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Triiodothyronine accelerates and enhances the antipsychotic effect of risperidone in acute schizophrenia

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Dr. R Bunevicius died before the work presented here reached completion. This manuscript is dedicated to his memory and to the many contributions he made to psychoendocrinology.

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ABSTRACT

In acute psychotic schizophrenia patients we investigated if the combination of triiodothyronine (T3) plus risperidone was more effective when compared to risperidone monotherapy. Thirty-two in-patients meeting the DSM-IV-TR diagnostic criteria for schizophrenia and without thyroid disease received risperidone (flexibly adjusted dose for tolerability) and were randomized to additionally receive either T3 (25 μg daily; risperidone plus T3 group) or placebo (risperidone plus placebo group). Treatment lasted until meeting the response to treatment criteria defined as score of ≤3 on the Clinical Global Impression Severity and Improvement scales. Acute psychotic episode symptom severity was evaluated using the Brief Psychiatric Rating Scale (BPRS) at treatment initiation and at the final study assessment. Fourteen patients were randomized to receive risperidone plus T3 and eighteen to receive risperidone plus placebo. The time until treatment response was shorter in the risperidone plus T3 group relative to the risperidone plus placebo group (25.5 ± 4.4 days *vs* 32.2 ± 8.2 days, respectively; $p = 0.001$). Moreover, there was a greater reduction of BPRS-total score ($p = 0.01$) in the risperidone plus T3 group relative to the risperidone plus placebo group. Treatment with T3 was associated with shorter time to treatment response ($\beta = -0.440$, $p = 0.022$) and with greater improvement in BPRS score ($\beta = 0.240$, $p = 0.053$), independent of patients' gender, age, baseline BPRS score and mean risperidone dose. The study confirms that addition of T3 to risperidone was associated with accelerated and enhanced treatment response in acutely psychotic schizophrenic patients.

1. Introduction

Approximately 1% of the general population suffers from schizophrenia (Mueser and McGurk, 2004) rendering this disorder among the leading causes of disability worldwide (World report on disability., 2011, Whiteford et al., 2013). Schizophrenia is characterized by a progressive and life-long clinical course accompanied by acute psychotic exacerbations, which are associated with significant disruptions in patients' functioning, increased emotional distress and dangerous behaviors (Barnes, 2011; De Hert et al., 2001; Lieberman et al., 2001; Wehring and Carpenter, 2011). Psychotic relapses are associated with accelerated disease progression, a reduction in treatment response (Emsley et al., 2013; Harvey et al., 2013; Lieberman et al., 2001), reduction of gray brain matter volume and impaired brain connectivity (Cahn et al., 2002; McGlashan, 2006; Sarpal et al., 2015). Acute psychotic episodes are emergencies that warrant immediate initiation of effective treatment strategies directed towards rapid symptom resolution and return of the patient to his/hers best level of functioning (Howes and Kapur, 2009; Schwartz et al., 2012; Thibaut, 2014).

Monotherapy with antipsychotic medication is currently

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recommended as the first-line treatment strategy for patients with acute psychotic episodes (Barnes and Paton, 2011; Hasan et al., 2012). Numerous augmentation strategies of antipsychotic medication have been tested to enhance symptom control in patients with schizophrenia, but with largely disappointing results (Barnes, 2011; Haller et al., 2014; Matsuda et al., 2013; Rabasseda, 2014; Tuominen et al., 2006).

Recent evidence suggests that hormones of the hypothalamic-pituitary-thyroid (HPT) axis play a role in the development and clinical course of schizophrenia (Bunevicius et al., 2014; Ichioka et al., 2012; Radhakrishnan et al., 2013; Sim et al., 2002; Steibliene et al., 2012). The thyroid gland hormones (triiodothyronine or T3 and thyroxine or T4) are produced and secreted in response to stimulation by thyroid stimulating hormone (TSH), produced by the anterior pituitary gland, itself regulated by both hypothalamic thyrotropin-releasing hormone (TRH) and by the thyroid gland hormones via negative feedback. Thyroid gland hormones are actively transported across the blood–brain barrier where they exert numerous genomic and non-genomic actions (Senese et al., 2014). They interact with a variety of neural circuits, regulate neuronal myelination in development and modulate pro-inflammatory responses that may be important in the pathogenesis of schizophrenia (Brisch et al., 2014; Monji et al., 2009; Santos et al., 2012). Subclinical alterations of HPT axis function have been linked to clinical outcomes in schizophrenic patients both during acute psychotic episodes and in the chronic phases of the disease (Ichioka et al., 2012; Radhakrishnan et al., 2013; Sim et al., 2002; Steibliene et al., 2012). We have recently demonstrated that antipsychotic treatment of acute psychotic episodes was associated with reduction of serum thyroid hormone concentrations, while greater reduction of serum T4 concentration predicted less symptom improvement (Bunevicius et al., 2014). Abundant clinical evidence suggesting that adjunctive use of T3 is associated with an enhancement of antidepressant efficacy in major depressive disorder (Abraham et al., 2006; Altshuler et al., 2001; Aronson et al., 1996). However, only a few studies have examined the clinical efficacy of adjunctive thyroid hormone treatment in patients with schizophrenia, and these studies have provided conflicting results. A study in patients with chronic schizophrenia found that adjuvant T3 administration did not enhance the clinical efficacy of phenothiazines (Wolpert et al., 1969). In contrast, Park et al. have reported that adjunctive treatment with T3 enhanced the antipsychotic effects of chlorpromazine in acute schizophrenic patients (Park, 1974). To the best of our knowledge, there are no studies investigating safety and efficacy of adjuvant T3 therapy for augmentation or acceleration of any atypical antipsychotic in the treatment of acute psychotic episodes in patients with schizophrenia.

We conducted a double-blind, randomized, placebo-controlled study of T3 added to the atypical antipsychotic risperidone at treatment initiation in acutely psychotic patients with schizophrenia. The primary hypothesis of the study was that the addition of T3 to risperidone would significantly reduce time to treatment response. Additionally we investigated the clinical efficacy and safety of risperidone and T3 combination.

2. Material and methods

2.1. Participants

Male and female patients between the ages of 18 and 60 years consecutively admitted to the Acute Psychosis Department of the District Mental Hospital, Kaunas, Lithuania, in a period from 2007 until 2010 for treatment of an acute psychotic episode were considered for this study. Diagnostic inclusion criteria for the study were: [1] diagnosis of schizophrenia at least six months before the initial study assessment as defined according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR2000) diagnostic criteria (DSM codes from 295.1 to 295.9) by using the MINI-International Neuropsychiatric Interview version 5.0.0 (MINI-Plus) (Sheehan et al., 1998); and [2] acute psychotic episode at screening and randomization assessment meeting the diagnostic criteria as defined in the module M of the MINI-Plus interview.

Psychiatric exclusion criteria consisted of all current DSM-IV-TR Axis I diagnoses other than schizophrenia, DSM-IV-TR diagnosis of substance dependence (with an exception of nicotine dependence) within the past six month, injection of depot antipsychotics in the past 120 days, significant risk for suicidal or violent behavior, use of monoamine oxidase inhibitors within the past four weeks and electroconvulsive therapy within the past three months. There were no exclusion criteria based on the number of previous psychotic episodes. We also excluded patients with past histories of significant or unstable medical conditions and medical conditions that can potentially alter absorption, metabolism or excretion of the medication. History of epileptic seizures, known treatment resistance and/or current treatment with clozapine, known previous ineffective treatment or intolerance to risperidone, known allergic reactions to risperidone or T3 and a past history of neuroleptic malignant syndrome or tardive dyskinesia were also among the study exclusion criteria. Women who were pregnant (based on a urine pregnancy test) or breastfeeding were also excluded. All study women had to agree to practice an effective method of birth control for the duration of the study. Patients were not included in the study if they had a history of thyroid disorder, were taking thyroid medication, had autoimmune thyroid disease (elevated thyroid peroxidase antibody or TPOAb serum concentrations), or had subclinical thyroid disease (TSH serum concentrations above or below the reference range).

The study was approved by the Lithuanian Bioethics Committee (Eudra CT registration number: 2007-001541-18). All study patients were provided with a complete description of the study procedures and signed written informed consent to participate. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

2.2. Study design

The study consisted of three phases: [1] screening phase; [2] wash-out phase and [3] randomization/treatment phase.

Before the screening assessment the study patients signed an informed consent form to participate in the study and were evaluated for psychiatric inclusion and exclusion criteria using the MINI-Plus 5.0.0 structured clinical interview (Sheehan et al., 1998). Patients who met the psychiatric inclusion criteria underwent a comprehensive evaluation that included assessment of past medical and psychiatric histories and treatments, physical examination, electrocardiography and laboratory evaluation that covered hematology, blood chemistries, including TSH and TPOAb serum concentrations, urinalysis and urine pregnancy test (for female patients). Subsequently, all eligible patients underwent ultrasound assessment of the thyroid gland and were evaluated by an endocrinologist for thyroid disorders.

Patients who fulfilled the study criteria at screening assessment entered the wash out period, which lasted for a maximum period of three days, depending on previously used antipsychotic medication. During the wash out period all psychiatric medications, including antipsychotics, were gradually tapered and discontinued with the exception of lorazepam (up to 6 mg/day), zolpidem (up to 10 mg/day) and trihexyphenidyl (up to 6 mg/day), which were allowed during the washout and treatment phases of the study.