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Tricyclic Wash-out and Growth Hormone Response to Clonidine

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We have observed a significantly higher growth hormone (GH) response to clonidine administration (150 μg i.v.) in 14 patients with a major depressive disorder who had never received antidepressant therapy than in 14 matched depressive patients who had not received tricyclic drugs for at least 15 days. Compared with a control group of eight subjects, untreated depressed patients, as a group, had a normal response, while matched patients had markedly blunted response. Results for the group of untreated depressed patients showed that some patients had a blunted response while others had a response in the normal range. The results suggest that studies on the GH response to clonidine in psychiatric patients need to take into account the confounding and long-lasting effects of tricyclics.

Alterations in noradrenergic function have been postulated in patients with depression. One experimental strategy that has been used to study the noradrenergic system is acute challenge with the pharmacological agent clonidine. It is recognised that clonidine, by stimulation of hypothalamic post-synaptic alpha-2 adrenergic receptors, induces secretion of growth-hormone-releasing factor (GRF) and a discrete pulse of growth hormone (GH) release over the usual low baseline levels in humans. The GH response to clonidine may thus provide an indirect index of central adrenoreceptor function.

The methodological issue of the length of the tricyclic wash-out period is crucial in studies of the GH response to clonidine challenge. In normal subjects tricyclics alter the GH response to stimulation of the alpha-2 adrenergic receptor by clonidine for at least 3 weeks (Corn *et al*, 1984). We recently published our finding that patients with panic disorder have a normal GH response to clonidine (Schittecatte *et al*, 1988). However, these results were at odds with other studies (for a review see Charney & Heninger, 1986) where a blunted response was reported in these patients. We have suggested that the discrepancy might be due to the fact that the patients in these studies had a tricyclic wash-out period of two or three weeks, whereas, with the exception of one patient, ours had never received antidepressant therapy. The exception was the only patient with a blunted response. Blunted GH response to clonidine in depressed patients is a well-established fact (for a review see Siever & Uhde, 1984). This finding has been confirmed by most of the studies cited in Table I.

Table I summarises the available studies on the GH response to clonidine. In five independent studies depressed patients (mainly of the endogenous subtype) were reported as manifesting a blunted GH response to clonidine when compared with control subjects. Only one study (Horton *et al*, 1986) found no difference between depressed and control subjects in their GH response to clonidine administration (1.3 μg/kg i.v.).

The presentation of the results in these studies, except in one study by Siever *et al* (1986), does not permit classification of patients and controls as 'responders' or 'non-responders' to clonidine stimulation. Differences between subgroups of depressed patients in their GH response to clonidine are more controversial. One study (Checkley *et al*, 1984) found a difference between endogenous and non-endogenous depressed patients, but another study (Dolan & Calloway, 1986) found no significant differences between the two groups. The contradictory results might be due in part to the small sizes of the samples (7 patients per group). The studies used a wash-out period of one (Boyer *et al*, 1986; Horton *et al*, 1986) to four weeks (Matussek *et al*, 1980 and Siever *et al*, 1982).

We wanted to test the hypothesis that the blunted GH response to clonidine in depressed patients might be due, in part, to the recent use of tricyclics. One method of testing this hypothesis is to compare a group of patients who have never received antidepressant therapy with a matched group of patients who have not received tricyclics for at least 15 days. Another method is to compare the two groups of patients with a control group.

Method

Subjects

In a prospective study, we carefully selected 14 depressed patients (Group 1: 7 men and 7 women) who

TABLE I

Studies on the plasma growth hormone response to clonidine in depressed patients

Reference		*No. of patients*	*Diagnostic criteria*	*No. of controls*	*Clonidine*	*Minimum length of tricyclic wash-out: days*	*Results*
Matussek *et al* (1980)	10	(2M, 8F) endogenous v. 12 (5M, 7F) neurotic–reactive depressives	(+)	32 (14M, 18F)	i.v. 150 μg	28	Endogenous depressive patients differ significantly from neurotic–reactive depressives and controls
Checkley *et al* (1981)	10	(6M, 4F) major depressives, endogenous subtype	(*!)	10 (6M, 4F)	i.v. 2 μg/kg	21	GH response of the group of depressed patients significantly less than that of normal subjects
Siever *et al* (1982)	14	(?M, ?F) major depressives	(*)	10 (?, ?F)	i.v. 2 μg/kg)	28	GH response significantly less for depressed patients than for controls
Charney *et al* (1982)	11	(6M, 5F) depressives, endogenous subtype	(*)	11 (6M, 5F)	*p.o.* 5 μg/kg	24	Difference in the GH response to clonidine only in the male patients and controls
Ansseau *et al* (1983)	15	(?M, ?F) primary, v. 9 (?M, ?F) secondary depressives	(*!)	–	i.v. 150 μg/kg	14	Decreased response for the group of primary depressed in comparison with secondary depressed patients
Checkley *et al* (1984)	7	(5M, 2F) endogenous v. 7 (5M, 2F) non-endogenous depressives	(*)	–	i.v. 1.3 μg/kg	21	The patients with endogenous depression have smaller GH responses to clonidine than the patients with non-endogenous depression
Dolan *et al* (1986)	7	(?M, ?F) endogenous v. 7 (?M, ?F) non-endogenous depressives	(*!)	–	*p.o.* 5 μg/kg	14	No significant difference in GH response to clonidine in patients classified as endogenous or non-endogenous
Boyer *et al* (1986)	10	(1M, 9F) endogenous v. 10 (9M, 1F) neurotic–reactive depressives	(!)	11 (?M, ?F)	i.v. 150 μg	8	GH response in the neurotic–reactive depressives identical to that in the control group. No GH response in the endogenous group
Horton *et al* (1986)	17	(?M, ?F) endogenous v. 17 (?M, ?F) non-endogenous depressives	(*!)	31 (9M, 22F)	i.v. 1.3 μg/kg	7	No significant difference between depressed and control subjects. Subjects with endogenous depression do not show statistically significant blunting
Siever *et al* (1986)	13	(?M, ?F) major depressives	(*)	7	i.v. 2 μg/kg	14	Significantly greater number of blunted peak GH responses to clonidine (< 5 ng/ml) in depressed patients than in controls. Peak GH response not different between groups

Diagnostic criteria: (+) = ICD 8 (WHO, 1978); (*) = RDC (Spitzer *et al*, 1977); (!) = Newcastle (Carney *et al*, 1965); (*!) = RDC and Newcastle.
M = Male subjects; F = Female subjects.

had never received antidepressant therapy. They were assessed by the French version of the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer & Endicott, 1978; Charles & Ansseau, 1987), and met DSM-III criteria (Spitzer, 1980) for a major depressive episode without melancholia. Patients with recurrent depressive episode constituted the majority of the sample (11 out of 14). Fourteen depressed patients, meeting DSM-III criteria for a major depressive episode without melancholia according to SADS, were selected randomly from a population of 86 patients to match for age, sex and diagnosis (Group 2). They had received tricyclic therapy in the recent past, but were drug free for at least 15 days before the experiment (mean of the tricyclic wash-out period:16.3 ± 3.8 days). Eight controls (six men and two women) also volunteered to participate in the study. They were not suffering from any medical or psychiatric illness. Analysis of variance (ANOVA) did not reveal any significant age difference between the two groups of patients and controls (33.43 ± 10.49 v. 37.29 ± 6.38 v. 31.75 ± 6.34; $F = 1.36$; d.f. = 2; P = NS). All females were premenopausal and were tested within the first ten days of the menstrual cycle. All patients had been free of benzodiazepine drugs for at least five days. None had any medical disorder or was overweight. Patients and controls participated in the study after granting informed consent. The investigation was approved by the hospital ethics committee.

Procedure

At 8 a.m., an intravenous catheter was inserted into a forearm of the reclining patients after they had fasted overnight. Five ml of blood were sampled for hormone determination 30 minutes before ($t-30$) and immediately before the infusion ($t-0$), starting at 9 a.m. Clonidine was administered intravenously at a fixed dose of 150 μg dissolved in 9 ml saline injection over a ten minute period. Subsequent blood samples were collected at +30 ($t+30$), +45 ($t+45$), +60 ($t+60$) and +90 ($t+90$) minutes after the infusion. Blood samples were centrifuged within two hours and the plasma was stored at −40 °C.

GH determinations were performed using a radioimmunoassay according to the methodology described elsewhere (Schittecatte *et al*, 1988). We calculated a mean baseline GH value which was the mean of the ($t-30$) and the ($t-0$) value, and a delta maximum value which was the difference between the ($t+30$) value and the mean baseline value. The data were analysed with the SPSS computer package (Hull & Nie, 1981). To compare the two populations, we used a two-way analysis of variance. To compare the different parameters, we used a Mann-Whitney *U*-Wilcoxon rank-sum *W* test.

Results

The three sets of ANOVA results to assess the effects of clonidine on plasma GH levels in the two groups of depressed patients and controls are listed in Table II. The ANOVA always showed a significant time effect (all $P<0.001$) of clonidine on plasma GH values.

Group 1 differed from Group 2 (group effect: $F = 18.9$; d.f. = 3; $P<0.001$; group × time effect: $F = 4.7$; d.f. = 3; $P = 0.004$). The results reflected the differences between the two groups in the response to clonidine. The controls differed from Group 2 (group effect: $F = 105.02$; d.f. = 3; $P<0.001$; group × time effect: $F = 13.98$; d.f. = 3; $P<0.001$) but not from Group 1 (group effect: $F = 0.04$; d.f. = 3; P = NS; group × time effect: $F = 0.24$; d.f. = 3; P = NS).

As shown in Table III, we used a Mann-Whitney test to compare the different parameters. In the severity of the depressive episode evaluated by the Hamilton Rating Scale for Depression (HRSD) and baseline GH values there were no differences between the two groups of patients. Mean baseline GH values (BL) were 4.7 ng/ml or less.

For GH values at time ($t+30$) (8.59 ± 8.13 v. 1.71 ± 1.94; $P<0.04$), and at time ($t+45$) (5.4 ± 5.59 v. 0.82 ± 0.8; $P<0.02$) there were significant differences between Groups 1 and 2. So are delta maximum GH values (7.02 ± 7.89 v. 0.03 ± 2.7; $P<0.005$). These GH values were significantly different between the controls and Group 2 (all $P<0.001$) but not between the controls and Group 1 (all P = NS). The results are shown in Fig. 1.

If we used a cut-off value for the delta maximum GH value of 4 ng/ml, 7 patients (5 men and 2 women) in the first group against 13 patients (7 men and 6 women) in the second group had an abnormal or blunted response (Fischer exact test: $P = 0.02$).

In Group 1 we found no statistical difference between the patients with a normal response and those with a blunted response, when analysed according to sex (cross-tabulation: $\chi^2 = 0.04$; P = NS), age (39 ± 11.68 v. 27.86 ± 5.46; $z = -1.91$; P = NS), HRSD (23.75 ± 3.69 v. 23.14 ± 3.98; $z = -0.12$; P = NS) or baseline GH values (1.86 ± 1.98 v. 1.29 ± 1.68; $z = -1.11$; P = NS).

In Group 2, we found no correlation between the length of the wash-out period and the delta maximum GH value ($r = 0.0077$; P = NS).

TABLE II

Analysis of variance of growth hormone response to clonidine in depressed patients and healthy controls (F *values*)

	Time effect d.f. = 3	*Group effect* d.f. = 1	*Gr × time effect* d.f. = 3
Gr1 v. Gr2:	8.8**	18.9**	4.7*
Gr1 v. controls:	11.67**	0.1	0.24
Gr2 v. controls:	18.62**	105.02**	13.98**

*$P<0.01$, **$P<0.001$, P = NS.
Gr1: group of 14 depressed patients who have never received tricyclic therapy (7M, 7F).
Gr2: group of 14 depressed patients free of tricyclic drugs for at least 15 days (7M, 7F).
Controls: group of 8 control subjects (6M, 2F).
M = male subjects. F = premenopausal female subjects.

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TABLE III

Effect of clonidine on plasma growth hormone response concentrations in depressed patients and healthy controls

	Gr1	*Gr2*	*Controls*	*Mann-Whitney U test*		
				Gr1 v. Gr2	*Gr1 v. controls*	*Gr2 v. controls*
Age	33.43 ± 10.49	37.29 ± 6.38	31.75 ± 6.34	NS	NS	NS
HRSD	23.36 ± 3.69	22.21 ± 4.61	NA	NS	NA	NA
Mean baseline GH value (ng/ml)	1.57 ± 1.79	1.68 ± 1.27	1.33 ± 2	NS	NS	NS
GH value at *t* +30 (ng/ml)	8.59 ± 8.13	1.71 ± 1.94	8.51 ± 2.26	$P<0.05$	NS	$P<0.001$
GH value at *t* +45 (ng/ml)	5.4 ± 5.59	0.82 ± 0.8	5.04 ± 1.95	$P<0.05$	NS	$P<0.001$
Delta max GH value (ng/ml)	7.02 ± 7.89	0.03 ± 2.7	7.19 ± 3.43	$P<0.01$	NS	$P<0.001$
No. of subjects with a blunted response delta max GH value <4 ng/ml)	7/14	13/14	0/8	FET = 0.02		

NA = not applicable.
Gr1: group of 14 depressed patients (7M, 7F) who have never received tricyclic therapy.
Gr2: group of 14 depressed patients (7M, 7F) free of tricyclic drugs for at least 15 days.
Controls: group of 8 control subjects (6M, 2F).
M = male subjects. F = premenopausal female subjects.

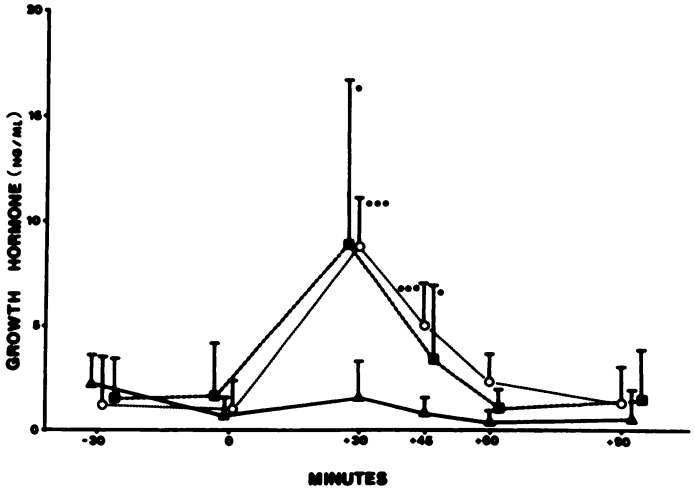

FIG. 1. Effects of clonidine on plasma growth hormone levels in two groups of depressed subjects and controls.
Group 1 (--- ■ ---): Depressed patients who have never received tricyclic therapy (7M, 7F).
Group 2 (—▲—): Depressed patients free of tricyclic drugs for at least 15 days (7M, 7F).
Controls (···○···): control subjects (6M, 2F).
M = male subjects. F = premenopausal female subjects.
Gr2 different from Gr1 and controls (*$P<0.05$, **$P<0.001$).
Gr1 not different from controls.

Discussion

The results showed that depressed patients who have never received tricyclic therapy have a significantly higher GH response to clonidine than patients in wash-out for at least 15 days. As our two groups were matched except for tricyclic wash-out, we might question whether the 'well-established' blunted GH response to clonidine in depressed patients could be due in part to this artifactual patient characteristic, i.e. to the recent use of antidepressant. The fact that, in concurring with Checkley & Corn (1985) and Horton *et al* (1986), we found no correlation between the length of the wash-out period and the GH response to clonidine, does not, in our opinion, argue against this hypothesis.

Compared with a control group of subjects, untreated depressed patients, as a group, had a normal response, while matched depressed patients had a markedly blunted response. Our control group

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included mainly male subjects. In normal subjects, Tulandi *et al* (1987) found that men had a greater GH response to i.v. clonidine administration than age-matched premenopausal women tested in the follicular phase. Hunt *et al* (1986) found that GH levels, 90 minutes after oral administration of 150 μg of clonidine, were similarly raised in their female and male subjects. Comparisons between our patients and controls should be made with caution. However, our purpose is not to establish that patients are different from controls but to emphasise the difference between the two groups of matched patients when they are compared with a control group.

Further examination of the results suggests that some untreated patients had a response in the normal range while others showed no response to clonidine. This is consistent with the concept of the biological heterogeneity of the depressive syndrome (Siever *et al*, 1985). It may be that owing in part to the small size of our samples, we could not show any statistical differences between untreated patients with a 'blunted' response and patients with a response in the normal range. Studies on larger groups of depressed patients are needed to better understand this heterogeneity.

At this stage, as was previously shown for the dexamethasone suppression test, it would be interesting, in our opinion, to define a dichotomy between patients with a 'blunted' response and patients with a response in the normal range, and to analyse the profile of the two groups.

However, the studies need first to take into account the confounding and long-lasting effects of tricyclics. One method would be to study groups of patients who have never received antidepressant therapy. Another method would be to conduct a study on the maximum length of time taken for the effects of tricyclics on the GH response to clonidine to disappear. The length of time could vary from one person to another.

Finally, since Ansseau *et al* (1984) have proposed the use of the clonidine test as a biological marker of endogenous depression, one might question whether the use, in clinical practice, of a wash-out period of two weeks or more would be convenient.

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