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The cardiovascular safety profile of escitalopram

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Abstract
The cardiovascular effects of escitalopram were examined in a large group of participants in double-blind, randomized, placebo-controlled studies. Escitalopram (n=3298) was administered at doses between 5 and 20 mg/day. Patients were treated in acute (8–12 weeks) and long-term (24 weeks) studies. Assessment of cardiovascular safety included heart rate, blood pressure (BP), treatment-emergent adverse events (TEAEs) and electrocardiograms (ECGs). In the short-term, there was a small, but statistically significant 2 beats per minute decrease in heart rate with escitalopram compared with placebo. The difference compared to placebo in systolic or diastolic BP was not clinically or statistically significant. Valid ECG assessments at both baseline and last assessment were available for 2407 escitalopram patients and 1952 placebo patients. Escitalopram-placebo differences in mean changes in ECG values were not clinically meaningful. The mean difference to placebo in the corrected QT [Fridericia's (QTcF)] interval was 3.5 ms (all escitalopram doses); 1.3 ms (escitalopram 10 mg) and 1.7 ms (escitalopram 20 mg) (p=0.2836 for 10 versus 20 mg). One out of 2407 escitalopram patients had a QTcF interval >500 ms and a change from baseline >60 ms. The incidence and types of cardiac-associated adverse events were similar between patients treated for 8–12 weeks with placebo (2.2%) or escitalopram (1.9%) and for 24 weeks with placebo (2.7%) or escitalopram (2.3%). Analyses of data from long-term studies and studies of the elderly showed similar results. In conclusion, these data demonstrate that escitalopram, like other SSRIs, has a statistically significant effect on heart rate and no clinically meaningful effect on ECG values, BP, with a placebo-level incidence of cardiac-associated adverse events.

1. Introduction

Escitalopram oxalate [S-(+)-1-[3-(dimethylamino)propyl]-1-(4′-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile] is the therapeutically active enantiomer of the racemic

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antidepressant citalopram. Like other selective serotonin reuptake inhibitors (SSRIs) and the serotonin-noradrenaline reuptake inhibitors (SNRIs) venlafaxine and duloxetine, escitalopram has a high affinity for the primary binding site on the serotonin transporter protein. Escitalopram also binds to the allosteric site on serotonin transporter (Chen et al., 2005a, 2005b), which decreases the dissociation rate of escitalopram from the primary site and may have a stabilising, or self-potentiating, effect on the escitalopram-transporter complex. Such allosteric binding has led to escitalopram being described as an allosteric serotonin reuptake inhibitor (Sánchez, 2006; Ali and Lam, 2011).

The cardiovascular safety of antidepressants has been the subject of recent debate and, in particular, the prescribing information and recommended dosing for citalopram have been modified to address concerns about the risk of QTc prolongation (Beach et al., 2013; Vieweg et al., 2012). Therefore, the present analysis of patient-level data was undertaken to evaluate the effect of escitalopram on cardiovascular safety measures in more than 3000 patients from randomised, double-blind placebo-controlled clinical studies in major depressive disorder (MDD), social anxiety disorder (SAD), generalised anxiety disorder (GAD), obsessive compulsive disorder (OCD), and panic disorder (PD).

2. Experimental procedures

2.1. Patients

The individual patient data come from all randomised placebo-controlled studies sponsored by H. Lundbeck A/S or Forest Laboratories, Inc in which ECGs were performed at baseline and at last assessment. Escitalopram was dosed once daily using a fixed dose or flexible dose design to a maximum of 20 mg/day. Patients treated with 20 mg/day were administered 10 mg/day for the first week. All protocols were approved by institutional review boards/independent ethics committees at each study site in accordance with the principles of the Declaration of Helsinki, and all patients provided signed informed consent before study participation. For each of the studies, medically qualified personnel were responsible for ensuring that the treatment-emergent adverse events (TEAEs) were coded using the lowest level term (LLT).

A TEAE is any untoward medical occurrence in a clinical study patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. TEAEs are presented by the preferred term corresponding to the LLT.

An integrated safety database included all clinical studies with a design allowing for pooling and comparison of safety data, which are the basis for the present analyses. A resting 12-lead electrocardiograms (ECG) was recorded at both baseline and at least at last assessment for 5 of the 6 short-term (8 weeks) placebo-controlled studies in major depressive disorder (MDD), for both of the elderly placebo-controlled MDD studies, and 6 of the 9 placebo-controlled studies of 'other indications' [generalised anxiety disorder (GAD), social anxiety disorder (SAD), and panic disorder (PD)] studies (Table 1).

2.2. Heart rate (ventricular rate)

A supine heart rate of >120 beats per minute (bpm) and an increase of ≥ 15 bpm from baseline was prospectively defined as a potentially clinically significant (PCS) high value. A supine heart rate of <50 bpm and a decrease of ≥ 15 bpm from baseline was prospectively defined to be a PCS low value. Sensitivity analyses were performed using >120 bpm and an increase of ≥ 10 bpm and <50 bpm and a decrease of ≥ 10 bpm from baseline.

2.3. Blood pressure (BP)

PCS limits were prospectively defined to be as follows: low supine systolic BP (≤ 90 and a decrease of ≤ 20 mmHg from baseline), high systolic BP (≥ 180 and an increase of ≥ 20 mmHg from baseline), low diastolic BP (≤ 50 and a decrease of ≥ 15 mmHg from baseline), and high diastolic BP (≥ 105 and an increase of ≥ 15 mmHg from baseline). In addition, sensitivity analyses were performed for high systolic BP using ≥ 160 and an increase of ≥ 10 mmHg from baseline and ≥ 150 and an increase of ≥ 10 mmHg from baseline.

2.4. ECG interval assessments

ECGs were obtained at baseline and at last assessment and quantitative assessments of RR, PR, QRS, and corrected QT [Fridericia's (QTcF)] intervals were performed by a central laboratory using the formula: $QTcF = QT/RR^{1/3}$. Limits for PCS values for QTcF intervals were prospectively defined as a post-baseline value >500 ms or an increase in QTcF >60 ms from baseline. Sensitivity analyses using QTcF values >480 and >450 ms were made, together with an increase in QTcF >30 ms from baseline.

2.5. Statistical analyses

All analyses of safety and tolerability were based on the all-patients-treated set (APTS or safety population), which comprised all patients who took at least one dose of escitalopram or placebo. For most analyses, all escitalopram dosage groups were pooled. Last assessment analyses used the last observation carried forward method (LOCF) while end of study used observed cases (OC). The change in heart rate, blood pressure, and ECG intervals from baseline to Week 8/10/12 in acute studies and to Weeks 8 and 24 in long-term studies was compared between escitalopram and placebo using a fixed-effects analysis of variance model with treatment and study as main effects. Both LOCF and OC methods were used in these comparisons. The treatment variable was either placebo/escitalopram or placebo/escitalopram dose regimen. The 95% confidence interval (95% CI) for difference to placebo is presented where relevant. Treatment-emergent adverse events (TEAEs) are presented for the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) *for Cardiac Disorders*.

3. Results

3.1. Short-term data

There are 17 randomised placebo-controlled studies (14 short-term and 3 long-term) (Table 1). ECGs were performed at baseline and at end of study or at last assessment in 12 of these studies [7 studies in MDD (8 or 12-weeks duration), 3 in GAD (8-weeks duration), 1 in PD (10-weeks duration) and 1 in SAD (12-weeks duration)], in which 2164 patients were treated with escitalopram and 2050 patients with placebo. Patients treated with escitalopram had a mean age of 42.2 years, 60.5% were women, and 89.7% were Caucasian. There were no differences between escitalopram and placebo in patient baseline characteristics including mean BP, heart rate (HR) and ECG intervals (Table 2). The overall withdrawal rate was 19.9% (escitalopram) and