DOI: 10.5455/bcp.20111208083355

Nephrotoxic Effects of Chronically Administered Olanzapine and Risperidone in Male Rats

Mustafa Gulec[1], Halil Ozcan[1], Elif Oral[1], Onur Burak Dursun[2], Deniz Unal[3], Selina Aksak[3], Jale Selli[3], Osman Nuri Keles[3], Bunyamin Unal[3], Abdulmecit Albayrak[4], Zekai Halici[4]

ÖZET:

Kronik olarak uygulanan olanzapin ve risperidonun erkek sıçanlar üzerindeki nefrotoksik etkileri

Amaç: Olanzapin ve risperidon atipik antipsikotik ailesinin üyeleridirler. Psikiyatri pratiği içinde geniş bir aralıktaki belirti ve bozuklukların tedavisinde yaygın olarak kullanılmalarına karşın böbrek üzerindeki etkileri hakkında çok az şey bilinmektedir. Bununla birlikte bu ilaçların böbrekler dışındaki dokular, organlar ve sistemler üzerindeki toksik etkileri daha önce gösterilmiştir. Bu sebeplerle, biz mevcut çalışmada uzun süreler ile düşük ve yüksek dozlarda olanzapin ve risperidon uygulamanın sıçan böbrekleri üzerindeki etkilerini değerlendirmeyi amaçladık.

Yöntemler: Yirmi beş adet sıçan eşit olarak bir kontrol grubu (KG), düşük doz bir olanzapin grubu (DOG), yüksek doz bir olanzapin grubu (YOG), düşük doz bir risperidon grubu (DRG) ve yüksek doz bir risperidon grubu (YRG) şeklinde beş gruba ayrılmıştır. Yarım ve 2.5 mg/kg/gün dozlarındaki olanzapin 6 hafta süresince intraperitoneal yolla sırasıyla DOG ve YOG'ye uygulanmıştır. Benzer şekilde, 0.5 ve 1 mg/kg/gün dozlarındaki risperidon yine 6 hafta boyunca ve intraperitoneal yolla sırasıyla DRG ve YRG'ye verilmiştir. KG'ye ise bu zaman zarfında aynı hacim ve dozlarda izotonik tuz çözeltisi (%0.09 NaCl) yapılmıştır. Deneyin sonunda böbrekler çıkarılmış ve histopatolojik incelemeye alınmıştır.

Bulgular: DOG'de herhangi anormallik bulunmamasına rağmen YOG, DRG ve YRG'de böbreklerin hem tubüler hem de glomerüler yapısındaki sınırların kaybolması, renal korteks ve medullanın bazı alanlarında fokal nekrozların görülmesi, hem glomerüler kapillerler hem de mezengiumda piknotik çekirdek ve eozinofilik sitoplazmalı hücrelere rastlanması, özellikle Bowman kapsülünün pariyetal yaprağında olmak üzere intraglomerüler kapiller bazal membran kalınlığında artış olması ve son olarak da bazı alanlarda hidropik vakuolizasyon ve eozinofilik akümülasyonlar gibi tubül hücrelerinin kaybının neden olduğu anormalliklerin ortaya çıkması gibi histopatolojik değişikliklerin dâhil olduğu, kayda değer nefrotoksik etkiler saptanmıştır.

Sonuçlar: Her ne kadar bu nefrotoksik etkilerin antipsikotik tedavi ile ilişkili olan oksidatif stres ve mitokondriyal disfonksiyondan kaynaklandığı varsayımında bulunulabilirse de nefrotoksisitenin kesin sebebi belirsizliğini sürdürmektedir. Diğer taraftan, kendini idrarda hücreler ve silendirler, oligüri, proteinüri, artmış serum kreatini ve yükselmiş üre ile gösteren nefrotoksisite bazı bireylerde kolayca gelişebilir ve bu ajanların özellikle böbrek hastalığı bulunan hastalarda dikkatle kullanılmalarında yarar vardır. Buradaki toksisitenin bir bölümü doza bağımlı olduğundan, böyle özel durumlarda böbrek üzerindeki yan etkileri azaltmak adına kronik uygulamalarda etkin olan en düşük dozların tercihi yoluna gidilmesi de bir avantaj olarak görülebilir. Yine de, atipik antipsikotik kullanımı ile nefrotoksisite arasındaki nedensel ilişkiyi konu alan daha ileri çalışmalara şüphesiz ihtiyaç vardır.

Anahtar sözcükler: Nefrotoksisite, histopatolojik, olanzapin, risperidon, sıçan, böbrek

Klinik Psikofarmakoloji Bülteni 2012;22(2):139-47

ABSTRACT:

Nephrotoxic effects of chronically administered olanzapine and risperidone in male rats

Objective: Olanzapine and risperidone are members of the atypical antipsychotic family. Even though they are widely used for the treatment of a broad range of symptoms and disorders in psychiatric practice, their effects on kidney are little known. Nevertheless, the toxic features of these medicines on the tissues, organs or systems other than the kidneys have been demonstrated previously. For these reasons, we aimed to evaluate the effects of long-term administration of low- and high-doses of olanzapine and risperidone on rat kidneys in the present study.

Methods: Twenty five rats were divided into 5 groups equally: a control group (CG), a low-dose olanzapine group (LOG), a high-dose olanzapine group (HOG), a low-dose risperidone group (LRG), and a high-dose risperidone group (HRG). Olanzapine in doses of 0.5 and 2.5 mg/kg daily for 6 weeks were intraperitoneally injected into the LOG and HOG, respectively. Similarly, risperidone in doses of 0.5 and 1 mg/kg daily for 6 weeks were intraperitoneally injected into the LRG and HRG, respectively. Same volume and dosages of saline (0.9% NaCl) were given to the CG during the same period. At the end of the experiment, the kidneys were dissected out and evaluated histopathologically.

Results: Although there were any abnormalities in the LOG, it was determined significant nephrotoxic effects, including losing regularities in both tubular and glomerular structure of kidneys, focal necrosis in some area of renal cortex and medulla, cells with pyknotic nuclei and eosinophilic cytoplasm in both glomerular capillaries and mesangium, an increase in thickness of basal membrane of intraglomerular capillary, especially in parietal layer of Bowman's capsule, and in some fields, abnormalities caused by the loss of tubule cells, such as hydropic vacuolization and eosinophilic accumulations in the HOG, LRG, and HRG.

Conclusion: Albeit it has been hypothesized that these nephrotoxic effects are due to the oxidative stress and mitochondrial dysfunction associated antipsychotic treatment, the definite mechanisms of the nephrotoxicity continue uncertain. On the other hand, nephrotoxicity that presents with cells and casts in the urine, oliguria, proteinuria, elevated serum creatinine, and elevated urea may occur easily in some individuals and these agents should be used cautiously, particularly in patients with renal disease. Because some toxicity here is dose-dependent, there might be an advantage of preferring minimum therapeutic doses with chronic administration to decrease their side effects on the kidney in these special conditions. However, further research is surely needed to study the causal relationship between atypical antipsychotic use and nephrotoxicity.

Key words: Nephrotoxicity, histopathological, olanzapine, risperidone, rat, kidney

Bulletin of Clinical Psychopharmacology 2012;22(2):139-47

[1]M.D., Department of Psychiatry, Ataturk University School of Medicine, Erzurum - Turkey
[2]M.D., Department of Child and Adolescent Psychiatry, Ataturk University School of Medicine, Erzurum - Turkey
[3]M.D., PhD, Department of Histology and Embryology, Ataturk University School of Medicine, Erzurum - Turkey
[4]M.D., Department of Pharmacology, Ataturk University School of Medicine, Erzurum - Turkey

Yazışma Adresi / Address reprint requests to: Mustafa Gulec, Department of Psychiatry, Ataturk University School of Medicine, Erzurum - Turkey

Elektronik posta adresi / E-mail address: mustafagulec78@yahoo.com

Gönderme tarihi / Date of submission: 14 Eylül 2011 / September 14, 2011

Kabul tarihi / Date of acceptance: 8 Aralık 2011 / December 8, 2011

Bağıntı beyanı:
M.G., H.Ö., E.O., O.B.D., D.U., S.A., J.S., O.N.K., B.U., A.A., Z.H.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
M.G., H.Ö., E.O., O.B.D., D.U., S.A., J.S., O.N.K., B.U., A.A., Z.H.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Antipsychotic drugs have been grouped according to both pattern of clinical action and mechanism of action. The original antipsychotic drugs such as chlorpromazine and haloperidol have been called typical or first generation. They cause both antipsychotic actions and many side effects (extrapyramidal and hormonal) that are ascribed to their high affinity dopamine D_2 receptor antagonism. Drugs such as olanzapine and risperidone were then developed that avoided the neurological and endocrine side effects (atypical or second generation antipsychotics) (1). Olanzapine is an antagonist of the D_1 and D_2 dopamine, muscarinic, cholinergic, and 5-HT_{2A} serotonin receptors and is used in the management of both positive and negative symptoms of schizophrenia (2). Similarly, risperidone has a high binding affinity for both dopamine D_2 and serotonin 5-HT_2 receptors and has also proven efficacy in the treatment of schizophrenia with both positive and negative symptomatology (3).

The cytotoxic properties of the typical antipsychotic drugs are well known. Chlorpromazine, fluphenazine, trifluoperazine, and related drugs have been reported to inhibit proliferation in a variety of cell lines and to alter cell morphology (4). Similarly, haloperidol, another typical antipsychotic agent, has been shown to be hepato- (5) and nephrotoxic (6) in rats, especially at high doses. The results of the latter study suggest that there is a significant relationship between haloperidol treatment and structural changes in the kidneys such as tubular deformations, prominent dilatation of the renal vessels and tubules, enlarged glomeruli, and glomerular basal membrane thickening. These structural abnormalities may cause changes in renal morphometry. Finally, the findings of the above-mentioned work clarify that the stereological and histopathological reasons underlying dose-dependent renal injury are associated with chronic administration of haloperidol. There have also been previous suggestions that these cytotoxic effects of the typical antipsychotic drugs are responsible for some of the adverse effects of these medications in patients, particularly the movement disorders and tardive dyskinesia. In contrast, the newer atypical drugs produce significantly fewer extrapyramidal symptoms (7). Although these data might be interpreted to mean that the atypical drugs are less toxic for cells, which tends to support a relationship between in vitro toxicity and in vivo side effects, there are also adverse effects reported for these compounds. Therefore, the cytotoxic and cytoprotective effects of the atypical antipsychotic agents, including olanzapine and risperidone, are being intensively investigated (8,9,10).

Although these atypical antipsychotic drugs have produced countless benefits for patients, some side effects are inevitable. For example, in other experimental studies performed in our laboratory, side effects of olanzapine (11) and risperidone (12) on hepatocytes have been reported. In addition, some researchers have demonstrated side-effects related to metabolic dysfunction (13,14). In addition to other side effects such as extrapyramidal effects and tardive dyskinesia (via blockade of dopamine D_2 receptors) or anticholinergic effects and memory impairment (via blockade of muscarinic receptors) (15), the effectiveness and/or adverse effects of olanzapine and risperidone, as well as other atypical antipsychotic drugs, have been examined in the literature since liver metabolism and excretion of metabolic products by the kidney may alter absorption, metabolism, and excretion (16,17).

Even though some recent workhas demonstrated toxic effects of these agents in different tissues of both laboratory animals and human beings (e.g. changes in liver function tests and weight gain), nephrotoxicity of this class of drugs is not common (18,19) and no systematic data on the nephrotoxic effects of olanzapine and risperidone have been published. Therefore, we aimed to examine possible histopathological dose-dependent toxic effects of olanzapine and risperidone on rat kidneys.

MATERIALS and METHODS

Animals

All experiments were performed with 25 adult male Wistar Albino rats, each weighing 200-210 g. They were obtained from Ataturk University Experimental Animal Laboratory of Medicinal and Experimental Application and Research Center (ATADEM). Care of the rats was in accordance with the ILAR/NRC Guide for the Care and Use of Laboratory Animals (2010 edition), and all procedures were also approved by the Ataturk University Local Animal Care Committee. The Ethics Committee of the Ataturk University Medical Faculty approved the whole study protocol. The rats were housed in standard plastic cages on

sawdust bedding in an air-conditioned room at 22.0±1.0°C under controlled lighting (14 h light/10 h dark cycle). Standard rat chow and tap water were given ad libitum. The rats were divided into five groups with each group containing five rats: a control group (CG), a low-dose olanzapine group (LOG), a high-dose olanzapine group (HOG), a low-dose risperidone group (LRG), and a high-dose risperidone group (HRG). The groups were kept in different cages.

Drug and Drug Administration

Olanzapine which was purchased from Eli Lilly Turkey, Istanbul, Turkey was dissolved in normal saline (0.9% NaCl) and given intraperitoneally (11,20) once per day for 6 weeks (2 and 4 mg/kg/day for the LOG and HOG, respectively). For the present study, olanzapine dosages were chosen as equivalent to the highest dosages used in humans (0.5 and 2.5 mg/kg/day) (11,21).

Risperidone which was bought from Janssen Turkey, Istanbul, Turkey was also dissolved in normal saline (0.9% NaCl) and given intraperitoneally (12,20) in doses once a day for 6 weeks (0.5 and 1 mg/kg/day for the LRG and HRG, respectively). Risperidone at doses of 1 mg/kg were chosen as equivalent to the highest dosage used in human beings (12,22).

The same volumes of normal saline (0.9% NaCl) were given to the CG (12).

Tissue Preparation Processes

Following the aforementioned period, the rats were killed by an overdose of a general anesthetic (thiopental sodium, 50 mg/kg). The rats were bled before organ sampling, and then the kidneys were dissected out immediately and transferred into a 10% formaldehyde solution for light microscopy.

Conventional Light Microscopy by Hematoxylin-Eosin (H&E) and Periodic Acid-Schiff (PAS)

On the following day, the kidney samples were placed into the same fixative (buffered formalin) for 24 h at room temperature. Subsequently the samples were prepared according to conventional light microscopic technique; i.e. they were dehydrated in a graded alcohol series, embedded in paraffin wax, and serially sectioned using a Leica RM2125RT microtome (Leica Microsystems, Wetzlar, Germany). Each paraffin block was serially cut into 5 µm-thick sections. Approximately 100 sections were obtained from each tissue block, and these sections were then stained with hematoxylin-eosin and periodic acid-Schiff. All sections from renal cortex and medulla were studied and photographed by a light photomicroscope (Olympus BH 40) (12,23).

RESULTS

Control Group (CG)

The renal cortex (Figure $1A_{H\&E}$, $B_{H\&E}$, and B_{PAS}) consisting of convoluted tubules, proximal and distal, together with the renal corpuscles (Figure $1A_{H\&E}$, $B_{H\&E}$, B_{PAS}, and E_{PAS}) appeared normal. Distributions of renal corpuscles in the cortex were regular (Figure $1A_{H\&E}$). Structural features of the proximal tubules which are lined by a simple cuboidal epithelium with brush border and which were intensely acidophilic and distal convoluted tubules with also a simple cuboidal epithelium were normal and regular (Figure $1D_{H\&E}$, $F_{H\&E}$, and $H_{H\&E}$).

Nephrons, which consist of one renal corpuscle that has several parts and its associated tubule and are the functional unit of the kidney, were normal (Figure $1C_{H\&E}$, C_{PAS}, $E_{H\&E}$, and F_{PAS}). No abnormal changes were detected in distinct parts of the renal corpuscle such as Bowman's capsule that is the outer epithelial wall of the corpuscle (Figure $1B_{H\&E}$ and $E_{H\&E}$), Bowman's space that is the space lying within Bowman's capsule, and the glomerulus that

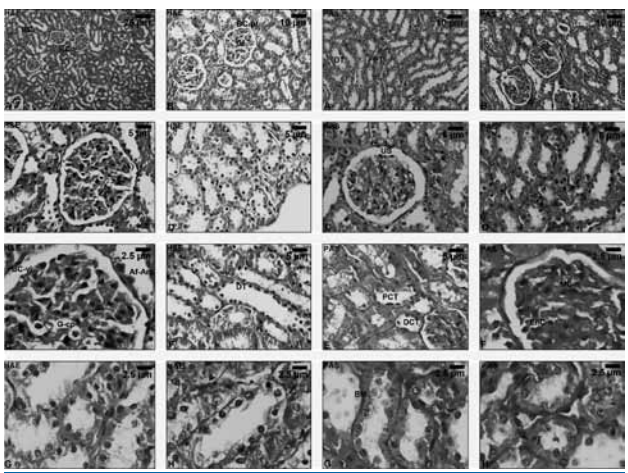

Figure 1: Light microscopic photomicrograph of control group

includes several distinct elements such as the glomerular capillaries and the mesangium, a supporting tissue consisting of mesangial cells and matrix (Figure $1C_{H\&E}$, C_{PAS}, $E_{H\&E}$, and F_{PAS}).

Abbreviations: Af-Art: Afferent Arteriole, BC-pl: Bowman's Capsule (Parietal Layer), BC-vl: Bowman's Capsule (Visceral Layer), BM: Basement Membrane, DCT: Distal Convoluted Tubules, DT: Distal Tubule, EnC-n: Endothelial Nuclei, G-cp: Glomerular Capillary, Gl: Glomerulus, MC-n: Mesangial Cell Nucleus, PCT: Proximal Convoluted Tubules, PT: Proximal Tubule, RC: Renal Cortex, RCo: Renal Corpuscle, US: Urinary Space.

Low-Dose Olanzapine Group (LOG)

In this group, there were no significant changes. Histopathological findings were quite similar to controls except for moderate dilatation of the glomerular capillaries (Figure $2F_{H\&E}$).

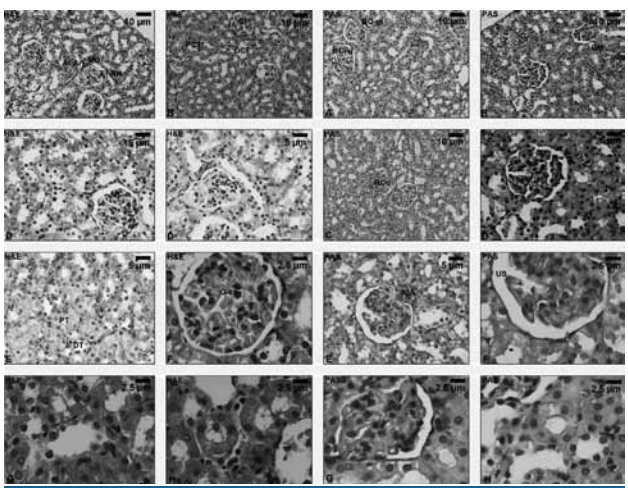

Figure 2: Light microscopic photomicrograph of low-dose olanzapine group

Abbreviations: Af-Art: Afferent Arteriole, BC-pl: Bowman's Capsule (Parietal Layer), BC-vl: Bowman's Capsule (Visceral Layer), BM: Basement Membrane, DCT: Distal Convoluted Tubules, DT: Distal Tubule, Ef-Art: Efferent Arteriole, EnC-n: Endothelial Nuclei, G-cp: Glomerular Capillary, Gl: Glomerulus, JgA: Juxtaglomerular Apparatus, MC-n: Mesangial Cell Nucleus, MD: Macula Densa, PCT: Proximal Convoluted Tubules, PT: Proximal Tubule, RCo: Renal Corpuscle, US: Urinary Space.

High-Dose Olanzapine (HOG) and Low/High-Dose Risperidone (LDR/HDR) Groups

Histopathological findings obtained from the high-dose olanzapine and low/high-dose risperidone groups were similar to each other but different from the control and low-dose olanzapine groups. In the former groups, the following changes were determined:

-loss of regularity in both the tubular (Figure $3C_{H\&E}$ and $D_{H\&E}$) and glomerular (Figure $3A_{H\&E}$, $B_{H\&E}$, A_{PAS}, B_{PAS}, and D_{PAS}) structure of the kidneys,

-focal necrosis in some area of the renal cortex and medulla (Figure $3F_{H\&E}$, $H_{H\&E}$, F_{PAS}, and G_{PAS}),

-occurrence of cells with pyknotic nuclei and eosinophilic cytoplasm in both the glomerular capillaries and mesangium (Figure $3G_{PAS}$),

-increased thickness of the basal membrane of the intraglomerular capillary, especially in the parietal layer of Bowman's capsule, and

-in some fields, abnormalities caused by the loss of tubule cells such as hydropic vacuolization and eosinophilic accumulations (Figure 3, 4, and 5).

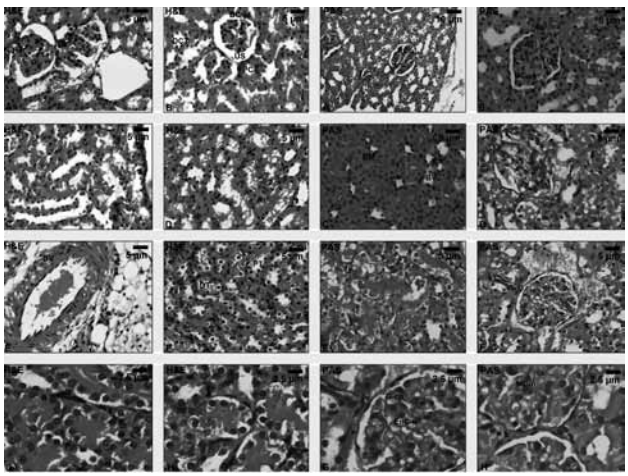

Figure 3: Light microscopic photomicrograph of high-dose olanzapine group

Abbreviations: BC-pl: Bowman's Capsule (Parietal Layer), BC-vl: Bowman's Capsule (Visceral Layer), BM: Basement Membrane, BV: Blood Vessel, DCT: Distal Convoluted Tubules, DT: Distal Tubule, EnC-n: Endothelial Nuclei, G-cp: Glomerular Capillary, Gl: Glomerulus, MC-n: Mesangial Cell Nucleus, PCT: Proximal Convoluted Tubules, PT: Proximal Tubule, RCo:

Renal Corpuscle, RI: Renal Interstitium, US: Urinary Space, He: Hemorrhage.

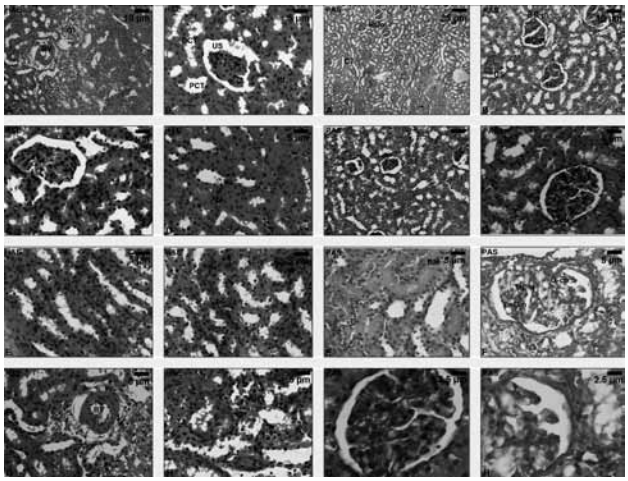

Figure 4: Light microscopic photomicrograph of low-dose risperidone group

Abbreviations: BC-pl: Bowman's Capsule (Parietal Layer), BC-vl: Bowman's Capsule (Visceral Layer), BM: Basement Membrane, BV: Blood Vessel, CT: Collecting Tubule, DCT: Distal Convoluted Tubules, EnC-n: Endothelial Nuclei, G-cp: Glomerular Capillary, Gl: Glomerulus, MC-n: Mesangial Cell Nucleus, PCT: Proximal Convoluted Tubules, RCo: Renal Corpuscle, RI: Renal Interstitium, US: Urinary Space.

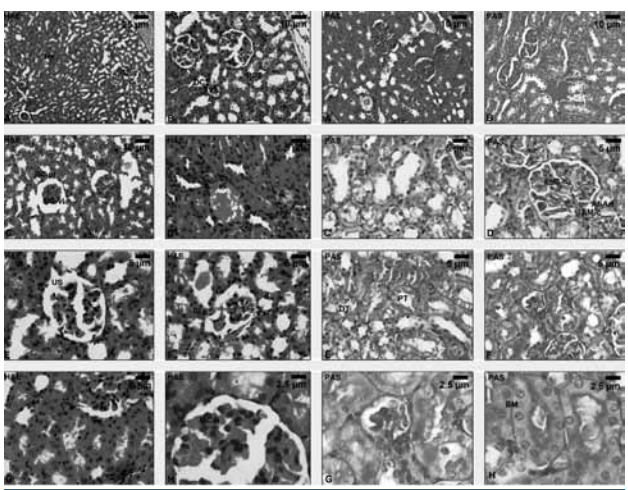

Figure 5: Light microscopic photomicrograph of high-dose risperidone group

Abbreviations: Af-Art: Afferent Arteriole, BC-pl: Bowman's Capsule (Parietal Layer), BC-vl: Bowman's Capsule, (Visceral Layer), BM: Basement Membrane, DCT: Distal Convoluted Tubules, DT: Distal Tubule, EM-c: Extraglomerular Mesangial Cell, EnC-n: Endothelial Nuclei, Gl: Glomerulus, He: Hemorrhage, MC-n: Mesangial Cell Nucleus, PCT: Proximal Convoluted Tubules, PT: Proximal Tubule, RI: Renal Interstitium, US: Urinary Space.

DISCUSSION

Our rationale for conducting the present research was based upon the hypothesis that if the cytotoxicity of olanzapine and risperidone is still controversial, they also might have toxic effects on the survival of rat kidney cells. Therefore, we evaluated and compared the impacts of different concentrations of olanzapine and risperidone. Although there were no abnormalities in the LOG, it was determined that there was significant nephrotoxicity in the HOG, LRG, and HRG. To our knowledge, this is also the first histological study examining the cytotoxic effects of both olanzapine and risperidone on the renal cells of rats. We did not have an opportunity to compare our results with previous research. However, some toxicological studies have described toxic features of these drugs on tissues, organs, or systems other than the kidneys.

In this context, Odaci et al. (11) reported that either low or high doses of olanzapine damaged rat livers at a cellular level in their histological and stereological study investigating the cytotoxic effects of olanzapine on the hepatocytes of male Wistar Albino rats. They found a significant difference in the total number of hepatocytes in rat livers between the CG, LOG, and HOG. The significant difference in the number of hepatocytes between the CG and LOG was an unexpected result for their study group because there had been no suggestion that a low-dose olanzapine treatment would decrease the number of hepatocytes in rat livers. Additionally, they did not have an explanation for this result that agrees with the results of the current literature. More recently, Weston-Green et al. (13) investigated how olanzapine might induce metabolic dysfunctional side-effects such as weight gain, obesity, and diabetes dose-dependently in rats. They showed that olanzapine increased body weight, food intake, and feeding efficiency with no effect on water intake, subcutaneous inguinal and intra-abdominal perirenal fat in female Sprague-Dawley rats. On the contrary, olanzapine decreased insulin and locomotor activity in the open field arena in their

study. The animal model used here appears to mimic some aspects of clinical experience. Similarly, Muller et al. (24) evaluated the interactions of chronic treatment with olanzapine and a cafeteria diet on metabolic parameters in male Wistar rats. They showed that chronic olanzapine treatment caused an increase in fat pad weight. Unfortunately, this change was found to be putatively involved in the etiology of many metabolic diseases previously. As a summary, chronic olanzapine administration seems to be related with hepatopathy and metabolic syndrome in rats.

Similar results have been encountered in some studies connected with risperidone toxicity. For instance, Bogdan et al. (25) examined the possible hepatotoxicity of some antipsychotics, including risperidone, in adult male Wistar rats. Although they did not provide detailed information about the dose, route, and duration of the antipsychotic administration , they reported granulo-vacuolar dystrophy in the parenchyma of hepatocytes of rats treated with risperidone. As a consequence, this study revealed the possible toxicity of the second generation antipsychotic risperidone on the liver. Correspondingly, Lauressergues et al. (14) inspected the effects of chronic treatment with risperidone on body weight, fat accumulation, and liver weight in female mice. They found a significant weight gain associated with an increase of liver and adipose tissue weight with the treatment with risperidone. This finding suggests that risperidone could alter lipid metabolism in the liver and induce weight gain. However, Boyda et al. (26) examined the acute effects of both high and low dose risperidone on alterations in glucose and insulin parameters using a rodent model. They established significant dose- and time-dependent effects with risperidone on fasting plasma glucose and insulin concentrations, homeostasis model of assessment-insulin resistance values, insulin resistance, and glucose intolerance. Together, these findings indicate that acute administration of risperidone has potent effects on the metabolic regulation of glucose and insulin sensitivities, which may contribute to the metabolic side-effects seen in humans. In conclusion, hepatotoxicity, weight gain, and metabolic disturbances, such as dyslipidemia and hyperglycemia are common side effects of risperidone. The above-mentioned effects were formerly connected to the direct toxic action of these drugs on the living cells of the related organs (e.g. liver and pancreas), but today subcellular and molecular methods have also been used intensively to reveal other possibilities underlying tissue or organ toxicity.

Although the mechanisms of the nephrotoxicity here still remain unclear, it might be hypothesized that oxidative stress and mitochondrial dysfunction associated with antipsychotic treatment might have a dose-dependent or -independent nephrotoxic effect in the pathogenesis of nephrotoxicity. Generation of reactive oxygen species (ROS) such as hydrogen peroxide, superoxide radicals, hydroxyl radicals, and lipid peroxides are known to damage various cellular components, including membrane lipids, proteins and DNA and thereby contribute to cellular dysfunction (12). There is increasing evidence to indicate that oxidative stress may be the most critical component in the pathophysiology and outcome of toxicities related to antipsychotic treatments. In a previous study, we investigated the effects of long-term and low dose treatment with the typical antipsychotic, haloperidol, and the second generation atypical antipsychotics, risperidone and olanzapine, on the expression of the key antioxidant defense enzymes and lipid peroxidation products in rat plasma; we found that these three antipsychotic drugs generally decreased plasma malondialdehyde levels (27). Therefore, the side effects associated with chronic treatment may be induced by oxidative cell injury. More recently, Heiser et al. (28) investigated the effects of some antipsychotics, including olanzapine on the formation of ROS in the whole blood of rats by using electron spin resonance spectroscopy. They also incubated the highest concentration of olanzapine with vitamin C to test its protective capacity. Their study demonstrated that olanzapine induces the formation of ROS in the whole blood of rats, which can be reduced by the application of vitamin C. There is also growing evidence that ROS are involved not only in side effects of antipsychotic medications, but also in the pathophysiology of psychiatric disorders such as schizophrenia. Similarly, Shertzer et al. (29) examined the ability of the antioxidant tetrahydroindenoindole (THII) to prevent metabolic changes in mice receiving olanzapine. Olanzapine treatment doubled the high-fat (HF) diet-induced increases in body weight and percent body fat. As increased body fat promotes insulin resistance by a pathway involving oxidative stress, they evaluated production of reactive oxygen and lipid peroxidation in white adipose tissue (WAT). The HF diet caused an increase in lipid peroxidation, NADPH-dependent oxygen uptake, and hydrogen peroxide production, which were further exacerbated by olanzapine.

Each of THII, the NADPH oxidase inhibitor, and diphenyleneiodonium chloride abolished oxidative stress in WAT. Finally, they concluded that THII intervenes in the development of obesity and metabolic complications associated with olanzapine treatment. In their classical work, Pillai et al. (30) compared the effect of 90 and 180 day exposure to haloperidol, a representative typical antipsychotic, to exposure to various atypical antipsychotics, including risperidone on the expression of antioxidant defense enzymes and levels of lipid peroxidation in the rat brain. The oxidative membrane damage was assessed by determination of levels of the lipid peroxidation products, hydroxyalkanals (HAEs), in the rat brain. Although risperidone did not show any change in the HAEs levels up to 90 days in contrast to haloperidol, further treatment up to 180 days resulted in significantly increased levels of HAEs. Understanding of long-term treatment effects of risperidone on the oxidative neural cell injury in rats may be important to explain the possible differential mechanisms underlying its long-term clinical and side effect profiles.

On the other hand, the nephrotoxic effects might also be due to the direct action of olanzapine and risperidone on renal mitochondria. Because the kidney contains more mitochondria compared to other organs, the reducing effects of these compounds on mitochondrial functions may also be important in the pathogenesis of nephrotoxicity. Modica-Napolitano et al. (31) tested a series of typical and atypical antipsychotics, including risperidone and olanzapine for effects on integrated bioenergetic functions of isolated rat liver mitochondria in their reference study. They showed that risperidone inhibited NADH-coenzyme Q reductase in freeze-thawed mitochondria, which is a direct measure of complex I enzyme activity. However, the inhibition of NADH-coenzyme Q reductase activity by the atypical antipsychotic risperidone was 2-4 fold less than that for the typical neuroleptics. Olanzapine had only slight effects on NADH-coenzyme Q reductase activity, even at 200 μM. This finding suggests that compromised bioenergetic function may be involved in the cellular pathology underlying nephrotoxicity. In line with the aforementioned work, we did not determine any histopathological changes in the LOG in the present study. Low-dose olanzapine might have not affected the mitochondrial functions in an amount equal to low-dose risperidone. Clinical reflections of mitochondrial dysfunction associated with antipsychotic use have also been shown previously. For instance, Ahn et al. (32) reported an adolescent girl with a mitochondrial disorder and depression who displayed both new-onset psychotic and increased mood symptoms during treatment with risperidone. Within 48 hours after discontinuation of the medication, she had complete resolution of psychotic symptoms, fatigue, and psychomotor retardation, and her depression improved. This observation of "on-off" risperidone treatment suggests that risperidone may have worsened both the psychiatric and physical manifestations of the mitochondrial disorder in this patient. These findings are also consistent with recent in vitro literature, which implicate a series of neuroleptic medications with mitochondrial dysfunction.

Although there are no reports about significant nephrotoxicity with both olanzapine and risperidone in the current literature, signs and symptoms of nephrotoxicity, such as cells and casts in the urine, oliguria, proteinuria, elevated serum creatinine, and elevated urea in humans, may occur in some individuals, especially patients with renal disease and these agents should be used cautiously with any patient having a history of renal disease. There might be an advantage to choosing minimum therapeutic doses of olanzapine and risperidone with chronic administration to decrease their side effects on the kidney in these special circumstances. Antioxidants or lipid peroxidation inhibitors also might provide nephroprotection in olanzapine- or risperidone-induced nephropathy, particularly in vulnerable patients. Large-scale prospective studies that will examine the association between nephrotoxicity and chronic use of olanzapine and risperidone are also needed in order to confirm the present findings.

CONCLUSION

Although no strong evidence suggests toxicity to the kidney during olanzapine or risperidone treatment, our data show that olanzapine is dose-dependently and risperidone is dose-independently toxic to rat kidney cells. However, we failed to compare our findings to a wide variety of studies, because no experimental study in the literature histopathologically investigated the effects of both olanzapine and risperidone on renal cells in the rats. Due to the fact that the mechanism of action of olanzapine and risperidone has not been fully elucidated and their

exact nephrotoxic mechanism is still being investigated, additional specific experimental studies of rat kidneys exposed to olanzapine and risperidone may provide useful data about possible effects on renal cells.

Limitations

The present administration route (intraperitoneal) is different from the routine clinical route (oral or intramuscular) and makes extrapolation to humans more questionable, particularly in the absence of toxicokinetics/metabolism. In addition, basic biological parameters might have been included, especially to evaluate the kidney functions (e.g. urea, creatinine, and potassium). Finally, macroscopic characteristics of the kidneys (e.g. shape, size, and weight) and general health of the animals (e.g. clinical status, appetite, and body weight) could have been considered.

References:

1. Mailman RB, Murthy V. Third generation antipsychotic drugs: partial agonism or receptor functional selectivity? Curr Pharm Des 2010; 16(5):488-501.
2. Heard KJ, Cleveland NR, Krier S. The effect of olanzapine pretreatment on acute cocaine toxicity in mice. Clin Toxicol (Phila) 2009; 47(6):542-4.
3. Abou El-Magd RM, Park HK, Kawazoe T, Iwana S, Ono K, Chung SP, et al. The effect of risperidone on D-amino acid oxidase activity as a hypothesis for a novel mechanism of action in the treatment of schizophrenia. J Psychopharmacol 2010; 24(7):1055-67.
4. Dwyer DS, Lu XH, Bradley RJ. Cytotoxicity of conventional and atypical antipsychotic drugs in relation to glucose metabolism. Brain Res 2003; 971(1):31-9.
5. Halici Z, Dursun H, Keles ON, Odaci E, Suleyman H, Aydin N, et al. Effect of chronic treatment of haloperidol on the rat liver: a stereological and histopathological study. Naunyn-Schmied Arch Pharmacol 2009; 379(3):253-61.
6. Uyanik A, Unal D, Halici Z, Cetinkaya R, Altunkaynak BZ, Keles ON, et al. Does haloperidol have side effects on histological and stereological structure of the rat kidneys? Ren Fail 2009; 31(7):573-81.
7. Chabroux S, Haffen E, Penfornis A. Diabetes and second-generation (atypical) antipsychotics. Ann Endocrinol (Paris) 2009; 70(4):202-10.
8. Schmidt AJ, Krieg JC, Clement HW, Hemmeter UM, Schulz E, Vedder H, et al. Effects of quetiapine, risperidone, 9-hydroxyrisperidone and ziprasidone on the survival of human neuronal and immune cells in vitro. J Psychopharmacol 2010; 24(3):349-54.
9. Wiklund ED, Catts VS, Catts SV, Ng TF, Whitaker NJ, Brown AJ, et al. Cytotoxic effects of antipsychotic drugs implicate cholesterol homeostasis as a novel chemotherapeutic target. Int J Cancer 2010; 126(1):28-40.
10. Turkez H, Togar B. The genotoxic and oxidative damage potential of olanzapine in vitro. Toxicol Ind Health 2010; 26(9):583-8.
11. Odaci E, Bilen H, Hacimuftuoglu A, Keles ON, Can I, Bilici M. Long-term treatments with low- and high dose olanzapine change hepatocyte numbers in rats. A stereological and histopathological study. Arch Med Res 2009; 40(3):139-45.
12. Halici Z, Keles ON, Unal D, Albayrak M, Suleyman H, Cadirci E, et al. Chronically administered risperidone did not change the number of hepatocytes in rats: a stereological and histopathological study. Basic Clin Pharmacol Toxicol 2008; 102(5):426-32.
13. Weston-Green K, Huang XF, Deng C. Olanzapine treatment and metabolic dysfunction: a dose response study in female Sprague Dawley rats. Behav Brain Res 2011; 217(2):337-46.
14. Lauressergues E, Martin F, Helleboid A, Bouchaert E, Cussac D, Bordet R, et al. Overweight induced by chronic risperidone exposure is correlated with overexpression of the SREBP-1c and FAS genes in mouse liver. Naunyn Schmiedebergs Arch Pharmacol 2011; 383(4):423-36.
15. Cohen R, Wilkins KM, Ostroff R, Tampi RR. Olanzapine and acute urinary retention in two geriatric patients. Am J Geriatr Pharmacother 2007; 5(3):241-6.
16. Lostia AM, Mazzarini L, Pacchiarotti I, Lionetto L, De Rossi P, Sanna L, et al. Serum levels of risperidone and its metabolite, 9-hydroxyrisperidone: correlation between drug concentration and clinical response. Ther Drug Monit 2009; 31(4):475-81.
17. Schwenger E, Dumontet J, Ensom MH. Does olanzapine warrant clinical pharmacokinetic monitoring in schizophrenia? Clin Pharmacokinet 2011; 50(7):415-28.
18. Seto K, Dumontet J, Ensom MH. Risperidone in schizophrenia: is there a role for therapeutic drug monitoring? Ther Drug Monit 2011; 33(3):275-83.
19. Stauffer VL, Sniadecki JL, Piezer KW, Gatz J, Kollack-Walker S, Hoffmann VP, et al. Impact of race on efficacy and safety during treatment with olanzapine in schizophrenia, schizophreniform or schizoaffective disorder. BMC Psychiatry 2010; 10:89.
20. Di Matteo V, Cacchio M, Di Giulio C, Di Giovanni G, Esposito E. Biochemical evidence that the atypical antipsychotic drugs clozapine and risperidone block 5-HT(2C) receptors in vivo. Pharmacol Biochem Behav 2002; 71(4):607-13.
21. Mitchell M, Riesenberg R, Bari MA, Marquez E, Kurtz D, Falk D, et al. A double-blind, randomized trial to evaluate the pharmacokinetics and tolerability of 30 or 40 mg/d oral olanzapine relative to 20 mg/d oral olanzapine in stable psychiatric subjects. Clin Ther 2006; 28(6):881-92.
22. Chang WH, Jaw SS, Tsay L. Chronic haloperidol treatment with low doses may enhance the increase of homovanillic acid in rat brain. Eur J Pharmacol 1989; 162(1):151-6.

23. Altunkaynak ME, Ozbek E, Altunkaynak BZ, Can I, Unal D, Unal B. The effects of high-fat diet on the renal structure and morphometric parametric of kidneys in rats. J Anat 2008; 212(6):845-52.

24. Muller AP, Tort AH, Gnoatto J, Moreira JD, Vinadé ER, Perry ML, et al. Metabolic and behavioral effects of chronic olanzapine treatment and cafeteria diet in rats. Behav Pharmacol 2010; 21(7):668-75.

25. Bogdan M, Popescu F, Bogdan FL. Contributions to the study of morphofunctional interrelations in the liver of the rats treated with certain antipsychotic drugs. Rom J Morphol Embryol 2011; 52(1):465-9.

26. Boyda HN, Tse L, Procyshyn RM, Wong D, Wu TK, Pang CC, et al. A parametric study of the acute effects of antipsychotic drugs on glucose sensitivity in an animal model. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34(6):945-54.

27. Halici Z, Ozabacigil F, Aydin N, Gulaboglu M, Gul M, Suleyman H. The effects of risperidone, olanzapine and haloperidol on enzyme activities in erythrocytes and plasma of rats. Eur Neuropsychopharmacol 2006; 16(4):247-8.

28. Heiser P, Sommer O, Schmidt AJ, Clement HW, Hoinkes A, Hopt UT, et al. Effects of antipsychotics and vitamin C on the formation of reactive oxygen species. J Psychopharmacol 2010; 24(10):1499-504.

29. Shertzer HG, Kendig EL, Nasrallah HA, Johansson E, Genter MB. Protection from olanzapine-induced metabolic toxicity in mice by acetaminophen and tetrahydroindenoindole. Int J Obes (Lond) 2010; 34(6):970-9.

30. Pillai A, Parikh V, Terry AV Jr, Mahadik SP. Long-term antipsychotic treatments and crossover studies in rats: differential effects of typical and atypical agents on the expression of antioxidant enzymes and membrane lipid peroxidation in rat brain. J Psychiatr Res 2007; 41(5):372-86.

31. Modica-Napolitano JS, Lagace CJ, Brennan WA, Aprille JR. Differential effects of typical and atypical neuroleptics on mitochondrial function in vitro. Arch Pharm Res 2003; 26(11):951-9.

32. Ahn MS, Sims KB, Frazier JA. Risperidone-induced psychosis and depression in a child with a mitochondrial disorder. J Child Adolesc Psychopharmacol 2005; 15(3):520-5.