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ADRENOCORTICAL SUPPRESSION WITH SMALL DOSES OF TOPICAL CORTICOSTEROIDS*

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There is increasing evidence that such fluorinated corticosteroids as triamcinolone acetonide, fluocinolone acetonide and flurandrenolone acetonide can cause sufficient percutaneous absorption to result in adrenocortical suppression when used topically in conjunction with polyethylene film occlusion (2, 3, 9, 10, 17–20). In 1965 Taylor *et al.* (20) suggested that as little as two mg of triamcinolone acetonide absorbed daily through dermatitic skin under occlusive wraps might depress pituitary-adrenocortical function. Carr and Tarnowski (2) have confirmed this suggestion.

This article reports the results of evaluation of adrenocortical function of several patients with generalized dermatitis while they were being treated with 2.25 mg of fluocinolone acetonide, flurandrenolone acetonide or betamethasone valerate in an ointment[1] applied to their entire integument under plastic occlusive dressings.

Material and Methods

Seven adult patients with generalized exfoliative dermatitis were studied in a hospital metabolic ward for evidence of adrenocortical suppression due to percutaneous corticosteroids absorption. In patients 1, 2, 5, and 6 the exfoliative dermatitis was due to atopic dermatitis, while in patients 3, 4, and 7 it was due to psoriasis. In all seven patients the dermatitis had been active and unchanged for several weeks before treatment was begun. No other systemic illness or abnormality was found in any of these patients. Although several of them had used topical corticosteroid therapy (without occlusion) during the previous several months, none had used topical corticoids for a period of at least four weeks prior to the beginning of the present study. No history of previous use of systemic steroids was obtained from any of the seven patients.

Adrenocortical function during control and treatment periods was evaluated by determining 8 : 00 AM plasma cortisol levels (8) and by the measurement of the urinary excretion of 17-hydroxycorticoids (17-OHCS) (16), and 17-ketosteroids (17-KS) (11). Completeness of the urine collections was checked by creatinine determinations. Estimation of endogenous adrenocorticotrophic hormone (ACTH) production was evaluated by administering metyrapone, 750 mg every four hours for six doses (12). Urinary 17-OHCS and 17-KS values were determined on the 24-hour urine collection which followed the day of metyrapone administration. Metyrapone testing was per-

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[1] The betamethasone valerate ointment was supplied as Valisone Cream by Dr. John Vogt of the Schering Corporation.

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formed during the control period and immediately following the period of corticoid treatment.

During each ten day treatment period, 45 gm of water washable ointment containing 2.25 mg (0.005 % concentration) of fluocinolone acetonide, flurandrenolone acetonide or betamethasone valerate (see the Table for identification of the specific steroid used on each patient) was applied to the entire skin surface of each patient once daily at 10:00 AM. Then the patient's entire integument (minus the head) was covered with plastic occlusive dressings in the form of a plastic sauna suit, polyethylene gloves, and plastic bags (for the feet). Occlusion was continued for 23 out of each 24 hour period.

Patients 1 and 2 each received two treatment courses, first with fluocinolone acetonide cream and then with flurandrenolone acetonide cream.

Results

The laboratory data are presented in Table 1 in relation to the treatment periods and metyrapone tests done on each patient. The pre-treatment plasma cortisol and 24-hour urinary 17-OHCS and 17-KS determinations were within normal limits in all seven patients. The pre-treatment and post-treatment metyrapone tests showed normal rises (more than twice the pre-metyrapone administration values) in the urinary 17-OHCS in all seven patients.

In regard to the results obtained during the treatment periods, three of the patients (patients 1, 2, and 3) treated with 2.25 mg of topical fluocinolone acetonide had two or more plasma cortisol and 24-hour urinary 17-OHCS values which were below normal levels while they were on therapy. The other patient treated with fluocinolone acetonide (patient 4) developed values which were considerably lower than pre- and post-treatment levels but not below the lower limits of normal.

All three patients (patients 1, 2, and 5) treated with flurandrenolone had two or more suppressed urinary 17-OHCS values but failed to show plasma cortisol depression.

In the case of betamethasone valerate treatment, patient 6 showed striking depression of urinary 17-OHCS excretion and definite, but less dramatic, reduction of the plasma cortisol values. On the other hand, patient 7 failed to show evidence of adrenocortical suppression.

The urinary 17-KS values did not reflect adrenocortical suppression during the treatment periods in any of the patients.

Clinically, the exfoliative dermatitis underwent rapid and dramatic improvement in each patient during the period of treatment. Following discontinuance of treatment there was a relapse in each patient over a several day period which necessitated resumption of the topical corticosteroid therapy under plastic occlusive dressings for maintenance of improvement. Both patients 1 and 2 were undergoing a rapid exacerbation of their generalized dermatitis at the time when the second treatment period was begun.

Discussion

Although some investigations have failed to demonstrate evidence of adrenocortical suppression with topical corticosteroid therapy under plastic occlusive dressings (6, 7, 13–15), there is growing evidence that the new fluorinated corticoids can suppress the pituitary-adrenal axis when used in sufficient amounts on extensive areas of dermatitic skin under such dressings (2, 3, 9, 10, 17–20). The suggestion of Taylor *et al.* (20) that percutaneous absorption of as little as 2 mg of triamcinolone acetonide may suppress adrenocortical function has been confirmed recently (2). Since such other fluorinated corticosteroids as fluocinolone acetonide, flurandrenolone acetonide, and betamethasone valerate are similar to triamcinolone acetonide in chemical structure, clinical efficacy, and cutaneous vasoconstrictor activity (4, 14), it seems logical that equally small amounts of these steroids applied topically under occlusive dressings may produce adrenocortical suppression. The data

Table 1. *Laboratory data in relation to treatment periods and metyrapone tests on seven patients*

Hospital Day*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Patient 1 (23 yr, Male)																		
Metyrapone test		×													×			
Fluocinolone acetonide cream				×	×	×	×	×	×	×	×	×	×					
Plasma cortisol**	16.3	17.9	24.5			19.1		7.7		10.7	3.1	3.5	3.9		14.6			
Urinary 17-OHCS***	6.8		13.7		4.6		5.5		4.3	2.8	0.9		0.0	3.3		17.5		
Urinary 17-KS****	18.5				14.4		20.9		1.2	17.3	11.5		13.8	8.9				
Patient 2 (33 yr, Female)																		
Metyrapone test		×																
Fluocinolone acetonide cream				×	×	×	×	×	×	×	×	×	×			×		
Plasma cortisol	19.7	13.0				4.9			9.7		7.0		5.4	3.0		16.6		
Urinary 17-OHCS	3.5		7.4			1.0		1.8		1.0		2.4	1.9		2.3		32.0	
Urinary 17-KS	5.8		8.9			5.3		5.4		8.7		7.6	8.1		7.2		12.2	
Patient 3 (58 yr, Female)																		
Metyrapone test		×																
Fluocinolone acetonide cream				×	×	×	×	×	×	×	×	×	×			×		
Plasma cortisol	13.1			10.5		14.1		11.6		7.6	7.4		6.8	4.9				13.8
Urinary 17-OHCS	4.6		15.4		5.4	3.9		3.2	0.8	0.5	2.2	2.5	3.2		4.8		37.0	
Urinary 17-KS	3.6		17.5		13.7	7.9		6.9	1.2	8.4	5.7	11.8	9.8		4.4		29.9	
Patient 4 (56 yr, Male)																		
Metyrapone test		×													×			
Fluocinolone acetonide cream				×	×	×	×	×	×	×	×	×	×					
Plasma cortisol	15.3	21.8					28.2		25.5	8.9			10.9					34.4
Urinary 17-OHCS	5.9		12.2		4.7		4.9	7.1		2.8		2.6	2.2	2.3		11.2		
Urinary 17-KS	7.3		8.3		6.6		7.2	7.2		8.2		8.4	4.7	8.5		11.4		
Patient 1 (23 yr, Male)																		
Metyrapone test		×																
Flurandrenolone acetonide cream				×	×	×	×	×	×	×	×	×	×		×			
Plasma cortisol		14.6				10.6	8.6	13.9		12.4	12.4	13.8	11.5		15.0		22.0	

Urinary 17-OHCS	3.3		17.5		1.0		6.3	8.5	7.3	5.4	3.4	2.6	0		13.8
Urinary 17-KS	8.9				12.3		15.2	23.9	24.3	11.1	11.5	15.1	17.3		24.5
Patient 2 (33 yr, Female)														×	
Metyrapone test		×													
Flurandrenolone acetonide cream				×	×	×	×	×	×	×	×	×	×		
Plasma cortisol		16.6		19.7		9.9		13.1		14.6	11.0		24.0	12.8	
Urinary 17-OHCS	2.3		32.0		1.1		4.6		1.2	1.0		0.0	0.0		4.1
Urinary 17-KS	7.2		12.2		4.2		5.4		4.0	5.9		6.9	3.4		7.0
Patient 5 (29 yr, Female)														×	
Metyrapone test		×													
Flurandrenolone acetonide cream				×	×	×	×	×	×	×	×	×	×		
Plasma cortisol	31.9	14.4		13.9		14.2		10.6		12.8	14.0		14.2	15.4	
Urinary 17-OHCS	2.3		6.3		1.1	1.5		3.8	3.7		0.8	2.3	0.0	0.9	8.7
Urinary 17-KS	6.9		10.7		7.3	17.3		8.6	9.7		8.7	10.5	10.3	11.1	21.3
Patient 6 (19 yr, Male)														×	
Metyrapone test		×													
Betamethasone valerate cream				×	×	×	×	×	×	×	×	×	×		
Plasma cortisol	19.2	17.8		18.6		7.7		9.7		9.7	12.1	11.9	12.4		
Urinary 17-OHCS	11.8		52.1	12.2	0.0	0.0	4.0	0.0	7.2	0.0	0.0	0.0	3.1	1.4	22.3
Urinary 17-KS	7.1		26.5	24.4	13.7	7.2	10.2	24.9	3.5	9.3	10.8	8.3	7.7	6.9	24.0
Patient 7 (60 yr, Male)														×	
Metyrapone test		×													
Betamethasone valerate cream				×	×	×	×	×	×	×	×	×	×		
Plasma cortisol	14.3			30.0		15.5		10.9		16.5	15.6	14.0	20.9	14.9	
Urinary 17-OHCS	4.8		28.9	11.0	2.5	6.3	3.8		3.5	3.7	4.1	4.5	2.6	8.3	35.0
Urinary 17-KS	7.6		3.6	7.2	9.6	8.8	9.6		6.0	7.7	6.7	5.4	8.2	17.7	20.0

* No tests were done on first day. "×" indicates day on which tests or therapeutic procedures were done.

** Normal values for plasma cortisol, 8 μg to 24 μg/100 ml.

*** Normal values for 24-hour urinary 17-OHCS, 2–9 mg/24 hr.

**** Normal values for 24-hour urinary 17-KS, 8 to 20/mg24 hr for men; 5–15 mg/24 hr for women.

presented herein partially support this conclusion. Three of the four patients treated with 2.25 mg of fluocinolone acetonide manifested intermittent adrenal suppression. The fourth patient showed reduction in adrenocortical function below pre-treatment values, although the levels of plasma cortisol and 24-hour urinary 17-OHCS were not reduced below the lower limits of normal. All three patients treated with 2.25 mg of topical flurandrenolone acetonide had intermittent suppression of their urinary 17-OHCS output but no significant suppression of plasma cortisol levels. Using 2.25 mg of betamethasone valerate topically, one patient demonstrated suppression of his urinary 17-OHCS and some reduction in his plasma cortisol, but the other did not show any evidence of adrenocortical suppression.

We wish to emphasize that each of these patients had a generalized and severe dermatitis and that the entire surface of the skin was inuncted and occluded nearly continuously. Even with this rather strenuous therapeutic program, adrenocortical suppression was usually mild and transient and not always present. The post-treatment response to metyrapone was normal in every case.

Since considerably less than total percutaneous absorption of topically applied corticosteroids occurs even with prolonged polyethylene film occlusive therapy, it would seem that even less than 2.25 mg of these steroids was actually absorbed in these patients. Taylor *et al.* (20) have estimated that 10 % to 20 % absorption through inflamed skin occurs, and recent experimental evidence approximates this estimation in the case of betamethasone valerate (1). Thus, perhaps as little as 0.25 mg per day of any one of these fluorinated topical steroids can cause intermittent pituitary-adrenal axis suppression when absorbed continuously through the skin. It seems unlikely that any smaller amounts of these corticoids can lead to adrenocortical suppression from percutaneous absorption, even with the use of occlusive dressings.

Even though as little as 2.25 mg of fluocinoline acetonide, flurandrenolone acetonide, betamethasone valerate or triamcinolone acetonide may induce adrenocortical suppression when applied to extensive areas of dermatitis under plastic dressings, the apprehension voiced (10, 18) that such suppression will lead to adrenocortical hypofunction after stopping such treatment or to inability of the pituitary-adrenal axis to respond normally to stress may not be well-founded. There is little clinical or laboratory evidence to justify this fear (18). In addition Danowski *et al.* (5) have shown that patients receiving corticoids in amounts sufficient to suppress the pituitary-adrenocortical axis, but too small to cause Cushingoid side effects, do not show evidence of adrenal hypofunction with stress or after stopping the corticosteroid treatment.

SUMMARY

Studies on percutaneous corticosteroid absorption resulting in pituitary-adrenocortical suppression are reported. Several patients with generalized exfoliative dermatitis were inuncted with an ointment containing 2.25 mg of fluocinolone acetonide, flurandrenolone acetonide or betamethasone valerate under continuous total body plastic film occlusion. With such treatment three of four patients treated with fluocinolone acetonide, all three patients treated with flurandrenolone acetonide, and one of two patients treated with betamethasone valerate showed laboratory evidence of intermittent, incomplete adrenocortical suppression.

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