Pharmacological Reports
2007, 59, 778–784
ISSN 1734-1140

Short communication

Amantadine as an additive treatment in patients suffering from drug-resistant unipolar depression

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Abstract:
The paper describes the effect of amantadine addition to imipramine therapy in patients suffering from treatment-resistant unipolar depression who fulfilled DSM IV criteria for major (unipolar) depression. Fifty patients were enrolled in the study on the basis of their histories of illness and therapy. After a 2-week drug-free period, 25 subjects belonging to the first group were treated only with imipramine twice daily (100 mg/day) for 12 weeks, and 25 subjects belonging to the second group were treated with imipramine twice daily (100 mg/day) for 6 weeks and then amantadine was introduced (150 mg/day, twice daily) and administered jointly with imipramine for the successive 6 weeks. Hamilton Depression Rating Scale (HDRS) was used to assess the efficacy of antidepressant therapy. Imipramine did not change the HDRS score after 3, 6 or 12 weeks of treatment when compared with the washout (before treatment). The addition of amantadine to the classic antidepressant reduced HDRS scores after 6-week joint treatment. Moreover, the obtained pharmacokinetic data indicated that amantadine did not significantly influence the plasma concentration of imipramine and its metabolite desipramine in patients treated jointly with imipramine and amantadine, which suggests lack of a pharmacokinetic interaction. The obtained results indicate that joint therapy with an antidepressant and amantadine may be effective in treatment-resistant unipolar depression.

Key words:
imipramine, amantadine, clinical and pharmacokinetic studies, therapy-resistant unipolar depression, humans

Introduction

It is well known that all currently used antidepressant drugs (ADs) show therapeutic efficacy in a maximum of 60–70% of patients in a major depressive episode (unipolar or bipolar). The remaining 30–40% of patients fail to demonstrate substantial clinical improvement following the first treatment (defined as at least 50% reduction in the score of symptoms) [e.g. 10]. Therefore, in order to improve the therapy, a combination of ADs belonging to various pharmacological groups, or a combination of an AD and a substance which can enhance its effect has been used in clinical practice. In recent years, much attention has been devoted to the glutamatergic system in general, and to NMDA receptor antagonists in particular in the mechanism of action of antidepressant drugs [15]. The antidepressant properties of those compounds were described in the past decade [28],

and antidepressant-like actions of competitive and uncompetitive NMDA receptor antagonists were subsequently demonstrated in animal models [e.g. 13, 24]. In addition, our earlier study showed that combined treatment with imipramine (IMI) and amantadine (AMA) produced better antidepressant efficacy in the forced swim model of depression than did either of the drugs alone, and that dopamine $D_{2/3}$ and α_1-adrenergic receptors may have contributed to the mechanism of the synergistic action of AMA and IMI in that test [22]. Therefore, in our study we decided to treat a selected group of therapy-resistant unipolar patients with IMI together with AMA, an uncompetitive NMDA receptor antagonist already admitted to the clinical use in the treatment of such diseases as Parkinson's disease [4]. By antagonizing glutamatergic inhibitory inputs on presynaptic dopaminergic neurons, AMA enhances dopaminergic neurotransmission [27]. Although the involvement of dopamine in the pathophysiology of major depressions has been well established, the role of antidepressant treatments in enhancing dopamine activity in the brain has only recently been explored [e.g. 3, 11, 16, 29, 30].

Our previous preliminary clinical studies showed that joint therapy with IMI and AMA (in 12 subjects) may be effective in treatment-resistant unipolar depression, and that the observed improvement suggested the lack of a pharmacokinetic interacton (in 6 subject who expressed their consent to be tested in that direction) [20]. Based on these data, the present study aimed to investigate the influence of AMA addition to IMI therapy in 25 patients suffering from treatment-resistant unipolar depression. For comparison, the effect of therapy with IMI alone in another 25 depressed patients was also examined. The plasma levels of IMI and its metabolite desipramine were also determined in order to check the therapeutic range in the patients during the therapy or to check possible pharmacokinetic interactions with AMA.

Materials and Methods

The study was approved by the Ethical Committee of Collegium Medicum, Jagiellonian University, Kraków and the informed consent was obtained from all participants. The patients admitted to the trial fulfilled DSM IV diagnostic criteria for major depression. Before enrolling in the study, all patients were interviewed by 2 psychiatrists, and were recruited on the basis of their histories of illness and therapy. An average duration of the illness was 2–30 years, whereas the number of depressive episodes was 3–14. The duration of the last episode of depression was 2–15 months. Over those years, the therapy of the patients consisted in treating them with various tricyclic ADs, followed by one or more selective serotonin reuptake inhibitors, or one of the "new generation" antidepressants (e.g. venlafaxine). None of those therapies was effective. An antidepressant therapy was also augmented by the addition of lithium or/and carbamazepine, but that treatment was never successful, either. Over the prolonged period of their illness, the patients were also treated with benzodiazepines, neuroleptics and mood stabilizers (full documentation of a treatment applied prior to the present study is accessible).

At the beginning of the present study, a 2-week washout period was introduced, and no benzodiazepines or other psychotropic agents were then allowed.

Thereafter, 50 patients (35 women and 15 men, aged 33–55 and 37–55 years, respectively) were treated with IMI (Imipramin, Polfa Stargard, Poland) twice daily (100 mg/day) for 12 weeks. The first group of 25 subjects (16 women and 9 men) was treated only with IMI twice daily (100 mg/day) for 12 weeks, and the second group of 25 subjects (19 women and 6 men) was treated with imipramine twice daily (100 mg/day) for 6 weeks, and then AMA (Amantix, 150 mg/day, twice daily, Merz Pharmaceuticals, Frankfurt am Main, Germany) was introduced and administered jointly with IMI for the successive 6 weeks.

Clinical ratings

Patient self-report instruments and clinician ratings were used to assess the clinical status, overall functioning, and the quality of life at five time points (i.e. at the beginning of the study, after 3 and 6 weeks of IMI administration, and finally after 3 and 6 weeks of joint IMI and AMA administration). Hamilton Depression Rating Scale (HDRS, 21 items) [7] was used to assess the efficacy of the antidepressant therapy.

Drug assay in the plasma of patients

Pharmacokinetic studies were conduced only in patients who expressed their consent to be tested in that direction. Blood samples were collected before the

morning dose of IMI and AMA. The plasma concentrations of IMI and its metabolite desipramine were determined by a HPLC method based on the procedure described by Suftin and Jusko [26]. To 1 ml of blood plasma containing IMI and desipramine, 300 μl of a 25% ammonium hydroxide were added; then the drugs were extracted with 2 ml of hexane containing 1.5% of isoamyl alcohol (v/v). The recovery of the parent compound and its metabolite after extraction was about 96%. The residue obtained after evaporation of the plasma extracts was dissolved in a mobile phase (described below) and injected into the LaChrom HPLC system (Merck-Hitachi), equipped with an L-7480 fluorescence detector. The analytical column Econosphere C18 (5 μm, 4.6 × 250 mm) was purchased from Alltech (Carnforth, England) and was kept at an ambient temperature. The mobile phase consisted of methanol and acetonitrile (1:1, v/v) containing 1 ml/l of triethylamine. The flow rate was 1 ml/min. The fluorescence of the samples was measured at an excitation wavelength of 240 nm and an emission wavelength of 370 nm. All plasma samples were assayed in duplicate.

Statistical analysis

The clinical and pharmacokinetic data were evaluated by a one-way analysis of variance (ANOVA), followed by Dunnett's test.

Results

The characteristics of patients participating in the study are presented in Table 1. Fifty patients were admitted, including 15 men aged 37–55 and 35 women aged 33–55 years; they were then divided into two groups (containing 25 subjects each): one group of 16 women and 9 men, aged 47.9 ± 1.2 and 43.0 ± 4.7 years, respectively (the mean duration of illness was 13.9 ± 1.4 and 12.0 ± 2.0 years, respectively). The number of depressive episodes averaged 8.2 ± 0.7 and 6.1 ± 1.1, respectively, and lasted at least 1 month; the duration of the last episode of depression was 2–12 months, averaging 6.9 ± 0.8 and 7.4 ± 1.1 months, respectively. The other group of 19 women and 6 men, aged 44.9 ± 1.6 and 50.0 ± 1.2 years, respectively (the mean duration of illness was 10.4 ± 1.7 and 12.5 ± 3.9 years, respectively), while the number of depressive episodes averaged 7.1 ± 0.8 and 6.7 ± 1.0 each, respectively and lasted at least 1 month. The duration of the last episode of depression was 2–15 months (6.3 ± 0.8 and 8.5 ± 1.9 months, respectively).

Clinical ratings

Clinical effects of the administration of IMI alone or jointly with AMA (five time points) are presented in Table 2. No differences could be seen between the baseline scores of male and female patients (HDRS scores). IMI did not significantly change HDRS scores after 3, 6 or 12 weeks of treatment when compared with the baseline depression rating (before treatment) (Tab. 2), while, a partial response defined as a drop by more than 25%, but less than 50%, was observed in 6 patients (24%, 4 women and 2 men) after 12-week on IMI therapy. The augmentation of IMI treatment by the addition of AMA only slightly reduced HDRS scores in women and men (by 11.8% and 14.2%, respectively) after 3-week administration. Combined treatment with IMI and AMA for 6 weeks produced a stronger reduction of HDRS scores in women and men than did co-administration of those drugs for 3 weeks (by 23.3% and 43.7%, respectively, when compared with the baseline score [before treatment]). A greater than 50% decrease in the baseline HDRS scores was observed in 6 patients (24%, 2 women and 4 men); however, a partial response defined as a drop by more than 25%, but less than 50%, was observed in other 11 patients (44%, 10 women and 1 man). The augmentation of IMI treatment by the addition of AMA was not effective in 8 patients (32%; no reduction in HDRS scores was reported in 7 women and 1 man).

The most common side-effects resulting from IMI treatment were dry mouth and a decreased blood pressure (by 5–10 mm); those effects were not changed by the addition of AMA to IMI therapy.

Pharmacokinetic measurements

The plasma concentrations of IMI and its demethylated metabolite desipramine (DMI) were within the therapeutic range in the majority of patients (IMI + DMI 100–300 ng/ml) at most of the time points studied, e.g. before the addition of AMA to IMI treatment, during the combined therapy. The relative concentrations of DMI (compared to IMI) varied among pa-

Tab. 1. Demographic and clinical characteristics of patients

A. Characteristic of patients before therapy with imipramine

Subject	No.	Age (years)	Duration of illness (years)	Number of episodes	Duration of the last episode (months)
Woman	1	42	12	10	5
	2	50	13	11	9
	3	51	19	9	8
	4	46	15	10	7
	5	39	7	6	3
	6	50	20	4	9
	7	52	13	13	8
	8	51	5	4	11
	9	55	14	7	12
	10	47	21	8	7
	11	48	17	12	10
	12	51	21	7	3
	13	54	7	8	2
	14	46	14	11	4
	15	40	20	7	10
	16	45	4	4	3
Mean ± SEM		47.9 ± 1.2	13.9 ± 1.4	8.2 ± 0.7	6.9 ± 0.8
Men	1	50	8	5	7
	2	51	23	11	5
	3	52	9	12	4
	4	50	11	4	11
	5	47	13	7	12
	6	46	6	5	10
	7	54	20	3	4
	8	54	6	3	10
	9	37	12	5	4
Mean ± SEM		43.0 ± 4.7	12.0 ± 2.0	6.1 ± 1.1	7.4 ± 1.1

B. Characteristic of patients before therapy with imipramine and amantadine

Subject	No.	Age (years)	Duration of illness (years)	Number of episodes	Duration of the last episode (months)
Woman	1	47	21	12	9
	2	52	28	12	11
	3	42	14	8	9
	4	42	4	4	12
	5	35	20	14	13
	6	46	4	3	12
	7	37	5	6	3
	8	48	20	12	4
	9	33	14	10	2
	10	34	6	7	6
	11	50	15	6	7
	12	47	2	3	2
	13	55	8	5	3
	14	47	6	4	3
	15	37	3	5	5
	16	54	5	7	4
	17	48	9	5	4
	18	53	8	7	7
	19	46	6	4	3
Mean ± SEM		44.9 ± 1.6	10.4 ± 1.7	7.1 ± 0.8	6.6 ± 0.8
Men	1	50	30	8	10
	2	51	16	11	12
	3	46	11	5	15
	4	55	5	4	3
	5	49	5	6	6
	6	49	8	6	5
Mean ± SEM		50.0 ± 1.6	12.5 ± 3.9	6.7 ± 1.0	8.5 ± 1.9

Tab. 2. The therapeutic effect of imipramine (100 mg/day, twice daily, IMI) **(A)** or IMI (100 mg/day, twice daily) with amantadine (150 mg/day, twice daily, AMA) **(B)** administration in patients with drug-resistant unipolar depression. Hamilton Depression Rating Scale (the mean ± SEM) was used to assess efficacy of antidepressant therapy

Treatment	Washout baseline	3 weeks	6 weeks	9 weeks	12 weeks
Woman					
A. IMI	37.0 ± 0.8	36.4 ± 1.2	36.7 ± 1.2	35.9 ± 1.7	35.0 ± 2.2
B. IMI+AMA	34.7 ± 1.1	34.1 ± 1.1	33.8 ± 1.8	30.6 ± 1.6	26.6 ± 2.4
Men					
A. IMI	33.4 ± 1.8	32.6 ± 2.0	31.9 ± 2.3	31.2 ± 2.7	29.9 ± 2.5
B. MI+AMA	33.2 ± 1.9	31.5 ± 1.9	29.3 ± 0.7	28.5 ± 3.2	18.7 ± 5.0*

A – patients treated only with IMI for 12 weeks, **B** – patients treated with IMI for 6 weeks, followed by IMI with AMA for the successive 6 weeks.
* $p < 0.05$ *vs.* baseline

during the combined therapy. The relative concentrations of DMI (compared to IMI) varied among patients, indicating interindividual differences in the activity of imipramine N-demethylase, i.e. in the activity of cytochromes P-450 3A4 and 1A2 (CYP3A4 and CYP1A2). AMA did not influence the average plasma antidepressant concentration (IMI + DMI). The differences in drug concentrations between patients after 12-week IMI treatment alone [87.1 ± 17.1, 114.1 ± 12.8 and 201.3 ± 22.1 (IMI, DMI and IMI + DMI, respectively) in women or 56.5 ± 17.5, 179.6 ± 27.4 and 236.1 ± 39.6 (IMI, DMI and IMI + DMI, respectively), in men] and those treated with IMI for 6 weeks and then given jointly IMI and AMA for another 6 weeks [116.1 ± 27.4, 104.5 ±13.0 and 220.6 ± 33.1 (IMI, DMI and IMI + DMI, respectively), in women, or 114.1 ± 13.5, 116.4 ± 14.5 and 230.5 ± 28.4 (IMI, DMI and IMI + DMI, respectively), in men] did not reach the level of statistical significance.

Discussion

The present results show the efficacy of AMA as augmentation to the ongoing antidepressant therapy in patients suffering from treatment-resistant unipolar depression. Clinical remission, defined as a cut-off point of 7 or less on the HDRS scale, was observed in one patient; moreover, a response defined as a decrease by more than 50% from the baseline HDRS score [6, 17, 18] was found in other 5 patients (20%), and a partial response regarded as a decline by more than 25% but less than 50% [14] was observed in other 11 subjects (44%). AMA augmentation of IMI treatment was not efficient in 8 patients (32%, no reduction of HDRS scores was found in 7 women and 1 man). Since in the last episode of depression (over all those months) the therapy of the above patients with tricyclic ADs, followed by one or more selective serotonin reuptake inhibitors or venlafaxine, was not effective, and since the therapy augmented by the addition of lithium or/and carbamazepine was not successful, either, the present results indicating the efficacy of AMA as augmentation to ongoing IMI therapy in 17/25 patients (68% of responses and partial responses) suffering from antidepressant-resistant depression seem promising.

In addition, our earlier preliminary studies showed that joint therapy with IMI and AMA could be successful in treatment-resistant unipolar depression, and the augmentation of IMI treatment by AMA was beneficial and lasted even after AMA withdrawal (of the 12 patients suffering from drug-resistant unipolar depression, two showed clinical remission; a response was evoked in eight patients, and a partial response in two patients [20]. Similar long-lasting effects were also described by other authors, who reported high ratio of improvement in subjects with treatment-resistant depression (57%; 4/7 patients, treated with AMA as an augmentating agent for 4 weeks [25], and approaches the reported response rate of augmentation therapy with lithium [2].

Since no significant side-effects of the above described therapy were observed throughout the study, it seems that AMA is a safe and effective augmenting agent to be used in the therapy of treatment-resistant depression.

The obtained pharmacokinetic data indicate that AMA does not significantly influence the plasma concentration of IMI and its metabolite DMI in patients treated jointly with AMA and IMI. Therefore, the observed improvement of the clinical state of treatment-resistant patients may be ascribed to their pharmacodynamic interaction.

On the other hand, AMA appears to act *via* several pharmacological mechanisms, and none of them has been identified as a chief mode of action. Moreover, AMA exhibits dopaminergic, noradrenergic and serotonergic activities, blocks monoamine oxidase A and NMDA receptors, and probably elevates β-endorphin/β-lipotropin levels [8]. It is still uncertain which of these mechanisms work at the therapeutic dose of the drug. All AMA actions may be decisive for its antidepressant properties, so it has been suggested that AMA is likely to act as an antidepressant *via* not one, but several mechanisms related to antidepressant activity. For example, it cannot be excluded that the antagonistic action of AMA on NMDA receptors may be an additional mechanism of antidepressant activity [1, 25]. Moreover, a large number of ADs have been demonstrated to alter the NMDA receptor in a manner that may be in line with the resulting decrease in functional activity at this site [15]. Indeed, the mechanism of action of AMA at its clinically effective doses involves the NMDA system. However, by antagonizing the glutamatergic inhibitory inputs on presynaptic dopaminergic neurons AMA enhances the dopaminergic neurotransmission [27].

We also demonstrated previously that repeated administration of IMI jointly with AMA induced up-regulation of the dopamine $D_{2/3}$ in rats [19]. In the light of our previous animal studies indicating the role of dopamine D_2/D_3 receptors in the mechanism of action of not only ADs, but also AMA [e.g. 12, 19, 21, 22], it has been proposed that brain dopaminergic system itself may underlie the beneficial therapeutic effects of joint IMI and AMA administration in drug-resistant depressed patients.

The pivotal role of dopamine in the brain reward systems, the association of major depression with Parkinson's disease and the enhancement of dopaminergic activity by several antidepressant treatments suggest that the deficit of dopaminergic function might be associated with major depression. Different approaches have been employed to address this issue in human studies. Neuroendocrine studies into dopamine functions have not given crucial support to the alteration of this function in depression; however, it is noteworthy that it is the tuberoinfundibular dopamine system that is investigated for the neuroendocrine strategy, and it does not necessarily reflect changes in the meso(cortico)limbic dopamine system, whereas the latter is probably more relevant to depression. On the basis of the single photon emission computerized tomography (SPECT) studies, it may be concluded that striatal dopamine release is decreased in the studied subgroup of patients, although conflicting results have also been reported [5]. Recent studies conducted on a post-mortem brain tissue revealed that the binding of [^{125}I]RTI 55 to a dopamine transporter was significantly lower in the basal ganglia and central amygdaloid nuclei, while the binding of [^{125}I]epidepride to D_2/D_3 receptors was significantly higher in the basal, central and lateral amygdaloid nuclei in patients suffering from major depression compared to control subjects [9]. Nevertheless, the basic findings obtained in the present study justify the conclusion that joint therapy with ADs and AMA may be efficacious in treatment-resistant unipolar depression. The augmentation of ADs treatment by the addition of AMA was beneficial and lasted even after AMA withdrawal [20, 25]. Similar long-lasting effects were also described by other authors [1, 31] who studied the antidepressant effect of single ketamine infusion. Possibly, the relatively short-term modulation of glutamatergic neurotransmission triggers neuroadaptive changes which make classic antidepressants effective in otherwise therapy-resistant patients. In addition, our earlier study showed that joint administration of IMI and AMA induced a more potent increase in BDNF gene expression in the rat hippocampus compared to treatment with either drug alone [23], and suggested that the enhancement of neurotrophic system support and the associated augmentation of synaptic plasticity and function might constitute a basis for antidepressant efficacy and serve as the present and future focus in the search for a more rapid-acting and effective medication of depression.

Despite a small number of samples, heterogeneity of the duration of the illness and a variety of ADs used to treat patients before as well as an open label design limiting the general application of our findings, it can be suggested that the use of AMA as augmentation therapy jointly with the most selective ADs (e.g. selective serotonin reuptake inhibitors, or venlafaxine) in patients suffering from treatment-resistant depression may be further investigated in larger, randomized, placebo-controlled double-blind research.

Acknowledgment:
The authors wish to thank Ms. E. Smolak, M.A., for the linguistic supervision of the paper.

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Received:
October 30, 2007; in revised form: November 19, 2007.