Effect of typical and atypical antipsychotic drugs on serum C-reactive protein and lipid profile in schizophrenic patients

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Abstract

Objectives: To assess the effect of quetiapine and fluphenazine on serum high sensitivity C-reactive protein (hs-CRP) and serum lipid profile in schizophrenic patients.

Patients and methods: The subjects comprised two groups of twenty seven newly diagnosed schizophrenic patients for each group. The first group was treated orally with quetiapine at a dose 200-500 mg/day. The second group was treated with fluphenazine intramuscularly at a dose 25 mg every 4 weeks. Twenty seven healthy volunteers were also included as a control group. The patient and the control groups were age and sex matched. The patients were diagnosed by a psychiatrist on the basis of semi-structured interview to determine DMS-IV diagnosis. Clinical symptoms were assessed in 14 of the 18 Brief individual Psychiatry Rating Scale (BPRS) items in order to measure the severity of schizophrenia. Fasting blood samples from the patients were taken for analysis before the beginning of quetiapine or fluphenazine treatment and after 8 weeks of the study. Other blood samples were taken from healthy subjects as a control group.

Results: Serum hs-CRP was significantly ($p < 0.01$) higher in the schizophrenic patients before treated by quetiapine or fluphenazine (difference = 382.9% and 395.1% of control, respectively) than controls. The measurement of hs-CRP decreased significantly ($p < 0.01$) after quetiapine treatment by 19.1%, while it was increased significantly ($p < 0.01$) after fluphenazine by 12.3% compared with before treatment values. In the schizophrenic patients, serum total cholesterol (TC) and triglycerides (TG) were significantly higher ($p < 0.01$) than controls, while high density lipoprotein cholesterol (HDL-C) was lower than controls. Quetiapine caused significant increase ($p < 0.01$) in serum TC and TG, while serum HDL-C decreased significantly ($p < 0.01$) compared with the results before treatment. Fluphenazine did not cause any significant change in the lipid parameters. Quetiapine treatment significantly increased ($p < 0.05$) body mass index (BMI), whereas fluphenazine did not change BMI compared with before treatment values. Base time and after 8 weeks of quetiapine or fluphenazine treatment showed significant decrease in the score of BPRS by quetiapine and fluphenazine.

Conclusion: Quetiapine depressed CRP and caused dyslipidemia. Fluphenazine raised CRP but it had no effect on lipid profile.

Keywords: Schizophrenia, C-reactive protein, quetiapine, fluphenazine

الخلاصة

هدف الدراسة: دراسة تأثير عقار quetiapine وعقار flupheazine على مصل البروتين الفعال نوع C ومصل واجهة الدهون في المرضى المصابين بأنفصام الشخصية.

المرضى وطرق العمل: شملت الدراسة مجموعتين من المرضى المصابين بأنفصام الشخصية المشخصين حديثا كل مجموعة مكونة من 27 مريضا . عولجت المجموعة الاولى بعقار quetiapine عن طريق الفم وبجرعة تتراوح بين 200-500 ملغم/اليوم . وعولجت المجموعة الثانية بعقار fluphenazine عن طريق الحقن بالعضلة وبجرعة 25 ملغم كل 4 اسابيع. وشملت الدراسة ايضا على 27 من الاصحاء كمجموعة ضابطة. وكانت مجاميع المرضى ومجموعة السيطرة متجانسة من ناحية العمر والجنس. وتم تشخيص المرضى عن طريق طبيب اختصاص في الامراض النفسية على قاعدة المقابلة شبه الهيكلية باعتماد التشخيص DMS-IV. تم قياس الاعراض السريرية باستخدام 14 من 18 من مقياس BPRS لغرض معرفة شدة المرض. وتم سحب عينات دم من المرضى لاجراء التحليل قبل علاج quetiapine او fluphenazine وبعد 8 اسابيع من العلاج. واخذت عينات اخرى من الدم من الاشخاص الاصحاء.

النتائج: كان مصل البروتين الفعال عالي الحساسية في المرضى المصابين بالانفصام قبل علاج quetiapine او fluphenazine اعلى معنويا ($p < 0.01$) من مجموعة السيطرة (الفرق= 382 % و 395 % من السيطرة وعلى التوالي) وقل هذا القياس معنويا ($p < 0.01$) بعد عقار Quetiapine ب 19% بينما زاد القياس معنويا ($p < 0.01$) بعد عقار fluphenazine ب 12.3% مقارنة بالنتائج قبل العلاج. وكان مصل الكوستيرول الكلي TC والشحوم الثلاثية TG للمرضى المصابين بالانفصام اعلى معنويا ($p < 0.01$) من السيطرة بينما كان مصل البروتين الدهني عالي الكثافة HDL-C في المرضى اقل معنوي ($p < 0.01$) من السيطرة. وسبب عقار quetiapine زيادة معنوية ($p < 0.01$) في مصل الكولستيرول الكلي والشحوم الثلاثية. بينما انخفض مصل البروتين الدهني عالي الكثافة معنويا مقارنة بالنتائج قبل العلاج. ولم يسبب عقار fluphenazine تغيير معنوي في قياسات الدهون. وزاد عقار quetiapine مؤشر كتلة الجسم معنويا ($p < 0.05$) بينما لم يؤثر عقار fluphenazine على مؤشر كتلة الجسم مقارنة ما قبل العلاج. ووقلل كل من عقار quetiapine و fluphenazine معنويا من مقياس BPRS.

الاستنتاج: ثبط عقار quetiapine مصل البروتين الفعال وسبب في تغيير واجهة الدهون. ان عقار flupheaziine رفع مصل البروتين الفعال نوع C بينما لم يؤثر على واجهة الدهون.

C-reactive protein (CRP) is one of the positive acute phase reactant protein. It is synthesized in the liver and has many pathophysiological role in the inflammatory process[1].

There have been some reports on the use of the elevated CRP level as evidence for an inflammatory etiology for schizophrenia and as indicator for more severe clinical symptoms and psychopathology in schizophrenia[2]. In antipsychotic free patients with schizophrenia, serum high sensitivity CRP (hs-CRP) level was higher than healthy controls and was positively correlated with the severity of the psychopathology[3]. However, elevated serum CRP in schizophrenic patients was associated with the severity of cognitive impairment but not of psychiatric symptoms[4,5].

Second generation antipsychotics (SGA) are now commonly used because they have lower incidence of extrapyramidal side effects than for first generation antipsychotics (FGA)[6]. Quetiapine is an atypical antipsychotic drugs, used in the treatment of schizophrenia and bipolar disorder[7,8]. Fluphenazine is a conventional typical antipsychotic drug used in the treatment of schizophrenia, it was considered to be used in poor compliance patients, though there is

little advantage of the drug over oral medication in term of compliance[9].

Treatment of schizophrenia with different antipsychotic drugs had different results on serum CRP. The atypical antipsychotic drugs, olanzapine or risperidone, decreased serum hs-CRP, while the typical antipsychotic drug, haloperidol, increased serum hs-CRP[10].

Western studies mainly focus on the effect of different SGA on metabolic outcome but little is known of FGA, still commonly used in Asia[11]. Atypical antipsychotic drugs were associated with metabolic risk more than FGA[12]. Quetiapine was associated with weight gain, hypercholest-erolemia and lower high density lipoprotein cholesterol (HDL-C)[13]. In addition, the rate of obesity and metabolic disorder in atypical antipsychotic drugs including quetiapine were high[14].

Since fluphenazine is still used in the developing countries and little attention was paid on the metabolic side effects of this drug. We suggested this study to compare the effect of this drug as one of FGA with quetiapine as a drug of SGA on serum hs-CRP and lipid profile as risk factors for cardiovascular diseases in schizophrenic patients.

Patients and methods

This study was a follow up study, conducted in the Outpatient Department of Ibn Sina Hospital, Mosul, Iraq, during the period from September 2010 to April 2011. The laboratory analyses were performed at the Pharmacology laboratory, Ninevah Collage of Medicine, University of Mosul, Iraq. The study was approved by the ethical committee of Ninevah Directorate of Health and the patients were informed by the study. Drugs were given to the patients by a psychiatrist according to their needs. Quetiapine was given as first line treatment, while fluphenazine was given for non-compliance patients in order to achieve the therapeutic dose.

The subjects comprised two groups of newly diagnosed of twenty seven schizophrenic patients for each group. The first group was treated orally with quetiapine at a dose 200-500 mg/day (age range: 15-57 years, mean ± SD: 29.9 ± 9.7 years). The second group was treated with fluphenazine intramuscularly at a dose 25 mg every 4 weeks (age range 19-55 years, mean ± SD: 30.1± 7.2 years). The treated patients were reevaluated after 8 weeks. Twenty seven healthy volunteers (age range: 18-40 years, mean ± SD: 28.8 ± 4.1 years) were also included as a control group. The patient and the control groups were age and sex matched. The patients were diagnosed by a psychiatrist on the basis of semi-structured interview to determine DMS-IV diagnosis. Clinical symptoms were assessed in 14 of the 18 Brief Individual Psychiatry Rating Scale (BPRS) items in order to measure the severity of schizophrenia.

All patients and controls were neither alcoholics nor smokers and they were not hospitalized. Patients and controls taking other medications during the study period were excluded.

Fasting blood samples (5 mL) from the patients were taken before the beginning of quetiapine or fluphenazine treatment and after 8 weeks of the study. Other blood samples were taken from healthy subjects as a control group. Serum was obtained from the blood samples and analyzed by using colorimetric method for hs-CRP[15]. Serum total cholesterol (TC), HDL-C, and triglycerides (TG) were determined by using enzymatic methods[16].

Data are presented as mean ± SD. Unpaired Student□s t-test was used to compare between patient and control parameters. Paired t-test was used to compare the follow up parameters within the patient group. Chie square test was used in order to find the significance of the drug response. P values less than 0.05 were considered significant. Statistical analysis was performed using SPSS package version 17.

Results

Table 1 shows that serum hs-CRP was significantly ($p < 0.01$) higher in the schizophrenic patients before quetiapine and fluphenazine treatment (difference = 382.9% and 395.1 of control, respectively) than controls. This measurement of hs-CRP decreased significantly after quetiapine treatment by 19.1%, while it was increased significantly after fluphenazine by 12.3% compared with before treatment values.

Table 1. Serum hs-CRP, TC, HDL-C, and TG in schizophrenic patients treated with quetiapine or fluphenazine

Variables / Study groups	hs-CRP (μg/L)	TC mmol/L	HDL-C mmol/L	TG mmol/L
Control subjects	0.41 ± 0.1	4.3 ± 0.71	1.22 ± 0.26	1.55 ± 0.52
Patients Before quetiapine treatment	1.57 ± 0.3[a]	4.7 ± 0.82 [a]	1.15 ± 0.28 [a]	1.71 ± 0.61 [a]
After quetiapine treatment	1.27 ± 0.25[b]	5.2 ± 0.75 [b]	1.23 ± 0.30 [b]	1.88 ± 0.70 [b]
Patients Before fluphenazine treatment	1.62 ± 0.32 [a]	4.8 ± 0. 72 [a]	1.12 ± 0.29 [a]	1.69 ± 0.69 [a]
After fluphenazine treatment	1.92 ±0.33 [b]	4.5 ± 0.69	1.14 ± 0.27	1.70 ± 0.71

hs-CRP: high sensitivity c-reactive protein, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, TG: triglycerides

[a] $p < 0.01$ vs control; [b] $p < 0.01$ vs pretreatment

In the present schizophrenic patients before quetiapine or fluphenazine treatment TC and TG were significantly ($p < 0.01$) lower, whereas HDL-C was significantly ($p < 0.01$) lower than controls. Quetiapine caused significant increase ($p < 0.01$) in serum TC and TG (difference: 11.1% and 10.99%, respectively), while serum HDL-C was decreased significantly ($p < 0.01$) compared with the results before treatment. Fluphenazine did not cause significant change in the lipid parameters.

Quetiapine treatment significantly increased ($p < 0.05$) body mass index (BMI) by 2.9% compared with pre-treatment values (22.64 ± 2.46 Kg/m^2 vs 23.31 ± 2.55 Kg/m^2, respectively), whereas fluphenazine did not change BMI compared with before treatment value (23.21 ± 2.32 Kg/m^2 vs 23.11 ± 2.42 Kg/m^2, respectively).

Base time and after 8 weeks of both quetiapine or fluphenazine treatment showed significant decrease in the score of BPRS (86 ± 4.9 vs 44.8 ± 4.3 for quetiapine; 81 ± 4.1 vs 40.1 ± 4.9 for fluphenazine) ($p < 0.01$).

Discussion

The main findings of this study were fluphenazine (FGA) raised hs-CRP while quetiapine (SGA) decreased it. Dyslipidemia and elevated BMI were found by quetiapine but not fluphenazine.

In the present schizophrenic patients before quetiapine or fluphenazine treatment, serum CRP was significantly higher than controls. These results are consistent with other workers[5,17]. There is emerging evidence of increased inflammation in severe mental disorder[18]. Many studies showed that CRP is a reliable marker of cardiovascular disease (CVD) and has thus been incorporated into CVD risk prediction protocols[19,20]. Hepatic CRP production is under the influence of cytokine especially interlukine[21]. Some of these cytokines also rise in parallel with CRP and could be related to symptomatology of schizophrenia[22].

Quetiapine decreased serum hs-CRP significantly in the studied, while fluphenazine increased hs-CRP significantly after 8 weeks of treatment. Haloperidol as a conventional antipsychotic drug raised CRP, while olanzapine an atypical antipsychotic drug depressed CRP[10]. Moreover, resperidone normalized proinflammatory CRP in n-3 fatty acid deficient rats[23]. The main point in this study was both quetiapine and fluphenazine decreased BPRS significantly; however, quetiapine depressed hs-CRP, while fluphenazine raised it. Therefore, the mechanism of action of quetiapine and fluphenazine on hs-CRP may be different. Further studies are needed in order to evaluate the cause of elevated CRP by typical antipsychotic drugs.

In the schizophrenic patients before quetiapine or fluphenazine treatment, serum TC and TG were increased, whereas HDL-C was decreased. These results are consistent with other workers[24,25]. The prevalence of metabolic syndrome is high in schizophrenic and bipolar disorder compared to general population[26].

Quetiapine increased serum TC and TG in this study, while

fluphenazine did not change serum TC and TG. There is controversial results for the effect of atypical and conventional antipsychotic drugs on lipid, since atypical but not conventional showed increasing in serum lipids[25]. Individual drugs of typical and conventional antipsychotic drugs had different effect on lipids in the treated patients[27]. Quetiapine was associated with high risk of hyperlipidemia, the possible underlying causes of lipid dysregulation include weight gain, dietary changes, and glucose intolerance[28]. However, Henderson et al.[29] found that aripirazole treatment for 4 weeks did not change serum TC, HDL-C, and VLDL-C in the schizophrenic patients. The metabolic disturbances by antipsychotic drugs such as dyslipidemia, hypertension and overweight are regarded as added risk factors of CVD for the schizophrenic patients.

In conclusion, quetiapine depressed the proinflammatory factor CRP, associated with metabolic risk by causing dyslipidemia. Fluphenazin had minimal effect on lipid but raised CRP. Further studies are needed to investigate the mechanism of raised CRP by typical antipsychotic drugs.

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