisone acetate. The administration of Δ FF was continued until the last blood specimen had been drawn.

The absorption of intra-articularly injected hydrocortisone acetate into the blood was studied in six patients suffering from rheumatoid arthritis or osteo-arthritis of the knees. The first blood specimen was drawn immediately before the intra-articular injection of the steroid, and blood specimens were then drawn at varying intervals.

One patient receiving a single oral dose of hydrocortisone acetate served as a control.

* The Δ^1 -9- α -fluoro hydrocortisone used in these experiments was kindly supplied by Dr. C. J. O'Donovan of the Upjohn Company.

Results

The results are presented in the Table and the Figure. It can be seen that Δ FF reduced the

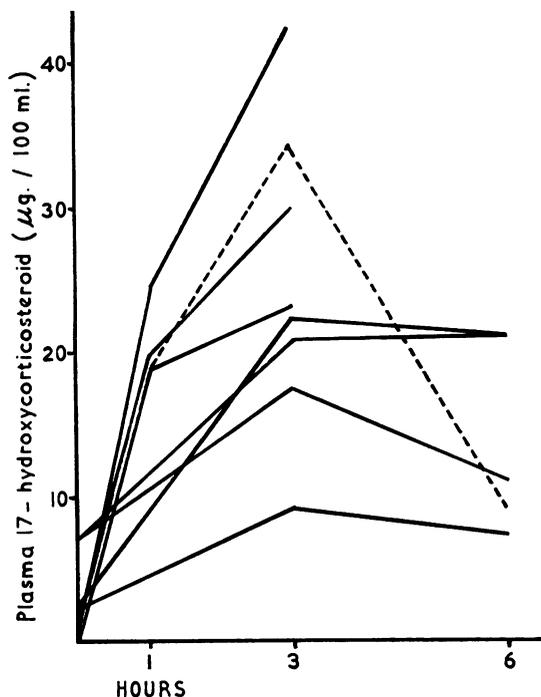


Figure.—Plasma 17-hydroxycorticosteroid levels after intra-articular (—) or oral (-----) administration of hydrocortisone acetate.

initial plasma 17-hydroxycorticosteroid levels almost to zero in six instances. In two instances (Cases 5 and 6), the values were the same as the lower limit of the normal range.

Intra-articular hydrocortisone acetate injection produced a strong rise in the plasma 17-hydroxycorticosteroid level in all cases except one (Case 3). The highest levels were obtained 3 hours after the intra-articular injection. 24 hours after the injection the values had decreased almost to the initial levels. The rate of absorption seems to be very individual. 25 mg. hydrocortisone acetate produced a stronger elevation of plasma 17-hydroxycorticosteroids in one patient (Case 6) than was produced by a dose of 100 mg. in another (Case 3).

25 mg. hydrocortisone acetate orally produced an elevation of plasma 17-hydroxycorticosteroids comparable to that produced by 100 mg. intra-articularly. Here, too, the top level was reached 3 hours after ingestion of the tablet. The plasma 17-hydroxycorticosteroid values 6 hours after the administration of the steroid showed a sharper decrease in the case in which hydrocortisone acetate was given orally.

Discussion

The results of these experiments show that intra-articularly injected hydrocortisone acetate is absorbed into the circulation to a considerable degree.

The plasma 17-hydroxycorticosteroid levels after intra-articular hydrocortisone acetate injections are so high that systemic hormonal effects can be expected if large and frequent doses are used.

Summary

The absorption of hydrocortisone acetate from the joint cavity into the circulation has been studied under experimental conditions in which the endogenous output of hydrocortisone was blocked by the administration of Δ^1 -9- α -fluoro hydrocortisone.

High plasma 17-hydroxycorticosteroid values were obtained after the intra-articular injection of 25 to 100 mg. hydrocortisone acetate.

TABLE

PLASMA 17-HYDROXYCORTICOSTEROID LEVELS AFTER INTRA-ARTICULAR OR ORAL ADMINISTRATION OF HYDROCORTISONE ACETATE TO RHEUMATIC SUBJECTS. THE ENDOGENOUS HYDROCORTISONE OUTPUT WAS BLOCKED BY Δ^1 -9- α -FLUORO HYDROCORTISONE

Case No.	Diagnosis	Dose (mg.)	Route	Plasma 17-hydroxycorticosteroids (μ g./100 ml.) after Administration of Hydrocortisone Acetate (hrs)				
				0	1	3	6	24
1	Rheumatoid arthritis	100	intra-articular	0	18	23	—	—
2	Rheumatoid arthritis	100	intra-articular	0	24	42	—	—
3	Osteo-arthritis	100	intra-articular	2	—	9	7	5
4	Rheumatoid arthritis	100	intra-articular	0	20	30	—	—
4	Rheumatoid arthritis	50	intra-articular	2	—	22	21	6
5	Osteo-arthritis	50	intra-articular	7	—	17	11	9
6	Rheumatoid arthritis	25	intra-articular	7	—	21	21	5
7	Rheumatoid arthritis	25	oral	1	19	34	9	—

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Absorption de l'hydrocortisone de la cavité articulaire dans la circulation

RÉSUMÉ

L'absorption d'acétate d'hydrocortisone de la cavité articulaire dans la circulation a été étudiée dans des

conditions expérimentales dans lesquelles la production endogène d'hydrocortisone fut bloquée par l'administration de Δ^1 -9- α -fluoro hydrocortisone.

On obtint des chiffres sanguins élevés de 17-hydroxycorticostéroïde après l'injection intra-articulaire de 25 à 100 mg. d'acétate d'hydrocortisone.

Absorción de la hidrocortisona de la cavidad articular en la circulación

SUMARIO

La absorción de acetato de hidrocortisona de la cavidad articular en la circulación fué estudiada en condiciones experimentales en las cuales la producción endógena de hidrocortisona fué bloqueada por la administración de Δ^1 -9- α -fluoro hidrocortisona.

Se obtuvieron cifras sanguíneas altas de 17-hidroxicorticoesteroide después de la inyección intra-articular de 25 a 100 mg. de acetato de hidrocortisona.