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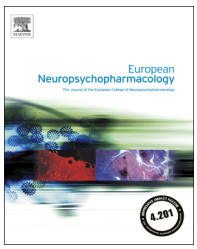

A pharmacokinetic/pharmacodynamic investigation: Assessment of edivoxetine and atomoxetine on systemic and central 3, 4-dihydroxyphenylglycol, a biochemical marker for norepinephrine transporter inhibition

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Abstract
Inhibition of norepinephrine (NE) reuptake into noradrenergic nerves is a common therapeutic target in the central nervous system (CNS). In noradrenergic nerves, NE is oxidized by monoamine oxidase to 3,4-dihydroxyphenylglycol (DHPG). In this study, 40 healthy male subjects received the NE transporter (NET) inhibitor edivoxetine (EDX) or atomoxetine (ATX), or placebo. The pharmacokinetic and pharmacodynamic profile of these drugs in plasma and cerebrospinal fluid (CSF) was assessed. In Part A, subjects received EDX once daily (QD) for 14 or 15 days at targeted doses of 6 mg or 9 mg. In Part B, subjects received 80 mg ATX QD for 14 or 15 days. Each subject received a lumbar puncture before receiving drug and after 14 or 15 days of dosing. Plasma and urine were collected at baseline and after 14 days of dosing. Edivoxetine plasma and CSF concentrations increased dose dependently. The time to maximum plasma concentration of EDX was 2 h, and the half-life was 9 h. At the highest EDX dose of 9 mg, DHPG concentrations were reduced from baseline by 51% at 8 h postdose in CSF, and steady-state plasma and urine DHPG concentrations decreased by 38% and 26%, respectively. For 80 mg ATX, the decrease of plasma, CSF, or urine DHPG was similar to EDX. Herein we provide clinical evidence that EDX and ATX decrease DHPG concentrations in the periphery and CNS, presumably via NET inhibition. EDX and ATX concentrations measured in the CSF confirmed the availability of those drugs in the CNS.

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1. Introduction

In noradrenergic nerve endings, norepinephrine (NE) is oxidized by monoamine oxidase (MAO) to the inactive derivative 3,4-dihydroxyphenylglycol (DHPG) (Kumagae et al., 1991). Blockade of presynaptic NE reuptake has the effect of increasing synaptic NE concentrations and correspondingly decreasing intraneuronal NE concentrations and reducing intraneuronal DHPG (Elsworth et al., 1983; Goldstein et al., 2003; Vincent et al., 2004). Although inhibition of NE reuptake is a common therapeutic target in the central nervous system (CNS), there currently is a lack of specific biomarkers for assessing NE reuptake inhibition. In view of the highly regulated mechanisms that involve NE metabolism, the measurement of central and peripheral DHPG concentrations may be a novel approach for evaluating NE metabolism (Elsworth et al., 1983; Geracioti et al., 2001; Goldstein et al., 2003; Raskind et al., 1999).

Edivoxetine (EDX) and atomoxetine (ATX) are selective inhibitors of the norepinephrine transporter (NET) (Wong et al., 1982; Bolden-Watson and Richelson, 1993). Atomoxetine is well established as a centrally active drug (Bymaster et al., 2002; Patil et al., 2007) and is a clinically proven agent for the treatment of attention deficit hyperactivity disorder (ADHD) (Michelson et al., 2001; Spencer et al., 2001). Edivoxetine was evaluated as a mono-therapy agent in adult patients with major depressive disorder (MDD) (Dubé et al., 2010; Pangallo et al., 2011) and pediatric patients with ADHD in an open-label Phase 1 study (Jin et al., 2013; Kielbasa et al., 2012) and a Phase 2 study (Lin et al., 2014). As adjunctive therapy for MDD, EDX did not meet its primary endpoints in Phase 3 studies (Martinez et al., 2014). ATX also did not show an evidence of effectiveness in MDD patients (Atomoxetine ADHD and Comorbid MDD Study Group et al., 2007; Michelson et al., 2007).

In the current study, we investigated the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of EDX and ATX based on drug and DHPG concentrations in plasma and cerebrospinal fluid (CSF) obtained from healthy adult subjects who received EDX or ATX.

2. Experimental procedures

2.1. Study design and subjects

The institutional review board for the study site approved the protocol, which was developed in accordance with the ethical guidelines of good clinical practice and the Declaration of Helsinki. All patients provided written consent after the study was explained and their questions were answered and before study procedures were initiated.

For logistical and operational purposes, the duration of dosing at the clinical site was 15 days, except for subjects who were assigned to receive a lumbar puncture (LP) to collect CSF samples for 24 h after last administration. In that case, the duration of dosing was 14 days. Fig. 1 illustrates this open-label, sequential design study, which consisted of 2 parts, A (n=27 randomised, n=22 completed) and B (n=13 randomised, n=11 completed). Part A was divided into 2 treatment arms, A1 and A2, which were initiated sequentially to obtain safety and tolerability information from A1 prior to starting A2. In A1, subjects received orally 6 mg EDX once daily (QD) for 14 or 15 days (n=15 randomised, n=11 completed). In A2, subjects received orally 6 mg EDX QD for 3 days followed by 9 mg EDX QD for the remaining 11 or 12 days, for a total duration of dosing of 14 or 15 days (n=12 randomized, n=11 completed). Dose escalation from 6 mg to 9 mg was based on individual subject safety and tolerability. In either A1 or A2, if the EDX dose was not well tolerated, it could be reduced to no less than 1 mg QD for the remainder of the dosing period at the discretion of the investigator. Part B (n=13 randomized, n=11 completed) was also divided into 2 arms, B1 and B2. In B1, subjects received 40 mg ATX QD for 3 days followed by 80 mg QD for the remaining 11 or 12 days for a total duration of 14 or 15 days (n=8 randomized, n=6 completed). In B2, subjects were to receive oral placebo QD for 14 or 15 days (n=5 randomized and completed). The purpose of the placebo arm in this study was to collect samples for future exploratory purposes in evaluating putative biomarkers for NET inhibition and was not an outcome measure or part of the data analysis for this trial. As such, the urine, CSF and blood samples collected from placebo-treated subjects were stored for future biomarker analyses and were not measured for DHPG concentration.

EDX was provided as 25 mg in open-label bottles and prepared in decarbonated US-manufactured Sprite® before dosing. The reconstituted solution was stable for 24 h and was not to be used after this period.

The dosing regimen for ATX (Strattera®) was based on the recommended clinical regimen in adults with ADHD: a starting dose of 40 mg QD for 3 days, which was then increased to 80 mg QD. Atomoxetine was provided as 40-mg capsules for oral administration obtained from local approved sources and was administered with decarbonated US-manufactured Sprite®.

Placebo was provided as decarbonated US-manufactured Sprite®. All study drugs were administered at the investigative site.

Subjects were overtly healthy men between the ages of 21 and 45 years and had body mass indexes of 18.5–29.9 kg/m^2, screening clinical laboratory tests and electrocardiograms (ECGs) within normal range, and normal blood pressures (supine systolic $\leq$140 mm Hg and diastolic $\leq$90 mm Hg) and pulse rates ($\leq$90 bpm). A subject was excluded from the study if he had received an LP up to 30 days before study entry, had experience with significant complications after an LP, or had medical conditions for which an LP, EDX, or ATX was contraindicated.

A complete physical examination was performed at screening. Routine medical assessments were performed at study entry, prior to the LP procedure, prior to discharge from the site and at the follow-up visit. More specifically, aural temperature was measured at screening, prior to LP and at the follow-up visit. Supine and standing blood pressure and pulse rate were measured the day prior to the first drug or placebo administration; prior to the LP procedure; 2 h after the first drug or placebo administration; prior to discharge from the site; and prior to the 3rd, 4th, 8th, 9th, 12th and 14th drug or placebo administration and at the follow-up visit. Other sitting and/or standing blood pressure and pulse rate measures were performed as clinically indicated. Body weight and height were recorded at screening, and body weight was recorded at the follow-up visit. Twelve-lead ECGs were obtained at screening, the day prior to the first drug or placebo administration, predose and approximately 2 h postdose after the first drug or placebo administration, predose of the 2nd drug or placebo administration and at the follow-up visit. Additional ECGs were obtained during the study as clinically indicated. Subjects were monitored by telemetry for up to 12 h after the first dose. Adverse events were monitored throughout the study. Additional assessments were performed at any time during the study at the investigator's discretion. Since it has been shown that ATX PK is largely influenced by cytochrome P450 2D6 (CYP2D6) polymorphisms, in which the average steady-state plasma concentration in poor metabolizer (PM) subjects is about 10 times greater than that in extensive metabolizer (EM) subjects (Sauer et al., 2005), CYP2D6 PM subjects were excluded from this study to minimize exposure variability in subjects receiving ATX. However, EDX appears to depend less on the CYP2D6 enzyme for metabolism than ATX does (Kielbasa et al., 2011). Subjects could not have used over-the-counter or prescription medications for 14 days before study entry, specifically excluding anticoagulants, MAO inhibitors and CYP2D6 inhibitors.