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COMPARISON OF THE SUBACUTE EFFECTS OF A NEW GLUCOCORTICOID, DEFLAZACORT, AND PREDNISONE ON THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS OF NORMAL SUBJECTS

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1. The effects of deflazacort (DFL), a new oxazoline derivative of prednisolone, were compared with those of prednisone (Pd) by measuring plasma cortisol (F) levels as an index of the function of the hypothalamic-pituitary-adrenal (HPA) axis.

2. Twelve normal volunteers received each glucocorticoid for 16 to 24 days in a double-blind cross-over trial with random allocation of subjects to treatment with DFL (24 mg/day) and Pd (20 mg/day) in clinically equivalent doses, with a washout period from 20 to 45 days between administration of the glucocorticoids.

3. The following tests were performed in a randomized sequence: cortisol (F) circadian rhythm, insulin tolerance test (ITT), lysine-vasopressin(LVP) and B^{1-24} ACTH stimulation.

4. Despite basal F suppression by DFL, the relative maximum F response (maximum F increment above basal/basal x 100) was significantly greater than control for the ITT and ACTH tests and was similar to the control after intramuscular injection of LVP, suggesting that the responses were appropriate for the basal F levels, with the HPA being reset at a lower level.

5. After Pd, despite higher basal F levels, the F diurnal rhythm disappeared and there was no significant response to ITT, LVP or ACTH, indicating that the limiting factor in the HPA response was the reduced adrenal F production independent of the effects on the steroid-sensitive tissues of the brain including the pituitary.

Key words: deflazacort, prednisone, hypothalamic-pituitary-adrenal axis, cortisol.

Introduction

It is well established that the administration of glucocorticoids (GCs) may produce abnormalities in hypothalamic-pituitary-adrenal (HPA) axis function (Melby, 1974; Wajchenberg *et al.*, 1984).

DFL is a new synthetic GC which is an oxazoline derivative of prednisolone presenting a bulky group at the C-17 position which sterically hinders reactivity of the side chain (Nathanson *et al.*, 1969).

However, while clinical studies in healthy volunteers have suggested that DFL affects glucose metabolism (Wajchenberg *et al.*, 1985) and acts on the HPA axis (Criscuolo *et al.*, 1980) to a lesser extent than Pd (relative potency ratio = 0.80) there is the possibility that DFL might also have a less deleterious effect than Pd on the HPA axis in normal subjects when the 0.80 dose ratio is administered for a long period of time, i.e. more than 2 weeks.

The aim of the present study was to evaluate the effects of a new synthetic GC, deflazacort (DFL) in comparison with prednisone (Pd) on the HPA axis to identify the

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nature of the HPA abnormalities that might occur after their administration.

Patients and Methods

We present a double-blind cross-over trial allocation of subjects to the first treatment, with Pd used for comparison. A washout interval of at least 20 days, ranging from 20 to 45 days, was allowed between each test in order to compensate for possible carry-over effects from the previous GC treatment. The control study was followed by a 16-24 day experimental period with Pd (20 mg/day) or DFL (24 mg/day)[1] which were administered to 12 subjects divided into two 6 patient groups: A, which started on Pd and B, which started on DFL. The doses chosen were assumed to be clinically equivalent on the basis of (a) preclinical animal studies and (b) human pharmacological studies (Cannigia *et al.*, 1977).

The plan of study called for 3 tests: circadian variation of plasma F, ITT and LVP tests performed in a randomized fashion. The effect of DFL treatment of Group A and that of Pd of Group B on the ACTH stimulation test was also evaluated.

We studied 6 normal healthy female volunteers. Mean age was 30 years (range, 20-40 years), body weight 64 Kg (range, 47-73) and height 1.63 m (range, 1.52-1.68). This was Group A, which started on Pd. Another group of 6 normal females, whose mean age was 26 years (range, 22-39 years), body weight 58 Kg (range, 50-66) and height 1.50 m (range, 1.51-1.65) (Group B), which started on DFL. Informed consent was obtained from all patients prior to the study.

For an evaluation of the diurnal F rhythm, blood samples were collected at 8:00, 16:00, 24:00 and 8:00 h the next morning for determination of plasma F. The ITT was performed by giving regular porcine monocomponent insulin (Actrapid NOVO, 0.1 U/kg) *iv*, with blood withdrawn immediately before (0) and 5, 10, 15, 20, 30, 45, 60, 90 and 120 min after insulin injection for plasma glucose (PG) and F determinations. The LVP test was performed by collecting a basal blood sample at 8:00 h, after which 10 Pressor Units of LVP were injected *im*. Additional blood samples were taken at 30 and 60 min after injection for F determination. The ACTH stimulation test was carried out by injecting fasting subjects *iv* with 250 μg B^{1-24} ACTH (Cosyntropin) at 8:00 h. Blood samples for F determination were drawn immediately before and 30 and 60 min after injection. This test was only performed on 5 subjects from Group A, before and after DFL treatment, while in Group B it was also carried out on 5 individuals before and after Pd treatment, both GCs being the second steroid to be administered.

Plasma F was measured by specific RIA (Okada *et al.*, 1979). The antiserum used (Miles-Yeda Ltd., Rehovot, Israel) was prepared against cortisol 21-hemisuccynyl-thyroglobulin having a high degree of specificity for F and showing less than 1% cross-reaction with Pd and prednisolone, which is the major product of Pd metabolization (Meikle *et al.*, 1975). Sensitivity evaluation for plasma samples using two standard deviations of 8 sets of duplicate maximum binding tubes showed a mean ± SD of 0.76 ± 0.29 μg/dl. Intra-assay precision studies for plasma F gave coefficients of variation (CV) of the order of 4.5%, 4.8% and 5.8% for plasma samples of high (39.1 μg/dl), medium (16.3 μg/dl) and low (7.2 μg/dl) F mean content, respectively. Interassay reproducibility CVs were 5.75%, 7.3% and 8.8% for similar plasma with mean F levels of 37.7, 17.0 and 6.7 μg/dl, respectively. The samples collected during all tests from the same patient were analyzed in the same assay.

The changes in plasma F following all stimulation tests were analyzed in terms of mean basal level prior to stimulation (basal), peak level attained (peak), maximum increment over basal (Δ) and relation between basal and maximum increment as the percent response above basal, i.e., the relative response. Calcula-

[1] The differences in time of GC treatment for the various subjects were due to the fact that a total of 5 tests including those for evaluation of glucose metabolism were performed on each patient in a random fashion.

tion of the relative maximum response (Δ/basal x 100 = Δ%) permitted the evaluation of the F responsiveness independent of factor(s) influencing the basal level.

Plasma glucose (PG) was determined by the ferricyanide method (Hoffman, 1937) using a Technicon analyzer.

All data are expressed as mean ± SEM. For interpretation of the diurnal F rhythm, the findings before and after GC treatment were compared by analysis of variance (ANOVA) with two-way classification, time and treatment (Snedecor, 1956). The significance of differences between group means in the remaining tests was determined by the Student paired and unpaired *t*-test (Dixon and Massey Jr., 1957).

Results

Diurnal cortisol rhythm

a) Effect of Pd treatment

For Group A, the control study showed the expected diurnal F rhythm, with values returning to basal levels on the next morning at 8:00 h (Table 1). After 21 ± 1.2 days of Pd treatment, there were significant differences in mean cortisol values between sampling times ($F = 12.18$; $P < 0.001$) and between the control and Pd ($F = 21.28$; $P < 0.001$) with values being lower after GC administration. However, there were no significant differences between sampling times after Pd treatment ($F = 2.04$; $P = 0.134$).

For Group B, after a washout period of 38 ± 1.6 days after DFL and 19 ± 0.8 days after Pd treatment, there were also significant differences between sampling times ($F = 12.48$; $P < 0.001$) and between control and GC treatment ($F = 26.80$; $P < 0.001$) with lower F values after GC. Similarly, there were no significant differences in mean cortisol values between times after Pd ($F = 1.83$; $P = 0.174$).

b) Effect of DFL treatment

For Group A, after a washout period of 29 ± 2.8 days, followed by 17 ± 0.4 days of DFL treatment, there was a significant difference in mean cortisol levels between sampling times ($F = 6.05$; $P < 0.01$) and between control and GC treatment ($F = 41.28$; $P < 0.001$) with cortisol values being lower after the drug treatment.

For Group B, after DFL treatment for 17 ± 0.4 days, there were significant differences

Table 1 - *Circadian rhythm of plasma cortisol in 12 healthy subjects before and after prednisone and deflazacort treatment.*

The data are reported as means ± SEM for plasma cortisol in μg/dl. Each group contained 6 subjects.

Treatment	Time (hours)			
	8	16	24	8
Group A				
Control	8.5 ± 0.62	4.7 ± 0.76	1.6 ± 0.11	8.7 ± 1.03
Prednisone	3.6 ± 0.35	2.8 ± 0.19	2.9 ± 0.32	3.9 ± 0.53
Control	8.1 ± 0.69	3.9 ± 0.58	2.5 ± 0.59	8.8 ± 0.73
Deflazacort	2.1 ± 0.40	2.1 ± 0.46	0.8 ± 0.10	1.2 ± 0.12
Group B				
Control	12.0 ± 1.27	6.2 ± 0.75	2.7 ± 0.49	10.4 ± 1.19
Deflazacort	3.2 ± 0.85	1.8 ± 0.47	1.0 ± 0.14	2.6 ± 0.75
Control	9.7 ± 0.82	5.6 ± 0.85	1.7 ± 0.71	9.8 ± 1.20
Prednisone	4.3 ± 0.53	3.1 ± 0.50	2.7 ± 0.33	3.6 ± 0.58

Table 2 - *Effect of the insulin tolerance test on plasma cortisol levels of healthy subjects before and after prednisone and deflazacort treatment.*

The data are reported as means ± SEM for plasma cortisol in μg/dl. Each group contained 6 subjects.

Treatment	Time (min)											
	0	5	10	15	20	25	30	35	45	60	90	120
Group A												
Control	7.7 ± 0.53	6.8 ± 0.51	6.3 ± 0.42	6.5 ± 0.62	7.1 ± 0.51	6.9 ± 0.95	9.9 ± 0.95	11.2 ± 1.48	12.5 ± 0.87	15.5 ± 0.80	15.2 ± 0.66	14.0 ± 0.70
Prednisone	4.0 ± 0.34	4.1 ± 0.24	4.0 ± 0.23	4.2 ± 0.31	3.7 ± 0.27	3.8 ± 0.30	3.8 ± 0.27	3.9 ± 0.20	4.1 ± 0.15	3.8 ± 0.14	3.9 ± 0.17	2.84 ± 0.35
Control	8.3 ± 0.56	7.4 ± 1.03	6.9 ± 0.49	6.3 ± 0.58	7.1 ± 0.52	7.4 ± 0.50	9.2 ± 0.72	10.9 ± 0.68	12.7 ± 1.46	15.9 ± 1.86	17.2 ± 1.84	13.0 ± 2.15
Deflazacort	1.7 ± 0.15	2.6 ± 0.51	1.9 ± 0.57	2.2 ± 0.65	2.3 ± 0.59	2.0 ± 0.66	2.3 ± 0.42	2.4 ± 0.68	4.1 ± 0.77	4.5 ± 0.57	4.9 ± 0.33	4.2 ± 0.44
Prednisone *vs* Deflazacort P =	<0.005	>0.05	<0.025	<0.05	>0.05	>0.05	<0.01	>0.05	>0.05	>0.05	>0.05	>0.05
Group B												
Control	10.5 ± 0.54	10.5 ± 0.80	10.3 ± 0.64	9.1 ± 0.58	9.0 ± 0.8	9.6 ± 0.26	11.5 ± 0.32	14.3 ± 0.98	18.6 ± 1.43	18.9 ± 1.02	17.7 ± 2.59	18.5 ± 2.55
Deflazacort	0.7 ± 0.12	0.6 ± 0.11	0.5 ± 0.09	0.5 ± 0.18	0.5 ± 0.11	0.4 ± 0.11	0.6 ± 0. 7	0.9 ± 0.26	1.8 ± 0.32	2.6 ± 0.47	2.0 ± 0.28	1.7 ± 0.26
Control	10.4 ± 2.04	10.5 ± 2.94	8.5 ± 2.31	8.6 ± 1.99	9.2 ± 1.76	9.6 ± 2.50	9.5 ± 2.90	14.4 ± 3.11	18.3 ± 2.52	19.9 ± 3.31	19.8 ± 3.40	19.4 ± 3.62
Prednisone	4.6 ± 0.94	5.3 ± 1.00	5.1 ± 0.95	5.2 ± 1.15	4.9 ± 0.82	4.8 ± 0.67	5.0 ± 0.74	4.9 ± 0.69	4.7 ± 0.69	4.9 ± 0.69	4.9 ± 0.69	4.5 ± 0.98
Deflazacort *vs* Prednisone P =	< 0.01	<0.01	<0.005	>0.01	>0.001	>0.001	>0.001	<0.005	>0.001	<0.01	<0.005	<0.05

in mean cortisol levels between sampling times ($F = 13.32$; $P < 0.001$) and between control and DFL treatment ($F = 64.20$; $P < 0.001$), with cortisol levels being significantly lower after GC.

There were significant differences in mean cortisol levels between sampling times after DFL in Group A ($F = 4.08$; $P = 0.020$), but not in Group B ($F = 2.32$; $P = 0.106$). However, because the values for both groups after GC were below or close to the minimum detectable level in the cortisol assay, these findings are more a statistically than a biologically meaningful observation. Similarly the differences in the effects of Pd and DFL could not be established either in Group A (statistically significant differences between treatment - $F = 44.46$; $P < 0.001$ - but not between times of sampling - $F = 2.20$; $P = 0.068$) or Group B (statistically significant differences between treatments - $F = 9.32$; $P = 0.004$ - and between times of sampling - $F = 3.94$; $P = 0.015$).

Insulin tolerance test

a) Effect of Pd treatment

For Group A, which started on Pd, there were no significant differences in PG response to insulin before or after Pd treatment (18 ± 0.8 days). Plasma F was significantly lower at all sampling times after Pd (Table 2). The mean ± SEM Δ and Δ% were 8.54 ± 0.80 μg/dl and 116 ± 14.6% in the control test and 0.66 ± 0.24 μg/dl and 19 ± 8.69% after Pd, respectively, i.e. significantly lower.

For Group B, after a washout period of 38 ± 2.8 days after DFL, Pd treatment did not significantly change glucose levels after insulin in relation to the control. F values were also significantly lower at all times after Pd, except at 5, 10, 15 and 30 min after insulin injection (Table 2). As for Group A, the mean Δ and Δ% were significantly lower after Pd when compared to the control (control Δ = 12.48 ± 2.65 μg/dl and Δ% 131 ± 30.28%; Pd: Δ = 1.09 ± 0.22 μg/dl and Δ% = 26 ± 6.32%).

Even though in study B mean F values were higher at all sampling times, except at 30 min, they were not significantly different from those obtained for patients in Group A. Correspondingly the higher mean Δ and Δ% obtained in study B were not significantly different from those obtained in study A.

b) Effect of DFL treatment

For Group A, after a washout period of 32 ± 1.6 days, there were no significant differences in PG response to insulin before and after DFL treatment (17 ± 0.4 day). Plasma F levels were significantly lower at all sampling times after DFL (Table 3). When Δ and Δ% were compared in both studies, while Δ was significantly higher in the control study (Δ control: 9.86 ± 1.32 μg/dl *vs* DFL: 3.98 ± 0.30 μg/dl), when the value was corrected for basal levels, Δ% was significantly higher for GC (Δ% control: 121 ± 18.40% *vs* Δ% DFL: 244 ± 68.28).

For Group B, there were also no significant differences in PG levels before and during ITT in control and after DFL (18.0 ± 0.8 days). As for Group A, the F values were significantly lower at all sampling times after DFL (Table 2), and Δ was significantly higher in the control (10.75 ± 2.22 μg/dl) than after DFL (2.02 ± 0.29 μg/dl), but when related to basal levels it was higher after DFL but not significantly so in relation to the control test (Δ% control: 106 ± 25.30 *vs* Δ% DFL: 306 ± 55.91%).

When the two groups were compared for PG responses to DFL, no significant differences were detected at any sampling time. However, mean F levels were higher in study A when DFL was used as the 2nd GC, significantly so at zero, 5, 15, 20, 30, 90, and 120 min. The comparison of Δ and Δ% after DFL in study A *vs* B showed a significantly higher Δ but not Δ% when DFL was the first GC (study B).

When the results of both GCs were compared within Group A, the PG values before anf after insulin injection were similar. F values were higher after Pd than after DFL, at all times, and significantly so at the basal level and at 10, 15 and 30 min. On the other hand, Δ and Δ% were significantly higher after DFL. In Group B, PG values were significantly higher after Pd than after DFL at all sampling times

Table 3 - *Effect of the lysine-vasopressin test on plasma cortisol levels of healthy subjects before and after deflazacort and prednisone treatment.*

The data are reported as means ± SEM for plasma cortisol in μg/dl. Each group contained 6 subjects.

Treatment	Time (min)		
	0	30	60
Group A			
Control	9.2 ± 0.40	18.5 ± 0.37	17.5 ± 1.15
Prednisone	3.8 ± 0.26	4.3 ± 0.27	3.8 ± 0.17
Control	9.7 ± 0.66	19.1 ± 1.19	19.9 ± 1.15
Deflazacort	1.1 ± 0.09	3.8 ± 0.34	2.9 ± 0.26
Prednisone *vs* Deflazacort	$P < 0.005$	$P > 0.20$	$P > 0.10$
Group B			
Control	11.0 ± 1.15	23.0 ± 2.86	26.4 ± 2.48
Deflazacort	3.2 ± 0.75	6.5 ± 1.13	8.3 ± 1.31
Control	9.4 ± 0.77	20.4 ± 0.44	19.9 ± 1.67
Prednisone	4.1 ± 0.50	4.47 ± 0.47	4.49 ± 0.41
Deflazacort *vs* Prednisone	$P > 0.4$	$P > 0.2$	$P > 0.10$

from 25 to 45 min. As in the previous group, F values were significantly higher at all sampling times after Pd. However, while Δ's were similar, Δ% were significantly higher for DFL than Pd.

Lysine-vasopressin test

a) Effect of Pd treatment

The values obtained in the control study on Group A are indicated in Table 3. Δ and Δ% were 9.97 ± 0.87 μg/dl and 110 ± 11.53%, respectively. After 20 ± 0.8 days of Pd treatment, F values were significantly lower than control at all sampling times, the same occurring for Δ (0.51 ± 0.32 μg/dl) and Δ% (16 ± 10.01%).

The results of the control LVP test carried out on Group B after a washout period of 36 ± 1.9 days after DFL are shown in Table 3. Δ was 11.29 ± 2.27 μg/dl and Δ%, 152 ± 31.42. After 17 ± 0.8 days of Pd treatment, F levels, Δ (0.54 ± 0.31 μg/dl) and Δ% (34 ± 28.57%) were also significantly lower.

No significant differences were observed in any of the parameters of the LVP response between the two controls in Groups A and B as well as after Pd.

b) Effect of DFL treatment

The results of the control LVP injection in Group A are shown in Table 3. Mean ± SEM Δ and Δ% were 10.71 ± 1.14 μg/dl and 113 ± 11.42%, respectively, after a washout period of 30 ± 1.1 days. After 20 ± 1.1 days of GC treatment, mean F values were significantly lower at all times, with Δ and Δ% values of 2.71 ± 0.54 μg/dl and 262 ± 61.63%, respectively. While the mean maximal incremental F values over basal (Δ) were significantly lower after DFL in

comparison to the control test, there were no significant differences in mean relative maximal responses (Δ%).

The results of the control LVP for Group B are presented in Table 3. Δ and Δ% were 15.65 ± 2.20 μg/dl and 160 ± 27.22%, respectively. After 17 ± 2.2 days of DFL treatment, mean F values were significantly lower at all sampling times in comparison to the control study, with Δ and Δ% of 5.06 ± 1.02 μg/dl and 311 ± 119.59%, respectively. In the same way as for Group A, mean Δ's were significantly lower after DFL while no significant differences in Δ% were observed between control and GC treatment. Comparison of the parameters of the control LVP tests for DFL indicated no significant difference between Groups A and B. While the mean F values after DFL were not significantly different in the two groups, the mean Δ's but not Δ% were significantly higher in Group B.

For Group A, mean F values were not significantly different when Pd was compared to DFL except at fasting, with mean Δ and Δ% being significantly higher after DFL. No significant differences were observed in mean F values of LVP testing after Pd and DFL treatment in Group B. As was the case for Group A, mean Δ and Δ% were significantly higher after DFL than after Pd.

ACTH test

In this study no paired comparisons were performed, the effect of GC treatment being evaluated only in the 2nd phase of each study, i.e., after DFL in Group A and after Pd in Group B, and compared to the corresponding controls.

a) Effect of Pd treatment

For Group B, after a washout period of 40 ± 2.2 days, maximum F increase above basal (Δ) and maximum increase (Δ%) were 15.80 ± 0.95 μg/dl and 160 ± 13.90%, respectively (Table 4). After 18 ± 0.9 days of Pd treatment, mean F values were significantly lower at all sampling times in comparison to the control, with Δ and Δ% of 1.52 ± 0.14 μg/dl and 43.00 ± 7.85%, respectively, i.e. significantly lower than in the control test.

b) Effect of DFL treatment

For Group A, after a washout period of

Table 4 - *Effect of the ACTH stimulation test on plasma cortisol levels of healthy subjects before prednisone or deflazacort treatment.*

The data are reported as means ± SEM for plasma cortisol in μg/dl. Each group contained 5 subjects.

Treatment	Time (min)		
	0	30	60
Group A			
Control	9.2 ± 1.22	20.8 ± 2.62	21.0 ± 2.42
Deflazacort	1.1 ± 0.21	7.9 ± 0.44	9.4 ± 0.91
Group B			
Control	10.4 ± 0.74	23.0 ± 1.66	25.8 ± 1.35
Prednisone	3.8 ± 0.30	4.9 ± 0.43	5.2 ± 0.18
Deflazacort (A) *vs* Prednisone (B)	$P < 0.001$	$P < 0.001$	$P < 0.005$

41 ± 2.7 days, Δ and Δ% were 15.74 ± 0.76 μg/dl and 182 ± 22.86%, respectively (Table 4). After 20 ± 0.9 days of DFL treatment, F values were significantly lower in all samples, with Δ and Δ% of 8.47 ± 0.63 μg/dl and 806 ± 126%, respectively. While the first parameter (Δ) was significantly lower, Δ% was significantly higher after DFL in comparison to control.

The two control studies were not significantly different in Groups A and B. When the effects of Pd and DFL were compared, mean F values were significantly higher in the samples after Pd, but were significantly higher after DFL in the post-ACTH samples. Finally, mean Δ and Δ% were significantly higher after DFL in comparison to Pd.

Discussion

This study was undertaken to determine whether the subacute treatment with equipotent anti-inflammatory pharmacological doses of Pd and DFL had similar suppressive effects upon the HPA axis and whether there was a preferential action of one of the GCs on the pituitary and/or hypothalamus and/or higher centers of the brain. We measured the diurnal rhythm of plasma F levels as a source of useful information concerning the hypothalamic mechanism, which presumably controls the early morning rise of plasma F.

While there was a fall in fasting plasma F, the very low F levels attained after Pd and DFL did not allow us to identify the presence of a diurnal rhythm after either GC in view of the sensitivity of the assay for F determination. Furthermore, the assessment of hypothalamic-pituitary release of ACTH by F response to ITT (Cesar *et al.*, in press) showed a significant reduction in response after both GCs. However, the relative maximum response (Δ%), which permitted evaluation of the F response to hypoglycemia independently of factors influencing the basal levels, was significantly greater after DFL than in the control test.

Because the ITT depends on adrenal F output as an *in vivo* assessment of physiologic ACTH release, this test was paired in the 2nd part of each study with an ACTH stimulation test using a pharmacological dose of synthetic B^{1-24} ACTH and, as previously shown by Kehlet and Binder (1973), the response to the test correlated well with the integrated HPA function (evaluated by the ITT) after either DFL or Pd considering Δ%.

Finally, the LVP test used to evaluate pituitary ACTH reserve gave a similar response to that observed after ITT, i.e., normal and lower maximum relative F response after DFL and Pd, respectively, when compared to the control testing.

By combining the 3 tests (ITT, ACTH and LVP) and taking Δ% into consideration, we suggest that, after a two-week DFL treatment, the responses were appropriate in relation to the basal F concentrations, with HPA being reset at a lower level.

On the other hand, a different pattern emerged in patients treated with Pd, with no significant response to the ITT or LVP. When these tests were paired with ACTH stimulation, the results suggested that the limiting factor in the overall HPA response was the reduced ability of the adrenal gland to produce F independently of the Pd effects on the steroid-sensitive tissues of the brain, including the hypothalamus. Since pharmacokinetic and metabolic studies did not show substantial differences in the metabolic rates of DFL in rat and man, the longer duration of action as compared to Pd in rats and confirmed in man (Schiatti *et al.*, 1980) may be a factor to be considered in the interpretation of the different results obtained with the tests when DFL and Pd were compared. Thus, DFL could block the hypothalamus and/or higher centers by decreasing corticotrophin - releasing factor, the HPA being reset at a lower level, and Pd, being a shorter-lasting GC (Assandri *et al.*, 1984) may have a less suppressive action on the hypothalamus and/or higher centers with less reduction in basal F levels when compared to DFL treatment. However, the lack of ITT and LVP responses is not compatible with our suggestion unless we postulate a significant pituitary action of the steroid with either loss to stress responsiveness or with a lesser effect on feedback responsiveness and impairment of

the ability to respond to stress, as demonstrated in patients on intermittent steroid therapy (Martin *et al.*, 1968).

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