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SHORT COMMUNICATION

Postprandial prolactin suppression appears absent in antipsychotic-treated male patients

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Summary
Introduction: Hyperprolactinemia is a common side-effect of antipsychotic treatment. Antipsychotics and hyperprolactinemia are both considered risk factors of metabolic disturbances and diabetes. Investigations on prolactin response to meal ingestion in antipsychotic-treated patients are missing.
Material and methods: In a case-control design, 49 antipsychotic-treated, clinically stable, non-diabetic, schizophrenia spectrum male patients were compared with 93 healthy male controls by age (33.1, SD 7.4 *vs.* 32.9, SD 6.6 years), body mass index (26.2, SD 4.6 *vs.* 26.1, SD 3.9 kg/m^2) and waist circumference (96.4, SD 13.0 *vs.* 96.7, SD 11.9 cm). Serum-prolactin was measured in the morning and 90 min after ingestion of a standardized liquid meal (2268 kJ).

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Results: Fasting prolactin levels varied considerably, and mean fasting prolactin levels did not significantly differ between patients and controls (12.33, SD 11.58 *vs.* 10.06, SD 8.67 ng/ml, $p = 0.623$). In the controls, postprandial serum prolactin was significantly reduced (Δ −2.53, SD 9.75 ng/ml, $p = 0.016$). In antipsychotic-treated patients postprandial serum prolactin tended to increase (Δ 2.62, SD 10.96 ng/ml, $p = 0.081$). Analyses of subgroups based on the prolactinogenic liability of their antipsychotic treatment indicated 22 to 65% higher postprandial prolactin levels with high and intermediate prolactinogenic antipsychotics.
Discussion: A physiological postprandial suppression of serum prolactin appears absent in antipsychotic-treated males. Marked variability in fasting prolactin levels may reflect individual variations in the diurnal cycle. Uniform acquisition procedures accounting for diurnal variation and food intake may enhance reliability of prolactin levels in antipsychotic-treated male patients.

1. Introduction

The introduction of antipsychotic medication has indisputably improved the clinical outcome of patients with schizophrenia and related psychotic disorders, but the treatment is frequently associated with side-effects. Whereas the management of extra-pyramidal and metabolic side-effects has attracted considerable clinical attention, hyperprolactinemia is a common, but less investigated side-effect of antipsychotic treatment.

Prolactin is a pituitary hormone involved in reproduction, endothelial function, immune modulation, hair, skin and bone regulation, and metabolism (Marano and Ben-Jonathan, 2014). Prolactin is secreted in a circadian rhythm with approximately 19 pulses in 24 h and peaks during sleep (Roelfsema et al., 2012). Due to circadian variation, serum prolactin is normally sampled between 0800 h and 1000 h. Prolactin level <20—25 ng/ml is considered normal, regardless of variations between assays, gender differences (women > men), and elevations associated with increased body weight (Roelfsema et al., 2012).

Antipsychotics and hyperprolactinemia are both risk factors of metabolic disturbances and diabetes (Arslan et al., 2014; Yavuz et al., 2003), but to what extent prolactin levels are associated with food intake in antipsychotic-treated patients is unknown. Previous reports on the physiological prolactin response to meal ingestion are scarce, small, and results are conflicting, possibly also reflecting differences in nutrition content between studies. The hitherto largest study in 20 healthy volunteers recently showed that prolactin decreases after meal ingestion (Plumelle et al., 2014), but earlier studies have reported both unchanging (Goettler et al., 1990), and increasing levels (Carlson et al., 1983; Ishizuka et al., 1983).

The clinical effect as well as the extrapyramidal side-effects of antipsychotic drugs are linked to the degree of dopamine D_2 receptor blockade in striatum (Kapur and Seeman, 2001). In the pituitary, blockade of the dopamine D_2 receptors leads to an increased release of prolactin resulting in clinical hyperprolactinemia (Meltzer and Fang, 1976). Since the anterior pituitary gland is located outside of the blood brain barrier, especially antipsychotics with low lipophilicity, high peripheral-to-central dopamine D_2 receptor occupancy ratio, and high dopamine D_2 receptor affinity, e.g. perphenazine, risperidone, and amisulpride are prone to induce hyperprolactinemia (McKeage and Plosker, 2004). Conversely, treatment with aripiprazole, quetiapine, and clozapine is associated with lower risk of hyperprolactinemia, while ziprasidone and olanzapine appear to assume an intermediate position (Leucht et al., 2013).

Here we investigate fasting and postprandial serum prolactin levels in a sample of non-diabetic antipsychotic-treated male patients and matched healthy controls. Associations between prolactin levels and high, intermediate and low prolactinogenic antipsychotic treatment are explored.

2. Methods

The study was approved by the Committee on Biomedical Research Ethics for the Capital Region of Denmark (H-C-2007-0069), the Danish Data Protection Agency, and the Danish Medicines Agency (2602-706). The study was registered at ClinicalTrials.gov (NCT00627757), conducted in accordance with the Declaration of Helsinki II, carried out according to Good Clinical Practice (GCP), and monitored by the GCP of Unit Copenhagen University Hospital. Participants received written and verbal information about the study and gave written informed consent prior to enrollment.

2.1. Participants

We included 49 antipsychotic-treated, clinically stable, non-diabetic male patients and 93 healthy male controls in the age of 18—45 years. Details of inclusion and exclusion criteria and participants were previously reported (Ebdrup et al., 2014). In short, patients had a diagnosis in the schizophrenia spectrum [ICD-10 diagnosis: F20, F21, F22, F25, F28, F60.1] and all were Caucasian outpatients treated with at least one antipsychotic. Controls were recruited by advertisement and were matched on age, body mass index (BMI), waist circumference, and race.

Based on the assumed prolactinogenic effect of the antipsychotic treatment (Leucht et al., 2013; McKeage and Plosker, 2004), we divided patients into three subgroups: a high (perphenazine, amisulpride, risperidone) ($n = 7$), an intermediate (olanzapine, ziprasidone) ($n = 14$), and a low prolactinogenic subgroup (aripiprazole, clozapine, quetiapine) ($n = 25$). Six patients, who were treated with more than