Lipid Peroxidation and Antioxidant Status in Schizophrenic Patients Treated by Quetiapine

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Abstract

Objectives: To find the effect of quetiapine on lipid peroxidation and serum total antioxidant status (TAS) in schizophrenic patients.

Patients and methods: The subjects comprised 27 schizophrenic patients and 27 healthy volunteers. Clinical symptoms for the patients were assessed in Brief Individual Psychiatry Rating Scale (BPRS) items. The patients were treated with quetiapine (200-500 mg/day) orally for 8 weeks then reevaluated after the treatment. Blood samples from the patients were taken before and after quetiapine treatments. Other blood samples were taken from healthy subjects as a control group. Serum was obtained and analyzed for malondialdehyde (MDA) and TAS.

Results: Base time and after 8 weeks of quetiapine treatment showed a significant decrease in BPRS score in the schizophrenic patients. Serum MDA was significantly higher in the schizophrenic patients (difference = 124.1% of control) than controls. The parameter decreased significantly after quetiapine treatment by 16.9% compared with before treatment values. Serum TAS, in the schizophrenic patients, was significantly lower (38.4%) than controls. Quetiapine increased serum TAS significantly by 21.1%. Quetiapine treatment significantly increased body mass index (BMI) by 2.9%.

Conclusion: Quetiapine depressed lipid peroxidation, and raised serum TAS in schizophrenic patients. The change in these parameters by quetiapine may play a role in its therapeutic activit.

Keywords: Quetiapine, Schizophrenia, Malodialdehyde, Total Antioxidant Status, C-reactive Protein.

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Introduction

Oxidative stress is involved in the pathophysiology of many psychiatric diseases including schizophrenia.[1] Lipid peroxidation is increased in schizophrenic patients,[2,3] but levels of individual antioxidants are conflicting.[4] Serum or plasma levels of superoxide dismutase (SOD),[5,7] glutathione,[6,8] and catalase (CAT)[9] were not consistent in schizophrenic patients.

Authors suggest the importance of measuring total antioxidant status (TAS) instead of individual antioxidant,[10, 11] since the total antioxidants comprise all the defense system of the body against oxidative stress.

In our previous study, olanzapine decreased lipid peroxidation and raised serum TAS,[12] but the decrease of oxidative stress by olanzapine was not connected with the therapeutic effect of the drug which was not studied.

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Quetiapine is an atypical antipsychotic drug used for the treatment of schizophrenia[13, 14] and bipolar disorder.[15] It is well tolerated and it has superior to haloperidol in efficacy in schizophrenic patients with wide dose range.[13] Quetiapine depressed lipid peroxidation and raised SOD in the schizophrenic patients.[3] This study was conducted to evaluate the effect of quetiapine on lipid peroxidation and serum TAS. The therapeutic effect of quetiapine was also studied.

Patients and Methods

Patients of this study were obtained from the Outpatient Department of Ibn Sina Hospital, Mosul, Iraq, during the period from September 2009 to March 2010. The laboratory analyses were performed at the Department of Pharmacology, Mosul 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.

The subjects comprised twenty seven schizophrenic patients (age range: 15-57 years, mean ± SD: 29.9 ± 9.7 years) and 27 healthy volunteers (age range: 18-40 years, mean ± SD: 28.8 ± 4.1 years). The patient and the control groups were sex matched (16 males and 11 females) The patients were diagnosed by a psychiatrist on the basis of semi-structured interview to determine DMS-IVTR diagnosis. Clinical symptoms were assessed in 14 of the 18 in Brief Individual Psychiatry Rating Scale (BPRS) items in order to measure the severity of schizophrenia. The patients were either newly diagnosed or had at least one month wash from the previous antipsychotic drug. The patients were treated with quetiapine at a dose 200-500 mg/day for 8 weeks then reevaluated after the treatment.

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

Blood samples (5 mL) from the patients were taken before the beginning of quetiapine 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 MDA, [16] and TAS [17]

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. The relationship between variables was determined by using pearson's correlation. Chie square test was used in order to find the significance of the therapeutic response of the drug. *P* values less than 0.05 were considered significant. Statistical analysis was performed using SPSS package version 17.

Results

Table 1. Serum MDA, and TAS in schizophrenic patients treated with quetiapine and controls (n= 27 per group)

	Serum MDA µmol/L	Serum TAS mmol/L
Control subjects	0.87±0.16	1.77±0.2
Patients Before treatment	1.95±0.21[a]	1.09±0.09[a]
After treatment	1.62±0.17[b]	1.32±0.12[b]

[a] $p < 0.001$ vs control; [b] $p < 0.001$ vs pretreatment

Table (1) shows that serum MDA was significantly ($p < 0.001$) higher in the schizophrenic patients (difference = 124.1% of control) than controls. These parameters decreased significantly after quetiapine treatment by 16.9% compared with before treatment values. Serum TAS, in the

schizophrenic patients, was significantly ($p < 0.001$) lower (38.4%) than controls. Quetiapine increased serum TAS significantly ($p < 0.001$) by 21.1% compared with the results before treatment.

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).

Base time and after 8 weeks of quetiapine treatment showed significant decrease in the score (85.8 ±4.9 vs 44.8 ± 24.3) ($p < 0.001$). A significant correlation was noticed between BPRS scores and serum MDA ($r= - 0.39$, $p < 0.05$) or TAS ($r= 0.471$, $p < 0.05$). However, no significant correlation was noticed between BPRS score and serum TAS or MDA after 2 months of treatment with quetiapine. Also a significant negative correlation between serum TAS and serum MDA ($r= - 0.413$, $p < 0.05$) in the schizophrenic patients before treatment was noticed, but not after the treatment.

Discussion

In the present study, serum MDA in the schizophrenic patients was significantly higher than controls. The neurons are sensitive to oxyradical-mediated injury, since their membranes are rich in polyunsaturated fatty acid,[18] and areas of human brain are very rich in iron, which plays an essential role in generating free radical species.[19] Intense oxidative stress and decreased antioxidants may contribute to neuronal death and alter the information processing in schizophrenia.[20] The change in the polyunsaturated fatty acid metabolism, also increased lipid peroxidation in schizophrenia.[21] Furthermore, experimental model showed oxidative stress induced behavioral and molecular anomalies similar to that in schizophrenia.[22] Membrane dysfunction can be secondary to free radical-mediated pathology and may contribute to specific aspect of schizophrenia symptomology and complication of its treatment.[20]

Quetiapine decreased serum MDA in our patients. The results are consistent with other studies.[23] Other atypical antipsychotic drugs also depressed lipid peroxidation in the schizophrenic patients.[23]

Serum TAS was used instead of individual antioxidant, since there are conflicting results in individual antioxidant in schizophrenic patients.[24] However, Lamont et al.[25] found that the monitoring of individual antioxidants in physiological samples is more important than plasma TAS, since the reaction kinetics in vivo are not the same and may interact with each other. Thus TAS of a sample is a quantitative measurement of the state of balance of these various components under specified reaction conditions.[25]

Serum TAS was significantly lower in the present schizophrenic patients than controls. These results are consistent with other workers.[10] The decrease in the antioxidant defense system is a reflection of the oxidative stress noticed by the increase in lipid peroxidation, since there is growing evidence of the role of free radical-mediated pathology and impaired antioxidant defense system in the schizophrenic patients.[26]

In this study, quetiapine raised serum TAS. In our previous study olanzapine, another atypical antipsychotic drug, also increased serum TAS in the schizophrenic patients. The increase in the antioxidant defense system is not known wither due to therapeutic response or due to the direct effect of the drug. According to BPRS, quetiapine decreased the score significantly. However, Xu et al.[27] found that quetiapine had a protective effect in cultured cells against oxidative stress cytotoxicity induced by a myloid beta 25-35 by blocking OH induced aggregation of amyloid beta 25-35. Other studies for the effects of atypical antipsychotic drugs on individual antioxidants were controversial.[3, 7]

In the present study, quetiapine produced a significant decrease in BPRS. The significant response of quetiapine is consistent with other studies.[14, 28]

The study was restricted to relatively low dose, since our patients could not tolerate higher dose rates. The optimum dose is probably greater than 250 mg/day.[29] The main daily dose for quetiapine is 375-495 mg/day.[30] Lee et al.[31] suggested that higher than the recommended quetiapine dose could be more effective in some patients. There is evidence describing the use of quetiapine in excess of 800 mg/day.[32]

The side effects of quetiapine in the present patients were minimal and the increase in the BMI and drowsiness were the only changes noticed. Timadal et al.[30] found that quetiapine was well tolerated in schizophrenic patients and did not increase extrapyramidal systems. In addition, no difference was seen for quetiapine from placebo regarding incidence of extrapyramidal symptoms or change in prolactin concentration.[33] Quetiapine did not cause parkinsonism and rarely tardive dyskinesia, since it is released from D_2 receptor within 12 to 24 hours, whereas traditional antipsychotics remain attached to D_2 for days preventing relapse but allowing accumulation that can lead to tardive dyskinesia.[34] Quetiapine affinity for 5-HT_{2A} receptors is much stronger than its affinity for D_2 receptor, consequently, it is thought to cause fewer extrapyramidal side effects.[35]

Quetiapine increased BMI slightly but significantly in our patients. Other workers showed minimal weight gain by quetiapine;[13, 36, 37] however, weight gain by quetiapine was still higher than risperidone and sertindole.[38] The increase in weight by quetiapine in our study can be explained by appetite stimulation due to affinity antipsychotic drugs for adrenergic and histaminergic receptors.[39] Endocrine metabolic mechanisms, such as the activation of the hypothalamus-pitutary-adrenal axis, changes in insulin sensitivity may also be involved.[39]

In conclusion, quetiapine depressed lipid peroxidation, and raised serum TAS in schizophrenic patients. This work also suggests that suppression of oxidative stress in schizophrenic patients by quetiapine may play a role in its therapeutic activity.

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زناخة الدهون ومضادات الأكسدة الكلي في المرضى المصابين بالانفصام وتحت علاج عقار كيوتابين

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الملخص

الهدف: صممت هذه الدراسة لتقييم زناخة الدهون متمثلة بمستوى المالوندلديهايد في المصل ومجمل مستويات مضادات الأكسدة في مصل المرضى المصابين بالانفصام، وتحت علاج عقار كيوتابين.

المرضى وطرائق العمل: شملت الدراسة 27 مريضا مصابا بالانفصام، وكذلك 27 من المتطوعين الأصحّاء. وتمت دراسة الأعراض السريرية باستعمال المعدل القياسي النفسي للأشخاص (Brief Individual Psychiatry Rating Scale). وتم علاج المرضى بعقار كيوتابين (200–500 ملغم/يوم) عن طريق الفم لمدة (8) أسابيع، وتم تقييم المرضى بعد ذلك. أخذت عينات الدم من المرضى قبل العلاج بعقار كيوتابين وبعده، وأخذت عينة أخرى من المتطوعين الأصحّاء كمجموعة سيطرة. وتم قياس مستوى كل من المالوندالدهايد ومنظومة مضادات الأكسدة الكلية في المصل.

النتائج: تبين ان عقار كيوتابين قد قلل معنويا المعدل القياسي النفسي للأشخاص المصابين بالانفصام بعد (8) أسابيع من العلاج. وكان مستوى المالوندالدهايد في المصل أعلى معنويا في مرضى المصابين بالانفصام (نسبة الاختلاف (124.1%) من السيطرة. إن هذه النتيجة انخفضت معنويا بعد استعمال عقار كيوتابين ب 16.9% مقارنة بالقيم قبل العلاج. أما مستوى منظومة الأكسدة في المصل في مرضى الانفصام؛ فقد كان أقل معنويا (38.4%) من مجموعة السيطرة. ورفع عقار كيوتابين معنويا من مستوى منظومة مضادات الأكسدة في المصل بـ 21.1%.

الاستنتاج: قلل عقار كيوتابين من زناخة الدهون، ورفع من مجمل مستويات مضادات الأكسدة في مرضى الانفصام، وإن التغييرات التي حصلت في هذه القياسات بوساطة عقار كيوتابين قد تؤدي دوراً في الفعل العلاجي للعقار.

الكلمات الدالة: زناخة الدهون، المصابون بالانفصام، مستوى المالوندلديهايد.

