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Progress in Neuro-Psychopharmacology & Biological Psychiatry 31 (2007) 1440–1443
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

The impact of ziprasidone in combination with sertraline on visually-evoked event-related potentials in depressed patients with psychotic features

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Received 7 January 2007; received in revised form 20 June 2007; accepted 22 June 2007
Available online 3 July 2007

Abstract

Background: The use of atypical antipsychotics in major depression complicated by psychotic features has not been extensively investigated. Event-related potentials (ERP) have been reported to be impaired in depressed patients, probably due to serotonergic hypofunction. The objective of this study was to examine the effects of a combination therapy with ziprasidone and sertraline on ERP in major depression with psychotic features.
Methods: 19 patients with major depression with psychotic features were treated with ziprasidone and sertraline. Before and after four weeks of treatment, visually-evoked ERP (P3 — oddball paradigm) were investigated.
Results: While a significant clinical improvement assessed with the Brief Psychiatric Rating Scale and Hamilton Depression Rating Scale was noted, no significant changes in weight, basal prolactin values and scores on the Extrapyramidal Symptoms Scale were observed. A significant prolongation ($p=0.041$) of the QTc-interval between baseline and endpoint showed no clinical symptoms. Combination treatment with ziprasidone and sertraline over 4 weeks was associated with a significant decrease ($p=0.033$) of P3 latencies from baseline to week 4. After a four week treatment, significantly ($p=0.008$) fewer patients showed pathologically P3 latencies (>450 ms) than at baseline.
Discussion: Our data, showing that ziprasidone in combination with sertraline lead to a decrease of prolonged P3 latencies, are in line with previous studies showing a decrease of prolonged P3 latencies by antidepressant treatment.

Keywords: ERP; Event-related potentials; Major depression; Psychotic; Sertraline; Ziprasidone

1. Introduction

The use of atypical antipsychotics in major depression complicated by psychotic features has not been extensively investigated. A few studies on the effects of atypical antipsychotics on depressive symptoms in bipolar depression (Calabrese et al., 2005; Thase et al., 2006), therapy-resistant depressive disorders (Papakostas et al., 2004; Baune et al., 2006; Todder et al., 2006) and schizoaffective disorders (Addington et al., 2004; Kinon et al., 2006; Simpson et al., 2004) showed an improvement of depressive symptoms. However, further studies investigating other antipsychotics, such as ziprasidone, for the treatment of major depression with psychotic features are still required (Konstantinidis et al., 2007). In addition to its pharmacological antipsychotic effects, ziprasidone might have antidepressive effects due to the 5-HT_{1A} agonist mechanism (Bantick et al., 2004), making ziprasidone possibly suitable for the treatment of depressive disorders. As antipsychotics may differ in their tolerability, especially in the

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders, EEG, electroencephalographie, EOG, electro-oculography, ERP, event-related potentials, mg/d, milligram per day, msec, millisecond, SSRI, selective serotonin reuptake inhibitor, µg/l, microgram per liter, µV, microvolt, 5-HT, 5-hydroxytryptamine.

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doi:10.1016/j.pnpbp.2007.06.021

risk of inducing weight gain, extrapyramidal side effects, prolactin elevation and QTc-prolongation (Addington et al., 2004; Ghaemi et al., 2006), further clinical studies are required.

In major depression, the P3 latency of event-related potentials (ERP) elicited in an oddball paradigm has shown to be increased as compared to healthy volunteers in various studies (Bange and Bathien, 1998; Bruder et al., 1991; Hetzel et al., 2005; Himani et al., 1999; Karaaslan et al., 2003; Vandoolaeghe et al., 1998). This phenomenon is probably due to a serotonergic hypofunction in major depression, as the visually evoked P3 latency negatively correlates with the cortisol increase after citalopram challenge (i.e., after serotonergic stimulation) (Hetzel et al., 2004). In contrast, the P3 amplitude was reported to be reduced for the most part (Blackwood et al., 1987; Devrim-Ucok et al., 2006; Gangadhar et al., 1993; Yanai et al., 1997), although one study demonstrated unchanged amplitudes (Bange and Bathien, 1998).

The objective of this study was to examine the effects of the combination therapy with ziprasidone and sertraline on ERP in major depression with psychotic features.

2. Materials and methods

2.1. Patient population

The study was carried out as an investigator-initiated trial according to the Tokyo revision of the Helsinki Declaration (World Medical Association, 1976) and was approved by the Ethics Committee of the University of Muenster. After written informed consent was obtained, 19 inpatients with major depression with psychotic features (7 males, 12 females, mean age 50.6±14.7 years) were included in the study. Diagnosis of unipolar major depression with psychotic features was assessed according to the DSM-IV criteria by an experienced psychiatrist (G.H.). All patients had previous episodes of their illness. Exclusion criteria in this study were a history of treatment with sertraline or ziprasidone, medical co-morbidity, history of any neurological disease or endocrine disorders, pregnancy, any psychiatric disease other than major depression with psychotic features or treatment with any other than the study medication.

2.2. Drug administration

Three days before start of medication previous antidepressant or antipsychotic medication was washed out and patients received, if any, exclusively lorazepam as medication for agitation or insomnia. Patients were treated with ziprasidone (81.5±33.4 mg/d; range 40–160 mg/d) and sertraline (167.9±19.5 mg/d; range 100–200 mg/d) in an open label design. Only lorazepam was allowed as additional medication. On day 1 six patients were additionally taking lorazepam (average dose 1.5 mg/d), whereas on day 29 four patients did (average dose 1.1 mg/d).

2.3. Study design

Patients' symptoms were rated before (day 1) and after a 4-week treatment period (day 29) by a trained psychiatrist using the 21-item Hamilton Depression Rating Scale (Hamilton, 1967), the Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg, 1979), the Brief Psychiatric Rating Scale (Flemenbaum and Zimmermann, 1973) and the Extrapyramidal Symptoms Scale (Mazure et al., 1995). On days 1 and 29, the weight, the basal prolactin value and an Electrocardiogram were measured. On day 29, the plasma level of sertraline was determined.

2.4. Measurement of basal prolactin values

Patients were asked to lay calm for 1 h before venipuncture for prolactin measurement at days 1 and 29 of the study. A blood sample was drawn at 08.00 h into vacuum tubes filled with polystyrene granules before it was fractionated by centrifugation. Plasma prolactin was examined by a blinded examiner for the study hypotheses using an electrochemiluminescence immunoassay ('ECLIA' by Boehringer Mannheim) following the manufacturer's instructions. Patients received medication after venipuncture.

2.5. Measurement of visually-evoked ERP

Briefly, on the day before the first administration of the antidepressant as well as after 4 weeks of treatment, ERP (Fig. 1) were evoked by a visual oddball paradigm using 400 flashes of light with 15% target stimuli (red flashes of light) and 85% non-target stimuli (white flashes of light). The duration of a single flash was 100 ms, while the inter-stimulus interval was 1800 ms. Subjects were asked to sit in a comfortable chair in a dark, air-conditioned room. They had to view a 30×30 cm screen and press a button whenever the red flash of light appeared and were asked to ignore the white flashes of light. EEGs were recorded by an amplifier using Ag/AgCl surface electrodes placed according to the international 10–20 system centroparietally (Pz) (recording electrode) and linked to the mastoid (reference electrode). Bulb movement artefacts were controlled by electro-oculography (EOG) and recorded using periorbital electrodes. The high-frequency filter was set to 70 Hz and the low frequency filter was set to 0.1 Hz. The EEG readings were recorded digitally onto a computer hard disk. EEG curves lasting from 300 ms before stimulus onset to 1100 ms after stimulus onset were analyzed for the target stimulus by an investigator who was blinded to the severity of depression and the type of medication. Only correct

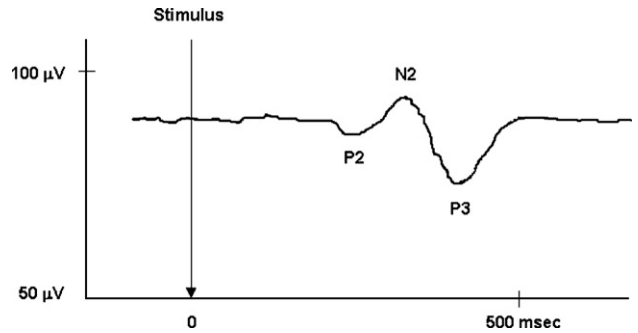

Fig. 1. A typical example of visually-evoked event-related potentials (ERP).