Pharmacokinetics and Efficacy of Fluvoxamine and Amitriptyline in Depression

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Abstract. Although often necessary for obtaining remission following major depressive disorder, combined antidepressant treatment is frequently associated with drug interactions and enhanced adverse drug effects. We investigated pharmacokinetic interactions following combined fluvoxamine and amitriptyline treatment and their impact on therapeutic efficacy and tolerability. Twenty-two inpatients with major depression [Hamilton Depression Scale (HAM-D) rating ≥18] were treated with either amitriptyline (75 mg/day), fluvoxamine (100 mg/day) or both. Blood samples, for determination of amitriptyline, its major metabolite nortriptyline, and fluvoxamine, were obtained after single dose administration and in steady-state. Therapeutic efficacy was evaluated using HAM-D and adverse drug effects were evaluated using the clinical global impression scale. Following combined treatment, steady-state plasma levels of nortriptyline were significantly decreased compared to monotherapy. HAM-D scores after two-week treatment showed that there was a better response to combined treatment. There was no significant difference in severity of adverse effects among groups. We observed a pharmacokinetic interaction between fluvoxamine and amitriptyline resulting in impaired metabolism of the later. However, no significant impact of the interaction on treatment safety was observed. Moreover, concomitant use of amitriptyline at 75 mg/day and fluvoxamine at 100 mg/day was well tolerated with a more prompt and stronger onset of clinical response compared to monotherapy in patients with major depression.

Keywords: amitriptyline, fluvoxamine, efficacy, safety, interaction

Introduction

Treatment of major depression often represents a challenge for clinicians, since many patients fail to respond adequately to monotherapy (1), and therefore the use of antidepressant combinations is common in clinical practice (2, 3). There are reports of good clinical response and improved remission rates following the combination of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) (4 – 6). The rational for such combination originates from the observation that in animal studies, the combination of fluoxetine and desipramine more promptly and strongly induced a down-regulation of cortical β-receptors (a putative marker of antidepressant effect) than monotherapy with these agents (7). Other studies showed changes in synaptic properties and functional changes of the noradrenergic and serotonergic systems induced by both TCAs and SSRIs that may be enhanced by concomitant administration (8, 9).

However, there is also significant reluctance to combine TCAs and SSRIs, deriving from the concern of poor tolerability (10, 11) since clinically relevant pharmacokinetic interactions between the two classes have been reported (12 – 16). The underlying drug interaction mechanism is considered to be SSRI inhibition of CYP2D6 (17, 18), one of the most important enzymes in the metabolism of TCAs (19, 20). As a
Fluvoxamine/Amitriptyline Interaction

We investigated the combined treatment of amitriptyline (AT), which is the most widely used TCA, and the SSRI fluvoxamine (FL), which was shown to be very efficient in treatment of inpatients with major depression (23, 24). Moreover, the use of AT and FL is a common practice, especially in developing countries due to comparable treatment outcome but lower prices compared to newer antidepressants. FL is a potent inhibitor of CYP1A2, CYP2C19, and CYP3A4 (25, 26), all involved in the demethylation of AT. However, compared to fluoxetine, FL is a much less potent inhibitor of CYP2D6 (17, 27), which is necessary for the hydroxylation and subsequent elimination of AT, and its active metabolite nortriptyline (NT). Concomitant AT and FL administration was associated with a tendency of increased AT plasma levels, but the effect of such interaction on clinical outcome was not assessed (12).

Materials and Methods

Study protocol

The study protocol was approved by the medical ethics board of the Institute for Mental Health, and ethical standards defined by the World Medical Association, Declaration of Helsinki, were met.

A total of 22 Caucasian inpatients diagnosed with major depression (according to the DSM-IV guideline) participated in this study. Hamilton Depression Rating Scale (HAM-D) was used for the evaluation of severity of the disease and therapeutic efficacy; all HAM-D ratings were performed by the same psychiatrist. Adverse drug effects were monitored and rated according to clinical global impression (CGI). Inclusion criteria were HAM-D score ≥18 prior to treatment initiation, exclusion of other psychiatric disorders, normal function of liver and kidneys, and no medication use in the previous four weeks. Patients were informed in detail about the study and written consent was obtained prior to study enrollment.

Patients were randomised into three groups: 1) The AT group consisted of nine patients who received AT 75 mg/day as monotherapy. On day 1, AT was administered as single oral dose (75 mg) after an overnight fast, 3 h prior to food intake. From day 3 the drug was administered three times (3 × 25 mg). 2) The FL group consisted of six patients who received FL (100 mg/day as monotherapy). On day 1, FL was administered in the morning, whereas from day 3, the dosage regimen was 1 × 100 mg, in the evening. 3) The AT/FL group consisted of seven patients who received combined treatment of AT (75 mg/day) and FL (100 mg/day). On day 1, single doses of AT (75 mg) and FL (100 mg) were administered in the morning. From day 3, AT was administered three times during the day (3 × 25 mg), whereas FL was administered in the evening (1 × 100 mg). There was no significant difference between the groups with respect to age, weight, sex, and baseline HAM-D score; their characteristics and treatment are summarized in Table 1.

Clinical response was attributed to patients whose HAM-D rating was <50% compared to baseline, two weeks after treatment initiation. In the FL and AT/FL group, HAM-D testing was performed four weeks after initiation of treatment. In the AT group, the HAM-D assessment was performed six weeks after initiation of treatment. Remission was achieved if the HAM-D score was ≤7 (28).

In order to establish a possible interaction between AT and FL, pharmacokinetic parameters were determined in plasma samples after single dose and in steady-state. Following the single dose, samples were obtained just prior to drug administration and at 1, 2, 3, 4, 6, 9,

<table>
<thead>
<tr>
<th>Table 1. Patients’ characteristics and treatment</th>
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<tbody>
<tr>
<td>AT group n = 9</td>
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<tr>
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</tr>
<tr>
<td>Age*</td>
</tr>
<tr>
<td>Weight*</td>
</tr>
<tr>
<td>Sex (Female/Male)</td>
</tr>
<tr>
<td>Baseline HAM-D*</td>
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<tr>
<td>Treatment</td>
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</table>

HAM-D, Hamilton Depression Rating Scale. * Mean value ± S.D.
12, 24, 36, and 48 h. Steady-state plasma samples were obtained on the 14th day of treatment. In the AT and AT/FL groups, samples were obtained just prior to AT administration in the morning, afternoon, and evening, as well as 3 h after the morning and afternoon dose. In the FL group, samples were obtained in the evening just prior to drug administration and at 12, 15, 18, and 21 h later. The difference in sampling time following drug administration was due to inability of sample collection during the night in the FL group, but the actual sampling times were the same for all three groups of patients.

All samples were collected in heparinized vials. Furthermore, vials containing samples with AT were silanized in order to prevent glass adsorption of the drug. Immediately after collection, samples were centrifuged and kept at −20°C until analysis.

Drug analysis

Samples were analyzed for AT, its major metabolite NT, and/or FL. AT and NT were extracted (solid-phase) from the plasma sample and analyzed by high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection according to the method of Miljković et al. (29) Another extraction and HPLC-UV method, developed by Miljković et al. (30), was used for the determination of FL. Both methods met all requirements according to the FDA Guideline for bioanalytical method validation (31).

Pharmacokinetic and statistical analysis

Pharmacokinetic parameters were calculated using WinNonLin® (version 4.1; Pharsight, Mountain View, CA, USA), and statistics was performed with SPSS™ (version 15.0; SPSS, Inc., Chicago, IL, USA). Due to small sample size, all statistical evaluation was performed using non-parametric testing. The level of significance was set to P<0.05.

Results

Pharmacokinetics

Pharmacokinetic parameters of AT and NT were calculated and statistically compared both after single and repeated dose of AT monotherapy and the combination of AT and FL (see Table 2). Single dose administration of FL had no significant effect on pharmacokinetics of AT and NT (Mann Whitney U test, P>0.05). Nevertheless, NT steady-state plasma concentrations were approximately twofold lower in the AT/FL group compared to the AT group (Mann Whitney U test, P<0.01). Steady-state parameters of AT were not significantly altered by the administration of FL (Mann Whitney U test, P>0.05).

Concomitant AT administration had no significant effect on FL pharmacokinetics either after single dose administration of FL compared to AT/FL or after repeated treatment (Mann Whitney U test, P>0.05).

Table 2. Pharmacokinetics and statistical comparison of AT, NT, and FL after single dose and in steady-state following AT and FL monotherapy or combined treatment

<table>
<thead>
<tr>
<th></th>
<th>AT group</th>
<th>AT/FL group</th>
<th>FL group</th>
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<tbody>
<tr>
<td></td>
<td>AT</td>
<td>NT</td>
<td>AT</td>
</tr>
<tr>
<td>Single-dose pharmacokinetic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>70.4 ± 13.8</td>
<td>63.4 ± 17.6</td>
<td>66.8 ± 14.0</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.3 ± 1.1</td>
<td>4.0 ± 1.5</td>
<td>2.9 ± 0.9</td>
</tr>
<tr>
<td>β (h⁻¹)</td>
<td>0.0449 ± 0.0790</td>
<td>0.0448 ± 0.0110</td>
<td>0.0486 ± 0.0103</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>15.9 ± 3.2</td>
<td>16.2 ± 3.7</td>
<td>14.7 ± 2.5</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>24.2 ± 4.4</td>
<td>28.2 ± 5.5</td>
<td>22.9 ± 6.4</td>
</tr>
<tr>
<td>CL (L/kg)</td>
<td>1.068 ± 0.177</td>
<td>1.215 ± 0.916</td>
<td>1.072 ± 0.203</td>
</tr>
<tr>
<td>AUC(0-∞) (ng h/mL)</td>
<td>1059 ± 221</td>
<td>931 ± 253</td>
<td>1113 ± 265</td>
</tr>
<tr>
<td>Steady-state pharmacokinetic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax ss (ng/mL)</td>
<td>43.4 ± 9.1</td>
<td>50.0 ± 8.2*</td>
<td>39.1 ± 8.4</td>
</tr>
<tr>
<td>Cmax ss (ng/mL)</td>
<td>54.5 ± 9.0</td>
<td>67.5 ± 9.4*</td>
<td>48.3 ± 9.5</td>
</tr>
<tr>
<td>Css (ng/mL)</td>
<td>50.8 ± 8.7</td>
<td>61.3 ± 8.2*</td>
<td>44.5 ± 8.8</td>
</tr>
<tr>
<td>FL (%)</td>
<td>22 ± 7</td>
<td>28 ± 14</td>
<td>21 ± 9</td>
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</table>

Cmax: maximum plasma concentration; Tmax: time of maximum plasma concentration; β: elimination rate constant; t1/2: elimination half-life; CL: total clearance; Vd: apparent volume of distribution; AUC: area under the plasma concentration vs. time curve; Cmax ss: minimum measured steady-state plasma concentration; Cmax ss: maximum measured steady state plasma concentration; Css ss: minimum measured steady state plasma concentration; FL%: average steady state plasma concentration; FL%: percent of fluctuation of steady state plasma concentration. Results are presented as the mean value ± S.D. *Values significantly different between mono- and combined therapy (P<0.001); for all other parameters P>0.05.
In addition to pharmacokinetic parameters, the sums of AT and NT steady-state plasma levels were calculated. Namely, it was shown that AT has a linear plasma concentration–response relationship at lower doses (75 – 150 mg) but was curvilinear at a wider dose range (32, 33). However, since NT is an active metabolite, therapeutic plasma concentration range (80 – 200 ng/mL) was established for the sum of AT and NT (34). In our patients on AT monotherapy, all steady-state concentrations of AT + NT (80 – 148 ng/mL) were within the therapeutic range. In contrast, due to lower NT plasma levels, patients on combined treatment had mainly subtherapeutic steady-state plasma levels of AT + NT (46 – 60 ng/mL). Only maximum plasma concentrations reached the therapeutic range in four patients (82 – 104 ng/mL).

**Treatment response**

Baseline HAM-D scores were not significantly different among the groups (Kruskall Wallis, $P > 0.05$). After two-week treatment, HAM-D scores were lower in all groups (Wilcoxon test; $P < 0.01$ after AT monotherapy, $P < 0.05$ after FL monotherapy, and $P < 0.05$ after combined AT/FL treatment). Monotherapy groups showed similar clinical response. However, in the AT/FL group, we observed a lower average HAM-D score (Mann Whitney U test: $P < 0.05$ AT/FL vs. AT treatment and $P < 0.01$ AT/FL vs. FL treatment). The results of HAM-D scoring are presented in Fig. 1.

The third HAM-D rating was performed four weeks after initiation of treatment in the FL and AT/FL group. HAM-D scores were lower in both groups compared to previous testing (Wilcoxon test, $P < 0.05$). At this time point, there was no significant difference in remission rate between the FL and the AT/FL group.

In the AT group, the third HAM-D test was performed six weeks after initiation of treatment. We observed clinical improvement compared to the prior scoring. Clinical outcome in this group did not differ significantly from the results in the FL and AT/FL group. Clinical response and remission rates are presented in Table 3.

**Tolerability**

In the AT group weakness, sleepiness, dizziness, and drowsiness were observed in some patients. In the FL group, patients complained about nausea, weakness, and dizziness. In the AT/FL group, sleepiness, weakness, dizziness, drowsiness, and dry mouth were reported. The severity of adverse effects never exceeded grade 2 of CGI, and there was no significant difference in frequency or severity of adverse effects among groups (Kruskall-Wallis test, $P > 0.05$). Moreover, serious adverse effects associated with the use of TCAs such as tremor, cardiovascular disorders, and dysarthria were not observed in our patients, and treatments were overall well tolerated.

**Discussion**

Usually elevated levels of TCAs were associated with concomitant administration of TCAs and SSRIs (11 – 16). In contrast, in our study, FL administration did

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**Table 3.** Clinical response and remission rates in patients on AT and FL monotherapy vs. combined treatment: statistical comparison between groups

<table>
<thead>
<tr>
<th>HAM-D* evaluation</th>
<th>AT (n = 9)</th>
<th>FL (n = 6)</th>
<th>AT/FL (n = 7)</th>
<th>AT vs. FL</th>
<th>AT/FL vs. AT</th>
<th>AT/FL vs. FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>3 (33%)</td>
<td>1 (17%)</td>
<td>5 (75%)</td>
<td>&gt;0.050</td>
<td>0.049</td>
<td>0.003</td>
</tr>
<tr>
<td>Remission</td>
<td>6 (67%)</td>
<td>5 (83%)</td>
<td>6 (86%)</td>
<td>&gt;0.050</td>
<td>&gt;0.050</td>
<td>&gt;0.050</td>
</tr>
</tbody>
</table>

*Response: ≥50% improvement of HAM-D after two weeks; Remission: HAM-D ≤7 after four weeks in the FL and AT/FL group or after six weeks in the AT group.
not elevate significantly AT plasma levels. Moreover, the levels of the major active metabolite NT were approximately twofold lower after combined treatment compared to monotherapy. Such results clearly indicate impaired demethylation of AT after concomitant FL administration. This is not surprising since FL is a potent inhibitor of CYP2C19 and CYP3A4, both of which are involved in the conversion of AT to NT (35). On the other hand, FL has low potency for inhibition of CYP2D6, the enzyme playing the most important role in the hydroxylation and subsequent elimination of AT and NT. Therefore, possibly CYP2D6 was not inhibited to the extent to induce accumulation of AT and NT. Our finding was somewhat contrary to the results of Vandel et al. (12) who observed a tendency of increased plasma concentrations of AT after FL administration in four patients. However, patients in our study were treated with lower doses of both AT and FL compared to the aforementioned study (75 mg/day AT vs. 100 – 200 mg/day and 100 mg FL vs. 150 mg/day). Since the magnitude of enzyme inhibition by SSRIs was shown to be dose- and concentration-dependent (36), it is possible that the lack of accumulation of AT observed in our study was a consequence of treatment with moderate doses of both drugs.

Pharmacokinetic interactions occur often in clinical practice, but they are significant if treatment is associated with increased or decreased efficacy and/or safety. In our study, both monotherapy and combination treatment was well tolerated and only transient minor adverse effects were observed. Although our patient sample was small, we observed no tendency of more frequent or more serious adverse effects in the AT/FL group compared to monotherapy. The lack of serious adverse effects, associated with AT treatment, can be explained by the administration of lower dosage of AT (75 mg/day in this study compared to the usual dose of 150 mg/day). It was shown in the study of Miljkovic et al. (32) that patients who received AT (75 mg/day) had similar clinical response and less adverse effects compared to those who were administered 150 mg/day. Treatment with lower doses of AT is rational if steady-state concentrations of the drug and its metabolite achieve the established therapeutic range, which was the case in all our patients in the monotherapy group. On the other hand, increased toxicity of AT was associated with supratherapeutic drug plasma levels (33, 37). Furthermore, it was reported that NT plasma levels correlated significantly with adverse effects (38). Since lower NT plasma concentrations were observed in the AT/FL group, it is reasonable to assume that combined treatment with moderate doses of AT and FL may be comparable in safety to the respective monotherapy.

SSRIs and TCAs were shown to have similar therapeutic efficacy (39–41). This was the case in our study as well, where no significant difference in clinical response or remission rate was observed in the monotherapy groups. In contrast, two weeks after initiation of treatment, a more rapid and better response of patients to the combination of AT and FL compared to monotherapy was observed. On the other hand, at four or six weeks after initiation of treatment, there was no significant difference in remission among the groups. Other investigators reported controversial findings regarding clinical response after combination of TCAs with SSRIs. Fava et al. (42) showed that “high-dose” fluoxetine was superior to the fluoxetine/desipramine combination in treatment-resistant patients, four weeks after treatment began. However, the same authors (43) could not confirm these findings later in a larger population where there was no difference between the clinical response in patients receiving a higher dose of fluoxetine alone compared to the fluoxetine/desipramine combination. Furthermore, other investigators could not establish a plasma concentration–clinical outcome relationship for fluoxetine, but suggested a dose-dependent increase of adverse effects frequency (44, 45). In contrast, Nelson et al. (5) reported that the combination of desipramine and fluoxetine initially induced a better response of patients compared to desipramine monotherapy. In a later study, the authors (46) could not confirm a more rapid onset of clinical response of the fluoxetine/desipramine combination, but they achieved better remission rates in the combination group compared to monotherapy. The discrepancy between the results of Nelson et al. and our data might derive from small patient samples in both studies. Nevertheless, our present results indicate that a synergistic effect (possibly relying on β-receptor down-regulation) of SSRIs and TCAs in terms of therapeutic efficacy may exist and additional controlled, randomized, double-blinded studies in larger patient populations would be needed to elucidate this possibility. Moreover, since plasma levels of AT and NT were slightly subtherapeutic in the combination group, it remains unclear whether a titration of the dose of AT to achieve therapeutic levels of the drug and its metabolite could improve the clinical outcome of the AT/FL treatment without jeopardizing safety.

In conclusion, we observed a pharmacokinetic interaction between moderate doses of AT and FL resulting in decreased plasma levels of the metabolite NT. Whereas other SSRIs usually induce an increase of TCA plasma levels, which can lead to toxicity, FL seems to be more appropriate for combining with TCAs when moderate doses of drugs are administered. Moreover,
lack of serious adverse effects in our patients treated with FL and AT seems to support such a theory, even though our study has shortcomings in terms of evaluation of safety and efficacy, due to the open-labeled trial with a small patient sample. Moreover, genetic polymorphism was not considered in this study, and although unlikely, we cannot exclude its possible impact on the results.

Nevertheless, the results indicate that a combination of AT and FL might be as safe as monotherapy, but possibly superior regarding a more prompt clinical response in the treatment of inpatients with major depressive disorder.

Acknowledgments

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References