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SHORT COMMUNICATION

Escitalopram plasma levels and antidepressant response

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Abstract
Major Depression Disorder (MDD) has a highly variable treatment response due to the large inter-individual variation in the pharmacokinetics and pharmacodynamics of drug treatments. In detail the correlation between plasma level and efficacy has been much debated. Among first-line drugs for MDD, one of the most used is escitalopram. In the present study we investigated the association between serum concentration of escitalopram (SCE) and antidepressant response (AR). 70 MDD patients treated with escitalopram monotherapy were recruited and followed for three months. Hamilton Depression Rating Scale - 21 (HAMD-21) was administrated at baseline, month 1, and month 3 to assess AR. SCE was measured at steady state. Linear regression analysis and nonlinear least-squares regression were used to estimate association between SCE and AR. We found an association between SCE and AR both at month 1 ($p<0.001$) and month 3 ($p=0.0003$), which persists also excluding 3 patients with SCE equal to 0. Interestingly, by excluding patients with SCE $<$ 20 ng/mL, i.e. with a SCE lower than the putative therapeutic threshold, these associations disappeared. The curvilinear function AR $= a +$ (SCE-SCE^2) explained a higher proportion of variance compared to the linear other models ($p<0.001$). Our results suggest that for escitalopram the association between SCE and AR likely follows a nearly-asymptotic function, with poor AR at sub-therapeutic SCE and stable AR response at therapeutic SCE. Thus, when a patient reaches the therapeutic SCE range, further increase of escitalopram dosage seems to be useless, although further studies are needed to confirm our findings.

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1. Introduction

Major Depression is among the most prevalent psychiatric disorders with a highly variable treatment response, with up to one-third of patients not achieving response with the first drugs for depression treatment (Souery et al., 2006). Nowadays, selective serotonin reuptake inhibitors (SSRIs) and other new generation drugs for depression (e.g. venlafaxine and vortioxetine) are the first choice in pharmacological treatment of depression (Patten, 2016). However, their therapeutic windows are still not clearly identified (Rifkin, 1997), despite the fact that they show an overall pretty safe therapeutic index (Lader, 1996). Furthermore, there is a large inter-individual variation in the pharmacokinetics and pharmacodynamics (Porcelli et al., 2011a, 2011b; Fabbri et al., 2014), making hard to understand the correlation between oral dosage and efficacy (Paulzen et al., 2016), despite that some evidences suggested a greater efficacy at higher dosages (Jakubovski et al., 2016). Differently from old drugs for depression (e.g. tricyclic (Linder and Keck, 1998)), for SSRIs and new generation drugs for depression a clear correlation between plasma levels and efficacy has not been demonstrated so far (Rasmussen and Brosen, 2000; Hiemke et al., 2011; Baumann et al., 2004). Consistently, the monitoring of serum concentrations for these drugs is recommended only for dose titration and for special indications or compliance issues (Hiemke, 2011). Among SSRIs, escitalopram is the newest one since it was approved in 2001. Escitalopram is the S-enantiomer of racemic citalopram and some studies reported that it is more effective and better tolerated than other drugs for depression, although some controversial results exist (Zhong et al., 2012). According to its Summary of Product Characteristics, Escitalopram recommended therapeutic range is 15–80 ng/ml (Baumann, 2004). However, further studies demonstrated that to reach a serotonin transporter (SERT) occupancy higher than 80% (i.e. the percentage usually associated with antidepressant effect (Meyer et al., 2004)), an escitalopram plasma level higher than 20 ng/mL seems to be required (Kasper et al., 2009; Baldinger et al., 2014). Nonetheless, some authors suggested that escitalopram effectiveness may be due to other mechanisms beyond the SERT blockage, e.g. to the allosteric modulation of SERT itself (Zhong, 2012).

Taking into account these considerations, in the present study we aimed to investigate the association between serum concentration of escitalopram (SCE) and antidepressant response (AR) in a sample of 70 depressed outpatients followed in a naturalistic setting for three months. Further, a set of analyses was performed taking into account the pharmacodynamic features of escitalopram in order to better elucidate the relationship between SCE and AR.

2. Experimental procedures

During a period of six years, outpatients consecutively admitted at the Department of Psychiatry of Bolzano, Italy, were considered for the present study. Inclusion criteria were a diagnosis of current Major Depressive Episode according to DSM IV criteria (Association, 2000), with a Hamilton Depression Rating Scale – 21 items (HAMD-21) Score $\geq$ 14 (Hamilton, 1967). Exclusion criteria were a) substance dependence with drug consumption during the last 3 months, b) pregnancy, c) suicidality, d) unstable medical conditions, e) age $<$ 18 years. Recruited patients were treated with escitalopram mono-therapy (benzodiazepine use was allowed at dosage lower than diazepam 10 mg equivalent) in a naturalistic setting which allows clinicians to increase the escitalopram dosage in case of inefficacy. Visits were scheduled from baseline to months 3. The baseline visit was defined as the day of inclusion in the study and the first day of medication with escitalopram. Patients were either drug free or under another ineffective drugs for depression. HAMD-21 was administrated at baseline, at month 1, and at month 3 by trained psychiatrist. The percentage of improvement at month 1 and at month 3 were calculated and used as main outcomes (i.e. antidepressant response - AR). Subjects signed the informed consent and the study was approved by the local Ethical Committee.

SCE were measured at steady state by liquid chromatography/tandem mass spectrometry (LC/MS/MS) on an ABSciex QTrap 6500 instrument (ABSciex, Darmstadt, Germany) at the University of Innsbruck (Saint-Marcoux et al., 2007). Samples (50 μl) were extracted with 600 μl of cold acetonitrile (−20 °C) containing 20 ng/ml d3-methadone as internal standard. After centrifugation, 50 μl of supernatant was then directly injected into the HPLC-MS/MS instrument. Chromatographic separation of the analytes was performed on a reversed-phase C18 column (Chromsystems Master Column MassTox Analytical Column A; Chromsystems(R) Diagnostics Munich, Germany) with a gradient of MassTox TDM Series A mobile phases 1 & 2 (90% to 0% methanol-based mobile phase 1, Chromsystems Diagnostics, Munich, Germany) at a flow rate of 0.8 ml/min. Intra-assay variation was 3.6%, lower level of quantification was 0.95 ng/ml at a signal-to-noise ration of 10:1, recovery was 80%.

Linear regression analysis was used to estimate the association between SCE and AR at 1) one month and 2) three months. The same analysis was repeated excluding patients with SCE equal to 0 ng/mL (non-compliant patients). Furthermore, we repeated the analysis excluding patients with SCE lower than 20 ng/mL, i.e. patients in which SERT occupancy was likely lower than the 80% required for clinical efficacy (Meyer, 2004; Kasper, 2009; Baldinger et al., 2014). Finally, nonlinear least-squares regression with the Levenberg–Marquardt algorithm (Moré, 1977) was applied to find the best fitting model explaining the association between SCE and AR. All data analyses were performed using the Statistica package, version 7.0 (StatSoft Italia, Vigonza, Padua, Italy) for Windows® (1995).

3. Results

Clinical features of the sample are shown in Table 1. Antidepressant response both at month 1 and month 3 was not associated with clinical or socio-demographic features of the sample (data not shown). Thus, these variables were not added as covariates in further analyses.

In the total sample, we found a strong association between SCE and AR both at month 1 ($p<0.001$, $F=20.70$, $r=0.48$) and at month 3 ($p=0.0001$, $F=15.62$, $r=0.43$). Also excluding the 3 patients who showed SCE equal to 0 ng/mL (likely for lack of compliance), these associations persisted ($p=0.0001$, $F=16.36$, $r=0.45$ and $p=0.001$, $F=11.41$, $r=0.39$, respectively). Thus, in the further analyses, these 3 patients were excluded. Figure 1 shows the scatterplots of SCE and AR at month 1 and month 3 in the sample, without the 3 patients who had SCE equal to 0 ng/mL.

Interestingly, after the exclusion of 28 patients with SCE $<$ 20 ng/mL (i.e. likely with a SERT occupancy lower than 80% (Kasper, 2009; Baldinger et al., 2014), the associations between SCE and AR at month 1 and at month 3 disappeared

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