

Comparison of Adinazolam, Amitriptyline, and Diazepam in Endogenous Depressive Inpatients Exhibiting DST Nonsuppression or Abnormal Contingent Negative Variation

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Adinazolam, a triazolobenzodiazepine that has an action similar to antidepressants in several pharmacological tests, was compared with amitriptyline and diazepam in endogenous depressive inpatients exhibiting dexamethasone suppression test nonsuppression and/or abnormal contingent negative variation. Three parallel groups of 22 patients received in double-blind conditions either adinazolam (60–90 mg/day), amitriptyline (150–225 mg/day), or diazepam (30–45 mg/day) over a 4-week period, with weekly assessments by the Hamilton Rating Scale for Depression. Results showed significant superiority of amitriptyline over diazepam on total Hamilton depression scores. On the endogenomorphy subscale, amitriptyline induced significantly better improvement than both diazepam and adinazolam, whereas both amitriptyline and adinazolam exhibited significantly better antidepressant efficacy on the core symptoms of depression. Moreover, the dropout rate for inefficacy after 2 weeks of treatment was higher in the diazepam group. Taken together, these findings suggest that adinazolam has an antidepressant efficacy intermediate between amitriptyline and diazepam. Adinazolam was, however, much better tolerated than amitriptyline, and produced significantly fewer anticholinergic side effects.

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CLASSICAL BENZODIAZEPINES have generally been regarded as ineffective in the treatment of endogenous depression.^{1,2} Controversy still exists, however, regarding possible antidepressant activity of alprazolam.³ Adinazolam is another triazolobenzodiazepine that exhibits several pharmacological characteristics sim-

ilar to tricyclic antidepressants and different from classical benzodiazepines: it potentiates clonidine-induced aggression and norepinephrine-induced blood pressure increase in rodents and, after chronic administration, sensitizes hippocampal neurons to serotonin.^{4,5} Several recent studies showed better antidepressant efficacy of adinazolam as compared to placebo in outpatients with major depression,^{6–9} and it was also found to be equivalent to imipramine in outpatients with major depression.¹⁰ However, in a recent comparison of adinazolam, amitriptyline and placebo in melancholic inpatients, adinazolam was found to be less effective than amitriptyline and not different from placebo.¹¹ These discrepancies may depend on the type of patients included in the studies. The selection of melancholic inpatients may provide a better way to discriminate potential antidepressants. Diagnostic confirmation by so-called “biological markers” could also help to define a more homogeneous sample.

The purpose of this present study was to confirm possible true antidepressant activity of adinazolam among carefully selected endogenous depressive inpatients. The clinical diagnosis should be confirmed by at least one biological abnormality: dexamethasone suppression test (DST) nonsuppression and/or pathological contingent negative variation (CNV).

DST is the most widely used “biological marker” of depression, and it identifies about 50% of major or endogenous depressive patients¹²; the specificity of the DST, however, remains a subject of controversy.¹³ CNV, which belongs to brain event-related potentials, exhibits abnormalities in amplitude and/or duration in 70% of major depressive inpatients.¹⁴

In summary, this study was aimed to compare the antidepressant activity of adinazolam with amitriptyline, a standard tricyclic antidepressant, and diazepam, a standard benzodiazepine, among endogenous depressive inpatients with biological abnormalities in order to precisely situate the therapeutic profile of adinazolam.

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Methods

Subjects

A total of 66 inpatients, consecutively hospitalized in the psychiatric unit of the University or "Petit Bourgogne" Hospital of Liège, Belgium, who fulfilled Research Diagnostic Criteria (RDC) for a definite major depression, primary and endogenous subtypes,¹⁵ entered the study. In addition, they had to exhibit a score of at least 21 on the 24-item Hamilton Rating Scale for Depression^{16,17} and a rating of at least 5 (markedly ill) on the Clinical Global Impressions scale (CGI).¹⁷ Moreover, patients had to present abnormal DST and/or CNV but normal EEG spectral analysis. Patients with significant or uncontrolled medical conditions, as evidenced by clinical examination, EKG, chest X-ray, EEG, or routine laboratory tests, as well as contraindications for the administration of tricyclics or benzodiazepines, were excluded from the study.

Patients were 9 men and 57 women, with age ranging from 21 to 59 years (mean, 45.1 years \pm 10.9). All patients remained hospitalized for at least a 2-week drug-free period and the first 2 weeks of active treatment. Finally, the protocol was approved by the Ethical Committee of the University of Liège Medical School and all patients gave fully informed consent.

DST and CNV

The DST was performed according to the simplified procedure described by Carroll.¹² 1 mg of dexamethasone was administered orally by a nurse at 11:00 p.m. and a blood sample was collected at 4:00 p.m. the following day. Cortisol was measured by radioimmunoassay, with intra- and interassay coefficients of variation of, respectively, 4.3% and 8.3%.¹⁸ DST nonsuppression was defined by a cortisol level higher than 5 μ g/dl.¹²

The CNV recording procedure has been described previously in detail.¹⁴ Briefly, the CNV paradigm was obtained by a warning stimulus (S1; 1,000 Hz, 50-msec tone), generated from a loud speaker 1 meter in front of the subject, followed 1 second later by an imperative stimulus (S2; 18 per second flashing light). The duration of S2 was 1 second unless it was terminated by the subject applying pressure to a pear-shaped bell push. The CNV session comprised 48 trials, with pseudo-randomized intervals ranging from 7 to 25 seconds. All CNV parameters were measured as the average of the 48 trials. CNV amplitude (or preimperative negativity) was measured by the voltage difference between a 1 second pre-S1 baseline and the 800–1000 msec after S1 level. The presence of postimperative CNV prolongation was assessed by the ratio of the postimperative positivity (difference in level between preimperative negativity and 550–700 msec after S2) to preimperative negativity. According to previously

published normative data,¹⁹ abnormal CNV amplitude was defined outside the voltage range from -11 to -22 μ V and prolonged (abnormal) CNV duration by a ratio postimperative positivity/preimperative negativity < -0.69 .

Study design

The study was performed under double-blind conditions, with patients being randomly assigned to one of 3 parallel groups treated by adinazolam (N = 23), amitriptyline (N = 22) or diazepam (N = 21). After a drug-free period of at least 2 weeks on placebo, with the clinical and biological screening assessment being made during the second week, patients were treated during 4 weeks, with weekly assessments including Hamilton Rating Scale for Depression (HAM-D), CGI, vital signs (weight, pulse, standing and supine blood pressure) and a checklist of symptoms and side effects. Two subscores were extracted from the HAM-D, corresponding to the endomorphomorphy subscale^{20,21} and to the consensus core symptoms cluster as defined in DSM-III melancholic depression.^{11,22} The drugs were presented as tablets containing either adinazolam 10 mg, amitriptyline 25 mg, or diazepam 5 mg. The treatment was begun on day 0 by one tablet at bedtime, then three tablets on day 1, four tablets on day 2, and six tablets from day 3 to day 7, administered in three daily intakes. Unless moderate to marked improvement as rated on the CGI was noted, the daily dose was increased to nine tablets from day 8 until the end of the 4-week period. Laboratory tests and EKGs were controlled after 2 and 4 weeks of treatment.

In all cases of discontinuation of the treatment, the drug had to be tapered over a withdrawal period of at least 2 weeks according to a specified schedule and patients were carefully monitored for any possible withdrawal reaction.

Data analysis

First of all, the homogeneity of the 3 treatment groups was controlled, using analysis of variance (ANOVA) or Chi-square statistics, eventually corrected by the Yates test for small samples. No significant differences were present related to age, weight, height, gender, and civil status distribution, the initial scores on the various depression scales, the previous psychotropic treatments, and the personal and family psychiatric history.

Changes over time in clinical ratings were assessed by a 2-way ANOVA with repeated measures. A first analysis was performed over the 4-week protocol for all cases having been treated for the entire period. A second analysis was then performed with reporting the endpoint scores for subsequent evaluations of patients who did not complete the 4-week protocol but since the conclusions were similar, they will not be reported herein. All ANOVAs with repeated measures were followed with

TABLE 1. Comparison of dropouts and side effects

	Adinazolam N = 22	Amitriptyline N = 22	Diazepam N = 20		<i>p</i>
Dropouts after 2 weeks					
Lack of efficacy	2	0	6	diazepam > amitriptyline	0.007
Side effects	0	2	0	diazepam > adinazolam	0.09
Dropouts after 3 weeks					
Lack of efficacy	5	3	3		
Side effects	0	0	0		
Side effects					
Drowsiness	5	7	8		
Nervousness	2	2	4		
Tremor	2	10	5	amitriptyline > adinazolam	0.008
Dizziness	3	3	3		
Headache	5	4	3		
Tachycardia	3	8	3	amitriptyline > adinazolam	0.08
Dry mouth	8	16	4	amitriptyline > diazepam	0.001
				amitriptyline > adinazolam	0.02
Constipation	5	5	6		
Others	10	18	13		

time by time ANOVAs associated with *a priori* contrasts in order to complete the comparison among groups at intermediate times. All statistical procedures used a SAS package.

Results

DST and CNV results

DST nonsuppression was noted in 50% of adinazolam-treated patients, 59% of amitriptyline-treated patients, and 71% of diazepam-treated patients ($\chi^2 = 2.07$, $df = 2$, $p =$ not significant) while abnormal CNV was present in 87% of adinazolam-treated patients, 100% of amitriptyline-treated patients, and 80% of diazepam-treated patients ($\chi^2 = 1.70$, $df = 2$, $p =$ not significant).

Dropouts

Two patients, both women, left the study before day 14 and were therefore not included in the statistical analysis: one, aged 29, exhibited a switch to mania after 8 days treatment by adinazolam, reported previously²³; the other, aged 41, left the hospital after 4 days of treatment with diazepam following an argument with a staff member.

A total of 10 patients left the study after 2 weeks for inefficacy or side effects and 11 more patients left after 3 weeks (Table 1).

Dosage

Mean dosages (SD) reached the first, second, third, and fourth week of treatment were respectively 52.8 (4.4), 89.6 (1.7), 89.6 (0.6), and 87.4 mg (6.4) in the adinazolam group, 125.4 (30.3), 203.9 (47.5), 209.6 (29.3) and 206.8

mg (31.1) in the amitriptyline group, and 27.4 (4.9), 44.1 (3.4), 43.2 (4.6) and 41.4 mg (6.4) in the diazepam group.

HAM-D

Changes over time on the HAM-D in the three treatment groups are presented in Figure 1. Amitriptyline induced a significantly better improvement compared to diazepam after 4 weeks of therapy ($F(1,40) = 4.26$, $p = 0.04$). The other contrasts did not show significant differences.

The endogenomorphy subscale as well as the consensus core symptom cluster, revealed better improvement after 4 weeks of treatment with amitriptyline as compared to diazepam: respectively, $F(1,40) = 5.91$, $p = 0.02$ and $F(1,40) = 5.16$, $p = 0.03$; moreover, the endogenomorphy subscale showed significant superiority of amitriptyline over adinazolam ($F[1,40] = 3.97$, $p = 0.05$) whereas the core symptoms cluster exhibited a trend toward superiority of adinazolam over diazepam ($F[1,40] = 3.52$, $p = 0.07$, trend).

Treatment responders

Patients considered to be much or very much improved on the CGI were 41% in the adinazolam group, 64% in the amitriptyline group, and 20% in the diazepam group, indicating significant superiority of amitriptyline as compared to diazepam ($p = 0.006$). No significant differences existed in the number of patients exhibiting decrease of at least 50% on the HAM-D: 36% in the adinazolam group, 55% in the amitriptyline group, and 35% in the diazepam group. In contrast, a decrease of at least 50% on the endogenomorphy subscale was noted in 32% of patients treated by adinazolam, 68% of patients treated by ami-

triptyline, and 30% of patients treated by diazepam, indicating superiority of amitriptyline over diazepam ($p = 0.02$) and adinazolam ($p = 0.03$). No differences were present in the number of patients characterized by a decrease of at least 50% on the core symptoms cluster: 59% in the adinazolam group, 64% in the amitriptyline group, and 50% in the diazepam group.

Side effects

The number of patients exhibiting side effects in the 3 treatment groups is presented in Table 1. Tremor, tachycardia, and dry mouth were significantly more frequent with amitriptyline than with adinazolam; dry mouth was also more frequent with amitriptyline than with diazepam.

Withdrawal symptoms and poststudy treatment

None of the patients exhibited withdrawal reactions following the tapering of the various drugs. A total of 27 patients entered the long-term phase of the study: 9 in the adinazolam group (41%), 14 in the amitriptyline group (64%), and 4 in the diazepam group (20%). Other patients were switched to tricyclic antidepressants, mainly clomipramine ($N = 20$), monoamine oxidase inhibitors (MAOIs), mainly nialamide ($N = 15$), or ECT ($N = 2$) with results rated as positive in 60% of tricyclic-treated patients, 73% of MAOI-treated patients, and 50% of ECT-treated patients.

Discussion

The results of the present study show lower antidepressant activity of adinazolam as compared to amitriptyline on the endogenomorphy subscale. Adinazolam however exhibited a trend toward superiority over di-

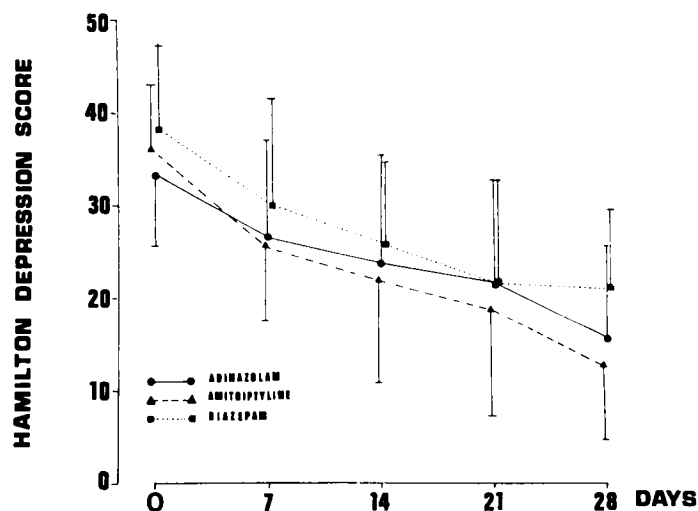


FIG. 1. Changes over time in HAM-D scores (mean \pm SD) in patients treated by adinazolam, amitriptyline, or diazepam.

azepam on the core symptoms cluster. This higher efficacy of adinazolam as compared to diazepam is confirmed by the trend toward lower rate of dropout for inefficacy after 2 weeks of treatment. It should be noted that all clinical differences, including the superiority of amitriptyline over diazepam, were only demonstrated after 4 weeks of treatment. It is generally accepted that classical benzodiazepines induce an initial improvement in depressive symptomatology which is not maintained after a few weeks.^{1,2} Among 20 double-blind studies reviewed by Schatzberg and Cole,¹ only one showed benzodiazepine superiority over an antidepressant in treating depression. This study²⁴ also used the highest dose of diazepam (30 mg/day), suggesting that benzodiazepines may exhibit antidepressant properties at higher doses. This hypothesis is supported by a recent trial²⁵ showing superiority of diazepam at a mean daily dose of 32 mg over moclobemide, an MAOI, in atypical depression. Moreover, alprazolam has been shown to exhibit antidepressant activity when used at high doses.³ The very high dose of diazepam used in our study (more than 40 mg daily from the second week of treatment) might explain the late and low differences in antidepressant efficacy among active drugs.

The methodology used in this study was able to differentiate adinazolam from a tricyclic antidepressant and from a classical benzodiazepine. This contrasts with a previous study showing a similar efficacy of adinazolam and imipramine.¹⁰ The methodology used in our study may reveal more sensitivity in detecting subtle differences between active compounds. First of all, the inclusion of severely depressed inpatients instead of moderately depressed outpatients decreases the rate of placebo effect. Whereas four studies performed in major depressive outpatients showed significant superiority of adinazolam over placebo,⁶⁻⁹ a study performed in melancholic inpatients showed no difference between adinazolam and placebo.¹¹

The diagnostic confirmation of depression by "biological markers," such as DST and CNV, could also help to define a more homogeneous sample and therefore improve the therapeutic sensitivity. With this respect, alprazolam, another triazolobenzodiazepine, has been found less effective than amitriptyline in endogenous depressive inpatients characterized by a shortened rapid eye movement sleep latency,²⁶ whereas several studies performed in depressive outpatients had shown similar efficacy as compared to standard tricyclics.²⁷⁻²⁹

A weakness of this study is the lack of monitoring of plasma levels of diazepam/desmethyl diazepam, adinazolam/desmethyl adinazolam, and amitriptyline/nortriptyline. Indeed, blood level measurements of antidepressants can be useful to check compliance, to maximize clinical response and to avoid toxicity.³⁰ While a specific

therapeutic window has been described with nortriptyline, the relationships between blood level of amitriptyline and clinical outcome are conflicting; some studies showed a linear relationship, others suggested a therapeutic window similar to that of nortriptyline and still others found no association.³⁰ Concerning benzodiazepines, and particularly diazepam/desmethyl-diazepam, there is a general agreement about the lack of indication for routine monitoring of plasma concentrations due to the wide interindividual variation of plasma drug concentration, the lack of correlation of plasma level with overall clinical improvement and the wide margin of safety of the drugs.³¹ None of the previous studies with adinazolam have assayed plasma levels and therefore nothing is known about possible relationship between adinazolam/noradinazolam plasma levels and clinical response.⁶⁻¹¹

Several studies have suggested an early onset of activity with adinazolam^{8, 9} and a trend for more rapid improvement with adinazolam as compared to imipramine after 1 week of treatment has been reported.¹⁰ Our study does not confirm these findings. This discrepancy may depend on differences in patient population. Our subjects were severely depressed inpatients exhibiting biological disturbances, whereas the previous studies included major depressive outpatients. Less severe depressed patients respond better and more quickly to a benzodiazepine.^{1, 2}

The selection of alprazolam instead of diazepam as reference benzodiazepine could have represented an interesting alternative. Indeed, such design could have helped to clarify the respective antidepressant power of alprazolam and adinazolam in comparison with amitriptyline. Our primary goal was, however, to better situate adinazolam with regard to a reference tricyclic and a benzodiazepine *without* antidepressant potential.

Adinazolam was much better tolerated than amitriptyline, with significantly fewer anticholinergic side effects. These findings confirm previous comparisons.^{10, 11} The lack of anticholinergic activity of adinazolam makes its use possible in patients exhibiting contraindications for tricyclic antidepressants and particularly in elderly depressives. None of the patients who discontinued adinazolam for lack of sufficient response exhibited withdrawal symptoms but the drug was always tapered according to a slow schedule; this is of particular importance due to a previous report of a grand mal seizure following rapid tapering.⁸

In conclusion, this study performed in severely depressed inpatients with a diagnostic confirmation by biological markers suggests that adinazolam exhibits antidepressant activity intermediate between amitriptyline and diazepam, with a much better tolerance than amitriptyline.

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