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EFFICACY AND ACCEPTABILITY OF AMINEPTINE IN INDIAN DEPRESSIVE PATIENTS : AN OPEN TRIAL

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Amineptine is a new antidepressant agent with a molecular structure which is related to the tricyclic antidepressants but with a different pharmacological action. Neurochemical studies have shown that amineptine stimulates dopaminergic neurotransmission in the mesolimbic and mesocortical systems by *inhibition of the re-uptake of dopamine at* presynaptic level (Mocaer, 1983; Labril et al., 1987; Offermeier et al., 1977 and Bonnet et al., 1987).

In contrast to the other tricyclic antidepressants, amineptine in normal therapeutic dosages, does not modify the release or the re-uptake of noradrenaline or serotonine. Although it is very difficult to extrapolate from neurotransmitter activities at cellular levels to pathological conditions or therapeutical effects, there is some evidence that diminished dopaminergic activity is related to depressive syndromes, especially combined with psycho-motor retardation (Willner, 1982, a, b, c). Amineptine has been used with success in the treatment of patients with reactive, neurotic, involutional and endogenous depressission (Kammerer et al., 1981; Decker and Wayner, 1981; Deniker et al., 1982, Vauterin and Bazot, 1979; Bornstein, 1979; Lemoine et al., 1981; Vain Amerongen, 1979; Porot et al., 1980 and Outes and Bosereton, 1983).

AIM

The purpose of our study was to evaluate the efficacy and acceptability of amineptine in depressive patients.

MATERIAL AND METHOD

Procedures and trial design

In this six week open study both men and women, aged between 21 and 65 years, were included. Patients who fulfilled DSM-III criteria for Major Depression, single episode; Major Depression, recurrent; Bipolar disorder, depressed or Dysthymic disorder (APA, 1980). Study was conducted at two centeres.

Study subjects could be either hospitalized or treated as out-patients. Exclusion criteria were: Huntington's chorea, severe or uncontrolled diabetes, severe disease of the liver, respiratory system, kidneys or heart, previous hepatitis related to amineptine, severe asthma or allergic conditions, cancer, disability or domicile which might interfere with regular attendance, alcoholism, drug addiction, history of narrow-angle glaucoma, patients requiring medication which might induce enzymatic liver activity, pregnant women and women in the reproductive period of life.

At entry the subjects were assigned to amineptine using a flexible daily dosage of 100 to 200 mg. This dosage could be adapted individually to the severity of the depressive symptoms. Additional medication with an anxiolytic, hypnotic or neuroleptic drug was allowed.

Measurements of efficacy and safety

Antidepressant activity and safety of amineptine were assessed on Day 0, 7, 14, 21, 28, 35 and 42.

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Clinical efficacy was assessed by :

—The 21-item Hamilton Rating Scale of Depression (HRSD) (Hamilton, 1967).

—A global scale of severity of illness with a 5-point scale (very severe, severe, moderate, mild, nil).

A clinical assessment of efficacy, was performed at the end of the treatment (D42) with a 6-point rating scale (symptoms cleared, marked improvement, moderate improvement, slight improvement, no change, worse).

Clinical safety was studied using :

—Sujective somatic complaints, body weight, heart rate, blood pressure (Phase V Korotkoff) both standing and supine, on Day 0, 7, 14, 21, 28, 35, and 42)

—Laboratory tests : haematology (haemoglobin, haematocrit, full blood count, including white cell differential), fasting blood glucose, blood urea, serum creatinin, serum alkaline phosphatase, and electrocardiogram, performed on D0 and at the end of the treatment (D42).

Study Population

During a period of six months, 40 depressive patients meeting the inclusion criteria and exclusion criteria were thus included in two psychiatric centres at Bombay (20 subjects) and Lucknow (20 patients). The age of the study population ranged between 22 and 65 years. The other demographic data of the study population are listed in Table I. All subjects included had a severe form of depression. Duration of the depressive episodes before entry in the study ranged between 15 days to more than six years. Diagnoses at entry of the study according to the DSM-III criteria are listed in Table II. In total 72.5% were classified in as major depression or bipolar disorders.

TABLE I. *Demographic data of study subjects at entry of the study (N=40)*

Men/Women	22/18 (55%/45%)
Mean age (years)	40.9 ± 1.7
Mean weight (kg)	53.6 ± 1.7
Professional Status :	
Unemployed/Retired	6 (15.0%)
Blue collar	9 (22.5%)
White collar	6 (15.0%)
Executive/Professional	2 (5.0%)
Housewife	17 (42.0%)

TABLE II. *Diagnoses of study subjects, according to DSM III criteria at entry of the study (N=40)*

Major Depression, single episode	11 (27.5%)
Major Depression, recurrent	13 (32.5%)
Bipolar Disorder, depressed	5 (12.5%)
Dysthymic Disorder	11 (27.5%)

Statistical analysis

The time course for the antidepressant parameters has been evaluated with the non-parametric test of Friedman. When time effect was significant this test was completed by a two-way comparison of the scores obtained at different moments.

The biological and cardiovascular parameters were compared by a two-way analyses of variance. When a time effect was significant the analysis was followed with the Newman-Keuls test.

RESULTS

Seventeen subjects were treated with amineptine alone. In 12 subjects amineptine therapy was combined with hypnotic therapy (flurazepam : 5; nitrazepam :7), while 15 subjects needed concomitant therapy with anxiolytic therapy (chlordiazepoxide :7; diazepam : 6; lorazepam :2).

One subject was treated throughout the study with propranolol because of benign essential tremors.

Seven subjects were withdrawn from the study, five because of lack of improvement and two others due to poor follow up.

Antidepressant efficacy

The total score of the Hamilton Rating Scale of Depression improved significantly

TABLE III. *Individual items of the Hamilton rating scale of depression at baseline and after 6 weeks treatment with amineptine indicated are average scores ± sem.*

	n	Baseline m (± S.E.M)	End of treatment m (± S.E.M.)	p Value*
1. Depressed mood	33	2.5 (0.1)	1.2 (0.2)	<0.001
2. Feelings of guilt	33	0.8 (0.2)	0.2 (0.1)	N. S.
3. Suicide	33	1.3 (0.2)	0.6 (0.1)	<0.001
4. Insomnia early	33	1.3 (0.1)	0.4 (0.1)	<0.001
5. Insomnia middle	33	0.9 (0.1)	0.3 (0.1)	0.015
6. Insomnia late	33	1.4 (0.1)	0.6 (0.1)	<0.001
7. Work & Activities	33	2.5 (0.1)	1.5 (0.2)	<0.001
8. Retardation	33	1.1 (0.2)	0.3 (0.1)	<0.001
9. Agitation	33	0.3 (0.1)	0.2 (0.1)	N. S.
10. Anxiety psychic	33	2.1 (0.1)	1.3 (0.2)	<0.001
11. Anxiety somatic	33	1.8 (0.1)	1.5 (0.2)	0.009
12. Somatic symptoms (Gastro-intestinal)	33	1.2 (0.1)	0.6 (0.1)	0.018
13. Somatic symptoms (General)	33	0.6 (0.1)	0.4 (0.1)	N. S.
14. Genital symptoms	33	1.2 (0.1)	0.8 (0.1)	N. S.
15. Hypochondriasis	33	1.6 (0.2)	0.8 (0.2)	<0.001
16. Loss of weight	33	0.4 (0.1)	0.2 (0.1)	N. S.
17. Insight	33	0.6 (0.1)	0.1 (0.1)	0.007
18. Diurnal variation	33	0.5 (0.1)	0.2 (0.1)	N. S.
18b. Severity of 18	31	0.2 (0.1)	0.1 (0.1)	N. S.
19. Depersonalisation/Derealisation	33	0	0	N. S.
20. Paranoid symptoms	33	0	0	N. S.
21. Obsessional and Compulsive symptoms	33	0	0	N. S.
Total Score	31	22.8 (0.7)	11.3 (1.5)	<0.001

*The time effect is based on the overall results of 6 weeks treatment.

from 22.8 ± 0.7 at week 0 to 11.9 ± 1.5 after 6 weeks of treatment ($p < 0.001$). The improvement became significant after 2 weeks of treatment (17.3 ± 1; $p < 0.05$) and progressed further throughout the study ($p < 0.01$). Subanalysis of the evolution of the individual items of this scale showed a significant improvement of 12 items, especially related to severity of depression, quality of sleep and psychomotor activity, anxiety and somatic symptoms (Table III). No individual item improved significantly within 2 weeks of treatment.

The score of the Clinical Global Evaluation decreased progressively with a significant difference with baseline values after 4 weeks treatment ($p < 0.01$). It suggests a gradual improvement of the average mood state of the subjects.

Overall clinical assessment showed that 21 out of 37 patients improved (56.8%) to a moderate degree or more, 21.6% of patients were reported to have slight improvement whereas 21.6% showed no change or worsening in their conditions (Table IV).

A subsequent analysis of the Hamilton Rating Scale of Depression and the Clinical Global Evaluation was performed on the moderate to marked responders.

The scores on Hamilton Rating Scale of Depression decreased from 23.4 ± 1.0 to 6.9 ± 1.8 ($p < 0.001$), while the Clinical Global

TABLE IV. *Results of the overall assessment scale of efficacy in the patients that completed the study (N=37)*

Symptoms cleared	7	(18.9%)
Marked improvement	5	(13.6%)
Moderate improvement	9	(24.3%)
Slight improvement	8	(21.6%)
No change	6	(16.2%)
Worsening	2	(5.4%)

Evaluation showed reduction from 2.3 ± 0.1 at the entry of the study to 0.6 ± 0.2 at the end.

Safety Parameters

Complaints of patients

Amineptine was well tolerated. In total 11 side effects were reported that might be related to amineptine in our opinion. (Table V). The most frequent reported effect was dryness of the mouth of which three patients complained. One patient developed jaundice after three weeks of treatment, but we could not establish the etiology of this symptom as this patient was lost to follow up.

TABLE V. *Reported adverse reactions that may be related to amineptine*

Dryness of mouth	3
Epigastric pain	1
Constipation	2
Jaundice	1
Headache	1
Insomnia	1
Flushing	1
Restlessness	1
TOTAL	11

Effect on body weight

There was a small but statistically significant increase in body weight from 53.6 ± 1.7 Kg at baseline to 53.8 ± 1.7 Kg at the end of treatment ($p = 0.02$).

Biological parameters

Except for a small but significant increase in average haemoglobin values from 12.27 ± 0.24 to 12.51 ± 0.26 g/100ml ($p < 0.05$), no significant changes occurred in any of the tested biological parameters. A careful examination of individual data revealed no pathological changes in any of the patients that completed the study.

Cardiovascular parameters

No adverse cardiovascular effects were noted. Heart rate reduced significantly during the trial from 92.9 ± 1.2 at baseline to 79.9 ± 0.6 at the end of treatment ($p < 0.01$). Standing systolic blood pressure decreased significantly from 123.8 ± 1.9 to 122.1 ± 1.9 mmHg at the end of treatment ($p = 0.03$). The other blood pressure values remained unchanged. The difference between supine and standing blood pressure did not change on amineptine. Case by case analysis of all cardiovascular parameters including E.C.G. recordings did not reveal any abnormality.

DISCUSSION

This open study involved 40 patients with major depressions, bipolar disorders and dysthymic disorders according to DSM III criteria.

From the start of therapy with amineptine the mood level of the included patients showed a positive trend, the antidepressant effect of amineptine reached significance after two weeks therapy in the Hamilton Rating Scale of Depression and after four weeks in the Clinical Global Evaluation. This relatively late onset of action is contradictory to earlier studies with amineptine (Oules and Boscredon, 1983; Kammerer et al., 1981; Dicker & Wagner, 1981; Deni Keretal, 1982; Vauterin & Bazot, 1979; Bornstein, 1979; Lemoine et al., 1981; Van Amerongen, 1979 and Perot et al., 1980). It is probably related to the low starting dosages

of amineptine used in the first week of treatment during this trial.

None of the individual items of the Hamilton Rating Scale of Depression improved significantly within 2 weeks of treatment, which suggests that the improvement of the quality of sleep and anxiety is related to the anti-depressant activity of amineptine and unrelated to the concomittant use of hypnotics or anxiolytics.

In general amineptine was well tolerated in this study. The most frequent reported side effect was dryness of the mouth.

Unfortunately, the patient who developed jaundice after three weeks of treatment was lost to follow-up and we were unable to establish the etiology of this symptom. As infectious hepatitis is quite common in India, it is unlikely that this case of jaundice is related to drug therapy. It is well known however that hepatitis may occur during therapy with antidepressant drugs, including amineptine. This side effect normally disappears after discontinuation of therapy (Yon and Anuras, 1975; Moskovitz et al., 1982; Andrieu et al., 1982).

The small increase in average body weight during this trial may be a secondary result of increased appetite or due to the antidepressant effect of amineptine.

The slight increase in haemoglobin value is of no clinical importance. As no other biological parameter changed, we may conclude that the biological tolerance of amineptine was excellent.

Amineptine caused a small decrease in heart-rate and standing systolic blood pressure, but both changes are of no clinical importance. All other cardiovascular parameters remained normal.

There was no difference between standing and supine blood pressure levels and thus amineptine caused no postural hypotension. Other tricyclic antidepressants may cause postural hypotension in as many as 20% of patients (Glassman et al., 1979).

The ECG recordings did not show any ST change, difference in QRS duration or T top inversion which suggests that amineptine has no harmful effect on myocardial function and confirms the results obtained in other studies (Boehnert & Lovejoy, 1985 and Agnoli et al., 1982).

Amineptine seems to be a useful addition to the existing antidepressant drugs.

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