Coll. Antropol. **31** (2007) 4: 1105–1109
Original scientific paper

Second Generation Antipsychotics and Risk of Diabetes Type II – Comparison between Olanzapine and Risperidone

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A B S T R A C T

Differences in the glucose metabolism were examined and analysed in this study between patients treated with olanzapine and risperidone in comparison with healthy volunteers. The aim of the study was to determine differences of the impaired glucose metabolism in the study groups as well as to point out to the possible mechanisms which bring to these differences. To the group of 15 schizophrenic patients treated with olanzapine, and group of 15 schizophrenic patients treated with risperidone and to 14 healthy volunteers oral glucose tolerancy test is applied in order to determine the level of the impaired glucose tolerance. In the group of the patients treated with olanzapine glucose tolerance was impaired in 33% of the patients, while in the group of the patients treated with risperidone in 20%. Impaired glucose tolerance mostly manifested as hyperinsulinemia. Authors discussed about possible mechanisms responsible for the impaired glucose tolerance in the patients treated with new antipsychotics. Authors conclude that insulin resistance is the main mechanism for development of the diabetes type II in the schizophrenic patients treated with antipsychotics. Insulin resistance is the result of the multiple effects of the antipsychotics, among which most common are: increased body mass and direct involvement of the antipsychotics in the glucose metabolism.

***Key words**: schizophrenia, second generation antipsychotics, glucose metabolism*

Introduction

Second generation antipsychotics, compared with first generation antipsychotics, brought significant advantages in the treatment of the patients suffering from schizophrenia and schizophrenia like diseases. Their biggest advantage is better tolerance because of the weaker manifested and rarer extrapiramidal side effects. But, some of the second generation antipsychotics induce increased body mass, induce risk of development of diabetes type II and risk of dyslipidemia and therefore increase prevalence of metabolic syndrome in the population of schizophrenic patients. Contribution of second generation antipsychotics to increased body mass, to the impaired glucose metabolism and dyslipidemia in the patients with schizophrenia is not easy to asses because of the other factors that influence the development of these disorders (family history, sitting lifestyle, inadequate eating habits, smoking, physical illnesses, abuse of the psychoactive substances, social disfunctionality…). Nevertheless, higher prevalence of diabetes in the schizophrenic population was described even before the development of the antipsychotics. That implies the idea that the impaired glucose metabolism in the schizophrenic patients could be connected with the nature of the disease. Introduction of the chlorpromazin in the therapy of the schizophrenia brought to the higher body mass, diabetes type II and dyslipidemia. But with second generation antipsychotics these metabolic disorders get into concerning proportions. Today the prevalence of diabetes among schizophrenic patients is twice higher than in the general population. Connection of these metabolic disturbances and some of the second generation antipsychotics is confirmed on the many levels: through case reports, retrospective studies and strictly controlled clinical trials. Therefore there is no doubt that some antipsychotics, especially second generation antipsychotics, apply to this twice as high prevalence of diabetes

Received for publication August 20, 2007

type II among schizophrenic patients compared with general population[1–5]. A lot of facts show that the risk of diabetes in schizophrenic patients has significantly grown after the inclusion of second generation antipsychotics in the therapy[6–8]. Although there are informations about development of diabetes type II with almost every antipsychotic[9–12], higher risk for development of diabetes type II and diabetic kethoacidosis is especially related with dibenzodiazepines – olanzapine and clozapine[13–16]. Potential mechanisms of the development of antipsychotic induced diabetes type II are multiple, but the most relevant risk factor is considered to be antipsychotics' induced higher body mass with increase of insulin resistency[17]. Increased body mass antipsychotics cause by blocking certain receptors which mediate in the control of the satiety. Therefore, some antipsychotics block histaminergic H_1 receptors, whose stimulation is connected with reduction of the food intake. Furthermore, antipsychotics which block 5-HT_{2C} receptors also through hipothalamus produce higher appetite and food intake in the body. Also, many antipsychotics block adrenergic receptors (α1,α2, β) which play significant role in the control of the appetite and in the controll of the glucose metabolism[1,18–20]. Controlled trials suggests that dibenzodiazepines (clozapine and olanzapine) might directly influence the insulin resistance and glucose tolerance, independently of body mass. It is assumed that in that case hyperglycemia develops because of the 5-HT_{1A} receptors blocking at the β cells of the pancreas. 5-HT_{2A} receptors may also be included in the glucose metabolism control. But the precise role of these receptors in the regulation of the glucose metabolism is not fully known. Probably, different antipsychotics produce hiperglycemia in different possible multiple ways. In that way can be explained their different power in the provocation of diabetes. For example, with olanzapine is connected 37% higher risk of development of diabetes compared with risperidone[21]. Higher risk of diabetes with olanzapine compared with risperidone may be connected with increased body mass, as well as with the direct affect of olanzapine to the glucose metabolism. Besides, for the development of the diabetes type II can be responsible the possibility of some antipsychotics to block the glucose transport in the peripheral tissues by blocking the influence of the insulin on the transport proteins[1,18].

Subjects and Methods

Study was conducted on the 44 subjects: 30 patients with schizophrenia, diagnosed according to the DSM IV criteria, and 14 healthy volunteers. Patients with schizophrenia were included by random choice. Inclusion criteria were: signed informed consent for the study, age from 18–65, at least one prior episode of schizophrenia according to the DSM-IV criteria – for the group of patients, for at least 6 months continuous therapy with risperidone or olanzapine. In the trial were not included patients with diabetes or with the information of diabetes in their relatives. Fifteen of the patients treated with olanzapine and fifteen with risperidone. There were no significant differences in the length of the treatment with investigated antipsychotic between the two groups. All of the patients were treated with the first generation antipsychotics in the prior episode. Routine measurement of the body weight gave us the insight in the body weight of the patients at the beginning of the treatment with risperidone or olanzapine. Group of healthy volunteers and groups of patients did not significantly differ according to the body weight and body mass index, although in the time of measurement the patients treated with olanzapine were the most heavier in the average. Oral glucose tolerancy test (OGTT-test according to the WHO recommendations) were applied to the all subjects. At the defined time points (0, 60, 120, 180 min) blood samples were taken for the measurement of the glucose concentrations (enzime measurements with hexokinases, Olympus); insulin (ELIZA, Mercadone) and C-peptide (ELIZA, Mercadone) in the serum. Referent ranges for lab**o**ratory values after fasting were: glucose = 4.2–6.4 mmol/L; insulin = 2–25 mU/L; C-peptide 343–1803 pmol/L. Criteria for the impaired glucose tolerance were: fasting serum concentrations of glucose ≥6.5 mmol/L, serum concentration of glucose in oral glucose tolerance test (75 grams) after 120 min ≥8.0 mmol/L; fasting serum concentration of insulin ≥26 mU/L, serum concentration of insulin in oral glucose tolerance test ≥100 mU/L. The results were analysed descriptively and with Exact Mann-Whitney U test for duration of therapy; Kruskal-Wallis test for age, body mass, BMI, glucose, insulin and C-peptide.

Results

According to the set criteria glucose tolerancy was impaired in 3 patients receiving risperidone (20%) and 5 patients receiving olanzapine (33%). In the group of healthy volunteers there were no impairement of the glucose tolerancy. A fasting hyperglycemia (7.2 mmol/L) is found in one patient receiving olanzapine. Impaired glucose tolerancy had in total 8 patients (23%). In the OGTT- test average glucose concentration in the group receiving olanzapine were higher than in the group of healthy volunteers in the 120 minute. Significant differences were found in the insulin concentrations in OGTT test between the group receiving olanzapine and the group of healthy volunteers in the 60., 120. and 180. minute as well as between the group receiving olanzapine and the group receiving risperidone in the 0. and 60. minute. Changes in the concentrations of C-peptide as expected followed changes in the insulin concentrations, which confirms endogen etiology of the insulin. (Table 1, Figure 1, Figure 2)

Discussion

The results of this study point out the significant number of patients with impaired glucose tolerance in the group of patients treated with olanzapine as well as in the group of patients receiving risperidone. The re-

TABLE 1
SERUM CONCENTRATIONS OF GLUCOSE, INSULIN AND C-PEPTIDE IN HEALTHY SUBJECTS (N=14), SCHIZOPHRENIC PATIENTS TAKING RISPERIDONE (N=15) AND OLANZAPINE (N=15) IN ORAL GLUCOSE TOLERANCE TEST.

	Healthy N=14	Risperidone N=15	Olanzapine N=15	p*
Male	5	6	5	
Female	9	9	10	
Age, median (25%–75%)	41.5 (37–44)	42 (37–53)	38 (31–42)	0.233
Duration of therapy (months), median (25%–75%)	–	17 (14–19)	14 (13–28)	0.504
TT1	72 (59.75–87.5)	73 (63–88)	75 (71–84)	0.833
TT2	73 (63.75–85)	76 (65–91)	84 (76–92)	0.179
BMI, median (25%–75%)				
BMI1	25.55 (21.45–29.425)	27.2 (21.8–29.6)	26.2 (25–27.1)	0.981
BMI2	25.7 (22.1–29.275)	27.9 (22.3–30.6)	28.0 (26.9–31.3)	0.182
Glucose, median (25%–75%)				
Zero point	5.25 (4.975–6.05)	5.4 (5.1–5.6)	5.4 (5.1–5.8)	0.989
After 60 minutes	6.35 (5.4–7.05)	8 (5.8–10.8)	9 (6.7–11.8)	0.077
After 120 minutes	4.75 (4.175–5.775)	6.2 (5.1–7.5)	6.6 (5.2–8.6)†	0.027
After 180 minutes	4.5 (4.05–5.0)	5.2 (4.2–5.5)	4.5 (4.0–5.8)	0.196
Insulin, median (25%–75%)				
Zero point	9.3 (7.7–11.4)	8.3 (5.7–9.5)	13.2 (9.3–19.2)‡	0.008
After 60 minutes	46.7 (28.35–75.25)	52.9 (36–83.9)	102.6 (62.6–117.0)†‡	0.014
After 120 minutes	11.75 (9.075–36.5)	32 (20.0–54.2)	51.6 (36.4–72.1)†	0.001
After 180 minutes	7.5 (2.95–8.8)	19.2 (5.4–39.6)	16 (10.7–33.9)†	0.002
C–peptide, median (25%–75%)				
Zero point	389.5 (109.5–1179.25)	462 (315–733)	566 (435–742)	0.278
After 60 minutes	1908 (986.5–3097.25)	2002 (1686–2765)	2865 (1509–3820)	0.171
After 120 minutes	1406 (376.75–2338.5)	1752 (1513–3447)	3222 (2320–3920)†‡	0.001
After 180 minutes	365.5 (115.5–1128.25)	1250 (358–2354)	2057 (1280–2371)†‡	0.001

* Exact Mann-Whitney U test for duration of therapy; Kruskal-Wallis test for age, body mass, BMI, glucose, insulin and C-peptide
† Significantly higher then in the healthy group ($p<0.05$; post-hoc exact Mann-Whitney U test with Bonferroni correction)
‡ Significantly higher then in the group of patients taking risperidone ($p<0.05$; post-hoc exact Mann-Whitney U test with Bonferroni correction)

sults are in concordance with the previous studies which compared risk from diabetes melitus type II in the patients treated with olanzapine, risperidone and conventional antipsychotics. According to these studies, higher risk of diabetes was among the patients treated with olanzapine. Higher risk, but in the lower degree exists also in the patients treated with risperidone and with first generation antipsychotics[5,18,19]. In this study, the results which have already published in the short version[20], there are also differences observed in the prevalence of impaired glucose metabolism between the patients receiving olanzapine and those receiving risperidone. This difference was not noticed in the fasting glucose measurements but in the OGTT test, and the most impressive pointer of the impaired glucose tolerance was hyperinsulinemia. Precise mechanisms in which antipsychotics cause hyperglycemia still remains unclear. Mostly mentioned are: increased body weight, increased body mass index (BMI), with insulin resistance afterwards[21,22], blockade of the serotoninergic 5 HT_{1A} receptors on the β cells of the pancreas independently of the body mass[14] and pancreatitis caused with antipsychotics[23,24]. It seems that body weight and accompanied insulin resistance play important role in the increased risk for diabetes type II patients treated with atypical antipsychotics. This hypothesis also supports higher compensatory secretion of insulin and C-peptide in the patients without diabetes with atypical antipsychotic therapy during the oral glucose tolerance test, as in the study by Yazicki[25]. In this study all of three measured parameters during the oral glucose tolerance test (glucose response and compensatory insulin and C-peptide secretion) were significantly higher in the patients compared with the healthy volunteers. Concentrations of glucose, insulin and C-peptide were higher, but not significantly, in the patients treated with olanzapine compared to

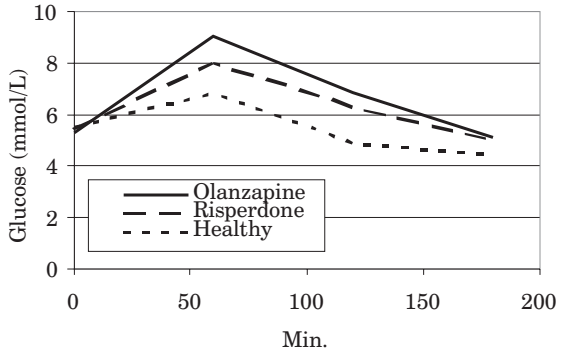

Fig. 1. Serum concentrations of glucose in healthy subjects (N= 14), schizophrenic patients taking risperidone (N=15) and olanzapine (N=15) in oral glucosae tolerance test.

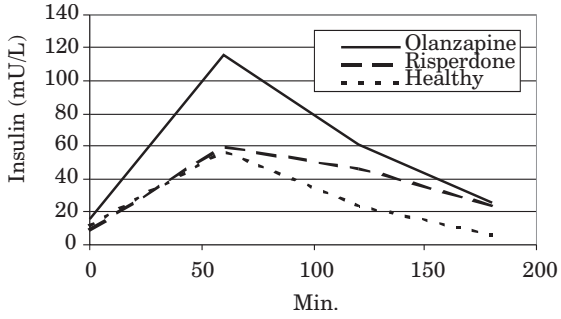

Fig. 2. Serum concentrations of insulin in healthy subjects (N= 14), schizophrenic patients taking risperidone (N=15) in oral glucosae tolerance test.

those treated with risperidone. BMI was higher in the patients treated with olanzapine compared with the healthy volunteers. In the group of patients treated with risperidone there were no significant difference in the BMI compared with the healthy volunteers. Therefore, difference in the body weight can be one of the explanations for the different results in the group of patients treated with different medications. Because of the small sample, study results hardly could distinguish direct influence of the antipsychotics to the impaired glucose tolerance from the direct impact through body weight gain, so they should be taken with restrictions. One can only speculate about the possible mechanisms responsible for the development of the diabetes mellitus in the patients receiving the antipsychotic therapy. However, since there was not significant difference in the BMI between the patients treated with risperidone and the patients treated with olanzapine, and there are significant differences in the hyperinsulinemia between those two groups, it can be assumed that for the higher hyperinsulinemia in the olanzapine group with higher body weight obesity is the one that might be responsible for direct influence of olanzapine to the insulin resistance. It still remains the question of the risk for diabetes type II during the treatment with the second generation antipsychotics. First of all this risk is not possible to asses on the basis the results of the fasting glucose concentrations in the serum. This research and other researches' results show that the best pointer of the higher risk for diabetes in the patients receiving the antipsychotics is higher insulin resistance. It can be best determined by the measurement of the insulin concentration in the OGTT test. The patients have higher insulin resistance as a sign of the overburden system for the control of the glucose metabolism years before the appearance of the diabetes[26]. Therefore to the every patient subjected to the antipsychotic with a higher risk for metabolic syndrome, OGTT test should be done**,** including the insulin measurement, in order to asses the risk for diabetes type II. OGTT test should be also done in every significant change in the body weight[27], no matter which antipsychotic the patient is taking. Although, other risk factors for development of the diabetes type II can, even with low diabetes risk antipsychotics, produce metabolic disturbances, as well as all of the other elements of metabolic syndrome[28–30].

Conclusion

Second generation antipsychotics affect the glucose metabolism of the schizophrenic patients in the different ways. In this study olanzapine has more often and stronger impaired glucose metabolism compared with the risperidone, although such impairments also existed in the patients treated with risperidone. The best pointer of the higher risk for diabetes in the patients treated with antipsychotics is higher insulin resistance manifested in the OGTT test with hyperinsulinemia. Therefore, to assess the risk for the diabetes type II in the patients receiving antipsychotics, the measurement of the insulin concentrations in the OGTT test should be included.

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DRUGA GENERACIJA ANTIPSIHOTIKA I RIZIK OD DIJABETESA TIPA II – USPOREDBA IZMEĐU OLANZAPINA I RISPERIDONA

S A Ž E T A K

U članku su prikazani i analizirani rezultati ispitivanja razlike u metabolizmu glukoze između bolesnika liječenih olanzapinom i risperidonom te zdravih ispitanika. Cilj ispitivanja bio je utvrditi razlike u oštećenju metabolizma glukoze u ispitivanim skupinama i ukazati na moguće mehanizme koji dovode do tih razlika. Na skupinama od 15 shizofrenih bolesnika liječenih olanzapinom, 15 shizofrenih bolesnika liječenih risperidonom i 14 zdravih dragovoljaca primjenjen je oralni test opterećenja glukozom (OGTT) u cilju procjene stupnja oštećenosti tolerancije glukoze. U skupini na olanzapinu tolerancija glukoze bila je oštećena kod 33% bolesnika, a u skupini na risperidonu kod njih 20%. Oštećena tolerancija glukoze najčešće se manifestirala hiperinzulinemijom. Autori raspravljaju o mogućim mehanizima odogovornim za oštećenu toleranciju glukoze kod bolesnika koji uzimaju nove antipsihotike. Zaključuju da je inzulinska rezistencija glavni mehanizam razvoja dijabetesa tip II u shizofrenih liječenih antipsihoticima. Inzulinska rezistencija je posljedica višestrukih učinaka antipsihotika, među kojima su najčešći: porast tjelesne težine i izravno uplitanje antipsihotika u metabolizam glukoze.