Clinical Biochemistry 50 (2017) 678–685

Contents lists available at ScienceDirect

Clinical Biochemistry

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

Impact of risperidone on leptin and insulin in children and adolescents with autistic spectrum disorders

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ARTICLE INFO

Article history:
Received 6 November 2016
Received in revised form 12 January 2017
Accepted 2 February 2017
Available online 3 February 2017

Keywords:
Autistic spectrum disorders
Risperidone
Metabolic risk factors
Diabetes
Children
Adolescent

ABSTRACT

Objective: To evaluate the influence of dose and duration of risperidone treatment on cardiovascular and diabetes risk biomarkers in children and adolescents with autistic spectrum disorders (ASDs).

Design and methods: In this cross-sectional analysis, a total of 168 ASDs patients (89% male) treated with a risperidone-based regimen for ≥12 months were included. Blood samples were analyzed for glucose and lipid metabolic markers, adiponectin, leptin, prolactin, cortisol and high sensitive C-reactive protein.

Results: The mean concentrations of glucose, insulin, prolactin and leptin and HOMA-IR significantly rose with risperidone dosage (all $P < 0.025$), but those of adiponectin and cortisol did not. Using regression analysis, insulin, leptin, prolactin and glucose concentrations and HOMA-IR show significant association with dosage. None of the markers except adiponectin showed dependence on duration of treatment. However, insulin and leptin concentrations and HOMA-IR clearly increased with increasing both dosage and duration. Dosage and duration of treatment had minimal effect on standard lipid profile and lipoprotein subclasses.

Conclusions: Risperidone treatment disturbed glucose homeostasis and endocrine regulation (particularly leptin) in children and adolescents with ASDs, in a dose- and duration-dependent manner, being suggestive of leptin and insulin resistance mechanisms. Metabolic adverse effects, especially development of type 2 diabetes mellitus should be closely monitored, particularly in individuals receiving high doses and/or long-term risperidone treatment.

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1. Introduction

Autistic spectrum disorders (ASDs) are a complex group of neurodevelopmental disorders with onset prior to 3 years of age [1]. The worldwide prevalence of ASDs in children has increased over the past few decades, ranging from 0.07% to 1.8% [2]. Risperidone is a second-generation antipsychotic drug approved by the US Food and Drug Administration (FDA) to treat ASDs in pediatric patients. It appeared to be the most effective treatment for irritability and aggression in these patients [3–4]. In addition, there has recently been a large increase in the use of risperidone in children with a wide variety of psychiatric and non-psychiatric disorders [5–6]. Consequently, prescriptions for risperidone, in particular the off-label therapeutic use in children, have increased dramatically in many countries.

Numerous studies have presented associations between antidopaminergic antipsychotic drug therapy and adverse effects, in particular rapid weight gain and metabolic and endocrine abnormalities [7–9]. Although, the specific mechanisms for the metabolic disturbances are not fully understood, children and adolescences appears to experience more adverse effects, even with shorter durations of treatment, than adults [7–8]. The presence of increased appetite during antipsychotic treatment has led investigations to consider a link between increased caloric intake, serotonin, and histamine receptors in the hypothalamus and the accumulation of adipose tissue [10]. Adipose tissue influences the regulation of several important physiological functions through adipokines, including appetite, satiety, energy expenditure, activity, insulin sensitivity and secretion, glucose and lipid metabolism, fat distribution, neuroendocrine regulation, and function of the immune system [11]. Current research proposes that

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http://dx.doi.org/10.1016/j.clinbiochem.2017.02.003
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adiponectin and leptin regulate metabolic activity, appetite, and other physiological functions, thus contributing to the development of obesity-related diseases such as type 2 diabetes mellitus (type 2 DM) and cardiovascular disease (CVD) [12]. Adiponectin is abundantly expressed in healthy individuals, has anti-thrombotic, anti-atherogenic, and anti-inflammatory properties, and is down-regulated in obese individuals [13]. Leptin plays an important role in appetite regulation by sympathetic nervous system activation impacting energy homeostasis [14]. Research suggests that antipsychotic medication may affect the common regulatory action of adipokines on appetite, contributing to the development of obesity-related diseases [10,15].

Atherosclerosis begins in childhood. As such, knowledge of the impact of treatments, such as resperidone, is essential for good long-term management of patients into adulthood [16]. Age-inappropriate weight gain and metabolic disturbance in childhood may accelerate or accentuate type 2 DM and CVD, causing premature mortality and morbidity in adults [16–17]. The aim of this cross-sectional observational study was to evaluate the influence of dosage and duration of risperidone treatment on metabolic risk markers in Thai children and adolescents with ASDs. The emphasis was on markers of energy disturbance and cardiovascular disease risk: glucose intolerance, adipokines, dyslipidemia and high-sensitivity C-reactive protein (hsCRP).

2. Materials and methods

2.1. Study subjects

A cross-sectional observational study was conducted. During May 2013 to April 2014, we enrolled 168 (149 males and 19 females) Thai children and adolescent outpatients aged between 4 and 18 years from the Yuwaprasart Waithayopathum Child and Adolescent Psychiatric Hospital, Samutprakarn, Thailand, who had been diagnosed with ASDs according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition [1]. Subjects and/or parents/legal guardians were informed of the specific risks and benefits of participation and provided their written consent. The study protocol was approved by the ethics committee of the Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. All participants receiving a risperidone-based regimen for one year or more were enrolled in this study. Demographics and treatment history including dosage and concomitant therapy were extracted from the medical and pharmacy records. Height, weight, and waist circumference measurements were also obtained at enrollment. Exclusion criteria for this study were a known history of pervasive developments disorders, mental retardation, schizophrenia, other psychotic disorders, or conditions associated with convulsions as well as cardiovascular disease, diabetes, cancer, end-stage chronic kidney disease or other serious physical conditions (i.e. thyroid disorders). We excluded patients receiving concomitant treatments that could potentially affect glucose and lipid metabolism.

Based on FDA-approved dosing recommendations for pediatric patients [3], we categorized subjects into three groups: low-dose, recommended-dose, and high-dose groups. The recommended starting dose of risperidone is 0.25–0.5 mg/day for patients with body weight <20 kg, or 0.5–1 mg/day for those with body weight of 20 kg or greater. Patients taking less or more than these recommended amounts were classified as receiving low or high doses, respectively.

2.2. Biochemical measurements

Blood samples were collected as serum or plasma in the fasting state, between the hours of 7 and 10 a.m. All samples were stored at 2-8 °C and analyzed within one day of collection for total cholesterol, triglycerides, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C), creatinine, uric acid, glucose, insulin, adiponectin, leptin, prolactin, and hsCRP. Serum total cholesterol, triglycerides, LDL-C and HDL-C and plasma glucose, were measured using Siemens enzymatic methods (Siemens Medical Solution Diagnostics, Tarrytown, NY, USA). High-sensitivity CRP were measured on the Siemens BN Prospec using the immune nephelometric method, and adiponectin and leptin levels were quantified using a sandwich ELISA system (Mediagnost Gesellschaft für Forschung and Herstellung von Diagnostika GmbH, D-72770 Reutlingen, Germany) [18]. The insulin and prolactin levels were determined using a chemiluminescent immunoassay on the Immulite H2975 (Siemens Medical Solution Diagnostics) and the Architect ci2000 (Abbott Laboratories Abbott Park, IL, USA), respectively. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR). The index of HOMA-IR was calculated according to the following formula: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L) / 22.5.

Patient sera were analyzed for lipoprotein subclass using polyacrylamide tube gel electrophoresis (Quantimetrix Lipoprint™, Redondo Beach, CA, USA). This method electrophoretically separates plasma lipoproteins into a maximum of 12 bands ranked by size: very low density (VLDL), midbands [primarily intermediate low density (IDL): MIDC, MIDB and MIDA], large, buoyant LDL (LDL1 and LDL2), small dense LDL (LDL3 to LDL7), and HDL. The relative area for each lipoprotein band was determined by densitometry and multiplied by the total cholesterol concentration to yield the amount of cholesterol for each band. A mean LDL-particle size was computed by integrating the relative contribution of each subfraction of LDL for a given subject.

2.3. Statistical analyses

The clinical data of study subjects were expressed as the medians plus the minimum-maximum range for continuous variables. The chi-square test was used to assess the differences in patient characteristics between boys and girls. Individual group data for all biochemical markers were reported as the mean and standard error of mean (SE), and differences among groups were analyzed using one-way analysis of variance or Mann–Whitney *U* tests where appropriate. A multiple linear regression model was used to determine the associations between the dosage and duration of treatment and each metabolic risk biomarker. P values < 0.05 were considered statistically significant. All analyses were performed using SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Characteristics of the study population

The demographic characteristics and biochemical test results of all participants are summarized in Table 1. The majority were male (88.7%), reflecting the more common prevalence of ASD in boys than in girls in the Thai population. More males received a high dose (1.0 mg/day) of risperidone than did females (0.5 mg/day). Median treatment duration was greater in males (62.2 months; interquartile range: 41.5–81.7 months) than females (46.7 months; interquartile range: 30.0–74.1 months). Body mass index (BMI) and waist circumferences were not significantly different between males and females. Although, the mean values of the most biomarkers did not differ significantly between genders, girls presented with greater the levels of leptin and cortisol than males.

3.2. Clinical and biochemical parameters and risperidone dosage

Of these 168 patients, 55 (52 males and 3 females) had a daily dose above FDA recommendation (Table 2), and higher dosage correlated with longer duration. Many of the metabolic risk markers showed statistically significant differences based on the dosage. The mean concentrations of glucose intolerance (fasting glucose, insulin and HOMA-IR) as well as prolactin and leptin rose significantly with increasing daily dosage (all $P \leq 0.022$), but those of adiponectin and cortisol did not. Dosage had minimal effect on lipid markers, including triglycerides, total

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