Venlafaxine and CYP2D6 in clinical practice: a case report

Venlafaxina e CYP2D6 nella pratica clinica: un case report

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Summary

Objectives
Venlafaxine (V) is a serotonin-norepinephrine inhibitor, mainly metabolized by the highly polymorphic CytochromeP450 isoenzyme 2D6 (CYP2D6) to its major active metabolite O-desmethylvenlafaxine (ODV) and to a lesser extent by CYP3A4 to the inactive metabolite N-desmethylvenlafaxine (NDV).

Depending on CYP2D6 activity, patients may be grouped into four classes of phenotypes, namely Poor (PMs, representing 7-10% of the general population), Intermediate (IMs, 35% of the population), Extensive (EMs, 48% of the population) or Ultrarapid Metabolizers (UMs, 5-7% of the population).

Literature suggests PMs show poor tolerance, while UMs need a greater dose of V. As part of the pilot study "Venlafaxine and CYP2D6 in clinical practice", which is being conducted at the Institute of Psychiatry at AOU Maggiore della Carità in Novara, in collaboration with the Molecular Diagnostics Laboratory, we describe the case of RP, diagnosed with Major Depressive Disorder (according to the DSM-IV-TR criteria) under treatment with V. The study design was approved by the local Ethics Committee (study n. CE 78/10, reference number 451/CE), in accordance with the declaration of Helsinki (2008). The aim of this observational study is to evaluate the impact of CYP2D6 phenotype on V efficacy/tolerability.

Methods
Together with all patients recruited for our study, after providing his written informed consent, RP underwent venous blood sampling, which was performed in an anonymous 3cc EDTA test-tube, which only could be identified through a numerical code and sampling date. CYP2D6 genotyping was performed using a new technology based on DNA microarray (BioFilmChip® CYP4502D6 INFINITI® - AutoGenomics - Medical systems s.p.a.), allowing to identify 16 allele variants. We also assessed sociodemographical features, duration of treatment and clinical outcome, through the Hamilton Rating Scale for Depression (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS). A clinical evaluation was performed at T0, T1 (1 week) and T2 (4 weeks).

Adverse events were evaluated by means of the self-rated SIDE scale of the Psychiatric Department of Vanderbilt University.

Results
*Being heterozygous for the CYP2D6*XN allele, encoding an enzyme with increased activity, RP was identified as a UM. RP responded to an average dose of V (300 mg/die) during acute phase of illness, with no need of a dosage augmentation.*

Conclusions
Our results are in contrast with current literature suggesting the importance of genetic risk stratification in order to administer the subject a correct dosage, yet it does not dismiss its possible role in predicting adverse events.

Key words
Venlafaxine • CYP2D6 • Metabolizer status • Effectiveness • Adverse events

Riassunto

Obiettivi
Venlafaxina (V) è un inibitore della ricaptazione di serotonina-noradrenalina, metabolizzato principalmente dall'isoenzima altamente polimorfico del CitocromoP450 2D6 al metabolita attivo O-demetilvenlafaxina (ODV), e in misura minore da CYP3A4 al metabolita inattivo N-demetilvenlafaxina (NDV). In base all'attività di CYP2D6, i pazienti possono essere raggruppati in quattro classi fenotipiche, denominate Metabolizzatori Poveri (PMs, che rappresentano il 7-10% della popolazione generale), Intermedi (IMs, 35% della popolazione), Extensive (EMs, 48% della popolazione) o Ultrarapidi (UMs, 5-7% della popolazione). Nel contesto dello studio pilota "Venlafaxina e CYP2D6 nella pratica clinica", condotto presso la S.C. Psichiatria dell'AOU Maggiore della Carità di Novara, in collaborazione con il Laboratorio di Ricerche Chimico-Cliniche, descriviamo il caso di RP, affetto da depressione maggiore in trattamento con venlafaxina. Il protocollo di studio è stato approvato dal Comitato Etico locale (studio n. CE 78/10, numero di riferimento 451/CE), in accordo con la dichiarazione di Helsinki (2008). L'obiettivo di questo studio osservazionale è quello di valutare l'impatto del genotipo CYP2D6 sull'efficacia e tollerabilità di venlafaxina.

Metodi
Analogamente a tutti i pazienti inclusi nello studio, dopo aver fornito il proprio consenso informato, RP è stato sottoposto a prelievo ematico, effettuato su provetta anonima da 3cc EDTA, identificata esclusivamente mediante un codice numerico e la data

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del prelievo. La genotipizzazione per CYP2D6 è stata effettuata mediante una nuova tecnologia basata sul DNA microarray (BioFilmChip® CYP4502D6 INFINITI® - AutoGenomics - Medical systems s.p.a.), che identifica 16 varianti alleliche. Sono state inoltre valutate caratteristiche socio demografiche, durata del trattamento e risposta clinica, attraverso la *Hamilton Rating Scale for Depression* (HAM-D) e la *Montgomery-Asberg Depression Rating Scale* (MADRS). La valutazione clinica è stata effettuata a T0, T1 (1 settimana) e T2 (4 settimane). La comparsa di effetti collaterali è stata valutata mediante la scala SIDE autosomministrata dello *Psychiatric Department of Vanderbilt University*.

Risultati

Risultando eterozigote per l'allele CYP2D6*XN, che codifica un enzima dall'attività aumentata, RP è stato identificato come

UM. RP ha risposto a dosaggi standard di Venlafaxina (300 mg/die) nella fase acuta di malattia, senza richiedere un aumento di dosaggio.

Conclusioni

Questi risultati sono in contrasto con la letteratura attuale, che suggerisce l'importanza della stratificazione genetica del rischio al fine di somministrare al paziente un dosaggio corretto, tuttavia non ne esclude un possibile ruolo nella previsione di effetti collaterali.

Parole chiave

Venlafaxina • CYP2D6 • Metabolizzatore • Efficacia • Effetti collaterali

RP (male, 44 yrs) came to our attention in March, 2010, because of severe depression with ideas of guilt, insomnia with several awakenings, anhedonia and abulia, slight psychomotor retardation, somatized anxiety.

His Hamilton Rating Scale for Depression (HAM-D) evaluation showed a total score of 37, with greater values at the item regarding suicide, work and interests, psychic anxiety and somatized anxiety.

His total score on the Montgomery-Asberg Depression Rating Scale (MADRS) was 35, with higher values on the items 1 (overt sadness), 2 (reported sadness), 8 (inability to feel emotions).

History revealed a similar episode at the age of 35, treated with Paroxetine 20 mg/die, which was withdrawn after the patient developed hyperprolactinemia and anorgasmia. Venlafaxine 300 mg/die was subsequently introduced, with good clinical response and remission in about one month. Six months later, given the lasting well-being, the dosage was reduced to 75 mg/die and finally withdrawn after two years of treatment.

In March, 2010, we introduced venlafaxine 300 mg/die again, to which the patient risponded well rapidly.

A clinical evaluation was performed at T1 (1 week) and T2 (4 weeks), with HAM-D and MADRS: at T1 his HAM-D score was 22, and his MADRS score was 25; at T2 he showed a full remission of symptoms (HAM-D: 6, MADRS: 7).

No adverse event, as assessed by means of the self-rated SIDE scale of the Psychiatric Department of Vanderbilt University, occurred throughout the four weeks of observation.

After providing his written informed consent, the patient was recruited for the pilot study "Venlafaxine and CYP2D6 in clinical practice", which is being conducted at the Institute of Psychiatry in Novara, conjointly with the Molecular Diagnostic Laboratory, with the approval of our local ethics committee. The patient underwent genotyping in order to evaluate polymorphisms of CYP2D6 genes. Genotyping was performed with INFI-

NITI™ CYP2D6 assay, FDA approved, which can identify 16 mutations, each associated to a different activity of the enzyme.

Our patient proved to be heterozygous for the CYP2D6*XN allele, encoding an enzyme with increased activity (UM), which can be identified in about 5-7% of the general population and conveys ultrarapid metabolism of substrates [1].

At present, this patient is under treatment with venlafaxine, which was reduced to the dosage of 150 mg/die after 3 months of treatment, and he is still on remission. Mirtazapine 15 mg/die was added to his treatment because of mild insomnia.

Conclusions

The potential benefit of genotyping prior to treatment, either for setting the individual dose or for making a decision about using a particular drug, is not universally accepted in literature [2 3].

Our patient responded to an average dose of venlafaxine (300 mg/die) during the acute phase of the illness, with no need for dosage increase to 130%, as some authors suggest [4].

As far as maintenance treatment is concerned, the patient did not relapse while receiving a minimum dosage of venlafaxine (75 mg/die), with no need for a mood stabilizer.

We did not observe any correlation between genotype and therapeutic dosage of the drug, as the patient responded to an average dose of venlafaxine both in the acute phase and maintenance treatment.

We also point-out the patient did not develop adverse drug reactions while receiving the maximum dosage of the drug.

Our case report disagrees with literature suggesting the importance of genetic risk stratification in order to administer a correct dosage, yet it does not dismiss its possible role in predicting adverse events.

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