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Short communication

Dexamethasone suppression test and prediction of treatment response to selective antidepressants

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Summary – The usefulness of the dexamethasone suppression test (DST) in the prediction of treatment response to selective antidepressants was tested in 56 major depressive inpatients. Following DST, patients were randomly assigned to treatment by either nomifensine, a catecholaminergic antidepressant, or zimeldine, a serotonergic antidepressant during a 3-week period and assessed by means of the second part of the Clinical Global Impressions (CGI-2). No significant difference was present between the 27 DST suppressor and the 29 DST non-suppressor patients in their overall clinical outcome. Moreover, no preferential response to nomifensine or zimeldine was noted in any of the two groups defined according to DST status. Therefore, these results do not support the usefulness of the DST in the prediction of the treatment response to antidepressants in general and to selective antidepressants in particular.

dexamethasone suppression test / prediction of outcome / antidepressants / nomifensine / zimeldine

Introduction

Several reports support the usefulness of the dexamethasone suppression test (DST) in the prediction of the treatment response to antidepressants (Balon, 1989; D'Haenen, 1991). Indeed, the majority of studies found that DST nonsuppressors responded well to antidepressant therapy. In contrast, controversial results have been published regarding the DST status of predictor of a preferential response to selective antidepressants of noradrenergic or serotonergic types (D'Haenen, 1991).

In this context, the purpose of the present study was to investigate a possible relationship between DST status and treatment outcome following selective antidepressants in major depressive patients. Two antidepressants were compared: nomifensine, which selectively inhibits noradrenaline and dopamine reuptake (Hoffmann, 1982), and zimeldine, which selectively inhibits serotonin reuptake (Heel *et al,* 1982).

Methods

Subjects

A total of 56 major depressive inpatients defined according to Research Diagnostic Criteria (RDC) (Spitzer *et al,* 1978) representing consecutive admissions to the Psychiatric Unit of the University Hospital of Liège, Belgium, and exhibiting a score of at least 18 on the 17-item Hamilton depression scale were included in the study. According to RDC subtypes of major depressive disorder, 56 patients were classified as primary, 42 as recurrent unipolar, three as bipolar with mania (bipolar I), two as bipolar with hypomania (bipolar II), none as psychotic, 47 as incapacitating, 45 as endogenous, 14 as agitated, 24 as retarded, 13 as situational, and 56 as simple. According to the predominant mood of current episode of major depressive disorder, 30 patients were considered as mainly depressed, 18 as mainly apathetic, five as anxious and depressed without either predominating, and three as mainly hostile. This sample comprised 29 male and 27 female patients, with age ranging from 19 to 66 years (mean age = 42.0 ± 11.9 years). All patients were free of medical illness, as evidenced by history, med-

Table I. CGI-2 mean scores ± SD following treatment by nomifensine (nom) or zimeldine (zim) among patients defined by their DST status.

	First ADP			*Switch in case of failure*	
DST nonsuppression	nom	(n = 8) = 3.38 ± 1.69	→	zim	(n = 5) = 2.20 ± 0.45
(n = 29)	zim	(n = 21) = 2.71 ± 1.31	→	nom	(n = 8) = 2.50 ± 1.07
DST suppression	nom	(n = 14) = 3.43 ± 1.45	→	zim	(n = 9) = 2.89 ± 1.05
(n = 27)	zim	(n = 13) = 2.62 ± 1.04	→	nom	(n = 5) = 2.40 ± 1.52

ical examination, electrocardiogram, chest X-ray, electroencephalogram, and routine laboratory tests and tested after a drug-free period of at least 2 weeks. The protocol was approved by the Ethical Committee of the University of Liège Medical School and all patients gave their informed consent.

DST procedure

The DST was performed according to the simplified procedure described by Carroll *et al* (1981). Oral dexamethasone (1 mg) was administered by a nurse at 11 pm and a post-DST sample was collected at 4 pm the following day. Plasma cortisol was measured by direct radioimmunoassay (RIA) according to a procedure previously described (Sulon *et al,* 1978). All samples were processed in duplicate, with maximum intra- and inter-assay coefficients of variation of 4.3 and 8.3%, respectively, and a detection limit of 2.0 μg%. Non-suppression was defined as a cortisol level > 5 μg%.

Treatment procedure

After completion of the DST, patients were randomly assigned to treatment by either nomifensine or zimeldine: 100 mg for 3 days then 200 mg for the remaining 3-week period. Other psychotropic medication was excluded throughout the study period, except the occasional recourse to low dose benzodiazepines if requested. All clinical evaluations were made without knowledge of endocrine data. Clinical outcome following the 3 weeks of therapy was assessed by means of the second part of the Clinical Global Impressions (CGI-2) (Guy, 1976), with scores ranging from 1 to 7 meaning: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse. In the case of treatment failure (CGI-2 ⩾ 3), patients were switched to the other antidepressant for 3 more weeks and reassessed with CGI-2.

Data analysis

The baseline homogeneity in Hamilton depression scores as well as the treatment response as measured by CGI-2 were assessed by 2-way analyses of variance (ANOVA) including DST status (suppressor *vs* non-suppressor), antidepressant (nomifensine *vs* zimeldine), and the interaction between DST status and antidepressants. The proportion of patients that had to be switched to the alternative antidepressant was compared using Student's t-test.

Results

Following DST, 29 patients (52%) exhibited cortisol non-suppression and 27 patients (48%) a normal cortisol suppression. Their assignment to nomifensine or zimeldine, their mean final CGI-2 scores as well as the number of patients who had to be switched to the other compound and their final CGI-2 scores are displayed in table I. Mean initial Hamilton depression scores (SD) were: 26.1 ± 3.8 in DST non-suppressors treated with nomifensine; 26.0 ± 3.6 in DST non-suppressors treated with zimeldine; 26.1 ± 3.4 in DST suppressors treated with nomifensine; and 26.2 ± 3.0 in DST suppressors treated with zimeldine, without any significant difference according to the treatment group ($F = 0.0$, P = NS), the DST status ($F = 0.1$, P = NS) or the interaction ($F = 0.1$, P = NS). In the whole sample, zimeldine exhibited a trend toward better antidepressant efficacy than nomifensine ($F = 3.9$. $P = 0.053$). No significant difference existed between DST non-suppressor and suppressor patients in their overall clinical outcome during antidepressant therapy: $F = 0.1$, P = NS. Moreover, no significant differences were present in any of the two groups defined by DST status with regard to a possible preferential response to nomifensine or zimeldine: $F = 0.0$, P = NS.

In the nonsuppressor group, 62% of nomifensine-treated patients had to be switched to zimeldine and 38% of zimeldine-treated patients had to be switched to nomifensine ($z = 1.2$, P = NS). In the suppressor group, 64% of nomifensine-treated patients had to be switched to zimeldine and 38% of zimeldine-treated patients

had to be switched to nomifensine ($z = 1.3$, P = NS). In the whole sample, the proportion of patients initially treated with zimeldine that had to be switched to nomifensine was lower than the proportion of patients initially treated with nomifensine that had to be switched to zimeldine (38 *vs* 64%, $z = 1.9$, $P = 0.03$), supporting a better antidepressant response to zimeldine.

Discussion

The results of the present study do not support the usefulness of the DST status in the prediction of the treatment response to antidepressants in general and to selective antidepressants in particular.

A predictive value of DST status in the short-term response to antidepressants in general was noted in 15 out of 26 studies (D'Haenen, 1991). However, a non-suppressor status or a higher cortisol value following DST was associated with a better outcome in 9 studies while a suppressor status was positively correlated with a favorable response in six studies. Probably, the most interesting finding, however, is that DST non-suppressors are unlikely to respond to placebo (Georgotas *et al,* 1986; Peselow *et al,* 1986) or to specific psychotherapy (Rush, 1983) so that the presence of an abnormal DST indicates the need for a biological treatment.

Our negative results concerning a possible predictive role for DST status in the choice of selective antidepressants are in agreement with the majority of published trials. Indeed, nine out of 15 studies were unable to find a predictive value of DST status with regard to the treatment outcome with selective antidepressants (D'Haenen, 1991). Among the few positive reports, Fraser (1983) found that non-suppression predicted a good response to noradrenergic antidepressants and suppression a good response to serotonergic antidepressants. These results were confirmed by Arato *et al* (1984) who claimed that non-suppressors responded better to maprotiline, a noradrenergic antidepressant, and suppressors to amitriptyline, a serotonergic antidepressant. However, Beckman *et al* (1984) published opposite findings with DST non-suppressors responding more favorably to amitriptyline and suppressors more favorably to nomifensine.

Several limitations in the design of our study should be pointed out. Firstly, the DST was performed according to the simplified procedure which identifies only about 78% of DST non-suppressors (Carroll *et al,* 1981). This may represent a bias regarding the relatively small group of patients. In addition, it would have been interesting to perform the DST again after the 3 weeks of treatment to assess possible differences in its evolution according to treatment response. Secondly, nomifensine and zimeldine were given at the same dose in a patient group which was heterogeneous according to age. It would have been interesting to determine serum antidepressant levels in order to individually adjust the dose of antidepressants. It should be noted however, that therapeutic plasma levels have never been published for nomifensine and zimeldine (Hoffmann, 1982; Heel *et al,* 1982). Thirdly, the choice of nomifensine as a noradrenergic antidepressant can be criticized since it exhibits significant dopaminergic properties (Hoffmann, 1982). In fact, a previous study showed an association between DST suppression and preferential response to nomifensine, suggesting that dopaminergic mechanisms may be implicated in DST pathophysiology (Beckmann *et al,* 1984).

Unexpectedly, the results of this study suggest zimeldine has a better antidepressant efficacy as compared to nomifensine. In comparative studies, both nomifensine and zimeldine were found to be equivalent to reference antidepressants such as imipramine and amitriptyline (Hoffmann, 1982; Heel *et al,* 1982) but no direct comparisons of the two drugs were reported. Since the completion of this study, both nomifensine and zimeldine have been unfortunately withdrawn from the market because of side-effects. However, the negative conclusions of this study may be applicable to antidepressants exhibiting similar biochemical profiles.

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