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Effect of Olanzapine and Risperidone on prolactin level in schizophrenic patients

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Abstract :

Hyperprolactinemia is a well-established adverse effect associated with the use of typical and atypical antipsychotics. Hyperprolactinemia is associated with both acute and chronic clinical consequences in men and women. Increased prolactin levels received little attention and were rarely monitored. Therefore, the primary objective of this study is to investigate the effects of two atypical antipsychotics (olanzapine and risperidone) on prolactin level in schizophrenic patients. For this purpose, a therapeutic clinical trial was done. We prospectively recruited 28 schizophrenic patients attended to Social and Psychiatric Service Centre in Mosul city. All patients fulfilled the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for schizophrenia. They were randomized to receive monotherapy with either olanzapine in a dose 5-20 mg or risperidone in a dose 4-12 mg for 8 weeks (two groups). Also 22 apparently healthy subjects with approximately age and sex matching to the patients groups without previous history of schizophrenia or any other psychiatric disorders were taken as a control group. This study shows that, at baseline, there were no significant differences between the three studied groups in term of prolactin level and, after treatment with these drugs for 8 weeks, both drugs caused a significant increase in the prolactin level compared to baseline levels and that risperidone causes significantly greater increase in the levels of prolactin than olanzapine

المستخلص

ارتفاع مستوى البرولاكتين في الدم من الاضرار الجانبية المؤكدة التي تصاحب استخدام مضادات الفصام النموذجية واللانموذجية. ارتفاع مستوى البرولاكتين في الدم يصاحبه نتائج سريرية حادة ومزمنة عند الذكور والاناث. الزيادة في مستوى البرولاكتين في الدم يحضى باهتمام قليل ونادرا ما يتم متابعته. لذلك الهدف الرئيسي لهذه الدراسة هو لبحث تاثير اثنان من مضادات الفصام اللانموذجية (الاولانزابين و الرزبيريدون) على مستويات البرولاكتين لدى مرضى الفصام. لهذا الغرض تم استخدام تجربة سريرية علاجية حيث تم تجنيد 28 مريضا مشخصين كمرضى فصام كانو يراجعون مركز الخدمة الاجتماعية والنفسية في مدينة الموصل. كل المرضى كانو مطابقين لمعيارDSM – IV في تشخيص مرض الفصام. لقد قسم المرضى عشوائيا ليتناولو اما اولانزابين بجرعة تتراوح بين 5-20ملغم او رزبيريدون بجرعة 4-12 ملغم (مجموعتين)،

كذلك 22 متطوع اصحاء مطابقين للمرضى من ناحية العمرو الجنس لم يعانو من مرض الفصام سابقا او اي مرض نفسي اخر. نتائج هذه الدراسة اظهرت انه قبل اعطاء الادوية لا توجد فروقات معنوية بين المجموعات الثلاث فيما يتعلق بمستويات البرولاكتين، بعد تناول هذه الادوية لمدة 8 اسابيع كلا الدوائين سببا زيادة معنوية في مستويات البرولاكتين في الدم مقارنة بتلك التي تم ملاحظتها قبل اخذ الدواء والرزبيريدون سبب زيادة معنوية اكثر من الاولانزابين.

Introduction

Schizophrenia is a devastating, chronically debilitating disorder. It may be thought of as a clinical syndrome، with many possible pathophysiological pathways that ultimately manifests with psychotic symptoms [(1)]. It is characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances [(2)]. Antipsychotic drugs are able to reduce psychotic symptoms in a wide variety of conditions, including schizophrenia, bipolar disorder, psychotic depression, psychoses associated with dementia, and drug-induced psychoses. [(3)]. The most important distinction in modern-day classification of antipsychotic drugs is between the classical (typical or first generation) agents such as chlorpromazine, haloperidol and zuclopenthixol, and the atypical (second generation) antipsychotics, which include clozapine, and now risperidone, olanzapine, quetiapine, amisulpride, aripiprazole and others [(4)]. Second-generation agents are generally used as first-line therapy for schizophrenia to minimize the risk of debilitating extrapyramidal symptoms associated with the first-generation drugs that act primarily at the dopamine D2 receptor. [(2)]. Prolactin is a peptide hormone produced in the anterior pituitary. It is the principal hormone responsible for lactation. Prolactin is elevated as a result of prolactin-secreting adenomas. In addition, a number of drugs elevate prolactin levels. These include antipsychotic and gastrointestinal motility drugs that are known dopamine receptor antagonists, estrogens, and opiates. [(5)]. Hyperprolactinemia is a well-established adverse effects associated with the use of typical and atypical antipsychotics [(6)]. It has been known that, antipsychotic-induced blockade of the dopamine tract in the tuberoinfundibular area of the anterior pituitary leads to hyperprolactinemia [(3)]. Hyperprolactinemia is associated with both acute and chronic clinical consequences in men and women [(7)]. Prolactin elevation inhibits the release of luteinizing hormone and follicle-stimulating hormone from the pituitary gland. This results in low gonadal steroids and hypogonadism. For both sexes, this can cause sexual dysfunction, infertility, galactorrhea, decreased bone mineral density, osteoporosis, and fractures. Meanwhile, patients diagnosed with schizophrenia possess additional risk factors for osteoporosis, such as high alcohol consumption and cigarette smoking. Men may develop gynecomastia, and women may experience hirsutism and acne [(8)] [(9)]. There is growing awareness of the detrimental effects of elevated prolactin on physical health in patients with schizophrenia treated with antipsychotics [(10)]. Therefore, the primary objective of this study is to investigate the effects of two atypical antipsychotics (olanzapine and risperidone) on prolactin level in schizophrenic patients.

Subjects and methods

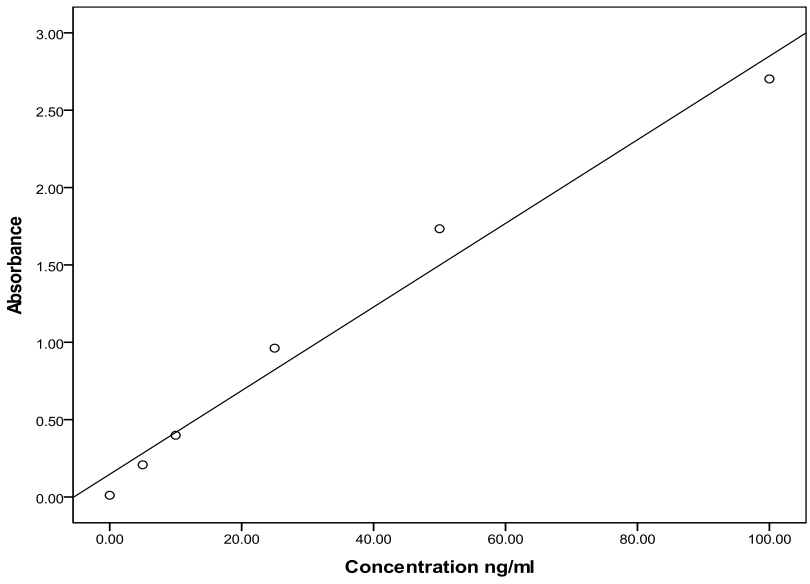
We prospectively recruited 28 schizophrenic patients who were either drug-free for at least 4 weeks or newly diagnosed attending the Social and Psychiatric Service Centre in Mosul city and their ages were between 18 and 50 years (28.9± 6.1). All patients fulfilled criteria for schizophrenia of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [(11)]. Each patient underwent diagnostic evaluation by one trained psychiatrist on the basis of a semistructural interview to determine the diagnosis. They were randomized to receive monotherapy with either olanzapine in a dose 5-20 mg or risperidone in a dose 4-12 mg for 8

weeks (two groups). This study was conducted during a period from January 2014 to May 2014. Also 22 apparently healthy subjects with approximately age and sex matching to the patients groups without previous history of schizophrenia or any other psychiatric disorders were taken as a control group. Patients have other diseases, those treated with other antipsychotics or with drug abuse and hospitalized patients were excluded from the study. All participants in the study gave written informed consent. At about 8.5-10 a.m. after an overnight fasting, 5 ml venous blood were taken from both, the patients groups before starting treatment and from the control group for measuring serum prolactin as a baseline level. By the end of 8 weeks of treatment, another blood sample was taken from the patients groups and the same measurement was repeated. Serum prolactin levels were measured by enzyme immunoassay for the quantitative determination of prolactin concentration in human serum (ELISA) using commercial kits supplied by BioCheck, Inc (USA) [(12)]. The statistical analyses used were ANOVA test, post hoc Waller Duncan test, and t-test using SPSS program version 15. P-value of less than 0.05 was accepted as being significant in all types of statistical tests.

Results

A standard curve of prolactin by ELISA was constructed by plotting the absorbance obtained from each standard against its concentration with standard concentration on the X-axis and absorbance on the Y-axis, as shown in fig.1.

Fig. (1):- Standard curve for prolactin



The characteristics of the studied groups were shown in table 1 which shows the number, sex, age and percent of participants in the olanzapine, risperidone and control group

Table (1):- Number, sex, age and percent of participants in the three studied groups

Groups	Male		Female		Age (year) mean±SD
	Number	Percent	Number	Percent	
Olanzapine	10	66.7 %	5	33.3%	27.4±6.4
Risperidone	10	77 %	3	23%	30.5± 5.8
Control	16	72.7 %	6	27.3 %	28.1± 4.9

The comparison of prolactin levels for olanzapine, risperidone and control group before starting treatment were shown in(table 2). This table shows that, at baseline, there were no significant differences between the three studied groups in term of prolactin level. This table also shows that, after treatment with these drugs for 8 weeks, both drugs causes significant increase in the levels of prolactin from those observed at baseline and that risperidone causes significantly greater increase in the levels of prolactin than olanzapine.

Table (2):- Comparison of prolactin levels between olanzapine and risperidone groups at different stages of treatment and with the control group

Prolactin (ng/mL)	Olanzapine Group(n=15) (mean±SD)	Risperidone Group (n=13) (mean±SD)	Control Group(n=22) (mean±SD)	P-value
Baseline	18.10 ±13.39	20.66 ±15.68	15.90 ±11.51	0.5
After 8 wks	23.77 ±18.06	130.36 ±18.66		
P-value	0.04	0.001		
Difference (Week 8-baseline)	5.67 ±12.97	109.70 ±19.73		0.001

Discussion

The selection of an antipsychotic agent to treat people with schizophrenia or schizoaffective disorder is a complex decision for which the physician must weigh individual patient factors and numerous drug factors, including efficacy, safety, tolerability, and cost [13]. Risperidone and olanzapine have been shown to be both well tolerated and efficacious in the treatment of psychotic disorders. Almost half of all new prescriptions for antipsychotics in the United States are for these two medications [14] [15]. Although, these antipsychotics are atypical in having less risk of extrapyramidal side effects, but these agents present their own spectrum of adverse effects, including hypotension, seizures, weight gain and increased risk of type II diabetes mellitus, hyperprolactinemia and hyperlipidemia [3] [16]. Antipsychotics are the most common cause of pharmacological hyperprolactinemia, and the majority of antipsychotic agents cause hyperprolactinemia [17]. The early age of onset of schizophrenia and related disorders and the need for long-term therapy make antipsychotic chronic adverse effects, such hyperprolactinemia, a major therapeutic problem [18]. Therefore, the present study compares the effect of two atypical antipsychotics (olanzapine and risperidone) on the levels of prolactin in patients with schizophrenia after 8 weeks of treatment with these drugs. The results of this study shows that both risperidone and olanzapine causes significant increase in prolactin levels after 8-week of treatment with both drugs and this finding was in agreement with the results of Konarzewska *et al* 2009 who found that both drugs significantly increased prolactin levels after

treatment [19]. Of the two drugs risperidone causes significantly higher increase in serum prolactin levels than olanzapine and this result serum prolactin levels decreased significantly following the switch from risperidone to olanzapine [20] [21]. All antipsychotics block the dopamine type 2 (D2) receptor, which is thought to be critical for their antipsychotic effects. D2 receptor occupancy also is associated with a number of adverse effects, one of which is prolactin level elevation. Risperidone has a relatively higher affinity for D2 receptors compared with other atypical antipsychotics, which may explain why it has a relatively higher incidence of hyperprolactinemia [22] [23]. It has been suggested that it may be due to the poor blood-brain barrier (BBB) penetrability of risperidone compared with that of the other marketed atypical agents. The pituitary gland lies outside the BBB and is exposed to the systemic circulation; consequently, lactotroph D2-receptor occupancy is greatest among agents that require higher systemic concentration for efficient penetration of the BBB [24]. In conclusion, the results of this study showed that risperidone causes significantly greater increase in prolactin level than olanzapine.

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