Journal of Psychiatric Research 47 (2013) 1337–1342

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

A double-blind randomized study comparing plasma level-targeted dose imipramine and high-dose venlafaxine in depressed inpatients☆

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ARTICLE INFO

Article history:
Received 30 October 2012
Received in revised form
26 May 2013
Accepted 28 May 2013

Keywords:
Imipramine
Venlafaxine
Plasma level targeted trial
Inpatients
Major depression

ABSTRACT

Objective: To compare the efficacy of plasma level-targeted dose imipramine and high-dose venlafaxine in depressed inpatients in a randomized double-blind study.
Methods: The study included 85 patients with a diagnosis of major depressive episode according to the DSM IV criteria and a 17-item Hamilton Rating Scale for Depression (HAM-D) score ≥ 17.
Patients were randomized to imipramine or venlafaxine. The dose of imipramine was adjusted for each patient to a predefined blood level of 200–300 ng/ml. The dose of venlafaxine was increased gradually to 300–375 mg/day. Efficacy was evaluated after 7 weeks of treatment.
Results: The mean age of the study group was 54.5 (range 29–82) years. There was no significant difference according to the primary outcome criterion of a ≥50% reduction on the HAM-D score: 17 of 43 (39.5%) patients on imipramine were responders compared to 21 of 42 (50%) patients on venlafaxine. When considering remission as outcome criterion (HAM-D score ≤ 7), 10 of 43 (23.3%) patients on imipramine were remitters compared to 15 of 42 (35.7%) patients on venlafaxine; again, no significant difference. When analysing a subpopulation of patients without psychotic features, with remission as outcome criterion, a significant difference was found: 5 of 34 (14.7%) patients on imipramine were remitters compared to 12 of 31 (38.7%) patients on venlafaxine.
Conclusions: The present study used optimal doses in depressed inpatients and showed that venlafaxine is at least equal in efficacy to imipramine. The results in the subgroup without psychotic features indicate a possible superiority of venlafaxine.

1. Introduction

Comparisons have been made of the efficacy of various antidepressants in major depressive disorder. For example, in depressed inpatients, imipramine is considerably more effective than mirtazapine (Bruijn et al., 1996) and imipramine is more efficacious than fluvoxamine (van den Broek et al., 2004). A meta-analysis concluded that tricyclic antidepressants (TCAs) were significantly more effective than selective reuptake inhibitors (SSRIs) in depressed inpatients; however, significantly more TCA-treated patients stopped treatment due to adverse effects compared to patients using SSRIs (Anderson, 1998). A meta-analysis of 102 randomized controlled trials (RCTs) of inpatients/outpatients with unipolar major depression showed no overall difference in efficacy between TCA-treated patients versus SSRI-treated patients; however, for the inpatient subgroup TCAs were more effective (Anderson, 2000). When comparing venlafaxine with SSRIs (fluoxetine, paroxetine and fluvoxamine) in eight comparable randomized double-blind studies of inpatients/outpatients with major depressive disorder, remission rates were significantly higher with venlafaxine than with an SSRI (Thase et al., 2001). Similarly, a pooled analysis of eight double-blind RCTs of inpatients/outpatients with major depression revealed that venlafaxine was significantly more effective than SSRIs (fluoxetine, paroxetine and fluvoxamine) in improving depression (Stahl et al., 2002). In summary, it can be concluded that both TCAs (especially in inpatient populations) and venlafaxine appear to be more effective than SSRIs for the treatment of depression.

TCAs, such as imipramine, are characterized by the inhibition of serotonin and noradrenaline reuptake (van den Broek et al., 2009).

☆ This study protocol is registered at http://www.controlled-trials.com. Identifier: ISRCTN73221288.

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0022-3956/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychires.2013.05.029

Unfortunately, the anticholinergic mechanisms of TCAs are accountable for the relatively common side-effects such as a dry mouth, constipation, blurry vision, urinary retention, glaucoma, and adverse cardiovascular effects, mainly orthostatic hypotension and cardiac conduction abnormalities (Potter et al., 1991). As mentioned, significantly more patients stop treatment due to adverse effects on TCAs compared to SSRIs (Anderson, 1998). A meta-analysis of 95 RCTs of inpatients/outpatients with unipolar major depression showed significantly lower rates of treatment discontinuations due to side-effects in the SSRI-treated population when compared to TCAs (Anderson, 2000). However, when comparing the tolerability of venlafaxine versus SSRIs, no significant difference could be found due to adverse reactions (Stahl et al., 2002; Thase et al., 2001). Therefore, it has been suggested that venlafaxine is better tolerated when compared to TCAs. Venlafaxine is an antidepressant with dual mechanisms of action: venlafaxine selectively inhibits serotonin at low doses (75 mg/day) whereas at high doses (375 mg/day) it inhibits both serotonin and noradrenaline reuptake (Harvey et al., 2000), and to a small degree dopamine (Harrison et al., 2004). An interesting effect of mixed uptake inhibitors, such as venlafaxine and imipramine, is the regulation of the permeability of the blood–brain barrier, found in animal studies, which could partially explain their antidepressant effect (Preskorn et al., 1981).

As mentioned, both TCAs (especially in inpatient populations) and venlafaxine appear to be more effective than SSRIs for the treatment of depression. However, it is uncertain whether TCAs and venlafaxine have comparable efficacy (van den Broek et al., 2009) and it is unclear whether venlafaxine is better tolerated in comparison to TCAs. When treating unipolar psychotic depression, there was no significant difference in response rates and remission rates between imipramine and venlafaxine (Wijkstra et al., 2010). A systematic review was performed to investigate the relative efficacy and tolerability of (low dose) venlafaxine compared with (low dose) TCAs; no overall significant difference in treatment effect or withdrawals could be found (van den Broek et al., 2009); however, the authors stated that, because of the heterogeneity of the odds ratios, one cannot conclude that TCAs and venlafaxine are of equal efficacy.

This study compares the antidepressant efficacy of venlafaxine and imipramine among inpatients with a major depressive episode. Although others have compared the efficacy of venlafaxine with imipramine (Schweizer et al., 1994; Benkert et al., 1996; Lecrubier et al., 1997), two of these studies were performed in an outpatient setting and none used dose adjustment based on targeted plasma levels of imipramine. Furthermore, all three studies used a relatively low mean daily dose of venlafaxine (75–182 mg/day) and did not restrict the use of benzodiazepines, which could mask the diagnosis and/or effects of the antidepressants.

1.1. Aim of the study

The present study is designed to compare the antidepressant efficacy of high-dose (375 mg/day) venlafaxine with plasma level-targeted dose imipramine in severely depressed inpatients (both with and without psychotic features).

2. Methods

2.1. Study design and patient selection

The study was performed in a single centre: the inpatient depression unit of the Department of Psychiatry of the Erasmus Medical Centre in Rotterdam. The unit has a regional function for treatment of uncomplicated depressed patients and a super-regional function for treatment of refractory depressed patients. Recruitment took place between March 2005 and March 2010. Routinely psychotropic drugs are discontinued after admission. After a drug-free wash-out period of seven days, during which period diagnosis was confirmed with the Structural Clinical Interview for DSM-IV Axis I disorders (First et al., 1999), depressed patients were screened for inclusion and exclusion criteria. Both depression with psychotic features and depression with melancholic features are defined according to DSM-IV criteria. *Included* were patients aged 18–65 years, diagnosed with a major depressive disorder according to the DSM-IV criteria, single or recurrent episode and a score $\geq$17 on the 17-item Hamilton Rating Scale for Depression (HAM-D). *Excluded* were patients with bipolar disorder, schizophrenia or other primary psychotic disorder, refractoriness to adequate treatment with imipramine or venlafaxine during the index episode, drug or alcohol dependence during the last 3 months, mental retardation (IQ $<$ 80), pregnancy or possibility of pregnancy, breastfeeding, serious medical illness affecting the central nervous system (e.g. Parkinson, SLE, brain tumour, CVA), relevant medical illness as contra-indications for the use of study medication such as recent myocardial infarction and severe liver or kidney failure, medication affecting the central nervous system [e.g. antidepressants and/or antipsychotics other than study medication, steroids, mood stabilisers, benzodiazepines (if not being tapered) $>$ 3 mg lorazepam or equivalent], and a direct indication for electroconvulsive therapy.

About two years after the start of the study, we wrote an addendum to the protocol in order to include patients aged $\geq$65 years, provided that their first episode of depression had occurred before age 65 years. This addendum was approved by the Ethics Committee.

Eligible patients provided written informed consent after study procedures were fully explained. Patients were randomly allocated to a double-blind treatment with either imipramine or venlafaxine. Randomization was performed by the department of Pharmacy from the Erasmus MC using a random number table which is generated by the computer. The dose of imipramine was adjusted for each patient to a predefined blood level of 200–300 ng/ml (imipramine + desipramine) (Hiemke et al., 2011). The dose of venlafaxine was increased gradually to 300–375 mg/day. Two weeks after the start of study medication the dose was held constant. The study medication was supplied by the department of Pharmacy from the Erasmus MC using a double-dummy technique. All study medication was taken in the presence of the nursing staff. Dose adjustment based on plasma levels of imipramine and adverse effects were performed by an independent psychiatrist, keeping the study blind for the treating physician and the investigators. The HAM-D and the Clinical Global Impression scale (CGI) were scored at baseline and weekly thereafter. Outcome was assessed after seven weeks of acute treatment. All assessments were done by the two research psychiatrists (WWvdB, TKB). To ensure comparable ratings, interrater reliability sessions took place 10 times per year during the study. Excellent interrater reliability was achieved ($\kappa = 0.95$) between the participating psychiatrist regarding the total score on the HAM-D. Of the 85 patients included in the analyses, 20 patients, suffering from psychotic depression, participated in a similar double-blind comparison between imipramine and venlafaxine, which was reported by Wijkstra et al. (2010).

2.2. Measures

For imipramine the dose administered was adjusted for each patient to obtain a predefined blood level of 200–300 ng/ml (sum of imipramine + desipramine). Plasma levels of imipramine were monitored weekly by an independent psychiatrist. Adverse effects