PLASMA CORTISOL LEVELS IN PATIENTS TREATED EXTENSIVELY WITH FLUPREDNYLIDENE-21-ACETATE TOPICAL CREAM (DECODERM)

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Summary

Topical steroids, which are highly effective clinically, have been claimed to be capable of being absorbed through the skin and to suppress the pituitary adrenal axis, though remarkably little evidence of adverse systemic effect is found. The functional status of the pituitary adrenal axis can best be judged by plasma cortisol estimations.

A study on the effect of topical application of 25 gm. of 0.1% flupredny-lidene-21-acetate cream twice daily (i.e. 50 gm. daily) in twenty patients with extensive skin lesions, revealed no statistically significant alterations in plasma cortisol levels during such therapy.

Topical steroids, absorbed through the skin may produce changes in endogenous corticosteroid production[1-3] under experimental conditions rarely used in everyday practice. Munro & Feiwel[3], for instance studied patients with 60% or more of their body surface affected by skin disease, and applied 30 gm. of steroid ointment a day for 14 days under whole body occlusion for 20 hours, out of each 24 hour periods. In practice, the majority of patients who are advised to apply topical steroids, are treated as out-patients with considerably less than 30 gm. of a steroid preparation a day. In India occlusive dressings, if used at all, are applied to circumscribed areas and only overnight.

There is remarkably little clinical evidence of adverse systemic effects resulting from steroid absorption through the skin. Sporadic reports have however, been published concerning growth retardation[4,5] and describing oedema following the intensive use of topical hydrocortisone in children (Feinblatt et al.[6] 1966). Keipert and Kelly[7] (1971) described an 11 week old baby who developed Cushingoid appearance after the application of large amounts of betamethasone 17-valerate cream. There is apparently no evidence of any adverse systemic effects in an adult. Nevertheless, most doctors are concerned about the possibility of placing any patient at risk.

There are a number of ways of measuring the systemic effect of topical steroids, although the relative merits of these methods vary considerably[9]. Determining the blood eosinophil count and plasma and urinary electrolyte concentrations are only of limited value

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as these techniques only give a measure of the indirect effect of adrenocortical suppression. Study of the epidermal penetration and percutaneous absorption of radioactive labelled topical steroid preparation gives a definite indication of the local depot effect of such a steroid, but this method only gives a limited idea of any systemic action.

Traditionally, assessment of adrenocortical activity in health and disease has depended on estimation of corticosteroid metabolites in the urine, i.e. determining the urinary 17 ketocorticosteroid and 17 hydroxycortico-steroid excretion. However, since the urine assays also include biologically inactive metabolites of the actual steroid hormones, and only indirectly relate to true cortisol secretion or excretion, they may often be misleading.

Since the introduction by Mattingly[10] in 1962, of a reliable and rapid plasma cortisol assay, assessment of adrenocortical activity has switched more and more to plasma cortisol measurements. The ease of their assay has made frequent sampling during dynamic test procedures a practical proposition. Besides, diagnostic reliability has greatly improved as a result.

Therefore, determining the plasma cortisol estimations is a more reliable and sensitive indicator of depressed adrenocortical function.

In the following, we present our study of plasma cortisol levels in patients treated extensively with fluprednylidene-21-acetate cream.

Method of study

The study was carried out in 20 patients with extensive steroid responsive dermatoses and 5 controls - all adults. None of the patients received any internal or external treatment with steroids or ACTH, for at least four weeks before the study.

Drugs like tranquilisers, oral contraceptives, spironolactone (Aldactone), Fucidic acid and Mepacrine were avoided for four weeks prior to the study. Diabetics were excluded from the study as ketone-bodies in the plasma would record false values.

From Table No. 1 it will be noted that 10 of 20 patients showed extensive involvement, 5 showed between 19–72% and another 5 between 10–18% body area involvement.

A majority of individuals with extensive skin involvement were selected in order to assess the possibility of suppression of adrenal function following prolonged steroid application.

In every subject treatment with 0.1% fluprednylidene - 21 – acetate cream, i.e. 25 gm. of cream was applied twice daily, morning and evening (equivalent to 50 mgm. active ingredient daily) over the entire body surface.

The plasma cortisol levels were determined three times in each patient. The first estimation was undertaken prior to the commencement of treatment; the second, one week after extensive topical treatment, and the third, two weeks after cessation or discontinuance of the therapy. Venous blood (10.0 ml.)

TABLE 1

Assessment of Percentage area of body involvement
(According to Wallace's Classification)

% involvement	10—18%	19—36%	37—72%	73—100%	Total
No. of treated cases	5	3	2	10	20
Controls	—	—	—	5	5

Results

TABLE 2

Diagnosis and Plasma Cortisol Estimations

	Diagnosis and cases	Plasma Cortisol Estimations in μg / 100 ml		
		1st	2nd	3rd
1.	Seborrhoeic Dermatitis	16.6	21.8	25.0
2.	,, ,,	16.6	25.0	23.0
3.	,, ,,	12.5	13.5	22.5
4.	,, ,,	16.6	24.6	25.0
5.	,, ,,	26.6	15.4	8.3
6.	,, ,,	13.8	28.3	25.0
7.	,, ,,	23.0	20.0	17.7
8.	,, ,,	37.7	25.0	30.0
9.	,, ,,	16.6	20.0	25.9
10.	,, ,,	33.3	19.2	8.8
11.	,, ,,	8.8	17.7	24.4
12.	,, ,,	13.2	26.0	21.8
13.	,, ,,	24.0	16.0	11.1
14.	Atopic ,,	25.0	26.0	24.4
15.	,, ,,	22.2	24.4	16.6
16.	,, ,,	18.0	16.6	17.4
17.	Contact Dermatitis	13.3	19.2	26.6
18.	,, ,,	22.2	23.2	13.2
19.	Exfoliative ,,	8.3	11.1	12.4
20.	Infectious Eczematoid Dermatitis	11.1	15.3	16.0
	Controls (1)	22.2	20.0	15.2
	(2)	25.0	16.6	20.0
	(3)	8.0	5.5	33.3
	(4)	32.0	14.0	16.8
	(5)	13.9	17.7	16.8

was collected from each fasting patient at 08.30 hours, without exception. The freely flowing blood after venepuncture was collected in heparinised syringes and later placed in heparinised tubes for centrifugation. The plasma was processed immediately thereafter.

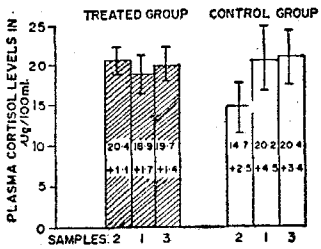
The Porter-Silber Reaction was used for the estimation of the plasma-free cortisol.

The free corticoids are extracted from the plasma in dichloromethane. The dichloromethane extract is shaken with alkali to remove phenolic compounds (oestrogens) and chromogens. Aliquots of the extract are shaken with phenylhydrazine hydrochloride sulfuric acid reagent. The 17, 21–dihydroxy-20-ketosteroid configuration reacts to form a yellow hydrazone which is easily and accurately measured, read at 410 mu. in micro cubettes in the Beckman D.U. Spectrophotometer using a water blank against all tubes.

From Table No. 2 it is seen that the patients selected had seborrhoeic dermatitis (13 patients), atopic dermatitis (3 patients), contact dermatitis (2 patients), exfoliative dermatitis (1 patient) and infectious eczematoid dermatitis (1 patient). The 'control' patients had other skin disorders which do not usually respond to steroid treatment.

Since ACTH and cortisol level fluctuations are known to occur in 24 hours cycles[11], the sampled blood was always collected at 08.30 hours in the morning.

Fig. (1) shows the diagrammatic representation of the results.



STATISTICAL ANALYSIS

COMPARISON OF	1 ST & 2ND. SAMPLES	4TH. & 5TH. SAMPLES
TREATED GROUP	T=0·994, P>0·05	T=0·3173, P>0·05
CONTROL GROUP	T=1·025, P>0·1	T=0·05, P>0·1

In the steroid treated group, the mean value of the plasma cortisol level prior to treatment was 18.98 μg/100 ml. (SE 1.7), and the mean value after one week's extensive steroid application was 20.41 μg/100 ml. (SE 1.1)*. Comparing the mean value of the steroid treated group prior to treatment, i. e. 18.98 μg/100ml. (SE 1.7) to the mean value after two weeks of stopping steroid application which was 19.76 μg/100ml. (SE 1.4) the statistical analysis showed no significant difference in the plasma cortisol values (T value = 0. 31 and $p > 0.05$).

In the control group, the mean value of the plasma cortisol level prior to treatment was 20.22 μg/100 ml. (SE 4.3) and the mean value after one week of extensive steroid application was 14.76 μg/100ml. (SE 2.5). These two levels did not differ significantly. The T value = 1.025 and $p > 0.1$. Comparing the mean value of the control group prior to treatment i. e., 20.22 μg/100 ml. (SE 4.3) to the mean value after two weeks of stopping steroid application which was 20.42 μg/100 ml. (SE 3.4). On statistical analysis showed T value = 0.05 and $p > 0.1$ suggesting no significant difference in the plasma cortisol values.

Discussion

There is a tendency for patients who use large amounts of topical steroids (by application) to have low plasma cortisol levels, although this is not always the case. However, in our study of 20 cases of steroid responsive dermatoses and 5 controls, even though 50 gms. of the fluprednylidene–21–acetate cream was applied daily for a week in both groups of cases, no statistically significant fall in the plasma cortisol levels occurred. In addition, there was no significant change in the post treatment cortisol levels as compared with the pre-treatment cortisol levels. There was no correlation between the duration of treatment and plasma cortisol levels.

Skin diseases for which topical steroids are used are often characterised by exacerbations and remissions with consequent varying rate of topical steroid usage. In addition, the degree of absorption through the skin may vary according to the degree of inflammation present. Scoggins and Kliman[13] showed that triamcinolone cream applied to an arm with extensive dermatitis caused a reduction in plasma cortisol whereas when, after the levels had returned to normal, the same quantity of steroid was applied to the patient's other unaffected arm no systemic effect could be detected. James et al[8] noted that, in two patients treated with betamethasone 17 valerate, plasma cortisol and urinary 17–hydroxycorticosteroid levels tended to increase during the last few days of treatment. Thus, it is likely that if adrenal suppression does occur it will be transient and plasma cortisol levels will return to normal as the acute condition resolves, despite continued therapy[14]. But in our study, no statistically significant difference was observed

* The statistical analysis by students test shows that the plasma cortisol level prior to treatment did not differ significantly from the level one week after extensive topical treatment ($T=0.79$ $p > 0.05$)

in the cortisol levels of patients before the commencement of corticoid application and one week after its usage.

Conclusion

Of the 25 cases–20 steroid responsive dermatoses and 5 controls—no significant lowering of the plasma cortisol levels were seen, even after using 50 gm. of Fluprednylidene—21—acetate cream daily for a period of a week. All the cases included in the study were adults with extensive eczematised dermatitis. There is some evidence[15],[16] that children, perhaps because of their greater ratio of surface area to body weight, may more readily absorb steroid through the skin. Studies in this group would be of interest.

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