ISSN: 2980-3063 (online) Original Article

Rats
2024; 2(2): 47-50
Doi: 10.5281/zenodo.14567347
https://ratsjournal.com

Effect of colistin injury on aspartate aminotransferase, alanine aminotransferase and gamma glutamyl transferase activities in ovariectomized rats

Serpil Aygörmez[1]*

[1]Kafkas University, Faculty of Veterinary Medicine, Department of Biochemistry, Kars, Türkiye
*Corresponding: serpilaygormez@hotmail.com

Recevied: 11.11.2024 Accepted: 24.12.2024 Published: 30.12.2024

Abstract
Colistin is an antibiotic with a dose-limiting side effect when used against multidrug-resistant gram-negative pathogens. The aim of this study was to investigate the effect of colistin on aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) activities in ovariectomized rats. Group I was the control group, Group II was ovariectomized only and Group III was ovariectomized and colistin administered. Colistin administration caused damage in ovariectomized rats. AST, ALT and GGT activities were higher ($p<0.001$) in Group III compared to the other groups. The increase in AST, ALT and GGT activities due to 73 mg/kg colistin application is an indicator of damage. For this reason, considering the effects found in the study, administration of colistin at a lower dose and duration can be considered as an alternative medicine option.
Keywords: *Ovariectomy, colistin, aspartate aminotransferases, alanine aminotransferase, gamma glutamyl transferase*

1. Introduction

Five medications (polymyxins A–E) make up the class of polypeptide antibiotics known as polymyxins. However, only polymyxin B and polymyxin E or colistin have therapeutic applications.[1,2] Colistin is a polymyxin E group glycopeptide antibiotic that significantly affects gram-negative bacteria that are resistant to many drugs, including *Klebsiella pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa*.[2-9] Colistin was discovered in 1949. It was introduced for clinical use in the 1969s. However, because of worries about its adverse effects, especially nephrotoxicity, it was replaced by less toxic antibiotics.[1] In 1970, colistin was temporarily discontinued due to side effects.[6,9,10] Colistin interacts with anionic lipopolysaccharides, displacing divalent cations (Ca^{+2} and Mg^{+2}) in the membrane of gram-negative bacteria. Colistin is mostly found in the extracellular area and has a large molecular weight, making it difficult to pass through cell membranes.[8] It is currently used as a last resort to treat life-threatening infections caused by gram-negative bacteria such as *Klesbsiella pneumonia* and *Escherichia coli*.[9] The precise mechanism of toxicity caused by colistin is unknown, however it appears to be connected to the overall dosage and/or length of time that colistin is administered.[7,8] It is possible that it may cause toxicity in humans and animals and affect its optimal therapeutic efficacy in the clinic.[3] Changes in estrogen, progesterone and some hormone levels occur in rats. Therefore, ovariectomy operation was performed in female rats to evaluate the effect of colistin more accurately and to minimize the effects of sex hormones.

The aim of this study was to investigate the effect of colistin on serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) activities in ovariectomized rats.

2. Material and Methods

2.1. Chemicals

Colistin (Colimycin® 150 mg/vial colistin base activity, Koçak Farma, Türkiye) was used in the experimental procedures.

2.2. Experimental procedures

In this investigation, eighteen Wistar Albino female rats weighing between 220 and 240 grams were employed. The animals were from the Experimental Animals Research and Application Center at Kafkas University. Animals were kept in cages in a controlled room with a constant temperature of 24-25ºC and a 12-hour dark-light cycle. They were provided with unlimited access to water and standard food. No experimental procedures were performed for one week for adaptation. At the end of one-week, experimental procedures were started. Before starting the experiment, rats were weighed and selected so that there was no statistical difference between the groups and groups were formed (n=6).

Group I (Control): Only saline will be administered intramuscularly for 7 days without ovariectomy.

Group II (Ovariectomy): Ovariectomy will be performed, and saline will be administered intramuscularly for 7 days.

Group III (Ovariectomy+Colistin): Intramuscular admi-

How to cite this article: Aygörmez S. Effect of colistin injury on aspartate aminotransferase, alanine aminotransferase and gamma glutamyl transferase activities in ovariectomized rats. *Rats*, 2024; 2(2): 47–50. Doi: 10.5281/zenodo.14567347

This work is licensed under a Creative Commons Attribution 4.0 International License

nistration of colistin 73 mg/kg twice daily at 8 hours intervals (1.0 and 2.0 mg/kg on day 1; 2.50 and 2.50 mg/kg on day 2; 3.5 and 5.5 mg/kg on day 3; 8.0 mg/kg twice daily on days 4, 5 and 6; single dose of 8.0 mg/kg on day 7).[8]

In the study, a total of 12 animals in two groups underwent ovariectomy. The study was started 10 days after the end of antibiotic administration.[11]

Experimental procedures were performed at Kafkas University Experimental Animal Research and Application Center. Laboratory analyses were performed at Kafkas University, Faculty of Veterinary Medicine, Biochemistry Laboratory (Kars/Türkiye).

2.3. Serum preparation

The day (day 8) following the final dose of colistin, the rats were anesthetized (ketamine/xylazine ((35-50/5-10mg/kg) (Ketalar-Pfizer/Alfazyne 2%-Ege-Vet, Türkiye)) and their lives were terminated by cervical dislocation method in accordance with ethical rules. Afterwards, blood samples were taken from all the animals in the tubes. The blood sample was centrifuged at 3000 rpm for 10 min and serum was separated and stored at -20ºC until analysis.

2.4. AST, ALT and GGT analysis

Serum AST, ALT and GGT activities were measured using a colorimetric kit (Erba, Türkiye) according to the manufacturer's instructions.

2.5. Statistical analysis

The data was statistically evaluated using the SPSS software package, version 26.0 (SPSS, Chicago, IL). The groups were compared using Tukey's post-hoc test after a one-way ANOVA analysis. A p-value of less than p<0.001 was deemed statistically significant. The results are shown as mean ± standard deviation.

3. Results

3.1. Results of the effect of colistin on serum AST activity

In this study, serum AST results are given in Figure 1. In this context, when group III was compared with group I and group II, a statistically significant increase was found in group III (p<0.001).

3.2. Results of the effect of colistin on serum ALT activity

In the current study, serum ALT results are given in Figure 2. According to the findings, when group III was compared with the other groups, a significant increase was determined in group III (p<0.001).

3.3. Results of the effect of colistin on serum GGT activity

In this study, serum GGT results are given in Figure 3. According to Figure 3, the colistin group showed a statistically significant increase compared to the control and ovariectomy groups (p<0.001).

4. Discussion

The emergence of multidrug-resistant gram-negative bacteria has renewed interest in the use of colistin due to its toxicity consequences.[10] In the present study, we measured serum AST, ALT and GGT activities to monitor colistin toxicity in ovariectomized rats.

The liver is the largest organ in the organism, accounting for about 2-3% of the average body weight.[12] The symptoms of liver disease are often vague. They can also be confused with symptoms of other diseases. This makes diagnosis difficult. The identification and monitoring of these disorders requires the use of biomarkers.[13] The most important liver enzymes are aminotransferases (AST, ALT and GGT).[14-18] The transfer of a-amino groups to the a-keto group of a-ketoglutaric acid is catalyzed by liver aminotransferases (AST and ALT). In the processes of gluconeogenesis and amino acid metabolism, this catalyzes the transfer of amino groups to create products.[19,20] AST and ALT are found in high concentrations in the liver. However, they can also be found in other tissues.[19,21] GGT is found primarily in the liver. It can also be found in biliary epithelial cells, kidney, intestine, prostate and pancreas.[22,23] Depending on the pattern of elevation, these tests can help narrow down the differential diagnosis and pinpoint a part of the liver where damage may be occurring.[17] AST and ALT are important in the early identification and diagnosis of liver disorders.[15,16] They play a vital role in determining the severity and prognosis of the disease. Their elevation is one of the most critical indicators of acute hepatocellular cell damage in the clinic.[16] AST, ALT and GGT are usually elevated in liver injury or liver disease, usually due to their release from hepatic cells where they are stored in the bloodstream.[17] AST and ALT are released into

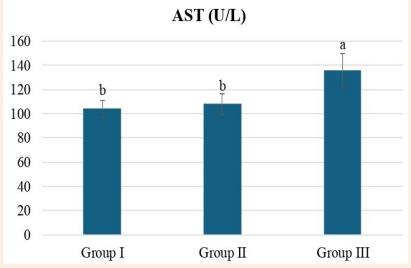

Figure 1: Effect of colistin on aspartate aminotransferase (AST) activity in ovariectomized rats. Each column with vertical lines represents different letters indicating statistical difference between groups (p<0.001).

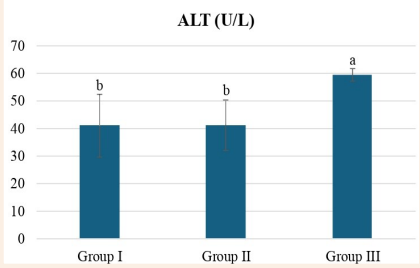

Figure 2: Effect of colistin on alanine aminotransferase (ALT) activity in ovariectomized rats. Each column with vertical lines represents different letters indicating statistical difference between groups (p<0.001).

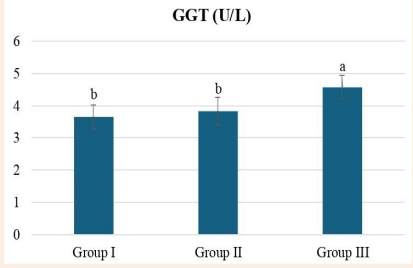

Figure 3: Effect of colistin on gamma glutamyl transferase (GGT) activity in ovariectomized rats. Each column with vertical lines represents different letters indicating statistical difference between groups (p<0.001).

the circulation as a result of liver cell damage caused by alcohol, medications, xenobiotics, and metabolites.[12] Hepatocytes, which are liver cells, are involved in the synthesis of various amino acids with the help of AST and ALT. Although elevated GGT levels are not specific for liver disease, they are considered one of the best indicators of liver-related mortality.[23] Damage to liver cells causes liver enzymes (AST, ALT and GGT) to leak into the circulation. This leads to elevations in serum enzymes routinely used in liver function tests.[24] In a study, a significant increase in GGT activity in urine sample was observed in the third treated group (450,000 IU/kg/day) in different dose administration of colistin, while no increase was observed in AST and ALT activities.[4] In a study conducted with levofloxacin, it was reported that AST, ALT and GGT activities increased in the levofloxacin treated group compared to the control group.[25] In another study, AST, ALT and GGT activities were found to be higher in the gentamicin-treated group compared to the control group.[26] In the present study, AST, ALT and GGT activities were higher in the colistin group compared to the other groups. This suggests that it may be an indicator of liver damage.

5. Conclusion

From the results of the above study, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) activities were found to be significant in the colistin-administered group compared to the other groups ($p<0.001$). It can be concluded that intramuscular administration of colistin should be avoided. However, if its use is to be continued, dose calculation should be made to avoid toxicity. Colistin 73 mg/kg intramuscularly causes serious damage. Therefore, it is recommended to use colistin below 73 mg/kg body weight.

Ethical approval

Ethical approval for the study was obtained from Kafkas University (KAÜ-HADYEK) Animal Experiments Local Ethics Committee with the approval numbered KAÜ-HADYEK/2024-193.

Authors contribution

SA: Research, planning, article review, writing- original draft and review.

Conflict of interest

According to the authors, there are no conflicts of interest associated with this research publication.

Data availability

Data will be provided upon request.

Acknowledgments

I would like to thank Assoc. Prof. Dr. Mushap KURU for performing ovariectomy operation in this study.

Funding statement

N/A

References

1. Mirjalili M, Mirzaei E, Vazin A. Pharmacological agents for the prevention of colistin-induced nephrotoxicity. *Eur J Med Res*. 2022;27(1):64. doi: 10.1186/s40001-022-00689-w

2. Soroudi S, Mousavi G, Jafari F, Elyasi S. Prevention of colistin-induced neurotoxicity: a narrative review of preclinical data. *Naunyn Schmiedebergs Arch Pharmacol.* 2024;397(6):3709-3727. doi: 10.1007/s00210-023-02884-w

3. Dai C, Li J, Li J. New insight in colistin induced neurotoxicity with the mitochondrial dysfunction in mice central nervous tissues. *Exp Toxicol Pathol.* 2013;65(6):941-8. doi: 10.1016/j.etp.2013.01.008

4. Ghlissi Z, Hakim A, Mnif H, Ayadi FM, Zeghal K, Rebai T, et al. Evaluation of colistin nephrotoxicity administered at different doses in the rat model. *Ren Fail.* 3013;35(8):1130-1135. doi: 10.3109/0886022X.2013.815091

5. Jeong ES, Kim G, Moon KS, Kim YB, Oh JH, Kim HS, et al. Characterization of urinary metabolites as biomarkers of colistin-induced nephrotoxicity in rats by a liquid chromatography/mass spectrometry-based metabolomics approach. *Toxicol Lett.* 2016;248:52-60. doi: 10.1016/j.toxlet.2016.02.018

6. Hanedan B, Ozkaraca M, Kirbas A, Kandemir FM, Aktas MS, Kilic K, et al. Investigation of the effects of hesperidin and chrysin on renal injury induced by colistin in rats. *Biomed Pharmacother.* 2018;108:1607-1616. doi: 10.1016/j.biopha.2018.10.001

7. Lee TW, Bae E, Kim JH, Jang HN, Cho HS, Chang SH, et al. The aqueous extract of aged black garlic ameliorates colistin-induced acute kidney injury in rats. *Ren Fail.* 2019;41(1):24-33. doi: 10.1080/0886022X.2018.1561375

8. Aksu EH, Kandemir FM, Küçükler S. The effects of hesperidin on colistin-induced reproductive damage, autophagy, and apoptosis by reducing oxidative stress. *Andrologia.* 2021;53(2):e13900. doi: 10.1111/and.13900

9. Eronmosele JE, Olurishe TO, Olorukooba AB. Investigation of treatment-time differences in colistin-induced nephrotoxicity in Wistar rats. *Chronobiol Int.* 2021;38(2):224-233. doi: 10.1080/07420528.2020.1838535

10. Edrees NE, Galal AAA, Monaem ARA, Beheiry RR, Metwally MMM. Curcumin alleviates colistin-induced nephrotoxicity and neurotoxicity in rats via attenuation of oxidative stress, inflammation and apoptosis. *Chem Biol Interact.* 2018;294:56-64. doi: 10.1016/j.cbi.2018.08.012

11. Makav M, Eroğlu HA. Recuperative effect of estrogen on rotenone-induced experimental model of Parkinson's disease in rats. *Environ Sci Pollut Res Int.* 2021;28(17):21266-21275. doi: 10.1007/s11356-020-11985-5

12. Pingili RB, Pawar AK, Challa SR, Kodali T, Koppula S, Toleti VA. Comprehensive review on hepatoprotective and nephroprotective activities of chrysin against various drugs and toxic agents. *Chem Biol Interact.* 2019;308:51-60. doi: 10.1016/j.cbi.2019.05.010

13. Thakur S, Kumar V, Das R, Sharma V, Mehta DK. Biomarkers of Hepatic Toxicity: An Overview. *Curr Ther*

Res Clin Exp. 2024;100:100737. doi: 10.1016/j.curtheres.2024.100737

14. Liu X, Hamnvik OPR, Chamberland JP, Petrou M, Gong H, Christophi CA, et al. Circulating alanine transaminase (ALT) and γ-glutamyl transferase (GGT), but not fetuin-A, are associated with metabolic risk factors, at baseline and at two-year follow-up: the prospective Cyprus metabolism study. *Metabolism.* 2014;63(6):773-782. doi: 10.1016/j.metabol.2014.03.008

15. Luan Y, Zhao J, Han H, Shen J, Tang S, Cheng L. Toxicologic effect and transcriptome analysis for short-term orally dosed enrofloxacin combined with two veterinary antimicrobials on rat liver. *Ecotoxicol Environ Saf.* 2021;220:112398. doi: 10.1016/j.ecoenv.2021.112398

16. Karapehlivan M, Başer ÖF, Dolanbay T, Alwaazer D. Effects of hydrogen-enriched water on lipid profile and some biochemical markers. *Rats.* 2023;1(2):47-50. doi: 10.5281/zenodo.10444706

17. Adeneye AA, Babatope FE, Adesii-Adelekan AE, Olorundare OE, Okoye II. Tadalafil pretreatment attenuates doxorubicin-induced hepatorenal toxicity by modulating oxidative stress and inflammation in Wistar rats. *Toxicol Rep.* 2024;13:101737. doi: 10.1016/j.toxrep.2024.101737

18. Bahari H, Rafiei H, Goudarzi K, Omidian K, Asbaghi O, Kolbadi KSH, et al. The effects of pomegranate consumption on liver function enzymes in adults: A systematic review and meta-analysis. *Complement Ther Med.* 2024;80:103008. doi: 10.1016/j.ctim.2023.103008

19. Center SA. Interpretation of liver enzymes. *Vet Clin North Am Small Anim Pract.* 2007;37(2):297-333. doi: 10.1016/j.cvsm.2006.11.009

20. Kunutsor SK, Apekey TA, Seddoh D, Walley J. Liver enzymes and risk of all-cause mortality in general populations: a systematic review and meta-analysis. *Int J Epidemiol.* 2014;43(1):187-201. doi: 10.1093/ije/dyt192

21. Rosenberg J, Sola O, Visconti A. Approach to elevated liver enzymes. *Prim Care.* 2023;50(3):363-376. doi: 10.1016/j.pop.2023.03.007

22. Beek JHDA, Moor MHM, Geus EJC, Lubke GH, Vink JM, Willemsen G, et al. The genetic architecture of liver enzyme levels: GGT, ALT and AST. *Behav Genet.* 43(4):329-39. 2013. doi: 10.1007/s10519-013-9593-y

23. Shawon SI, Reyda RN, Qais N. Medicinal herbs and their metabolites with biological potential to protect and combat liver toxicity and its disorders: A review. *Heliyon.* 2024;10(3):e25340. doi: 10.1016/j.heliyon.2024.e25340

24. Boye A, Asiamah EA, Martey O, Avertey F. Citrus limon (L.) osbeck fruit peel extract attenuates carbon tetrachloride-induced hepatocarcinogenesis in Sprague-Dawley rats. *Biomed Res Int.* 2024;6673550. doi: 10.1155/2024/6673550

25. Farid AS, Hegazy AM. Ameliorative effects of Moringa oleifera leaf extract on levofloxacin-induced hepatic toxicity in rats. *Drug Chem Toxicol.* 2020;43(6):616-622. doi: 10.1080/01480545.2019.1574811

26. Ali FEM, Hassanein EHM, Bakr AG, El-Shoura EAM, El-Gamal DA, Mahmoud AR, et al. Ursodeoxycholic acid abrogates gentamicin-induced hepatotoxicity in rats: Role of NF-κB-p65/TNF-α, Bax/Bcl-xl/Caspase-3, and eNOS/iNOS pathways. *Life Sci.* 2020;254:117760. doi: 10.1016/j.lfs.2020.117760