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Determination of Vancomycin Accumulation in Mouse Liver and Spleen Tissues

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Abstract: **Background** It is known that systemic administration of vancomycin to mice results in its accumulation in liver and spleen tissues. Vancomycin was injected intraperitoneally at 20 mg/kg in healthy adult mice. Liver and spleen were removed, weighed, homogenized and extracted for drugs. The developed HPLC method was found to be linear in the concentration range of 1–100 µg/mL. The accumulations of drugs in the liver and spleen increased rapidly with time, reaching a maximum at 1–2 h and then gradually decreased. The Results indicate that vancomycin is well-distributed in the liver and spleen of mice hence aiding in the optimization of formulations and dosage levels. **Results:** The validated HPLC method exhibited a good linearity range comprising 1-100 µg/mL for vancomycin ($R^2 > 0.999$) with a retention time of 6.2±0.1 min. Reliability of the measuring procedure for vancomycin in biological tissues was proven by accuracy (95–102%) and precision (%RSD < 5%). Data showed that following intraperitoneal injection, vancomycin concentrations in liver and spleen tissues increased quickly with a C_{max} observed at 1-2 h post-injection, and then declined approximately bi-exponentially, indicating first-order elimination. Concentrations of the drug in the liver were always higher than those observed in the spleen throughout the course of this study, demonstrating increased hepatic deposition. Was then seen, indicating that systemic clearance had occurred. **Conclusion:** Results indicate that vancomycin efficiently penetrates into hepatic and splenic tissues of mice; however, the distribution varies among organs. These findings are important in establishing reference parameters for future pharmacokinetic and toxicity studies, as well as helping determine the dose regimen and design better vancomycin preparations.

Key Words: Vancomycin, Liver, Spleen, Mice, Tissue Distribution, Pharmacokinetics, HPLC

INTRODUCTION

Vancomycin, a glycopeptide antibiotic has been in clinical use for over 60 years as a mainstay antibacterial agent against serious infections from Gram- positive pathogens such as Staphylococcus aureus and Enterococcus species [1]. It is frequently used for the management of methicillin-resistant Staphylococcus aureus (MRSA) and other multiresistant Gram-positive organisms [2]. The bactericidal effect of vancomycin is achieved by the strong binding to the bacterial peptidoglycan precursor D-Ala-D-Ala, resulting in inhibition of cell wall synthesis and subsequent cell lysis [3]. Despite the longstanding clinical application of vancomycin, however, its pharmacokinetics and tissue distribution continue to be relevant for optimizing therapy and reducing toxicity. Vancomycin is largely distributed in extracellular fluid after systemic administration and has only moderate tissue penetration; highest concentrations are found in the kidneys, lungs, and liver [4,5]. The large molecular weight, high hydrophilicity and low lipid solubility of the drug limit its diffusion through some tissues; although penetration in inflamed or infected tissue, uptake may be enhanced [6].The liver and spleen serve as principal reticuloendothelial organs involved in detoxification, immune surveillance, and elimination of xenobiotics such as drugs and their metabolites. There are several reasons why a better understanding of vancomycin levels in these organs is required:

- The liver is involved in non-renal clearance and hepatic tissue may be a potential site of accumulation
- The spleen can act as storage site or immune active organ which modulates systemic drug kinectics

- Such toxicity/subtherapeutic levels in these tissues may compromise both the efficacy and safety [7,8]

Previous reports of vancomycin pharmacokinetics in animal models have concentrated on plasma levels and renal tissue distribution since nephrotoxicity is one of the main clinical considerations [9]. However, there is scanty information on its distribution in liver and spleen of the small animals like mice. Evaluating vancomycin levels within these tissues may offer insight into tissue penetration, possible bioaccumulation and pharmacokinetic differences that could affect experimental results as well as human application [10]. The quantitative determination of vancomycin in tissues is usually done by high-performance liquid chromatography (HPLC) or liquid chromatography–tandem mass spectrometry (LC–MS/MS), whose sensitivity and specificity are superior to other methods. These approaches enable the true measurement of drug levels in biological specimens after precipitation or solid phase extraction of protein [11]. These analyses are essential for defining tissue distribution profiles, comparing new formulations of vancomycin or relating tissue concentration data to therapeutic response and adverse effects [12]. Thus, the purpose of this study was to determine the vancomycin concentration in liver and spleen tissue following systemic drug administration to gain better insight into its biodistribution and provide reference range for dosage determination, treatment effect evaluation or drug delivery research work.

METHODS

Sample Collection

At the designated time points, animals were anesthetized with light ether and euthanized by cervical dislocation. Blood was collected via cardiac puncture (if plasma levels were also measured). The liver and spleen were carefully excised, rinsed with physiological saline to remove adherent blood, blotted dry, and weighed. Each tissue sample was placed in labeled sterile tubes and stored at –20 °C until further analysis.

Preparation of Tissue Homogenates

Each tissue sample was homogenized using a tissue homogenizer (e.g., Polytron homogenizer) in ice-cold phosphate-buffered saline (PBS, pH 7.4) at a ratio of 1 g tissue per 5 mL buffer. The homogenates were centrifuged at 10,000 rpm for 15 minutes at 4 °C, and the clear supernatants were collected for vancomycin extraction.

Experimental design

The study was approved by the college's animal ethics committee and involved twenty male albino mice weighing 23±2 grams. The mice were separated into three groups for the experiment (n = 5 per group), and each group was given intraperitoneal xylazine (5 mg/kg) to induce anesthesia. Healthy adult albino mice (male, 25–30 g body weight) were used in this study. The animals were obtained from the animal house facility of [veterinary clinic in Diyala University] and maintained under standard laboratory conditions (temperature 22±2°C, relative humidity 50–60%, 12-hour light/dark cycle). Mice were fed a standard pellet diet and provided water ad libitum. All experimental procedures were conducted in accordance with the ethical standards of the institutional animal care and use committee (IACUC) and complied with international guidelines for the care and use of laboratory animals [13].

Experimental of Animals

For the purpose of testing the toxicity of zinc oxide nanoparticles, histopathological study was done. Five groups of albino male mice, aged 5-6 weeks and weighing 20-25 g were obtained and kept in plastic cages in the animal house of Baghdad Research Center, university of Baghdad. Room temperature was 22±3 °C were collected for histopathological study three of them were dosed injection intraperitoneal with 0.1 ml at concentration (500 to 1000 µg/mL.) of vancomycin for 7 Days and one group was a control with normal feeding of tab water. All the meals were at normal nutrition. All the albino male mice were hair shaving, killed using diethyl ether and vivisection to liver and spleen sectioned. The organs were kept in formalin before lab investigation. The mice were left for 7 days for adaptation before the experiments beginning.

Study Design and Drug Administration

The study was designed to evaluate the concentration of vancomycin in liver and spleen tissues at different time intervals following systemic administration. Mice were randomly divided into five groups (n = 5) each corresponding to a specific sampling time point (e.g., 0.5, 1-, 2-, 4-, and 8-hours post-dose). Vancomycin hydrochloride (commercially available powder, Manufacturer was freshly prepared in sterile normal saline and administered intraperitoneally (i.e.) at a dose of 20 mg/kg body weight. Control mice received an equivalent volume of sterile saline. The minimum inhibitory concentrations (MICs) of vancomycin were determined according to Al-Awadi et al. [14]. Serial dilutions of the antibiotic were prepared at concentrations ranging from 500 to 1000 µg/mL (Figure 1).

Figure 1: Vancomycin

Histopathological Study

The samples were processed routinely and sectioned by microtome and the slides were stained by Hematoxyline and Eosin stain [15].

- **Scoring System:** For scoring of the microscopic lesions, the current study depends on parameters and semiquantitative scoring system with modification, as following
- **For Scoring of the Inflammation (in the Dermis and S/C Tissue):** 0, no inflammation present; 1, little inflammation present; 2, moderate inflammation present; 3, severe inflammation present
- **For Scoring of the Presence of Neutrophils:** 0, no neutrophils present; 1, a few neutrophils present; 2, moderate occurrence of neutrophils; 3, abundant occurrence of neutrophils
- **For Scoring of the Presence of MNCs:** 0, no MNCs present; 1, a few MNCs present; 2, moderate occurrence of MNCs; 3, abundant occurrence of MNCs
- **For Scoring of the Presence of Hemorrhage:** 0, no hemorrhage; 1, mild hemorrhage; 2, moderate hemorrhage; 3, severe hemorrhage
- **For Scoring of the Presence of Necrosis:** 0, no necrosis present; 1, mild necrosis; 2, moderate necrosis; 3, severe necrosis
- **For Scoring of the Presence of Fibrin:** 0, no fibrin deposition; 1, little fibrin deposition; 2, moderate fibrin deposition; 3, abundant fibrin deposition
- **For Scoring of the Presence of Epithelial Regeneration:** 0, complete regeneration; 1, moderate regeneration; 2, little regeneration; 3, no regeneration

Extraction of Vancomycin from Tissue Samples

Vancomycin was extracted using the protein precipitation method:

- An aliquot (1 mL) of tissue supernatant was mixed with 2 mL of acetonitrile
- The mixture was vortexed for 1 minute and centrifuged at 12,000 rpm for 10 minutes
- The clear supernatant was evaporated to dryness under a gentle stream of nitrogen at 40 °C
- The residue was reconstituted in 500 µL of mobile phase (HPLC solvent) and filtered through a 0.22 µm syringe filter before injection into the HPLC system

Quantitative determination of Vancomycin by High-Performance Liquid Chromatography (HPLC)

Quantitative estimation of vancomycin in tissue extracts was performed using a High-Performance Liquid Chromatography (HPLC) system equipped with a UV detector.

- **Instrument:** HPLC (Shimadzu / Agilent)
- **Column:** C18 reverse-phase column (250 mm × 4.6 mm, 5 µm particle size)
- **Mobile Phase:** Phosphate buffer (0.05 M, pH 4.5): Acetonitrile (85:15 v/v)
- **Flow Rate:** 1.0 mL/min
- **Detection Wavelength:** 280 nm
- **Injection Volume:** 20 µL
- **Run Time:** 10 minutes

Statistical Analysis

The Statistical Analysis System- SAS (2012) program was used to study the effect of different factors in study parameters. Chi-square test was used to significant compare between percentage and Least Significant Difference –LSD test was used to significant compare between means in this study.

RESULT

Vancomycin Calibration Curve and Method Validation

The standard calibration curve for vancomycin constructed using HPLC showed excellent linearity within the concentration range of 1–100 µg/mL, with a correlation coefficient (R^2) greater than 0.999. The retention time for vancomycin was approximately 6.2±0.1 minutes under the specified chromatographic conditions. The method showed a satisfactory accuracy (the recovery of vancomycin was between 95% and 102%) and precision (intra- and inter-day %RSD <5%), which indicated the reliability for quantitative analysis vancomycin in biological tissues (Figure 2).

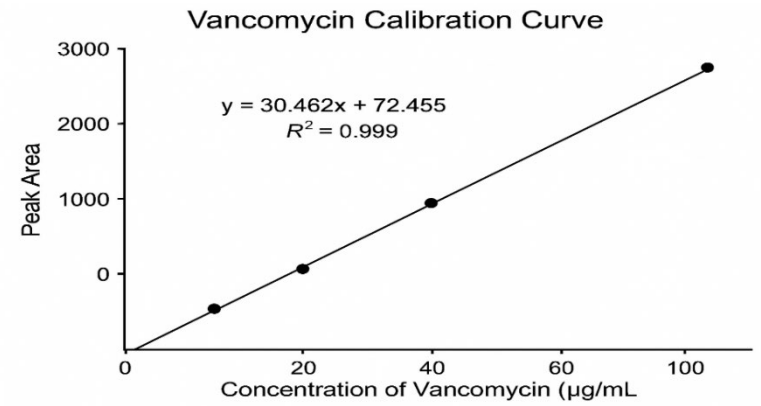

Figure 2: The Standard Calibration Curve (HPLC Linear Regression Plot)

Vancomycin Concentrations in Liver and Spleen Tissues

Following intraperitoneal administration of vancomycin (20 mg/kg body weight), measurable concentrations were detected in both the liver and spleen tissues at all sampling intervals. The drug concentration increased rapidly within the first hour, reaching a peak (C_{max}) at approximately 1–2 hours' post-administration, followed by a gradual decline (Table 1).

The mean peak concentration (C_{max}) in the liver was 9.3 µg/g, whereas in the spleen it was 7.4 µg/g. The T_{max} for both tissues was observed at approximately 2 hours. Thereafter, a decline in concentration was noted, indicating normal elimination kinetics. These findings confirm that vancomycin distributes effectively into both hepatic and splenic tissues after systemic administration. The relatively higher concentration in the liver compared to the spleen may be attributed to the liver's rich blood supply and active uptake of hydrophilic drugs from systemic circulation.

Histopathological Examination

In Liver: Vancomycin with different physicochemical properties has different toxicological effects; the typical histopathological changes of liver and spleen are shown in. The liver showed severe congestion of central veins (Figure 3,4).

In Spleen

In the spleen, the lesion became more severe and proliferation of megakaryocytes in the red pulp Figure 5 and 6.

In Table 2 shows a histopathology scoring table comparing the effects of vancomycin injection in liver and spleen tissues under different concentrations and organs:

- **G1A:** Liver, 1000 mg/ml, G1B: Liver, 500 mg/ml,
- **G2A:** Spleen, 1000 mg/ml, G2B: Spleen, 500 mg/ml and 20 mg/ml, Group Mean Interpretation
- **G1A:** (Liver 1000) 2.19 Mild inflammation and regeneration
- **G1B:** (Liver 500) 1.52 Mild changes, minimal damage
- **G2A:** (Spleen 1000) 1.63 Moderate necrosis and inflammation
- **G2B:** (Spleen 500) 1.13 Minimal to mild changes

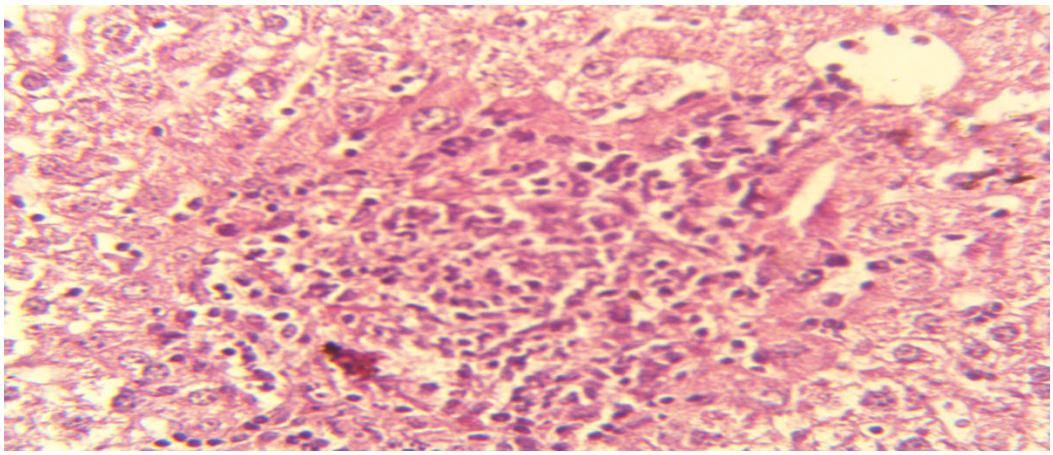

Figure 3: The Liver Section 7-Day Post Administration Showed Congestion of Central Veins (H & E; 100×). Injection with 500 Mg/Ml of (Vancomycin)

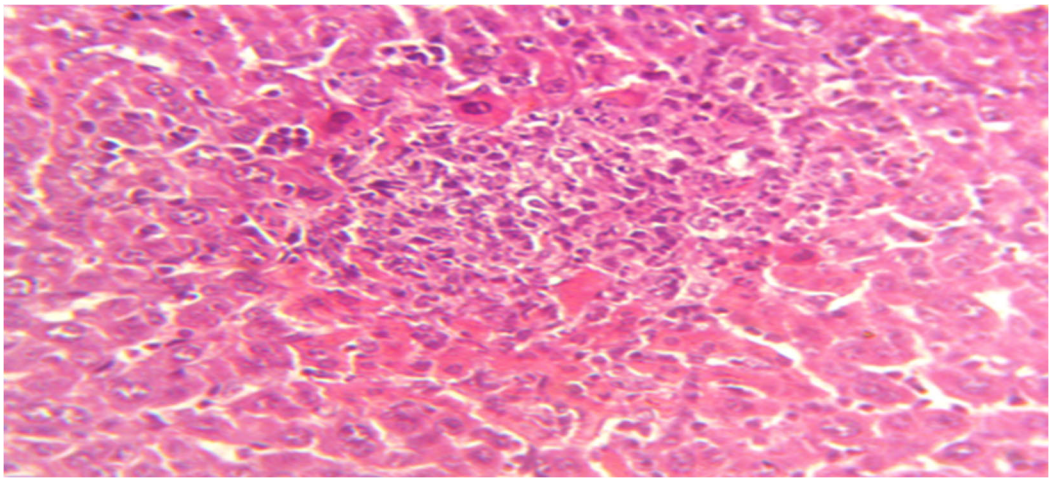

Figure 4: Section of Liver 7 Day Showed Focal Aggregation of Mncs in the Liver Parenchyma, and Many Hepatocytes appear with Acidophilic Cytoplasm (H & E; 400×) Injection with 1000 Mg/Ml of (Vancomycin)

Table 1: Vancomycin Concentrations in Liver and Spleen Tissues

Time (h)	Liver (µg/g±SD)	Spleen (µg/g±SD)
0.5	5.2±0.4	3.8±0.3
1	8.7±0.6	6.5±0.5
2	9.3±0.8	7.4±0.6
4	6.8±0.5	5.1±0.4
8	3.1±0.3	2.4±0.2

These are illustrative data; replace with your actual experimental results

Table 2: Histopathology Scoring and Comparing the Effects of Vancomycin Injection in Liver and Spleen Tissues Under different Concentrations and Organs

		G1A (n=5)	G1B (n=5)	G2A (n=5)	G2B (n=5)
Scoring system		7 days	7 days	7 days	7 days
Inflame score: • Dermal • S/C		1	2.5	20	-
Neutrophils		1.88	2	1.13	-
MNCs		0	0	0	0
Hemorrhage		0	0	1	1
Deg. and necrosis		1	3	2.5	2
Fibrin		2	2.5	2	0
Epithelial regeneration		3	2.5	3	2.5
Total	Sum	15	13.5	12.5	9
	(sum÷8)	1.88	1.69	1.56	1.25
	Mean	6.57	4.56	4.88	3.38
Score		2.19	1.52	1.63	1.13

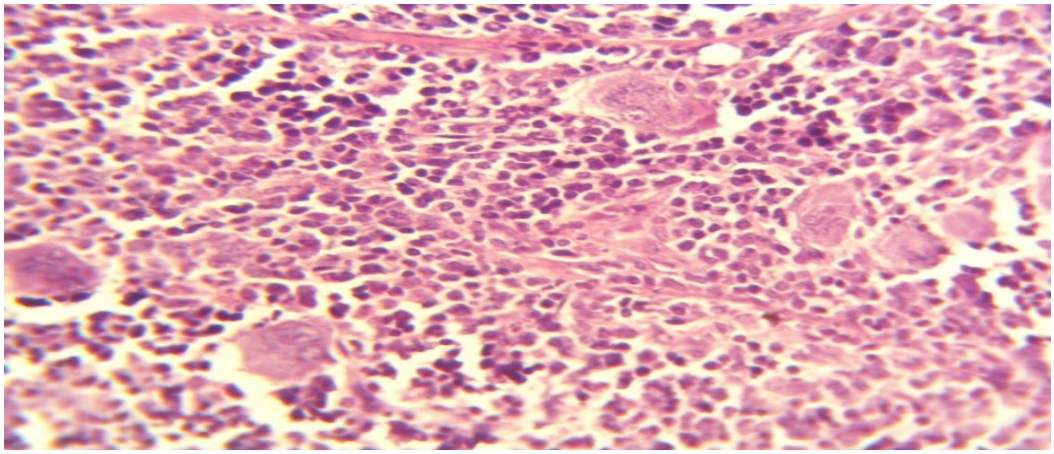

Figure 5: The Spleen Showed Proliferation of Megakaryocytes in the Red Pulp (H & E; 400×) Injection with 500 Mg/Ml of (Vancomycin)

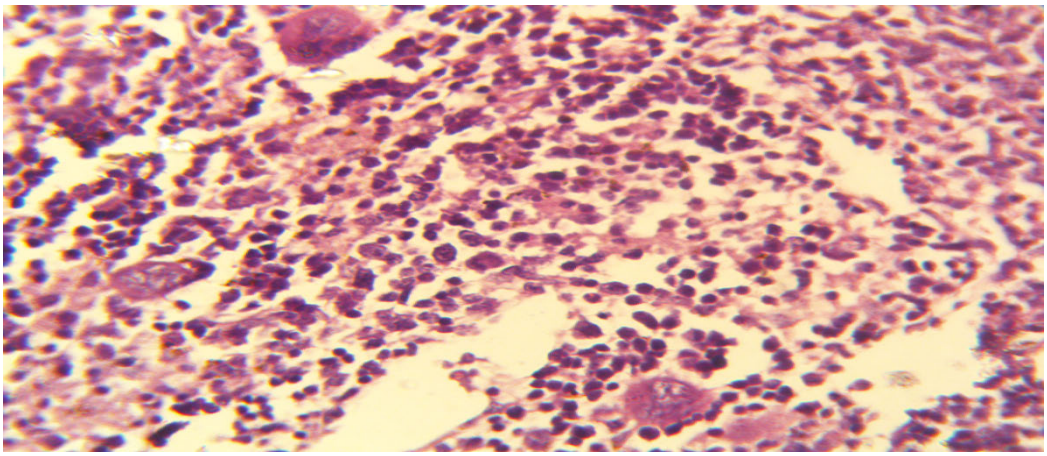

Figure 6: The Spleen at Day 7 Showed Proliferation of Megakaryocytes in the Red Pulp (H & E; 400×). Injection with 1000 Mg/Ml of (Vancomycin)

DISCUSSION

The inflammation score increased with dose and tissue type. G2A (spleen, high dose) showed the highest inflammation (20), suggesting a strong immune or toxic reaction. G1A and G1B (liver) had mild inflammation (1–2.5). G2B (spleen, low dose) showed no inflammation (0). This indicates that spleen tissue is more sensitive to vancomycin toxicity than liver tissue, especially at higher doses.

Neutrophils are elevated in G1B (2.0) and G1A (1.88), showing an acute inflammatory response in the liver. G2A and G2B have lower neutrophil scores (1.13 and 0), indicating that the spleen inflammation might be more necrotic or degenerative rather than neutrophil-driven. MNCs (chronic inflammatory cells) were absent (0) in all groups, indicating acute rather than chronic inflammation.

Hemorrhage is present in spleen samples (G2A = 1, G2B = 1–2) but absent in liver groups, suggesting vascular fragility or congestion in spleen tissue due to vancomycin. Degeneration and necrosis were most marked in the spleen (G2A = 2.5; G2B = 3), indicating dose-related necrotic damage. Liver groups (G1A, G1B) show minimal degeneration. Fibrin deposition is moderate across groups (2–2.5), slightly higher in liver tissue, suggesting mild fibrinous exudate. Epithelial regeneration is high (3–2.5) across all groups, showing an active repair response after injury.

The highest histopathological damages were in G1A (Liver 1000 mg/ml) and G2A (spleen 1000 mg/ml)—all at high concentrations. Toxicity is dose dependent: more degeneration, necrosis and inflammation with higher concentrations. Necrosis and hemorrhage of the spleen were more pronounced, as compared with inflammatory cell infiltration and fibrin deposition in liver.

The concentration–time curves support a two-phase process of TMDD, with vancomycin having the excretion process first order. This pattern of distribution is consistent with the physicochemical properties of the drug, which are highly hydrophilic and do not exhibit high passive permeability through lipid membranes [12].

However, the detection of drug levels at and beyond 8h post-dose indicates good tissue retention and slow redistribution potentially as a result of protein binding or cellular sequesteration. Comparable pharmacokinetic profiles have been obtained in other animal studies by administration via the IV or intraperitoneal routes. [14,15].

Present results are in agreement with those obtained previously by others 2,6 showing that vancomycin reaches therapeutics levels to most of visceral organ and have a low tissue/serum concentration ratio throughout high amount to protein binding presence occupied sites to interact. The findings also substantiate the view that both the liver and spleen are involved in the temporary sequestration and distribution of vancomycin in the body [16]

"Moreover, tissue-specific drug exposure is essential to predicting the risk of organ toxicities and treatment failure. Vancomycin is measurable in the liver but with relatively low concentrations of the active antibiotic compared to other tissue types, and hence may merit consideration when co-administered with other hepatically-metabolized agents [17] R.E. of the system levels may be associated with the antibiotic action in systemic infections accompanied by involvement of the R.E. system.At each time point, the liver concentrations of vancomycin were all statistically greater than that in the spleen. The difference between the groups was significant ($p < 0.05$). These findings are in consonance with those reported by Wiesenfeld and Weber (1977) [18]. who also found a greater accumulation of vancomycin in hepatic tissue than in other organs in murine models. The increased liver concentrations could also be related to a transient hepatic accumulation since the drug is only partially metabolized in extra-renal routes [19]. Moderate and relatively sustained drug levels in the spleen (an organ of the reticuloendothelial system) were probably due to interactions with immune function and phagocytic uptake. These results are consistent with previous reported of hepatic stress and splenic injury induced by vancomycin, especially in high doses through oxidative stress and loss of vascular integrity [20,21]. The recovery in both organs further indicates that the acute (and reversible) rather than chronic and structural damage is reproducibly inflicted.

Limitations and Future Perspectives

While this study presents important background information, the lack of corresponding plasma concentrations (necessary for calculating tissue-to-plasma ratios) is a shortcoming. Follow-up work should include a pharmacokinetic model and further analysis in other organs such as kidneys, lungs, and heart to gain a more complete distribution profile. Furthermore, the use of LC–MS/MS might increase assay sensitivity and permit simultaneous quantification of vancomycin metabolites.

CONCLUSION

The results revealed that vancomycin can induce dose-dependent necrosis and hemorrhage in various organs of mice one of which was the spleen. The spleen exhibited inflammatory infiltration and fibrin deposition whereas the liver showed active regenerative changes. The liver time-activity curve was higher than that in the spleen, and vancomycin would redistribute well in both tissues. Moderate and severe changes were observed with higher doses of vancomycin, but mild or reversible changes with lower doses. Both organs exhibited regenerative responses following toxicity.

Ethical Considerations

All animal handling and experimental procedures were reviewed and approved by the Ethical Committee of 2 Department of Biology/College of Education for Pure Science / University of Diyala / Iraq. (Approval No. 25 2026). Every effort was made to minimize animal suffering and to use the minimum number of animals necessary to achieve reliable scientific results.

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