J Nephropharmacol. 2024; 13(1): e10633.

https://jnephropharmacology.com DOI: 10.34172/npj.2023.10633

Journal of Nephropharmacology

Investigation of the effects of oral dapoxetine on kidney function and histopathologic changes in male rats; an animal study and future perspectives

Alireza Akhavan Rezayat[1], Amirabbas Asadpour[2], Samaneh Boroumand-Noughabi[3], Mona Kabiri[4,5], Elham Ghafarian Baghaei Moghadam[6], Alireza Nough Javazm[2*]

[1]Department of Urology, School of Medicine, Kidney Transplantation Complications Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Department of Urology, School of Medicine, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Department of Hematology and Blood Bank, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Nanotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Science, Mashhad, Iran
[5]Clinical Research Development Unit, Ghaem Hospital, Mashhad University of Medical Science, Mashhad, Iran
[6]Department of Gynecology and Obstructive, School of Medicine, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Article Type:
Original

Article History:
Received: 3 July 2023
Accepted: 10 October 2023
ePublished: 27 October 2023

Keywords:
Dapoxetine
Renal function
Histopathologic change
Animal study

ABSTRACT

Introduction: Dapoxetine is a novel therapeutic agent employed in treating specific diseases. However, its potential impact on renal excretion processes has yet to be thoroughly investigated, necessitating further exploration in this study.
Objectives: This research aimed to assess the effects of dapoxetine on renal function and explore any potential disturbances in kidney excretion processes.
Materials and Methods: In this study, 32 male Albino rats weighing between 200-250 g were utilized. The rats were randomly divided into four groups. Group one served as the control and received a normal diet, while groups two to four were administered dapoxetine through gavage at doses of 1 mg/kg, 2 mg/kg, and 4 mg/kg, respectively. The study evaluated blood urea nitrogen (BUN), and serum creatinine levels and examined renal pathological changes in the rats.
Results: The results demonstrated a significant increase in average BUN levels in group four compared to other groups ($P<0.001$). For creatinine, group three displayed higher levels compared to other groups. However, the difference was not statistically significant ($P>0.05$). Importantly, no indications of apoptosis, necrosis, edema, hydropic degeneration, or glomerular changes were observed in any of the renal cells from the rat groups.
Conclusion: Dapoxetine administration led to changes in BUN and creatinine levels; however, it did not adversely affect the renal cells' pathological outcomes. These results suggest that dapoxetine could be considered for use in the future treatment of certain diseases, considering its minimal impact on renal function. Further investigations and clinical trials are warranted to corroborate these findings and inform medical decision-making.

Implication for health policy/practice/research/medical education:
Dapoxetine demonstrated no adverse effects on renal cells, indicating its potential safety for use in the treatment of certain diseases. However, it is important to consider the dose-dependent increase in blood urea nitrogen (BUN) with increasing dapoxetine dosage. Nevertheless, the absence of pathological changes in renal cells suggests that dapoxetine may offer a viable option for future treatments with minimal kidney-related side effects.

Please cite this paper as: Akhavan Rezayat A, Amirabbas Asadpour A, Boroumand-Noughabi S, Kabiri M, Ghafarian Baghaei Moghadam E, Nough Javazm A. Investigation of the effects of oral dapoxetine on kidney function and histopathologic changes in male rats; an animal study and future perspectives. J Nephropharmacol. 2024;13(1):e10633. DOI: 10.34172/npj.2023.10633.

Introduction

Recently, dapoxetine, a family of selective serotonin reuptake inhibitors (SSRIs), has been conducted to treat many diseases, including premature ejaculation (1). The administration of this medication comes with challenges, since there is not enough evidence regarding its mechanism and side effects (1,2). On the other hand, in some cases, it is necessary to be used for the treatment of patients for a

***Corresponding author**: Alireza Nough Javazm, Email: me.end100@gmail.com, NoughjA981@mums.ac.ir

long period. Like other medications, dapoxetine may have a series of effects on body cells and tissues in the short and long-term periods (3,4).

According to recent evidence, dapoxetine does not affect creatinine clearance. However, in other studies, exacerbation of clinical symptoms has been reported in patients with severe kidney impairment who use dapoxetine. On the other hand, considering that it is metabolized in renal and hepatic cells, this medication may impact renal function (5,6).

Objectives

This research aimed to assess the effects of dapoxetine on renal function and explore any potential disturbances in kidney excretion processes.

Materials and Methods

Animal design procedure

In this study, 32 male albino rats with a weight between 200-250 g were evaluated. The rats were obtained from the animal center related to Mashhad University of medical sciences. The rats were randomly divided into four groups. The administration of each group was as follows. The first group was the control group; they were only fed a normal diet.

Groups two to four were gavaged with dapoxetine in doses of 1 mg/kg, 2 mg/kg, and 4 mg/kg, respectively. The duration of the intervention for all four groups was 70 days and dapoxetine was administered to rats through gavage. After the end of the experimental period, the rats entered the deep anesthesia phase using ketamine (87 mg/kg) and xylazine (13 mg/kg) for sampling. The blood sample was drawn from the heart to prepare serum for the test. Additionally, under sterile conditions both kidneys were removed from the body for histopathological examination and they were sent to the laboratory in a tube containing 10% formalin.

Evaluation of BUN and creatinine

The samples obtained from the heart blood were collected in microtubes. After centrifugation at 2000 rpm for 2 minutes, serum was extracted and used to measure the level of blood urea nitrogen (BUN) and creatinine. These two factors were measured by clinical assay in the laboratory.

Hematoxylin and eosin stain

After preparing renal tissue, they were fixed using 10% formalin. After dehydrating, they were embedded in paraffin. Through microtome, 4-µm transversal sections were prepared from paraffin blocks. Finally, the samples were deparaffinized using xylenes. The samples were stained with hematoxylin and eosin (H&E) and examined with a light microscope.

Statistical analysis

Data analysis was conducted using SPSS version 22 software. The results were reported as mean ± SD. One-way ANOVA and chi-square tests and also Tukey test were conducted to evaluate the differences between the groups. Besides $P<0.05$ was considered a significant level.

Results

Evaluation of BUN and serum creatinine in groups

Table 1 shows that the average BUN in group four was significantly higher ($P<0.001$) compared to other groups. On the other hand, the average BUN in group two and group four was higher than in group one, however there was no significant relationship ($P>0.05$). Additionally, the results indicated that the average serum creatinine in group three was higher compared to other groups, but the difference was not significant ($P>0.05$).

Evaluation of congestion in the studied groups

According to the results, rats in groups one and three exhibited moderate levels of congestion, whereas in groups two and four, 75% showed moderate levels, 12.5% showed mild to moderate levels, and another 12.5% showed mild levels ($P = 0.487$) (Table 2).

Evaluating the effects of dapoxetine on renal cells

Based on the results, there was no evidence of apoptosis,

Table 1. Evaluation of BUN and serum creatinine level in the studied groups

Variable	Group	Mean± SD	*P* value[a]	*P* value[b]
Bun (mg/dL)	Group (1)	44.87±1.24	-	<0.001
	Group (2)	45.75±4.43	0.916	
	Group (3)	42.37±0.74	0.273	
	Group (4)	49.12±2.74	0.020	
Creatinine (mg/dL)	Group (1)	0.80±0.06	-	0.053
	Group (2)	0.80±0.05	0.999	
	Group (3)	0.87±0.05	0.086	
	Group (4)	0.80±0.03	1.000	

[a] Tukey post hoc test: comparison of the mean in the control group with other groups.
[b] One-way ANOVA: comparison of the means in all groups.

Table 2. Assessment of congestion in the groups under study

Variables		Group (1)	Group (2)	Group (3)	Group (4)	*P* value
Congestion	Mild	0 (0%)	1 (12.5%)	0 (0%)	1 (12.5%)	0.487
	Mild to moderate	0 (0%)	1 (12.5%)	0 (0%)	1 (12.5%)	
	Moderate	8 (100%)	6 (75%)	8 (100%)	6 (75%)	

necrosis, edema, hydropic degeneration, or glomerular changes in any of the renal cells from the groups of rats (Figure 1).

Evaluating the presence of hyaline cast in the renal cells

The results showed that no hyaline casts were observed in group one, while hyaline casts were observed in the two mice (25%) belonging to groups two and four. In contrast to the previous groups, only one mouse (12.5%) in group three showed hyaline casts. However, statistically no significant correlation was found between them (P = 0.715).

Evaluation of lymphocyte infiltration into renal cells

Based on the results, it was determined that no lymphocyte infiltration was observed in the control group. In group two lymphocyte infiltration was observed in the pelvis of one rat and the medulla of another rat. In groups three and four lymphocyte infiltration was observed in the pelvis area in 2 and 1 rats, respectively. However, no significant correlation was found between them (P=0.511).

Discussion

Dapoxetine has recently been used as a new drug to treat some diseases (7). It has been demonstrated that the metabolism of dapoxetine occurs through the P450 and CYP2D6 series of cytochromes present in the kidneys and liver (8). The results have shown that cytochromes are the main enzymes involved in the metabolism of dapoxetine. It is primarily eliminated by urine. Based on this evidence, prescribing dapoxetine for patients with renal dysfunction is prohibited (5,9).

In the present study, the effect of dapoxetine on BUN and serum creatinine was different. According to the results, as the dose of dapoxetine increased the average BUN also increased. It was also found that the mean serum creatinine level was higher in group three compared to other groups.

Previous studies have shown that the use of SSRIs in patients can increase the risk of dialysis. Considering that renal cells are one of the main sites for the metabolism of SSRIs, it can be expected that their administration in patients may lead to side effects including renal dysfunction (10). So far, limited studies have been conducted on the effects of dapoxetine on renal function and there is little information in this area. Based on the results of the present study, the use of dapoxetine may affect renal function. Accordingly, increasing the dose of

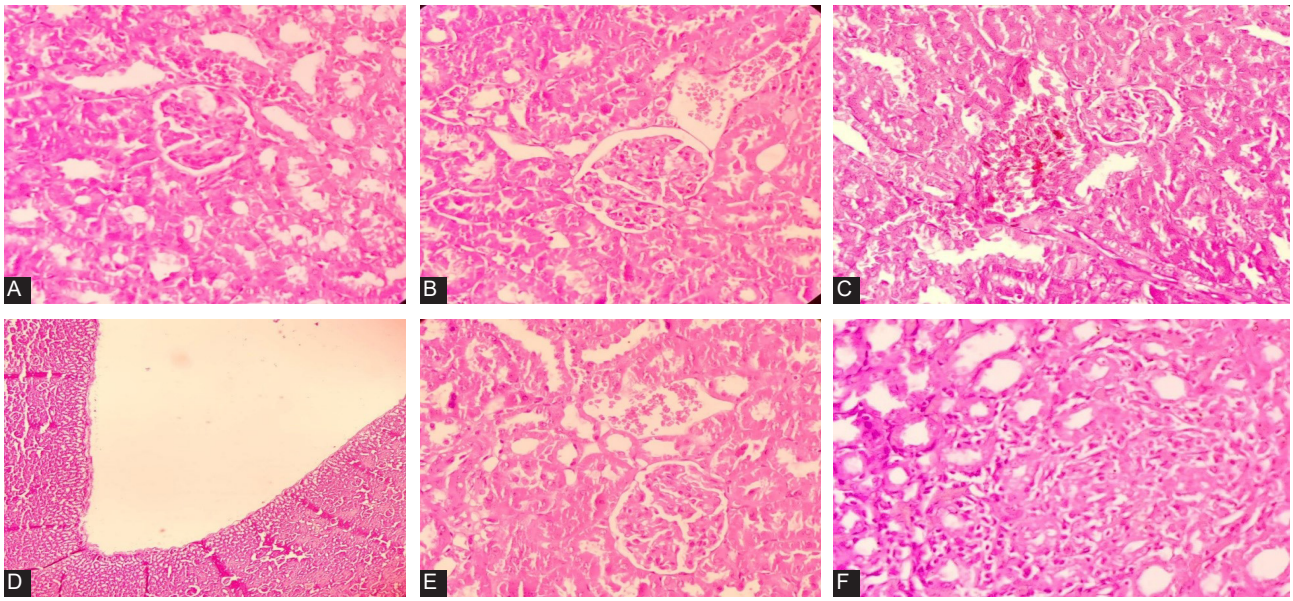

Figure 1. High power view of kidney tissue of 1 mg (A), 2 mg (B), and 4 mg (C) treated rats as well as control rats (D), which shows similar findings including normal appearing glomerulus and tubules and moderate congestion. (E), Low power view of the kidney of 1 mg treated rat which shows a simple kidney cyst. (F), High power view of the kidney of 2 mg treated rat which shows a focus on lymphoid infiltration in the cortex (H&E ×100).

the drug can potentially disrupt renal function.

In this study, pathologic evaluations of kidney cells were conducted for the first time. The results showed that no pathological processes involving apoptosis, edema, necrosis, and glomerular changes were observed in the renal cells. Additionally, the results of this study demonstrated that very small numbers of hyaline casts were observed in rats of each group; however, no significant correlation was observed (P>0.05).

The presence of hyaline casts is a non-specific finding in patients. In other words, their presence may be related to different reasons. However, it has been demonstrated that severe disturbance of renal function, including glomerulonephritis can increase the number of hyaline casts in the urine of patients. This study showed that the number of hyaline casts in the pathology results was very low, which was almost within the normal range (11,12).

Moreover, it was found that lymphocyte infiltration was more common in group three compared to other groups; however, no significant correlation was observed among them (P>0.05). The evidence suggests that drugs related to the SSRIs family have been recognized as immune system regulators. These drugs suppress the activation of immune cells, especially T cells, and prevent the production of inflammatory mediators. It seems that the administration of dapoxetine may impact regulating the immune cells and preventing lymphocyte infiltration into renal cells (13,14).

Conclusion

In general, dapoxetine can affect BUN and creatinine levels; depending on the dosage, it may increase them. However, it does not affect pathological processes such as apoptosis, necrosis, edema, and glomerular changes in the renal cells.

Limitations of the study

This study was not conducted on human samples. In addition, it would have been better to investigate different doses of the drug and compare it with other drugs of the SSRI family.

Authors' contribution

Conceptualization: Alireza Akhavan Rezayat.
Formal analysis: Mona Kabiri.
Investigation: Samaneh Boroumand-Noughabi.
Methodology: Alireza Nough Javazm.
Project administration: Alireza Akhavan Rezayat, Amirabbas Asadpour.
Writing–original draft: Alireza Nough Javazm, Elham Ghafarian Baghaei Moghadam.
Writing-review and editing: Alireza Akhavan Rezayat.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was conducted in accordance with animal study guidelines and was approved by the Ethics Committee of Mashhad University of Medical (Ethical code# IR.MUMS.REC.1400.517). The animal experiments were conducted according to the guidelines approved by the United States National Institutes of Health (NIH, 1978). Additionally, this study was conducted as a residency thesis at the university's urology department.

Funding/Support

This study was supported by Mashhad University of Medical Sciences.

References

1. McMahon C, Kim SW, Park NC, Chang CP, Rivas D, Tesfaye F, et al. Dapoxetine 3003 Study Investigators. Treatment of premature ejaculation in the Asia-Pacific region: results from a phase III double-blind, parallel-group study of dapoxetine. J Sex Med. 2010;7:256-68. doi: 10.1111/j.1743-6109.2009.01560.x.
2. Andersson KE, Mulhall JP, Wyllie MG. Pharmacokinetic and pharmacodynamic features of dapoxetine, a novel drug for 'on-demand' treatment of premature ejaculation. BJU Int. 2006;97:311-5. doi: 10.1111/j.1464-410X.2006.05911.x.
3. Hellstrom WJ. Emerging treatments for premature ejaculation: focus on dapoxetine. Neuropsychiatr Dis Treat. 2009;5:37-46. doi: 10.2147/ndt.s3251.
4. Wang YB, Mao Y, Wei Q, Wu TX, Dong Q. [Dapoxetine in treatment of premature ejaculation: a systematic review]. Beijing Da Xue Xue Bao Yi Xue Ban. 2010;42:425-32. [Chinese].
5. Simsek A, Kirecci SL, Kucuktopcu O, Ozgor F, Akbulut MF, Sarilar O, et al. Comparison of paroxetine and dapoxetine, a novel selective serotonin reuptake inhibitor in the treatment of premature ejaculation. Asian J Androl. 2014;16:725-7. doi: 10.4103/1008-682X.128467.
6. Hoy SM, Scott LJ. Dapoxetine: in premature ejaculation. Drugs. 2010 Jul 30;70:1433-43. doi: 10.2165/11204750-000000000-00000.
7. Raveendran AV, Agarwal A. Premature ejaculation - current concepts in the management: A narrative review. Int J Reprod Biomed. 2021;19:5-22. doi: 10.18502/ijrm.v19i1.8176.
8. Thyssen A, Sharma O, Tianmei S, Aquilina JW, Vandebosch A, Wang SS, et al. Pharmacokinetics of dapoxetine hydrochloride in healthy Chinese, Japanese, and Caucasian men. J Clin Pharmacol. 2010;50:1450-60. doi: 10.1177/0091270009359183.
9. McCarty E, Dinsmore W. Dapoxetine: an evidence-based review of its effectiveness in treatment of premature ejaculation. Core Evid. 2012;7:1-14. doi: 10.2147/CE.S13841.
10. Tully PJ, Cardinal T, Bennetts JS, Baker RA. Selective serotonin reuptake inhibitors, venlafaxine and duloxetine are associated with in hospital morbidity but not bleeding or late mortality after coronary artery bypass graft surgery. Heart Lung Circ. 2012;21:206-14. doi: 10.1016/j.hlc.2011.12.002.
11. Dvanajscak Z, Cossey LN, Larsen CP. A practical approach to the pathology of renal intratubular casts. Semin Diagn Pathol. 2020;37:127-134. doi: 10.1053/j.semdp.2020.02.001.
12. Uribe-Uribe NO, Herrera GA. Ultrastructure of tubular casts. Ultrastruct Pathol. 2006;30:159-66. doi:

10.1080/01913120600689749.
13. Taler M, Gil-Ad I, Lomnitski L, Korov I, Baharav E, Bar M, et al. Immunomodulatory effect of selective serotonin reuptake inhibitors (SSRIs) on human T lymphocyte function and gene expression. Eur Neuropsychopharmacol. 2007;17:774-80. doi: 10.1016/j.euroneuro.2007.03.010.
14. Gobin V, Van Steendam K, Denys D, Deforce D. Selective serotonin reuptake inhibitors as a novel class of immunosuppressants. Int Immunopharmacol. 2014;20:148-56. doi: 10.1016/j.intimp.2014.02.030.