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Comparative Effects of Amitriptyline and Amineptine in Patients Affected by Anxious Depression

Key Words
Anxious depression
Amitriptyline
Amineptine

Abstract
In a double-blind, placebo-controlled study, the therapeutic efficacy of two antidepressants with different neurochemical mechanisms of action, amitriptyline and amineptine, was investigated in patients affected by anxious depression. Sixty-six patients with the primary dignosis of major depression or bipolar affective disorder (DSM-III-R) and meeting additional operational clinical criteria such as anxiety, trepidation, restlessness, early and/or late insomnia, impulsivity, hostility, dysphoria, compulsivity, hyperperspiration, palpitation, pollakiuria and phobias were included. They were randomly assigned to three groups (n = 22) and treated either with placebo, amitriptyline (up to 100 mg/day) or amineptine (up to 200 mg/day) for 6 weeks. Patients showed better response to amitriptyline, a preferential inhibitor of serotonin reuptake, than to amineptine, a selective inhibitor of dopamine reuptake. The present results suggest that alterations in serotonergic rather than dopaminergic transmission contribute to the pathophysiology of anxious depression.

Introduction

Depression is a complex neuropsychoendocrinological syndrome which includes a wide range of clinical conditions resulting from alterations in monoaminergic neurotransmission. The diagnostic criteria proposed by the DSM-III-R [1] do not provide any reference to therapeutic indications and the biological markers are not useful predictors of antidepressant outcome [2–4].

Although clinical depressive pictures present some common symptoms, such as depressive mood (suicidal thoughts, hopelessness, sense of guilt, underrating oneself, despair), they exhibit different profiles that justify the use of antidepressants with selective or preferential activity on distinct monoaminergic systems [2, 5–11].

It was recently shown that amineptine, a specific dopamine reuptake inhibitor, is effective in a subgroup of patients affected by 'delayed depression' defined by a prevalence of negative symptoms [12]. We have assessed the therapeutic efficacy of amineptine (a selective dopamine, DA, uptake inhibitor) [13–15] and amitriptyline (a preferential serotonin, 5-HT, uptake blocker) on patients affected by anxious depression defined on the basis of DSM-III-R criteria and of additional operational clinical criteria.

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Material and Methods

The present study includes 66 depressed outpatients (36 women and 30 men, age range 18–62 years), with a psychiatric diagnosis of primary major unipolar depression or bipolar affective disorders, according to DSM-III-R [1]. Based upon additional operational subtype criteria, patients were diagnosed as being affected by anxious depression. All patients exhibited at least 8 of the following symptoms: anxiety, trepidation (as internal tremor feeling), restlessness, early and/or late insomnia, impulsivity, hostility, dysphoria, compulsivity, hyperperspiration, palpitation, pollakiuria, phobias. Patients included needed a minimum score of 20 on either the Hamilton Rating Scale for Depression (HDRS) [19] or the Hamilton Anxiety Rating Scale (HARS) [20]. Patients with alcoholism, organic brain syndromes, serious cardiac, hepatic, renal or endocrinological diseases, convulsive disorders, Parkinson disease, prostate hypertrophy or glaucoma and pregnant or lactating women were excluded. Psychotropic medication was withdrawn for at least 14 days prior to entering the study. Patients were advised against alcohol intake while participating in the study. Informed consent was obtained from each patient. Patients were randomly assigned to three groups (n = 22) and treated double-blindly with amitriptyline, amineptine and placebo for 6 weeks. No statistically significant difference was present in all parameters evaluated among the three groups.

Medication of each patient was precoded and provided in numbered packages according to systematized randomization. During the 1st week, the initial dose was 25 mg once per day and, after 4 days, twice per day for amitriptyline, or 100 mg once in the morning for amineptine. During the 2nd week the dose was increased to 100 mg per day in three administrations (25 + 25 + 50 mg) for amitriptyline and to 200 mg (twice per day, in the morning and afternoon) for amineptine. Patients were evaluated at the beginning of the study (time 0), then after 2, 4, and 6 weeks of treatment, by using the HDRS, HARS and the evaluation of the above-reported symptoms. Statistical analysis was performed by using paired t test or one-way analysis of variance (ANOVA) associated with Dunnet's t test. Blood pressure and laboratory tests (blood count, S-GOT, S-GPT and urinalysis) were monitored continuously during the study.

Results

Six amineptine patients in the 2nd week and 3 placebo patients in the 4th week dropped out of the study, because of side effects (amineptine) or worsening of symptoms (amineptine or placebo) (table 1). None of the amitriptyline patients dropped out, although moderate anticholinergic side effects (such as dryness of the mouth, blurred vision, constipation) or sedation, menstrual problems, oversleeping, bitterness of the mouth, weight gain, tachycardia, occurred singly or in association in most of the patients (table 1). Repeated administration of amitriptyline led to a significant decrease in the mean total HDRS and HARS scores after 2–3 weeks of treatment. Placebo also reduced the above-mentioned scores, albeit to a lesser extent (table 2). In contrast amineptine did not affect sig-

Table 1. Individual side effects observed at the end of treatment

	Placebo (n = 19)	Amitriptyline (n = 22)	Amineptine (n = 16)
Dry mouth	0	11	2
Bitter mouth	0	10	0
Drowsiness	1	8	0
Sedation	1	6	0
Weight gain	0	5	0
Tachycardia	1	3	1
Constipation	2	4	1
Visual disturbance	0	2	0
Insomnia	3	2	7
Anxiety	2	1	6
Menstrual problems	0	2	0

Table 2. Total HDRS and HARS during treatment with placebo, amitriptyline or amineptine

	HDRS				HARS			
	baseline	week 2	week 4	week 6	baseline	week 2	week 4	week 6
Placebo	23.34±0.3 (n = 22)	21.76±0.2 (n = 22)	19.67±0.3 (n = 19)	17.43±0.2* (n = 19)	24.40±1 (n = 22)	22.82±1.2 (n = 22)	20.12±0.4 (n = 19)	19.24±1.3* (n = 19)
Amitriptyline	22.48±1.1 (n = 22)	18.97±0.7 (n = 22)	13.43±0.5 (n = 22)	9.65±0.6*,+ (n = 22)	25.26±1.1 (n = 22)	21.32±0.6 (n = 22)	16.3±0.5 (n = 22)	10.13±0.8*,+ (n = 22)
Amineptine	21.33±0.8 (n = 22)	22.85±1.2 (n = 16)	20.28±1.3 (n = 16)	16.35±0.8*,NS (n = 16)	23.2±0.7 (n = 22)	24.65±0.9 (n = 16)	23.21±1.1 (n = 16)	24.41±0.6NS (n = 16)

Values are means ± SEM of 16–22 determinations.
* $p < 0.01$ vs. the respective baseline (paired t test); + $p < 0.01$ vs. amineptine and placebo.
NS vs. placebo (one-way ANOVA applied to the difference week 6-baseline, associated with Dunnett's test to isolate the differences).

Table 3. Mean total scores at baseline and after 6 weeks of treatment with placebo or amitriptyline or amineptine

Symptoms	Placebo		Amitriptyline		Amineptine	
	baseline (n = 22)	week 6 (n = 19)	baseline (n = 22)	week 6 (n = 22)	baseline (n = 22)	week 6 (n = 16)
Anxiety	14.62 ± 1.8	13.45 ± 1.9	15.41 ± 1.8	6.15 ± 0.7*	14.22 ± 1.1	16.40 ± 1.2
Impulsivity	10.21 ± 0.7	9.25 ± 1.2	12.69 ± 1.3	5.04 ± 1.3*	9.35 ± 0.8	10.16 ± 0.6
Compulsivity	6.31 ± 0.9	5.94 ± 1.3	10.99 ± 1.7	4.6 ± 0.7*	7.49 ± 1.4	5.28 ± 0.5
Restlessness	12.75 ± 1.1	10.1 ± 0.8	9.25 ± 0.5	4.25 ± 0.2*	11.46 ± 0.9	12.07 ± 2.2
Palpitation	7.11 ± 1.5	6.33 ± 0.6	8.03 ± 1.4	6.32 ± 0.9	6.03 ± 0.4	7.11 ± 0.7
Hyperperspiration	5.21 ± 1.9	5.71 ± 1.4	6.47 ± 1.2	5.12 ± 1.1	4.24 ± 0.6	3.21 ± 0.5
Hostility	9.9 ± 1.8	8.1 ± 0.3	11.62 ± 1.4	6.21 ± 1.9*	10.66 ± 1.3	11.9 ± 0.6
Insomnia	17.16 ± 1.6	16.15 ± 0.5	16.95 ± 1.6	7.06 ± 1.3*	15.24 ± 1.5	16.21 ± 1.8
Dysphoria	10.44 ± 0.2	10.01 ± 0.7	9.33 ± 1.1	5.03 ± 1*	8.73 ± 1.6	10.35 ± 2.1
Pollakiuria	8.55 ± 1.3	7.54 ± 1.8	7.25 ± 1.4	4.71 ± 0.7*	9.94 ± 2.5	9.29 ± 1.8*
Trepidation	8.24 ± 0.5	7.25 ± 0.7	14.13 ± 1.4	5.29 ± 1.4*	6.6 ± 1.7	8.64 ± 0.5
Phobias	6.14 ± 1.3	6.89 ± 1.3	7.55 ± 0.5	4.44 ± 0.8*	5.7 ± 1.1	5.3 ± 1.6

For each symptom 0 = absent, 10 = mild, 20 = severe.
Values are means ± SEM of 16–22 determinations.
* $p < 0.01$ vs. the respective baseline (paired t test).

Table 4. Synoptic table of two critical symptomatologic clusters (1–13 and 14–26) for predicting antidepressant response

Symptoms		Supposed biochemical dysfunction	
		DA	5-HT
1	Anergia	+++	+/0
2	Hypokinesia	+++	0
3	Reduction of speech	+++	+/0
4	Hypophonia	+++	0
5	Salivation	+++	0
6	Hypersomnia	+++	0
7	Parinaud	++	0
8	Slowness	+++	+/0
9	Hypomimia	+++	+/0
10	Red. of sexual activity	+++	+/0
11	Hypotension	++	0
12	Dysphagia	++/+	0
13	Drowsiness	+++	+/0
14	Anxiety	0	+++
15	Dysphoria	0	++
16	Impulsivity	0	+++/++
17	Compulsivity	0	++/+
18	Early insomnia	+/0	+++
19	Late insomnia	+/0	+++/++
20	Hostility	0	+++/++
21	Hyperperspiration	0	+++/+
22	Palpitation	0	++/+
23	Pollakiuria	0	++/+
24	Restlessness	0	+++/++
25	Phobias	0	++/0
26	Trepidation	0	+++

+++ = Severe; ++ = moderate; + = mild; 0 = absent.

nificantly the HDRS or HARS scores but even worsened some symptoms (table 3), such as insomnia, agitation, and hostility, and produced significant signs of psychomotor excitement. Interestingly, these symptoms were improved by amitriptyline (table 3). None of the treatments affected laboratory data or vital signs, with the exception of a mild tachycardia that occurred in 5 amitriptyline patients.

Discussion

Patients affected by anxious depression exhibit a low cerebrospinal fluid (CSF) level of 5-hydroxyindoleacetic acid (5-HIAA) as compared to normal controls and respond promptly to antidepressant drugs that increase serotonergic transmission [22]. The efficacy of buspirone, a partial agonist of 5-HT1 a subtype of serotonergic receptors, on generalized anxiety disorders [23, 24], and the antidepressant effect of selective serotonin reuptake inhibitors [25, 26] further support the relation between 5-HT, anxiety and depression.

A therapeutic efficacy of amitriptyline, which inhibits serotonergic reuptake and thereby down-regulates 5-HT receptors, has been demonstrated in numerous clinical investigations [11, 18, 27–34]. In our study amitriptyline exhibited a greater efficacy than amineptine and placebo in a defined subtype of depression, anxious depression, the pathophysiology of which has been related to a reduced central serotonergic transmission [22]. Amineptine, which increases dopaminergic transmission by selectively inhibiting dopamine reuptake, was ineffective in improving most of the symptoms of anxious depression. Our results support the view that serotonergic transmission is a preferential target for antidepressant agents effective in improving anxious depression, although a role for the anticholinergic activity of amitriptyline and the noradrenergic effect of its metabolite, nortriptyline, cannot be excluded (an investigation with a pure 5-HT and NA compound would be necessary to clarify this matter). The reported efficacy of amineptine in patients affected by retarded depression suggests that a balance between serotonergic and dopaminergic transmission regulates the relative proportion of anxiety or negative symptoms in depressed patients (table 4). The presence of symptoms related to anxiety may thus predict a favorable clinical response in depressed patients treated with drugs that enhance serotonergic transmission. This may help the outcome prediction for serotonergic antidepressant, which is often difficult to make due to the low reliability of the common biological markers, such as low CSF or plasma 5-HIAA levels, platelet MAO activity, ^{3}H-imipramine binding, abnormal dexamethasone suppression test or total plasma MHPG levels in anxious and nonanxious depressed patients [35].

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