Venlafaxine titration dosage in depressive in-patients. A series of cases

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Escalada de dosis de venlafaxina en pacientes deprimidos hospitalizados. Una serie de casos

Summary

This series of patients was gathered to assess the use of last and slow titration dosage of venlafaxine in in-patients with major depression and to evaluate the action onset. An observational open study was performed in 3 centers in 18 in-patients. Nine patients were included in fast titration dosage group (FT) and 9 in slow titration dosage group (ST). As results, it was found that the FT group showed faster improvement than the ST group in HAM-D score. This improvement was sustained to the final visit, with a lower score in the FT group (6.75) than the ST group (10.67). MADRS scores up to the 15th visit were similar; however, the score was lower in the ST group on the 20th visit. Improvement was sustained to the final visit, the FT group score being lower (6.50) than the ST group score (14). CGI-improvement and CGI-severity scores were similar to the above mentioned results. The most common events in both groups were considered mild. The data of these patients show faster response to antidepressant therapy with faster titration dosage, with maintenance of the molecule's tolerability profile.

Key words: *Venlafaxine. Fast titration dosage. Slow titration dosage. In-patients. Major depression.*

Resumen

Esta serie de pacientes se ha recogido para evaluar el uso en escalada rápida y lenta de venlafaxina en el tratamiento de la depresión en pacientes hospitalizados y valorar en qué momento empieza la respuesta al tratamiento. Se realiza con diseño de un estudio abierto, observacional, realizado en tres centros hospitalarios de Barcelona. Dieciocho pacientes incluidos, nueve del grupo de escalada rápida (ER) y nueve de escalada lenta (EL). Se obtiene que el grupo ER muestra una mejoría más rápida que el grupo EL en HAM-D. Dicha mejoría se ha mantenido hasta la visita final, con puntuaciones más bajas el grupo ER (6,75) que el grupo de EL (10,67). En MADRS las puntuaciones para ambos grupos han sido similares hasta la visita 15, mientras que en la visita 20 la puntuación ha sido más baja en el grupo EL. Se ha mantenido la mejoría en la visita final, siendo el grupo de ER el que ha puntuado más bajo (6,50 frente a 14 del grupo de EL). Esto mismo se ha observado en la valoración de gravedad y mejoría en la CGI. En cuanto a la tolerancia, las reacciones adversas con venlafaxina en ambos grupos han sido en general leves. Los datos de esta serie de pacientes muestran una respuesta más rápida cuando se aumenta la dosis más rápidamente, manteniéndose el perfil de tolerancia de la molécula.

Palabras clave: *Venlafaxina. Escalada rápida de dosis. Escalada lenta de dosis. Pacientes hospitalizados. Depresión mayor.*

INTRODUCTION

Venlafaxine is an antidepressant agent whose action mechanism is based on serotonin and noraldrenaline reuptake inhibition (SNRI)[1,2] without almost any affinity for the cholinergic, histaminergic or adrenergic receptors[3,4].

It seems that antidepressants with an action mechanism that involves a larger number of neurotransmitters in their action are generally more effective than those having a «cleaner» or selective mechanism —see the action mechanism and efficacy of drugs such as tricyclic antidepressants (TAD) or therapies such an electroconvulsive therapy (ECT) compared to the action mechanism and efficacy of the selective serotonin reuptake inhibitors (SSRI)—. On the other hand, and for the same reason, those that involve more neurotransmission systems are related with more side effects[5].

Along this line, venlafaxine would occupy an intermediate site in the action mechanism spectrum: it would basically act on 2 neurotransmitter systems and thus would be more effective than the SSRI and would have less side effects than the TAD or the monoamine oxidase inhibitor (MAOI)[6].

The most common side effects are: gastrointestinal discomfort (nausea) (for which there is tolerance), dizziness,

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insomnia or drowsiness and xerostomia. In those patients who are subjected to a fast titration dosage, the risk of side effects increases and appears with greater frequency: headache, insomnia, mouth dryness and sexual disorders such as anorgasmia or delayed ejaculation[7].

In regards to the early onset of the antidepressant effect attributed to venlafaxine, the presence of antidepressive response at the end of the first week of treatment has been described in different studies [8-15].

The clinical profile of venlafaxine is that of a general use antidepressant[16,17], useful for out-patient treatment and hospitalization, in patients suffering mild and severe depressive disorders, including depression with melancholy, psychotic symptoms and treatment resistant depression[18-23].

METHOD

This series of patients has been carried out with an observational study design, with the following objectives: 1) assess the use of fast titration and slow titration dosage of venlafaxine in the treatment of depression in hospitalized patients; 2) assess treatment compliance, safety and tolerability of venlafaxine, and 3) assess at what point the treatment response begins.

This project was approved by the Institutional Review Board of each one of the centers in which the patients were enrolled during 1997: Hospital Clínic of Barcelona, Hospital de la Mutua of Terrassa and Hospital de Terrassa.

The total sample was made up of 18 hospitalized patients of both genders, whose ages were greater than 18 years, diagnosed of major depression in its single, recurrent or bipolar episode variant, according to the DSM-IV diagnostic criteria and with a minimum score of 18 on the DSM-IV Hamilton scale. Pregnant or breast feeding women, patients with serious suicide ideation, known hypersensitivity to the drug, treatment with MAOIs in the last 2 weeks or any research drug, use of benzodiazepines (except lormetazepam and lorazepam) that could not be withdrawn before the baseline state were excluded. Those patients with a history of myocardial infarction in the last 6 months, rhythm and cardiac conduction disorders, systolic blood pressure at rest lower than 100 mmHg or greater or equal to 180 mmHg, diastolic pressure greater or equal to 100 mmHg and history of drug or alcohol abuse in the last two years were also discarded.

Each one of the patients included in the study and after informed consent was assigned to one of the two active treatments with titration dosage of venlafaxine according to medical criterion. The active titration dose treatment lasted 20 days. Dose increase could be performed until the effective dose for the patient was reached, considering that the maximum dose permitted is 375 mg/day. The rapid titration group increased the dose from 75 mg/day to 375 mg/day in 6 days, while the patients in the slow titration group reached the 375 mg/day dose after 15 days. After inclusion, twenty daily follow-up visits and one final visit at six weeks of onset were performed. In them, the existence of adverse reactions, evolution of the disorder, as well as the titration treatment and therapeutic compliance were assessed. A total of 12 patients completed the study; 5 (55.6%) patients from the fast titration group and 7 (77.8%) from the slow one.

Hamilton Scale for depression (HAM-D, 21 items), Montgomery and Asberg depression rating scale (MADRS 10 items) and Global Clinical Impression scale (seriousness and improvement) of both the physician as well as the patient were used. To assess *tolerability and safety,* the Registry of adverse reactions (UKU), global clinical impression (tolerability to drug) of the physician and clinical data and laboratory tests were used.

Statistical method

Rejection level of the null hypothesis for the statistical tests was placed at $\alpha = 0.05$. As this was an open, non-randomized study design, the results from the applied statistical tests were only interpreted with descriptive or exploratory character.

The statistical tests used for the quantitative variables were tests of previous hypothesis: Bartlett's test of homogeneity of variances and Cochrans' test of homogeneity of variances, Kolmogorov-Smimov normal distribution goodness of fit test; intergroup comparisons: «Fisher's Student "t"» for independent data, for those variables that fulfilled the condition of normality and homocedasticity, «Mann-Whitney's U test» for the non-parameter treatment of the variables or when these maintained order between values. In this test, correction for ties was applied; intragroup comparisons: «Fisher's Student "t"» for paired data, when the application conditions of the test were fulfilled, Wilcoxon test of equal pairs and rank. In this test, correction for ties was applied and it was chosen when the data characteristics made it impossible to use the previous test. For qualitative variables in the intergroup comparisons, the χ^2 test and Fisher's exact test (or Yates' correction when the characteristics of the data made it necessary) were used. When the expected frequencies did not fulfill the application conditions of the tests, regrouping of the adjoining cells was performed.

RESULTS

Nine out of a total of 18 patients belonged to the fast titration group and 9 to the slow titration one. A total of 72.2% of all the sample were women and 27.8% men. Mean age was 46.56. Distribution in the sociodemographic variables for each one of the titration groups was similar to that of all the sample. The most frequent primary diagnosis was single depressive disorder for a total of 11 (61.1%) subjects, followed by major recurrent depressive disorder with 6 patients (33.3%) and bipolar disorder with only 1 (5.6%) patient. The mean duration of hospital stay was 19.71 (± 2.27) days.

In the first visit, the baseline physical symptoms presented by the patients were recorded. A total of 6 (33.3%) patients presented one or more of them (4 in the fast titration group and 2 in the slow titration group). The most frequent

physical symptom was headache with 33.3%, followed by anxiety, constipation, dyspepsia, atypical precordial pain, mouth dryness with a frequency of 16.7% for each one of them.

The Hamilton Scale for depression (HAM-D) was administered to assess treatment with venlafaxine, and a score lower than 18 was considered as criterion for response to treatment. A progressive decrease in the HAM-D scale scores was observed in all the visits. The fast titration group showed faster improvement than the low titration group. This group registered improvement in visit 7 (score lower than 18, 17.88) while the slow titration group presented it on visit 11 (14.78). This improvement was maintained until the final visit, and the patients of the fast titration group obtained lower scores (6.75) than the slow titration one (10.67). The scores were similar until visit 15 in the Montgomery and Asberg Depression Rating Scale (MADRS), while in visit 20, the score was lower in the slow titration group (9 points less than in the fast titration group). As in the HAM-D, improvement was maintained in the final visit, the fast titration group having the lowest score (6.50 compared to 14 of the slow titration group). The differences between groups were not statistically significant.

Regarding the results on the clinical global impression scale (CGI), the following were found. In regards to the seriousness degree, both coincided that the patients of the fast titration group *were not depressed or were just within the limits of depression* and for the slow titration group *just on the limit of depression or slightly depressed* in the final visit, while the improvement level was located in much improved or quite improved for the fast titration group and *very improved or minimally improved* for the slow titration group at the end of the study.

All the patients took the medication dose prescribed by their physician adequately, as has been indicated in the titration of the dose, reaching 375 mg/day in most of the cases. There were some dosage changes due to worsening of the depressive symptoms, increase of anxiety or insomnia. A total of 22.2% of the fast titration group and 22.2% of the slow titration one changed dosage one or more times. There was no change in 55.5% of the total sample.

Regarding tolerability and safety, 10 out of the 18 sample subjects presented adverse reactions, in general mild, during the study, 4 (22.2%) in the fast titration group and 6 (33.3%) in the slow titration group. Some patients presented more than one adverse event, most of them being inferior to 10%.

The type of most frequent adverse reaction for the fast titration group was constipation, diplopia, mouth dryness, drowsiness, dizziness, headaches and abdominal pain that reached 5.4%, while this was insomnia (10.8%) and headaches (8.1%) for the slow titration group. In regards to the *intensity* of the adverse reactions, 66.2% were *mild,* 32.4% *moderate* and one case (3.6%) of the fast titration group presented a *serious* adverse reaction (hypotension) whose causality with the medication was considered as «possible» and withdrawal of the medication was decided.

For the remaining adverse reactions, the *causality* was determined as *probable* in 34.1%, *possible* in 40.7% and *improbable* in 25.2%, the therapeutic attitude taken being mostly (95.8%) maintenance of the dose and less frequently decrease (3.5%) and withdrawal of the drug (0.7%).

Tolerability to venlafaxine was shown to be good for both groups. For the fast titration group, it was *excellent* for 33.3% of the patients in visit 20 and 44.4% in the final visit, while for the slow titration group, it was *good* for 55.6% of the patients and *excellent* for 33.3% in visit 20 and 22.2% in the final visit.

A total of 6 patients withdrew from the study prior to the final visit, 4 (22.2%) of the fast titration group and 2 (11%) from the slow titration one. A total of 12 (66.7%) of the patients (55.6% of fast titration and 77% of slow titration) finished the study.

The causes for withdrawal were: 2 patients due to inefficacy, 2 due to loss to follow-up, 1 due to adverse reactions and 1 due to desire of the patient.

DISCUSSION

As has already been shown in previous studies[8-11], venlafaxine has a rapid action onset. In our series of patients, the faster response with venlafaxine was obtained in the fast titration group, although after day[15], the response tended to become the same, it being maintaining during the six weeks of the study.

A progressive decrease was observed in the Hamilton scale scores. Improvement in the final visit was sharper in the fast titration group (6.75 HAM-D score) than in the slow titration (10.67 on the HAM-D score). This same circumstance was observed in the assessment of the seriousness and improvement of the clinical global impression scale (CGI).

Although this is not a study designed to assess patient compliance, adequate compliance of the patients according to the medication prescribed was found.

In regards to tolerability, adverse reactions with venlafaxine in both groups were generally mild. They appear in the fast titration group during the first 13 days and they were present during all the study in the slow titration group.

The fast titration group presented fewer adverse effects while the slow titration one presented a greater number of adverse effects, the most frequent being insomnia (10.8%) and headache (8.1%).

It should be stated that no case of hypertension occurred in either of the two groups.

Venlafaxine has been shown to be a drug that was well tolerated by both groups, the number of withdrawals being limited (33.3%), only 1 subject withdrew due to unexpected adverse reaction (hypotension) and 2 due to inefficacy, all of them in the slow titration group.

This series of patients, as such, presented limitations such as: bias in the inclusion of patients, allocation of patients to one group or another was performed according to medical criterion and a very limited number, 18 patients, that takes external predictive strength away from the study. This series of patients opens the possibility of performing a controlled study, comparing the two therapeutic techniques.

ACKNOWLEDGEMENTS

We acknowledge the collaboration given by M. Prats of Biomedical Systems.

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