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The impact of Cephalexin on Pharmacokinetic of Rosuvastatin In Induced Hyperlipidemia In Rabbits

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ABSTRACT

Hyperlipidemia is characterized by an abnormal blood lipid level. the most prevalent kind of dyslipidemia, hyperlipidemia (hl), it is marked by increasing levels of TG, LDL-C, and peripheral blood total cholesterol (TC), along with a decrease in HDL levels The aim of the study was to determination how Cephalexin affected on the normal microbiota that could affect Rosuvastatin pharmacokinetics in rabbits with induced hyperlipidemia. Ten rabbits were divided into two groups ware given a diet containing 1.3% cholesterol and 3% saturated fat for 40 days. and the experiment was divided into groups: G1 hyperlipidemia rabbits treated with Rosuvastatin orally 0.86 mg/kg for 7 days. G2 hyperlipidemia rabbits treated with Cephalexin (orally) after two hours are given Rosuvastatin orally 0.86 mg/kg for 7 days. using a 3 ml plastic syringe, 1 ml of blood was drawn from each animal in each group's femoral vein, heart, jugular vein, and marginal ear vein. At 0.10, 0.30, 1, 2, 4, 6, 8, and 24 hours after treatment, the samples were taken. The amount of Rosuvastatin in the plasma was ascertained using HPLC (high-performance liquid chromatography).The results showed that co-administration of Rosuvastatin, Half-Life (T1/2): G1 has the longest half-life, while G2 have shorter half-lives. Cmax (maximum concentration): G1 shows the highest Cmax, with G2 having the lowest. Tmax (time to reach maximum concentration): G2 has the longest Tmax, indicating a delayed peak concentration compared to G1. Vd (volume of distribution): G1 has the highest Vd, suggesting a wider distribution the drug in the body. CL (clearance): G2 shows the highest clearance rate, indicating faster elimination drug. area under the curve, or AUC 0-inf: G1 has the largest AUC, indicating increased drug exposure with time. There is a significant difference between the means with different letters in the same row ($P<0.05$), indicating statistical differences in the pharmacokinetic parameters among the groups. In conclusion, findings provide insights into the pharmacokinetic behavior of Rosuvastatin in hyperlipidemic rabbits and suggest potential interactions when combined with antibiotics.

Keywords: *Hyperlipidemia, Rosuvastatin, pharmacokinetic and Cephalexin*

1. INTRODUCTION

hyperlipidemia is characterized by an abnormal blood lipid level. The most prevalent kind of dyslipidemia, hyperlipidemia (HL), It is marked by increasing levels of TG, LDL-C, and peripheral blood total cholesterol (TC) and a decrease in HDL levels. In reality, HL is linked to a wide range of metabolic illnesses, including type 2diabetes, hypertension, fatty liver, and atherosclerosis (Rauf et al, 2022). A high blood cholesterol level raises the risk of cardiovascular diseases (CVD) (Rozha *et al*, 2021). In the past several years, diseases linked to elevated blood cholesterol, plasma triglycerides, atherosclerosis, and ischemic heart disease have received a lot of attention. The best course of treatment for hyperlipidemia is diet along with other natural routines (Taher *et al*, 2015 ; Kafi., 2014). Hewage and Yaodeclared that certain endothelial dysfunctions are brought on by sustained, extended HL, This is the main risk factor for atherosclerosis-related cardiovascular issues (Yao et al, 2020).

The main causes of HL include consuming more than 40% of calories from fat, more than 10% from saturated fats, more than 300 mg of cholesterol per day, or medical disorders that can be treated. A diet with a high fat percent, along with other unhealthy lifestyle choices like drinking excessive amounts of alcohol, being overweight, not exercising, andsmoking contributes to abnormal cholesterol levels. Pregnancy, diabetes, polycystic ovarian syndrome, renal illness, and an underactive thyroid gland are other contributing factors . Higher levels of estrogen and other female hormones have been found to raise or alter cholesterol levels . Age and gender have a major influence on the development and spread of HL, according to earlier research (Onwe et al, 2015). Through the action of lipoprotein lipase and by changing the expression of genes linked to lipids and cholesterol (Jadaan and Khudair., 2023).

Rosuvastatin differ from other statin drug by its single external administration dose peak plasma Level is reached to five hours. This is longer too much than other HMG-CoA reducing drugs that achieve final plasma levels in time less than three hour. (Mak et al., 2016). Rosuvastatin considered relatively one of the potent inhibitors drugs that reduce HMG-CoA

reductase and has very high level of selectivity effect inside liver cells in comparative with another of non-liver cells, such as skeletal muscle cells (McTaggart, 2003). In addition for that, Rosuvastatin had relatively limited metabolism by the CYP 450 3A system of liver, which gave an additive advantage by reducing the risk of undesired interactions with other many types of different drugs (Chauvin et al., 2013) Mechanism of action Rosuvastatin stop the function of HMG-CoA reductase enzyme by direct competition. This enzyme that responsible for changing the HMG_CoA to mevalonic acid during the first cholesterol synthetic process (Pehlivanovic et al., 2021). Thus, HMG that regulated the synthesis of cholesterol (Bera et al., 2020). In addition, rosuvastatin had the capacity to decrease HMG CoA causing fall in sterol synthesis inside hepatic cell. In response to this drop in cholesterol levels, the hepatic cells increased the number of LDL (low density lipoprotein) receptors in their plasma membranes. This improved the hepatic cells' ability to reabsorb LDL from the circulation, which in turn led to a greater breakdown of LDL and a drop in lipids in the body's circulating blood. (Stone et al., 2014).

Even with the use of contemporary science, such as genetic engineering, the antibiotics are not new classes have been discovered in the past 30 years. The creation of novel products derived from the recognized classes of antibiotics has been the primary focus of pharmaceutical corporations (Ibrahim et al., 2016). A Gram-negative, non-spore-forming rod, obligate anaerobic and fastidious bacterium called D. nodosus (Sulaiman et al., 2024). beta-lactam antibiotics like cephalexin, which are part of the first-generation cephalosporin family, are distinguished by their beta-lactam rings. Peptidoglycan gives the cell wall of a bacterium its mechanical stability. In order to prevent the manufacture of peptidoglycan, Cephalexin and other beta-lactam antibiotics employ their beta-lactam ring, which is necessary for the bacterial cell wall to form. Cephalexin's beta-lactam ring binds to penicillin-binding proteins (PBPs) to effectively suppress the transpeptidation process, the final stage of peptidoglycan synthesis. This mechanism is necessary for the bacterial peptidoglycan to cross-link. This pathway is blocked by cephalexin, which reduces cell viability and ultimately results in bacterial cell autolysis (Herman and Hashmi, 2023). antibiotic with a wide range of activity that combats both Gram-positive and Gram-negative bacteria (Kbyeh and Abedsalih., 2023).) Antibiotics in animal feedhave also been demonstrated to influencegut microbiome, emphasizing the demand for effective antimicrobials to minimize damagingmicroorganisms and promote animal healthand wellbeing (Dakheel, et al., 2024). Different groups of antibacterial are used to treat infections with determinant criteria to select the suitable antibiotic for a specific bacterial infection depending on its pharmacokinetics-pharmacodynamics properties, potential adverse effects, toxicity, infection severity, and antibiotic spectrum (Al-Jumaili, et al., 2024).

When atorvastatin was administered to antibiotic-induced abiotic mice, the expression of genes that decrease cholesterol did not change. It has been shown that statins alter the gut microbial composition, which can control the statins' ability to decrease cholesterol (Zimmermannet al., 2020). Simvastatin had a comparable impact and was linked to genes controlling the production of bile acids (He et al., 2017). Furthermore, lovastatin's active β-hydroxy acid form can be produced and degraded by the gut flora (Beltrán et al., 2019). Additionally, individuals with greater gut biodiversity are more likely to respond favorably to statins, exhibiting decrease levels of LDL cholesterol and total cholesterol. Reduced Lactobacillus and Bifidobacterium and a substantial rise in Bacteroides, Holdemanella, and Clostridium indicate a poor response to statin treatment and greater side effects (Wilmanski et al., 2022). The systemic quantities of intact medicines, their metabolites, or both may change as a result of antibiotic therapy's potential to affect xenobiotic metabolisms more widely and powerfully than previously thought and to reduce gut microbiota-mediated transformation of oral drugs (Kim, 2015).

2. MATERIALS AND METHODS

Animals

There were ten (10) mature rabbits (weighing 1.5–2 kg and aged 10–12 months) in all used in this study. Animals at every step of the experiment were housed in plastic cages in a conditioned space (22–25 °C) at the College of Veterinary Medicine-University of Baghdad's animal house. The lighting was controlled by an automatic electrical timer that provided twelve hours of light per day (7–19.00) and a twelve-hour night cycle. Give at least two weeks to adjust before beginning the trial. Throughout the trial, the animals had unrestricted access to water and a typical, cholesterol-containing pellet meal (unless otherwise noted).

Ethics

At the College of Veterinary Medicine (Number P.G/340) of the University of Baghdad, the local committee for animal care and uses received ethical permission.

Induction of hyperlipidemia

fifteen rabbits were divided into two groups will fed a diet containing 1.3% cholesterol and 3% saturated fat for 40 day (Shediwah *et al*., 2019 ; El Nabetiti *et al*., 2023) (each group five rabbits).

Experimental Design

determination the effect of Cephalexin and Amoxicillin on pharmacokinetic of rosuvastatin on hyperlipidemia in Rabbits , the sampling time periods ware at 0.10, 0.30, 1, 2, 4, 8, 24 hours of treatment treatment (after the first day of giving rosuvastatin , blood samples will be collected before giving rosuvastatin and after that it is given, blood samples ware

collected after ten minutes, and so on for 7 days.) .

1-Group one : hyperlipidemia rabbits treated with Rosuvastatin for 7 days.

2-Group two: hyperlipidemia rabbits treated with Cephalexin (orally) after two hours are given Rosuvastatin for 7 days.

3. Group three:hyperlipidemia rabbits treated with Amoxicillin (orally) after two hours are given Rosuvastatin for 7 days.

Blood sampling and timing

Each animal in each group will have a 1 ml blood sample drawn using a 3 ml plastic syringe. The sampling time periods will be at 0.10, 0.30, 1, 2, 4, 8, 24 hours of treatment (After the first day of giving Rosuvastatin , The plasma will be collected in a 1 ml Eppendorf tube after the blood samples are taken in anticoagulant EDTA test tubes and centrifuged for 10 minutes at 3000 rpm. Until the analysis could be completed, the tubes were stored in a freezer at -20 degrees Celsius and marked with the time and date of blood collection. For HPLC analysis, the plasma samples were diluted to determine the rosuvastatin concentrations and expressed as µg/ml (Firas and Huda., 2024; Al-Doseri and Khudair., 2016).

3. CHROMATOGRAPHIC CONDITIONS

A-HPLC instruments and conditions

SYKAM HPLC model (Germany) It was employed for rosuvastatin analysis and detection. The fluorescence detector was set to 366 nm for excitation and 410 nm for emission, the column was C18-ODS (25 cm * 4.6 mm), and the mobile phase was acetonitrile-water 60:40 (v/v) at a flow rate of 1.0 mL/min.

B-Plasma sample preparation

100 µL of blood sample was combined with 125 mL of a 9-Anthryldiazomethane (ADAM) solution with a concentration of 100 mg/mL. Acetonitrile was used to increase the volume by 1 mL, and the mixture was left to stand at room temperature for an hour in the dark. The HPLC system was then filled with 100 µL of the reaction mixture(Caglar and Toker , 2022).

D- Method Validation

The Ministry of Food and Drug Safety's published regulations serve as the foundation for the validation criteria. To assess the specificity of the approach, spectral scans of peaks were performed using the PDA detector (2998, Waters). Each calibration curve's linearity, range, accuracy, precision, LOD, and LOQ were assessed in further detail (Jang *et al*., 201 ; Firas and Huda., 2024).

Calibration of standards alnd quality control of samples

For technique validation, internal standard 50µg/ml working solutions, calibration curve standards, and quality control samples were made by spiking them in plasma. The following quantities of pure Rosuvastatin were obtained by diluting a stock solution of the drug with methanol at a concentration of 1 µg/mL, 2 µg/mL, 3 µg/mL, 4 µg/mL, and 5 µg/mL. Until they were utilized, all standard solutions were stored in a refrigerator at or below 8°C.

Linearity

Stock solutions of standard compounds in Rosuvastatin were prepared at a concentration of 3 µg/mL in DMSO, and the stock solution was diluted to the required concentration using 10% (v/v) DMSO in methanol. The concentration ranges of the standard compounds were set appropriately to include the Rosuvastatin to be analyzed through preliminary experiments. The method was found to be linear in the 1–5 µg/mL range for all standard compounds. Each concentration was analyzed in triplicate, and the analytical curve was created from the peak area corresponding to each standard compound at five different concentrations.

Accuracy, Precision, and Recovery

Accuracy was evaluated as the percent recovery (%) at three concentrations (10 ppm) of spiked standard solutions and blanks (dilution solvent), while precision is displayed as the relative standard deviation (RSD) of intra-day repeatability (analysis was performed on the same day (n = 3) with the same instrument) and inter-day reproducibility (three different days (n = 3 × 3) using the same instrument) According to (Jang et al., 2019).

Limits of Detection and Quantification

LODs and LOQs were calculated for the analyte Rosuvastatin based on the slope of the calibration curve and the standard deviation of the response. The standard curves were constructed in the range of 0.61 to 20.00 µg mL−1, and the LOD was found to be 3.3 × σ/s (where σ is the standard deviation of the response and s is the slope of the standard curve). The LOQ was found to be 10 × σ/s.

Histological examination:

Rabbits were anesthetized and sacrificed using ketamine and xylazine for the histopathological study. The heart and aorta

were immediately preserved in a 10% neutral formalin buffer solution until the histological section was ready, and multiple tissue sections were prepared in accordance with (Mescher, 2010).

Statistical analysis Data

SAS was used for statistical analysis of the data (Statistical Analysis System, version 9.1). The experiment was designed using one-way analysis of variance (ANOVA). To evaluate significant differences between means, the Least Significant Differences (LSD) post hoc test was employed. $P < 0.05$ is regarded as statistically significant.

4. RESULTS

Induction of hyperlipidemia

The current study's findings showed that when the negative control group was given a diet with 3% saturated fat and 1.3% cholesterol for 40 days, there were substantial improvements in the positive hyperlipidemia group. The Aorta of the induction group shows marked deposition of cholesterol in the sub-intimal area, which leads to elevation of calcified lipid material in the sub intimal region (Figures 1), and the liver show bridging inflammation and fibrosis between central and portal area is seen in the positive control group (Figures 2).

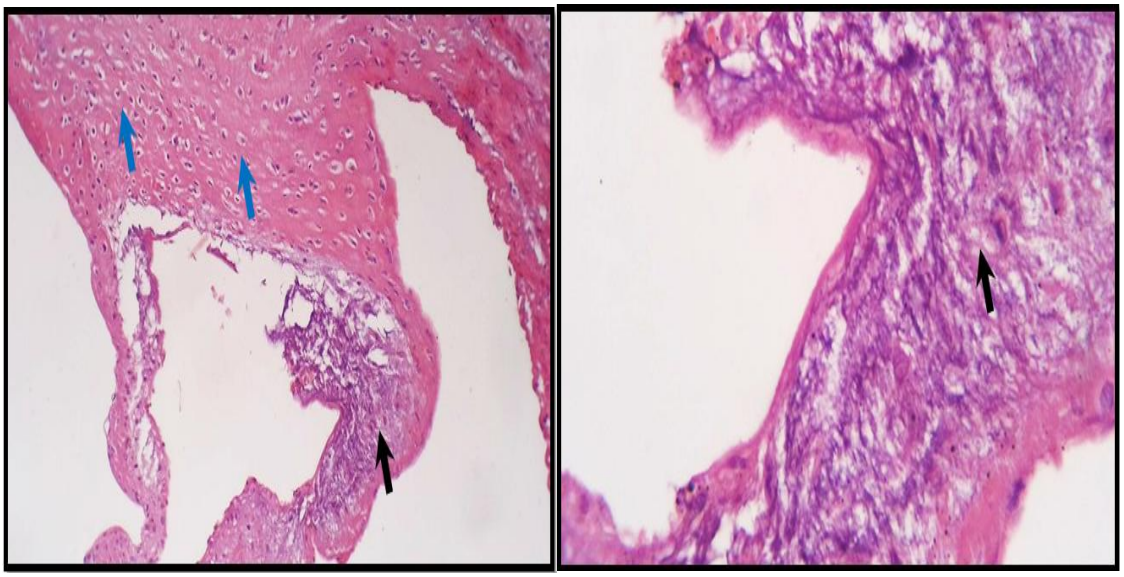

Fig (1) Aorta of positive control group shows area of calcified lipid material in the sub intimal region (back arrow), vacouation of muscular fibers in the tunica media (blue arrow). 10X and 40X

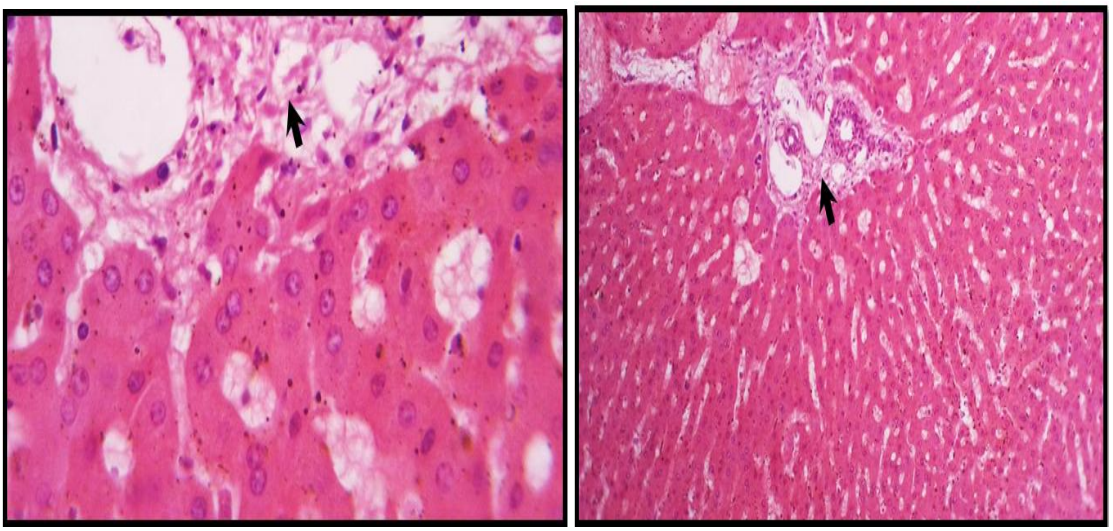

Fig (2) Liver of positive control group shows mild bridge fibrosis in the peri-portal area (back arrow). 10X and 40X

Chromatographic Analysis

Under the chromatographic conditions used, rosuvastatin was found in the sample with distinct, sharp peaks; its retention time was 5.69 minutes, and its retention time in rabbit plasma was 5.62 minutes. The developed method was validated for linearity, LOD, and LOQ, and recovery the method demonstrates excellent precision, Intra-day precision (RSD%) is calculated by comparing the variability of the measurements within a single day. Value: 0.094% Inter-day precision (RSD%) is calculated by comparing the variability of the measurements across different days. Value: 0.066% with both intra-day and inter-day RSD% values being well below 1%, indicating high reliability and reproducibility of the HPLC method for rosuvastatin determination (Figure 3).

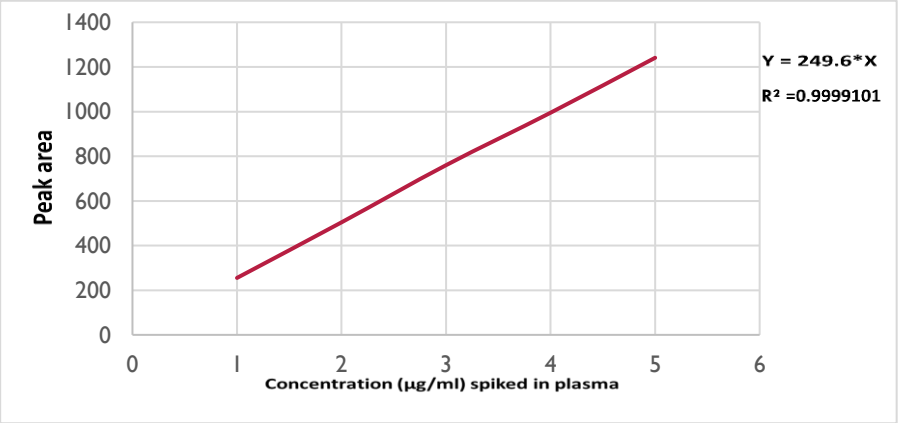

Figure (3): Calibration curve of rosuvastatin in plasma as a standard

Pharmacokinetic of Rosuvastatin

The pharmacokinetic parameters of Rosuvastatin after multiple oral administrations for 7 days in hyperlipidemic rabbits were analyzed in three groups: (1) Rosuvastatin alone, and (2) Rosuvastatin with Cephalexin, demonstrate significant alterations in key pharmacokinetic parameters due to antibiotic administration. The elimination rate constant (Ke) was lowest in the Rosuvastatin-alone group (0.027 ± 0.0005 h^{-1}) compared to the Cephalexin (0.030 ± 0.0004 h^{-1}). This resulted in a longer half-life (T1/2) in the control group (25.20 ± 0.43 hr) compared to the Cephalexin-treated (22.46 ± result accept0.34 hr). The shorter half-life in antibiotic-treated groups suggests enhanced drug clearance. The Cmax of Rosuvastatin was highest in the control group (0.90 ± 0.02 µg/mL), whereas it was significantly lower in the Cephalexin-treated (0.67 ± 0.01 µg/mL). Additionally, Tmax was delayed in both antibiotic-treated groups, indicating a slower absorption rate. The volume of distribution (Vd) was highest in the Cephalexin group (0.84 ± 0.11 L) compared to the control (0.68 ± 0.07 L). The increased Vd in the Cephalexin group suggests a greater tissue distribution of Rosuvastatin. Clearance (CL) was significantly increased in the antibiotic-treated groups, further supporting the hypothesis of enhanced drug elimination. The AUC, which represents the overall drug exposure, was highest in the control group (8.40 ± 1.16 µg/mL·h) and significantly lower in the Cephalexin-treated (6.90 ± 1.13 µg/mL·h) The reduced AUC in antibiotic-treated groups indicates a lower systemic availability of Rosuvastatin.

Table (4) Pharmacokinetic parameters of Rosuvastatin after a multi oral administration for 7 days in hyperlipidemia rabbits (mean ± SE).

Pharmacokinetics parameters	G1: Ros Mean ± SE	G2:Ros+Cep Mean ± SE	LSD
Ke h^{-1}	0.027±0.0005b	0.030±0.0004a	0.001
Half-Life (T1/2) (hr)	25.20±0.43a	22.46±0.34b	1.7
Cmax (µg/ml)	0.90±0.02a	0.67±0.01b	0.04
Tmax (hr)	109.60±5.87b	148.00±0.00a	14.79
Vd (L)	0.68±0.07b	0.84±0.11a	0.28
CL (µg/ml)/h	0.018±0.0004b	0.025±0.0003a	0.001
AUC 0-inf (µg/ml*hr)	94.40±1.61a	68.01±0.99b	6.67

Means with a different letter in the same row are significantly different (P<0.05)

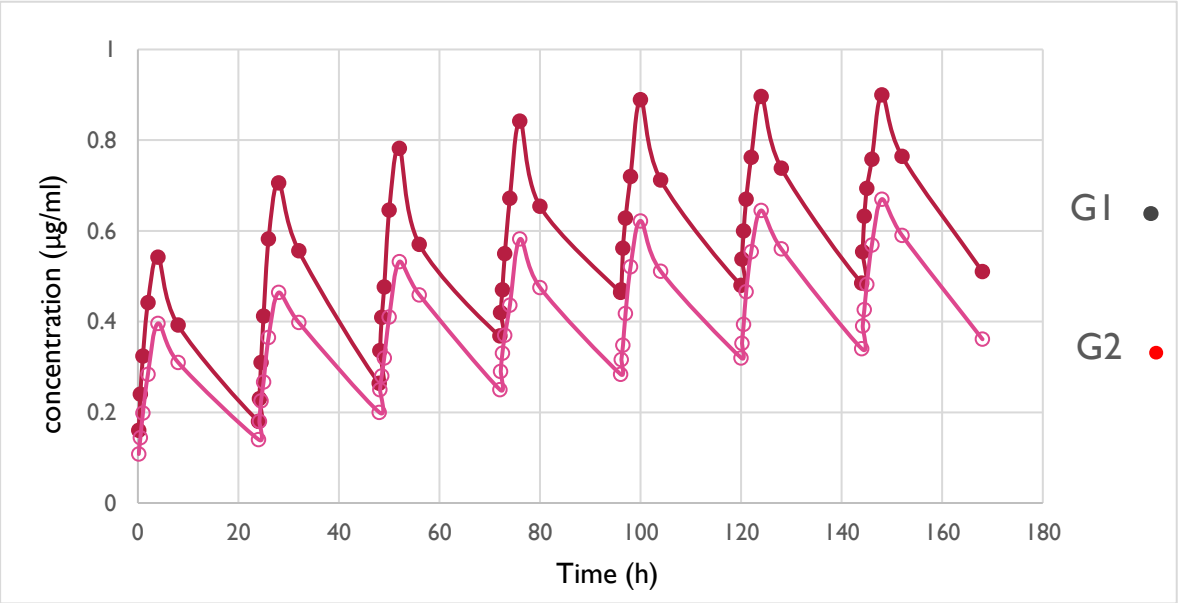

Fig (4) Plasma Rosuvastatin concentration (mean ± SE) after a multi oral administration (0.88mg/kg BW rabbit) for 7 days of the Rosuvastatin G 1 and Rosuvastatin + Cephalexin (44.24 mg/kg orally) G2.

5. DISCUSSION

The results indicate the Cephalexin significantly alter the pharmacokinetics of Rosuvastatin, leading to reduced bioavailability and increased clearance . antibiotics such as Cephalexin are known to disrupt gut microbiota, which play a crucial role in the metabolism and enterohepatic recycling of many drugs, including statins. The microbiota in the gut can modulate drug absorption, metabolism, and excretion, thereby affecting drug plasma levels and pharmacokinetic profiles (Yoo *et al*., 2014 ; Mu *et al*., 2019). the reduction in Cmax and AUC suggests that antibiotic administration may reduce the efficacy of Rosuvastatin, potentially leading to subtherapeutic levels. A decrease in T1/2 and increased CL in antibiotic-treated groups further emphasize the need for caution when co-administering antibiotics with statins, as these changes could result in decreased drug exposure and altered therapeutic effects (Džidić-Krivić *et al*., 2023). It's possible that enhanced gastrointestinal motility caused a little reduction in absorption, which is why co-administration with Cephalexin resulted in reductions in rosuvastatin AUC and Cmax.(Cooper *et al*., 2003).

Additionally, the increased $\mathbf{K_e}$ and reduced **T1/2** in the Cephalexin and Amoxicillin groups suggest that Rosuvastatin is eliminated more rapidly when these antibiotics are co-administered. This could be due to increased hepatic metabolism or altered drug transporter activity in the intestine, which has been related to alterations in gut microbiota composition (Vieira-Silva *et al*., 2020).This disruption can affect the overall systemic availability of the drug, possibly necessitating dose adjustments for patients receiving both antibiotics and statins. furthermore, the increase in Vd observed in the Cephalexin-treated group suggests changes in drug distribution, possibly due to alterations in plasma protein binding. The expression of transporters and enzymes involved in drug metabolism can be influenced by gut microbiota, according to studies, which can further alter the pharmacokinetic profile of medications like rosuvastatin (Zhang *et al*., 2021).

The gut microbiota plays a key role in metabolizing xenobiotics, including drugs such as Rosuvastatin. The depletion of gut bacteria due to antibiotics may reduce microbial enzymatic activity that contributes to drug metabolism, thereby altering its pharmacokinetics (Zhang *et al*., 2021). Intestinal transporters such as OATP1B1 and BCRP are critical for Rosuvastatin absorption and elimination. Antibiotics have been shown to modulate the expression of these transporters, which may explain the decreased **Cmax** and increased **CL** observed in the antibiotic-treated groups (De Bruijn., 2024 ; Balasubramanian *et al*., 2021). . Rosuvastatin undergoes enterohepatic circulation, which is influenced by bile acids produced by gut microbiota. Disruptions in bile acid metabolism due to antibiotics may impair Rosuvastatin reabsorption, leading to enhanced clearance and reduced plasma concentrations (Jourova, L., Anzenbacher, P., and Anzenbacherova, E, 2016).

According to the study's findings, using antibiotics and rosuvastatin together may lessen the medication's therapeutic impact. Patients receiving statin therapy for hyperlipidemia should be monitored when prescribed antibiotics, especially those known to disrupt gut microbiota. If necessary, dose adjustments or alternative lipid-lowering strategies should be considered to maintain therapeutic efficacy. Additionally, further studies should investigate whether probiotic supplementation or dietary modifications can help mitigate these effects and restore gut microbiota balance. Future research should also explore the

long-term consequences of antibiotic-induced changes in drug metabolism on cardiovascular outcomes in patients receiving statins.

6. CONCLUSION

The study's findings suggest that antibiotics reduce rosuvastatin's effectiveness and absorption. Examine how rosuvastatin and antibiotics work together to lower or reverse hyperlipidemia. investigate antibiotic role in decrease the absorption and effectiveness of rosuvastatin.

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