Psychoneuroendocrinology 66 (2016) 101–110

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

A low TSH profile predicts olanzapine-induced weight gain and relief by adjunctive topiramate in healthy male volunteers

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ARTICLE INFO

Article history:
Received 8 September 2015
Received in revised form
11 December 2015
Accepted 15 December 2015

Keywords:
Olanzapine
Topiramate
Body weight
Thyroid stimulating hormone
Thermoregulation
Food intake

ABSTRACT

Second generation antipsychotics, like olanzapine (OLZ), have become the first line drug treatment for patients with schizophrenia. However, OLZ treatment is often associated with body weight (BW) gain and metabolic derangements. Therefore, the search for prospective markers for OLZ's negative side effects as well as adjunctive treatments to inhibit these has been of major interest.

The aim of this study was to investigate in healthy male volunteers (age: 36 ± 11years; BW: 84 ± 12 kg; BMI = 25.5 ± 2.5) whether adjunctive topiramate (TPM) administration opposes OLZ-induced weight gain over the course of 14 days treatment. In addition, we investigated behavioral, endocrine and metabolic characteristics as underlying and potentially predictive factors for weight regulation and/or metabolic derangements associated with OLZ and TPM treatment.

While adjunctive TPM indeed reduced OLZ-induced weight gain ($P < 0.05$, Mann–Whitney U), behavioral/metabolic/endocrine characteristics of OLZ treatment were not affected by TPM. Using multiple regression analysis, BW gain was the key factor explaining metabolic disturbances (e.g., plasma insulin—LDL interaction: $P < 0.01$, $R^2 = .320$), and cumulative food intake during treatment was the best denominator of BW gain ($P < 0.01$, $R^2 = .534$). Neither TPM treatment, nor its circulating levels, contributed to variation observed in ΔBW. In a second multiple regression analysis, we observed that a low baseline thyrotropin profile (TSH_{AUC}) before the start of drug treatment was associated with an increase in ΔBW over the course of drug treatment ($P < 0.05$, $R^2 = .195$). Adding TSH_{AUC} as covariate revealed that adjunctive TPM treatment did attenuate OLZ induced BW gain ($P < 0.05$, ANCOVA). Further exploration of the circulating thyroid hormones revealed that individuals with a low plasma TSH profile were also those that were most sensitive to adjunctive TPM treatment blocking OLZ-induced ΔBW gain. Others have shown that OLZ-induced BW gain is associated with improvement in brief psychiatric rating scores (BPRS); adjunctive TPM treatment may be a solution specifically for those subjects susceptible to OLZ-induced rapid weight gain who—on a therapeutic level—benefit most of OLZ treatment.

1. Introduction

Second generation ('atypical') antipsychotics have become the first line drug treatment for patients with schizophrenia (Wallingford et al., 2008). Among these, olanzapine (OLZ) is known for its clinical efficacy (Leucht et al., 2009; Lieberman et al., 2005), but its use is strongly associated with body weight (BW) gain (Bak et al., 2014; Komossa et al., 2010), increased appetite and food intake (Stauffer et al., 2009), and is additionally related to hyperglycemia, insulin resistance, elevated cholesterol levels, and acute hypothermia (Atmaca et al., 2003; Graham et al., 2005; Hosojima et al., 2006; Lindenmayer et al., 2003; Melkersson et al., 2000; van Marum et al., 2007).

BW gain as a result of OLZ treatment can be remarkably large and increases the risk for diabetes mellitus (DM) (Meyer, 2010). This is particularly relevant since individuals suffering from schizophrenia are already predisposed for developing DM irrespective of treatment with antipsychotic agents (Mukherjee et al., 1996). In fact, metabolic syndrome and cardiovascular diseases are important causes of morbidity and mortality among patients with severe mental illnesses (Pramyothin and Khaodhiar, 2010). The search for an adjunctive treatment to reduce OLZ-induced BW gain, and

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http://dx.doi.org/10.1016/j.psyneuen.2015.12.024
0306-4530/

concomitant reduction of metabolic side effects, without affecting clinical efficacy, is therefor of major interest. Not only for the health benefit on a metabolic level, but also to improve treatment compliance (McQuade et al., 2004) benefitting mental health.

Topiramate (TPM), an anticonvulsant prescribed mainly for the treatment of epilepsy and known to induce weight loss (Li et al., 2005), was found capable of diminishing olanzapine-induced weight gain in schizophrenic patients without aggravation of psychotic symptoms (Kim et al., 2006; Narula et al., 2010). Additionally, co-administration of TPM with OLZ resulted in a reduction of OLZ-induced weight gain and appetite, but also improved insulin sensitivity and favorably decreased fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol and leptin levels in schizophrenic patients (Narula et al., 2010).

Although the phenomenon of severe weight gain by OLZ is well-recognized (Bak et al., 2014; Choong et al., 2012; McEvoy et al., 2005) some individuals actually lose weight during OLZ treatment (Kinon et al., 2005), which shows that not all individuals are equally prone to this adverse side effect. This individual variation in metabolic responsiveness to OLZ treatment is most likely due to OLZ's a-typical receptor binding profile (Bymaster et al., 1999) and complicates the identification of responsible mechanisms of OLZ-induced weight gain. Nonetheless, a number of neuroendocrine factors related to energy homeostasis released from pineal, pituitary, gonadal, adrenal, and thyroid glands have been identified to be affected by OLZ treatment (Mann et al., 2006; Raskind et al., 2007; Starrenburg and Bogers, 2009; Vidarsdottir et al., 2010b). We therefore hypothesize that the cause of the individual variation in susceptibility to OLZ-induced weight gain (Ascher-Svanum et al., 2005; Kinon et al., 2005; Stauffer et al., 2009) may originate from inter-individual differences in responsiveness of neuroendocrine pathways to drug treatment.

The first aim of this study in healthy male volunteers was to investigate the potency of adjunctive TPM administration to reduce OLZ-induced body weight gain and related metabolic side effects. Secondly, to identify -post hoc- baseline parameters predictive of OLZ-induced BW gain and related co-morbidities. The latter is important, because the moment a specific pathway can be identified as a predictor for OLZ-induced side effects, it becomes possible to avoid/decrease the occurrence of unwanted side effects, either by (1) excluding patients that are at risk of developing negative side-effects or (2) by treating these patients with an adjuvant selected specifically to counter these unwanted side-effects.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled clinical study conducted at PRA Clinics in Zuidlaren, the Netherlands. An independent ethics committee (BEBO, Assen, the Netherlands) approved the clinical study protocol. All subjects provided written informed consent before participation. The study was conducted in accordance with the principles of the Declaration of Helsinki, and with the laws and regulations of the Netherlands and the EU. This work was performed within the framework of the Dutch Top Institute Pharma project: T2-105. EudraCT number: 2010-019664-37.

2.2. Study procedures

Study medication was administered by personnel not involved in the preparation of the medication.

Table 1
Descriptive statistics body composition and demographics.

Variable	Group	n	Mean	Stdev	Median	Min	Max
Age (year)	OLZ	15	35.3	10.0	36.0	21.0	54.0
	OLZ + TPM	15	36.1	11.5	37.0	20.0	52.0
Weight (kg)	OLZ	15	85.1	12.7	84.0	67.8	110.5
	OLZ + TPM	15	84.3	12.3	82.1	70.9	119.3
Height (cm)	OLZ	15	181.5	7.9	180.0	170.0	196.0
	OLZ + TPM	15	181.3	7.5	178.0	171.0	199.0
BMI	OLZ	15	25.7	2.7	25.1	21.7	29.8
	OLZ + TPM	15	25.5	2.5	26.0	21.8	30.1
Waist circ. (cm)	OLZ	15	87.9	7.4	87.5	75.0	98.0
	OLZ + TPM	15	88.8	10.6	86.1	73.0	110.0
Adiposity (%)	OLZ	15	17.6	5.6	18.7	8.1	27.4
	OLZ + TPM	15	18.2	6.3	17.2	7.4	29.8

Ethnicity				
	OLZ	European	$n = 13$	86.6%
		African/European	$n = 1$	6.6%
		Asian	$n = 1$	6.6%
	OLZ + TPM	European	$n = 12$	80.0%
		African/European	$n = 2$	13.3%
		African	$n = 1$	6.6%

2.3. Treatments

Thirty healthy male subjects were randomized to receive OLZ plus placebo ($n = 15$) or OLZ plus TPM ($n = 15$) over a 14-day in house treatment period. The doses were 10 mg OLZ o.d. with TPM (or placebo) at 25 mg b.i.d. during days 1–6 and 50 mg b.i.d. during days 7–14. Subjects arrived at the clinic at day-2, drug treatment started at day 1 until day 14, subjects left the clinic at day 15. Recovery from effects was assessed in a follow-up visit on day 28 after washout of all medication had occurred.

It was assumed that the trial medication of OLZ plus TPM could induce unwanted side-effects (e.g., augmented sedation), which might cause subjects to drop-out and make the results difficult/impossible to interpret. For that reason a gradual increment in dosing of TPM was chosen in this study. Drug doses were selected on the basis of prior dose-response studies (Vidarsdottir et al., 2010a), and were chosen in order to minimize side effects but retain clinically relevant therapeutic levels.

2.4. Subject grouping

Key exclusion criteria were evidence of clinically relevant pathology, history of psychiatric diseases, significant psychopathology in first grade family members, and positive screen on drugs of abuse or alcohol intake of more than 24 units of alcohol per week. Baseline body weight characteristics (Table 1) and demographics were comparable across treatment groups. Body weight was measured at day-2 (baseline), 13 and 28 at 09:00 h just before drug dosing. Standardized meals, various snacks, and non-alcoholic beverages were available ad libitum on request. All caloric intake and left-overs were carefully recorded by the staff continuously from day-2 to day 15, when subjects were in the facility.

2.5. Laboratory investigations

Blood samples for assessment of OLZ levels were taken on day 1 of treatment, 4 h after dosing at 09:00 h, at day 6 (at 09:00 h at dosing and 4 h later) and at day 13 (at 09:00 h at dosing and 4 h later). Levels of TPM were assessed only at days 6 and 13 at 09:00 h (for assessment of baseline level). Blood samples for glucose, insulin and C-peptide were taken just prior to dosing at 09:00 h and at 0.5, 1, 1.5, 2, 2.5 and 3 h after a meal tolerance test 1 h post dosage (MTT;