Pharmacogn J. 2022; 14(5): 548-552
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Pathophysiological Electrolyte Changes Connoted via Antagonism of Serotonin Receptor in Experimental Animals

Mohammed D Mahmood*, Mohammed A. Younes, Mohammed Saarti

ABSTRACT

Background: Atypical antipsychotics are a subclass of antipsychotics that have emerged primarily since the 1970s for the treatment of psychiatric disorders. They are sometimes referred to as second-generation antipsychotics (SGAs). Several atypical antipsychotics have received regulatory approval for the treatment of disorders such as bipolar disorder, schizophrenia, irritability in autism, and as adjunctive treatment for major depressive disorders. **Objectives:** The purpose of the following study was to evaluate the effect of two widely known atypical antipsychotics, aripiprazole, and risperidone, on pathophysiological fluctuations in electrolytes. Several other studies were based on the following ideas, which brought a variety of different perspectives. As can be seen in the following evaluation, although atypical antipsychotics reduce the chance of extrapyramidal symptoms, it leads to impairment of renal function and destruction of renal histo-morphology. **Materials and Methods:** Thirty rats (10 per group) were used for this study, control group received normal saline, aripiprazole group received 10mg/kg//day, and risperidone group received 20mg/kg//day. The duration of therapy was long up to 3 months. **Results:** the results confirmed that both drugs reduced plasma sodium and chloride concentration with no effects on plasma potassium and calcium concentration. Moreover, the histomorphology at microscopic level shown no defects after 3 months of therapy. **Conclusion:** the outcome confirmed no deleterious defects associated with aripiprazole and risperidone when used for 3 months.

Key words: Aripiprazole, Risperidone, Electrolyte, Sodium, Potassium, Calcium, Chloride.

Mohammed D Mahmood*, Mohammed A. Younes, Mohammed Saarti

Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, IRAQ.

Correspondence

Mohammed D Mahmood

Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, IRAQ.

E-mail: mohameddaowd@uomosul.edu.iq

History

- Submission Date: 19-08-2022;
- Review completed: 26-09-2022;
- Accepted Date: 06-10-2022.

DOI : 10.5530/pj.2022.14.134

Article Available online

http://www.phcogj.com/v14/i5

INTRODUCTION

Between 1954 and 1975, the first antipsychotic drugs (e.g., chlorpromazine) were successfully marketed, which led to extensive development and testing of further antipsychotic drugs.[1] However, the remarkable success of this new class of drugs was soon followed by reports of adverse events, including unanticipated medical events that could occur at any dose and were temporarily related to, but not necessarily causally related to, the use of the drug product, particularly severe extrapyramidal symptoms in subjects, including opioids, seizures, involuntary movements, muscle spasms, and delayed side effects such as Parkinson's disease or delayed onset of abnormal excretion.[2-4] There have also been cases of fatal neuroleptic malignant syndrome characterized by joint and muscle stiffness, fever, and elevated plasma creatine kinase activity. The most common adverse reactions and side effects are unintended consequences of the pharmacological properties of the drug occurring at normal doses and include sedation, cardiovascular effects (including hypotension) and sexual dysfunction (e.g., ejaculatory dysfunction, erectile dysfunction, and others).[5] Anticholinergic side effects (e.g., constipation, urinary retention, dry mouth, blurred vision, and cognitive impairment), seizures, severe blood problems, weight gain and hyperprolactinemia.[4] Namely. Hypotension, prolonged ventricular repolarization, arrhythmias, and sudden cardiac death. High dropout rates, poor treatment compliance and high relapse rates are caused by most reported adverse events.[6]

Atypical antipsychotics are a subclass of antipsychotics that arose primarily after the 1970s to treat psychiatric problems. They are sometimes referred to as second-generation antipsychotics (SGAs) and 5-hydroxytryptamine-dopamine antagonists.[7] Although the latter term is usually reserved for typical antipsychotics, general antipsychotics are also referred to as primary sedatives and neuroleptics. A number of atypical antipsychotics have received regulatory approval for the treatment of disorders such as bipolar disorder, schizophrenia, irritability in autism, and as adjunctive treatment for major depressive disorder.[8,9]

Both generations of drugs have a tendency to inhibit the brain's dopamine system receptors. Compared with haloperidol, the most commonly used typical antipsychotic, atypical drugs are less likely to cause patients to develop extrapyramidal motor control deficits such as erratic movements, rigidity, and involuntary tremor similar to Parkinson's disease.[10] However, only a few atypical drugs have been shown to be superior to less popular and less potent first-generation antipsychotics in this regard. Recognizing that each medication has its own unique efficacy and side effects, some studies have questioned the usefulness of classifying antipsychotics as "atypical/second-generation" rather than "first-generation" because more people use these medications.[11] It is argued that from a more nuanced perspective, it is preferable to match the requirements of unique patients with the characteristics of unique medications. Neuroleptic malignant syndrome, delayed dyskinesia (a severe movement disorder), increased risk of stroke, sudden cardiac death, blood clots, and diabetes are just some of the serious side effects of atypical antipsychotics, although they are generally considered safer than typical

Cite this article: Mahmood MD, Younes MA, Saarti M. Pathophysiological Electrolyte Changes Connoted via Antagonism of Serotonin Receptor in Experimental Animals. Pharmacogn J. 2022;14(5): 548-552.

antipsychotics.[12] There may be significant weight gain. Critics say the distinction between first- and second-generation antipsychotics is unnecessary and should be abandoned.[13]

The aim of the following study is to evaluate the impact of two widely known atypical antipsychotics, Aripiprazole and Risperidone on the pathophysiological fluctuations of the electrolytes.

METHODOLOGY AND MATERIAL

Chemicals

Aripiprazole is used to treat psychiatric disorders such as schizophrenia, major depressive disorder, and bipolar I disorder, either alone or in combination with other medications. The chemical formula of Aripiprazole is C23H27Cl2N3O2 with molar formula of 448.4 g/mol.[14]

Risperidone is a known as an atypical antipsychotic drug used to treat schizophrenia that works in the brain. It is also known as second-generation antipsychotic (SGA). Risperidone restores the balance of 5-hydroxytryptamine and dopamine to improve cognition, behavior, and depressive disorders.[15] The chemical formula of Risperidone is found to be C23H27FN4O2 known molar mass 410.5 g/mol.

Animal

Thirty healthy and disease free male Sprague Dawley albino rats were used as the sample animal for this research. Each rate reportedly weighted between 200g to 300g.

Study design

This study was based on the randomized controlled trial. The total of thirty rats were recruited for the experiment who were kept in the artificial, and optimal environment. The temperature of the environment was maintained in the range of 5°F to 75°F which is approximately 18°C to 28°C. The observed humidity of the area was 30% to almost 70%. The rats were provided with food in defined time and there was free access to water.

The rats were divided into three groups, each group had equal number of rats which was 10 rats each. The first group was the control group which received the placebo, in the second group, there were 10 rats too, which was known as the Risperidone group. Each rat received 20mg/kg/day through I/V. The third group known as the Aripiprazole group which received the drug from intravenous route, 10mg/kg//day.

Biochemical investigation

To evaluate the impact of both drugs including Risperidone and Aripiprazole on the electrolytes, Na, K, Ca and Cl, (kit supplied by Giesse diagnostic) were used. The levels of Na, K, Ca and Cl, were recorded individually for each group.

Statistical Analysis: The mean value for all the findings were recorded with the standard deviation. Furthermore, to evaluate the statistical difference between the theoretical values and obtained experimental values, two-sided t test has been used. To establish the difference and the comparison between the before and after, Paired t-test was used.

RESULTS

The results of the following study have evaluated the level of electrolytes in each group and recorded the data separately. On the evaluation of Sodium, the results indicated that in the control group the mean level of sodium before was 154.2 with the standard deviation 3.70, with after the study period the mean value was 144 with standard deviation 3.6. On Aripiprazole group, the mean level of sodium before the intervention was 154.38 with the standard deviation 2.4, and after the intervention the level increased to mean 141.2 and standard deviation 1.64. On the evaluation of Risperidone, the mean value of Sodium before the intervention was 142.6 with standard deviation 4.03, while after the induction of drug the value increased to mean 140.2 and Standard deviation 3.2 (Figure 1A).

On the evaluation of the level of potassium in the blood, the finding of this study represented that, the mean Potassium was 6.47 in the control group before, and after the study it was 6.555 with SD 0.38. The results from the Aripiprazole found that the mean finding before were 6 .4 and SD.04 while after the intervention the mean was 6.8, and SD 0.82. Lastly, On the risperidone group the initial findings were mean equal to 6.47 and SD 0.26, while after the intervention the mean was 76.48 and SD 0.12 (Figure 1B).

On the evaluation of Chlorides, the results indicated that in the control group the mean level of sodium before was 105.9 with the standard deviation 2.8, with after the study period the mean value was 106.5 with standard deviation 4.3. On Aripiprazole group, the mean level of sodium before the intervention was 104.8 with the standard deviation 2.16, and after the intervention the level increased to mean 0.411 and standard deviation 0.04. On the evaluation of Risperidone, the mean value of Chlorides before the intervention was 104.67 with standard deviation 3.9, while after the induction of drug the value increased to mean 100.8 and Standard deviation 0.61 (Figure 1C).

Lastly, on the evaluation of Calcium, the finding indicated that in the controlled group there was mean 0.42 in the controlled group with SD 0.04, and afterwards the value remained almost the same which was 0.43 and SD 0.06. The results from the Aripiprazole found that the mean finding before were 0.433 and SD.0.04 while after the intervention the mean was 0.41, and SD 0.04. Lastly, On the risperidone group the initial findings were mean equal to 0.444 and SD 0.01, while after the intervention the mean was 0.04 and SD 0.03 (Figure 1D).

The renal histological findings in the controlled group showed normal architecture of renal tissue characterized by glomeruli, proximal renal tubules, and distal renal tubules. In Aripiprazole the findings represented atrophy of glomeruli, dilatation of Bowman's space, cell swelling of epithelial cells lining renal tubules and mild necrosis of others and congestion of blood vessels. Lastly, the results of the Risperidone group indicated atrophy of glomeruli, dilatation of Bowman's space and renal cyst (Figure 2).

DISCUSSION

The following study highlights the impact of atypical antipsychotic, Aripiprazole and Risperidone on the levels of electrolytes including Na, Cl, Ca, and K, and further evaluated the effects of the renal tissue. The impact of these atypical antipsychotics has been widely discussed in the existing literature.

On a similar study which evaluated the impact of Aripiprazole on the renal functions, it was found that blood urea nitrogen and creatinine were decreased by aripiprazole.[16] Serum MDA, IL-1 and TNF- levels were significantly reduced in the aripiprazole group. Aripiprazole treatment also reduced the extent of renal necrosis. In the existing study it has been shown that the apparent renal failure was noted as a potential side effect of anorexia nervosa; nevertheless, renal failure and pyelonephritis were identified as the primary disorders and therefore considered independent of psychopathological symptoms.[12,17] The symptoms reported in our case were comparable to those previously described, and Raynaud's disease was found to be associated with AN early in three clinical cases. patients with AN exhibited higher skin sensitivity, however the exact cause of the association between AN and Raynaud's syndrome is still unknown. Further, the apparent side effects of Aripiprazole represented that an unusual antipsychotic drug is called Abilify (aripiprazole).[18] Some of the most common adverse effects of Abilify include headache, nausea, and vomiting.

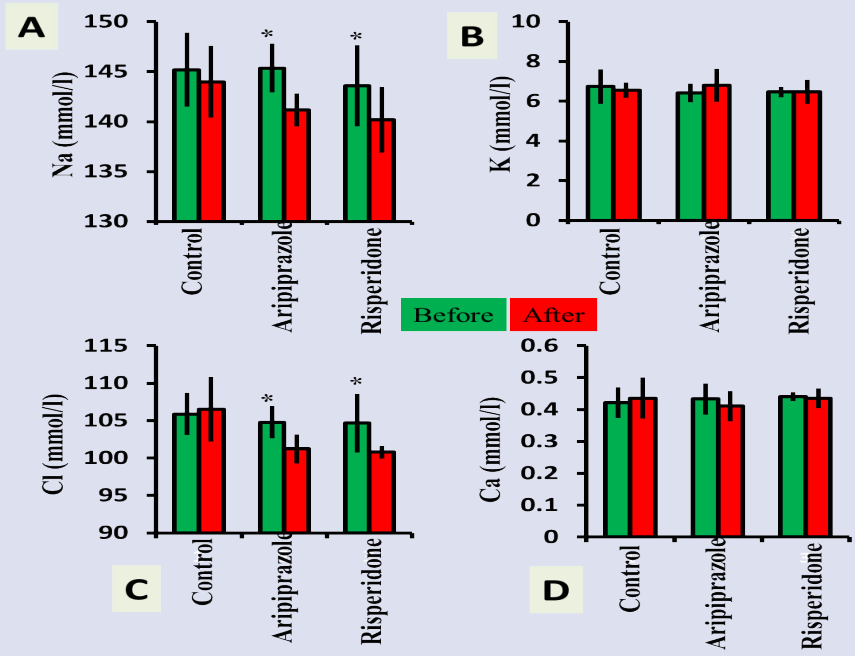


Figure 1: Electrolyte changes in experimental rat models after treatment with Aripiprazole, Risperidone compared to control group. Data expressed as mean±SD, *p<0.05. *as compared to after therapy groups. Na=Sodium, k=Potassium, Cl=Chloride, Ca=Calcium.

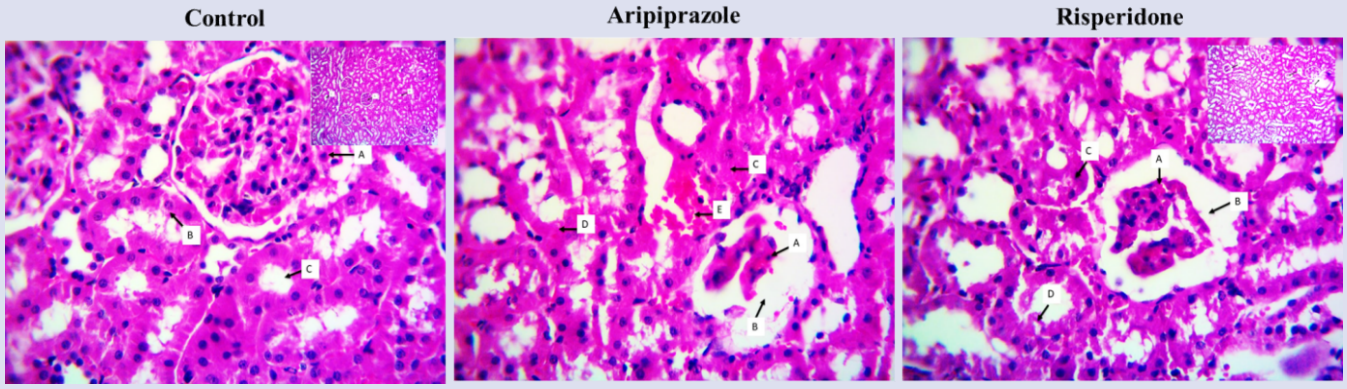


Figure 2: Renal histology following 3 months' exposure to aripiprazole and risperidone compared to control group.

Further it has been studies that, Acute kidney injury is one of the side effects linked to atypical antipsychotics, specifically quetiapine, risperidone, and olanzapine (AKI). These effects include rhabdomyolysis, neuroleptic malignant syndrome, acute urine retention, and hypotension.[19] Similarly, another study indicated that Risperidone may be less effectively eliminated in patients with impaired renal function than in healthy individuals. When patients with moderate to severe renal disease received oral risperidone, the total clearance of risperidone and its active metabolites was 60% lower than in younger, healthy participants.[20] The kidneys are responsible for the clearance of RIS and its main active metabolite, 9-hydroxypiperidone. Maternal drug and metabolite clearance has been shown to be 60% lower in individuals with moderate to severe renal impairment than in healthy individuals.[21,22] Various kidney injury has been linked to electrolyte disturbances, for instance, in a study conducted by Alnori *et al.*, 2021 on patients with acute kidney injury, has shown electrolyte disturbances and various metabolic derangements.[23] Alternatively, patients undergoing diagnosis on contrast x-ray for cardiac angiography has shown slight degree of renal changes with subsequent electrolyte disturbances necessitating sodium chloride replacement which provides improved diseases profile due to optimum hydration.[24,25] furthermore, daily used drinks, such as, beverages,[26] tea,[27,28] and coffee[27,28] perhaps could be a modulator for plasma electrolyte levels. Moreover, drug induced renal damage could be the most deleterious impact for electrolyte disturbances.[29]

Several other research studies have been based on the following idea, which brings about multiple different perspectives. From the following evaluation, it can be stated that although the atypical antipsychotics reduces the chances of extrapyramidal symptoms, however It results in the impairment of renal function and destruction in the morphology of the renal tissues.

CONCLUSION

The aim of the following study is to evaluate the impact of two widely known atypical antipsychotics, Aripiprazole and Risperidone on the

pathophysiological fluctuations of the electrolytes. This study was based on the randomized controlled trial. Thirty healthy and disease-free male Sprague Dawley albino rats were used as the sample animal for this research. Each rate reportedly weighted between 200g to 300g. To evaluate the impact of both drugs including Risperidone and Aripiprazole on the electrolytes, Na, K, Ca and Cl, (kit supplied by Giesse diagnostic) were used. Several other research studies have been based on the following idea, which brings about multiple different perspectives. From the following evaluation, it can be stated that although the atypical antipsychotics reduces the chances of extrapyramidal symptoms, however It results in the impairment of renal function and destruction in the morphology of the renal tissues.

ACKNOWLEDGEMENTS

We would like to express our appreciation and gratitude to the College of Veterinary Medicine and College of Pharmacy at University of Mosul for their cooperation with this study.

ADHERENCE TO ETHICAL STANDARDS

The study was approved and registered in College of Pharmacy, University of Mosul.

FUNDING

Self-funded.

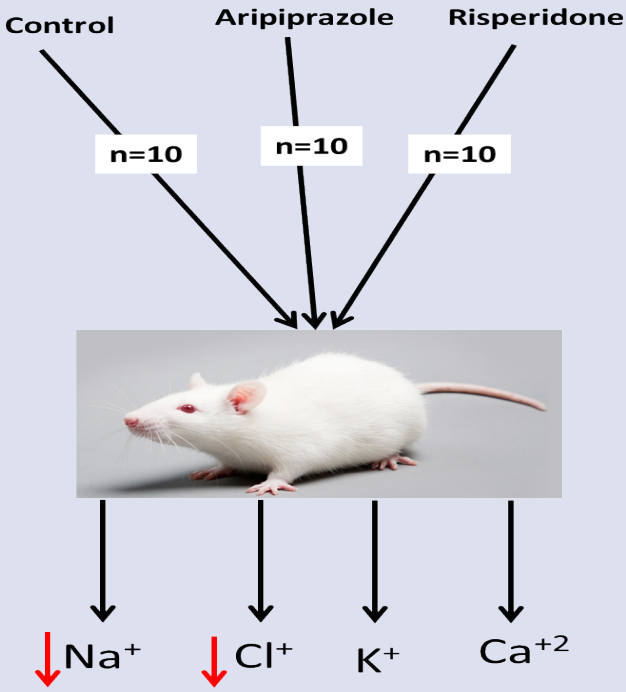
CONFLICTS OF INTEREST

The authors declare no conflicts of interest concerned in the present study.

REFERENCES

1. Ferreira V, Grajales D, Valverde ÁM. Adipose tissue as a target for second-generation (atypical) antipsychotics: A molecular view. Biochim Biophys Acta Mol Cell Biol Lipids. 2020;1865(2):158534.
2. Alvarez-Herrera S, Escamilla R, Medina-Contreras O, Saracco R, Flores Y, Hurtado-Alvarado G, *et al*. Immunoendocrine peripheral effects induced by atypical antipsychotics. Front Endocrinol. 2020;11:195.
3. Dai W, Liu J, Qiu Y, Teng Z, Li S, Huang J, *et al*. Shared postulations between bipolar disorder and polycystic ovary syndrome pathologies. Prog Neuropsychopharmacol Biol Psychiatry. 2021;18:110498.
4. Naidoo V, Martínez-Iglesias O, Cacabelos R. Targeting epigenetics as future treatments of trauma-and stress-or-related disorders. Epidrugs Epinutr. InEpigenetics Stress Dis. 2022;31:317-92.
5. Bigio B, Zelli D, Lau T, de Angelis P, Miller D, Lai J, *et al*. ACNP 57th Annual Meeting: Poster Session I.
6. Muneer A. Mood Disorders: Practical Issues in Diagnosis and Management. Routledge; 2018.
7. Vedal TS, Steen NE, Birkeland KI, Dieset I, Reponen EJ, Laskemoen JF, *et al*. Free thyroxine and thyroid-stimulating hormone in severe mental disorders: A naturalistic study with focus on antipsychotic medication. J Psychiatr Res. 2018;106:74-81.
8. Çöpür M, Çöpür S. Emergence of tic disorder in a pediatric patient associated with risperidone and aripiprazole treatment. Anadolu Psikiyatri Dergisi. 2019;20(6):671.
9. Can SS, Atagün Mİ, Çamur C, Uğurlu GK, İslamoğlu S. Extremely high prolactin level due to risperidone in a chronic renal failure patient. Klinik Psikofarmakoloji Bulteni. 2018;28:128.
10. Mullapudi M, Madan R, Vardhan V, Vidhyavathi M. Aripiprazole-induced Diplopia: A Rare Case Report. J Med Sci. 2019;5(3):73-4.
11. Güneş S, Ekinci Ö, Teke H, Yıldırım V. Risperidone related Raynaud's phenomenon: an adolescent case. Clin Psychopharmacol Neurosci. 2018;16(1):118.
12. Gundogmus I, Unsal C, Akgun A, Bolu A, Celik C, Uzun O. Risperidone-induced pretibial edema: A case report. Ann Med Res. 2020;27(1):429-30.
13. Tost M, Monreal JA, Armario A, Barbero JD, Cobo J, García-Rizo C, *et al*. Targeting hormones for improving cognition in major mood disorders and schizophrenia: thyroid hormones and prolactin. Clinical drug investigation. 2020;40(1):1-4.
14. Koller D, Almenara S, Mejía G, Saiz-Rodríguez M, Zubiaur P, Román M, *et al*. Metabolic effects of aripiprazole and olanzapine multiple-dose treatment in a randomised crossover clinical trial in healthy volunteers: association with pharmacogenetics. Adv Ther. 2021;38(2):1035-54.
15. Mejıa DK, Saiz-Rodrıguez M, Ochoa PZ, Navares-Gómez M, Pintos-Sánchez ES, Abad-Santos F. Metabolic Effects of Aripiprazole and Olanzapine Multiple-Dose Treatment in a Randomised Crossover Clinical Trial in Healthy Volunteers: Association with Pharmacogenetics. Adv Ther. 2021;38(2):1035-54.
16. Mullapudi M, Madan R, Vardhan V, Vidhyavathi M. Aripiprazole-induced Diplopia: A Rare Case Report. J Med Sci. 2019;5(3):73-4.
17. Hori H, Katsuki A, Atake K, Yoshimura R. Effects of continuing oral risperidone vs. switching from risperidone to risperidone long-acting injection on cognitive function in stable schizophrenia patients: a pilot study. Front Psychiatry. 2018;9:74.
18. Thakur A, Niranjan V, Rastogi P, Razdan R. Acute oedema associated with risperidone use: a report. Gen Psychiatr. 2020;33(4):e100203.
19. Akan M. Development of enuresis secondary to risperidone: two case reports. Klinik Psikofarmakoloji Bulteni. 2019;29:241-2.
20. Śmierciak N, Szwajca M, Popiela TJ, Bryll A, Karcz P, Donicz P, *et al*. Redefining the Cut-Off Ranges for TSH Based on the Clinical Picture, Results of Neuroimaging and Laboratory Tests in Unsupervised Cluster Analysis as Individualized Diagnosis of Early Schizophrenia. J Pers Med. 2022;12(2):247.
21. Patel RS, Heer AS, Lesko A, Kim SW, Ishaq M. Risperidone and Levothyroxine for Managing "Myxedema Madness". Cureus. 2020;12(8):e10152.
22. Vedal TS, Steen NE, Birkeland KI, Dieset I, Reponen EJ, Laskemoen JF, *et al*. Free thyroxine and thyroid-stimulating hormone in severe mental disorders: A naturalistic study with focus on antipsychotic medication. J Psychiatr Res. 2018;106:74-81.
23. Alnori MK, Dawood MN, Ajeel MA. The role of symmetrical and asymmetric dimethyl-l-arginine as biomarkers in dialysis-dependent AKI patients. MMSL. 2021;90(4):165-71.
24. Shilbayeh SAR. Prevalence of anemia and its impact on the quality of life of renal transplant recipients: a cross-sectional study. MMSL. 2022;91(1):11-7.
25. Shilbayeh SAR. Efficacy of sodium bicarbonate versus normal saline in the prevention of contrast-induced nephropathy among cardiac patients: a cohort study in Saudi Arabia. MMSL. 2022;91(1):18-28.
26. Al-Dabbagh EHT, Alnori MKJ. Effect of pepsi beverages on urine pH, crystalluria, and urinary calcium excretion. MMSL. 2022;91(3):191-6.
27. Maughan RJ, Griffin J. Caffeine ingestion and fluid balance: a review. J Hum Nutr Diet. 2003;16(6):411-20.
28. Armstrong LE, Casa DJ, Maresh CM, Ganio MS. Caffeine, fluid-electrolyte balance, temperature regulation, and exercise-heat tolerance. Exerc Sport Sci Rev. 2007;35(3):135-40.
29. Merkhan MM, Abdullah E, Althanoon Z. Effect of Esomeprazole on serum creatinine and urea in patients with Peptic Ulcer. Res J Pharm Technol. 2022;15(1):160-4.

GRAPHICAL ABSTRACT



ABOUT AUTHORS

Mohammed D Mahmood is currently a Lecturer of pharmacology at the department of Pharmacology and Toxicology, College of Pharmacy at the University of Mosul, Mosul, Iraq. He has been graduated from College of Pharmacy, University of Mosul and He did his Master and PhD degree in Pharmacology from College of Medicine at the University of Mosul.

Mohammed A. Younes is currently a Lecturer of physiology at the department of Pharmacology and Toxicology, College of Pharmacy at the University of Mosul, Mosul, Iraq. He is the Dean Assistant for Scientific Affairs since 2017-present. He has been graduated from College of Pharmacy, University of Mosul and He did his Master and PhD degree in Medical Physiology from College of Medicine at the University of Mosul.

Mohammed Saarti is currently a Lecturer of pharmacology at the department of Pharmacology and Toxicology, College of Pharmacy at the University of Mosul, Mosul, Iraq. He is the rapeuter of the department of Pharmacology and Toxicology in the College of Pharmacy since 2021-present. He has been graduated from College of Pharmacy, University of Mosul and He did his Master in Pharmacology from College of Medicine at the University of Mosul. He did his PhD degree in Pharmacology from University of Nottingham.

Cite this article: Mahmood MD, Younes MA, Saarti M. Pathophysiological Electrolyte Changes Connoted via Antagonism of Serotonin Receptor in Experimental Animals. Pharmacogn J. 2022;14(5): 548-552.