ORIGINAL ARTICLE

# Effect of Ranitidine on the Pharmacokinetic and Pharmacodynamic Profile of Metformin in Rabbits

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## Abstract

**Background:** The aim of this study was to investigate the effect of ranitidine, an H2-receptor antagonist, on the pharmacokinetics of metformin, a widely used antidiabetic drug in albino rabbits. **Methods:** Albino rabbits were divided into 3 groups, group I received metformin alone, group II received ranitidine alone, and group III received ranitidine 30 minutes prior to metformin. Blood samples were collected at various intervals post-administration for the estimation of blood glucose levels and metformin concentration. **Results:** The study found that the plasma metformin concentrations (CMet) were below the limit of quantification at 8 hours in group I, indicating a near complete elimination of the drug from systemic circulation. However, quantifiable levels of metformin were observed at 8 hours in group III, suggesting a significant increase in the mean residence time of the molecule caused by a decrease in metformin elimination. The study also found that the area under the curve of metformin was significantly increased by ranitidine pre-treatment in group III, suggesting an increase in systemic exposure to metformin. Conclusion: This study suggests that concomitant administration of ranitidine and metformin in rabbits leads to an increase in the mean residence time of metformin due to the inhibition of the organic cation transporter 1 by ranitidine, resulting in an increase in systemic exposure to metformin. The study highlights the potential for drug-drug interactions between ranitidine and metformin, which may impact the efficacy and safety of metformin treatment. Further studies in humans are needed to confirm these findings.

**Keywords:** Ranitidine, metformin, pharmacokinetics, interaction, clearance

## INTRODUCTION

Metformin is a biguanide oral hypoglycemic drug that is considered first line in the treatment of non-insulin dependent diabetes mellitus (NIDDM).[1] In spite of its safe and wide therapeutic index, metformin causes adverse drug reactions such as hypoglycemia and lactic acidosis.[2,3] Although rare, metformin-induced lactic acidosis is a life-threatening condition that occurs usually in patients with renal failure due to the drug's near complete renal elimination (90%).[3] It has been reported that the histaminergic antagonist cimetidine increases systemic metformin levels in humans by decreasing metformin's renal tubular secretion.[4] As metformin is a hydrophilic base present in its cationic form at physiological pH, its pharmacokinetic behavior is dictated largely by the influence of transporters.[5] Glycemic control is produced when metformin enters into hepatocytes through the organic cation transporter (OCT).[6] The OCT is a member of the solute carrier 22 (SLC22) family.[7] The OCTs are involved in the uptake of structurally diverse organic cations of endogenous and xenobiotic compounds, such as prostaglandins and drugs.[8] The OCT1, OCT2, and OCT3 are encoded by the SLC22A1, SLC22A2, and SLC22A3 genes, respectively.[9] It has been shown that functional SLC22A1 alleles with the amino acid substitution of Arg61Cys, Gly401Ser, 420del, and Gly465Arg significantly decreased metformin clearance and increased the area under the curve, maximum plasma drug concentration, and the systemic exposure to metformin than those who carried the SLC22A1 wild allele.[10] However, the glycemic response to metformin is

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quite variable. Some patients respond extremely well, whereas others show no benefit. Metformin is not metabolized and is excreted unchanged in the urine, with a half-life of ~5 h.[11] Active tubular secretion in the kidney is the principal route of metformin elimination. The hepatic uptake of metformin is mediated primarily by OCT1 (*SLC22A1*) and possibly by OCT3 (*SLC22A3*).[12,13] Both transporters are expressed on the basolateral membrane of hepatocytes.[14] In addition, it has been shown that metformin may not be eliminated favorably if cationic transporters of the OCT superfamily are strongly inhibited. However, this interaction has not been specifically reported for ranitidine which is commonly prescribed with met for min.[15] This study was designed to study the effect of ranitidine coadministration on the pharmacokinetic profile of metformin using rabbits of either sex.

## MATERIALS AND METHODS

### Mode of drug administration

As oral route is the commonly preferred route of administration for metformin and ranitidine, they were administered through the same route. Both metformin and ranitidine are freely soluble in water and hence distilled water was used as the aqueous vehicle of administration. The solutions were freshly prepared as and when required.

### Study design and experimental procedure

Albino rabbits of either sex weighing between 1.5 and 2.0 kg were selected for the study. They were separated into three groups, each with five animals, and appropriately marked for identification. The animals were kept in the animal house's usual rabbit cages and husbandry conditions. The animals were fasted for 14 h before the scheduled time of medication administration on the day of the experiment. Water, however, was available at all times. For the purpose of determining the basal glucose concentration, blood samples were taken from the marginal ear vein the next day. After then, the animals in the various groups received the further treatments, which are listed in Table 1.

After administration of metformin or ranitidine or metformin after 30 min of receiving ranitidine to respective groups, 2 mL of blood was withdrawn from marginal ear vein at intervals of 0.5, 1, 2, 3, 4, 6, and 8 h.

### Estimation of blood glucose levels

Blood samples were collected in eppendorf's tube containing heparin (200 IU/mL of blood) and subjected to refrigerated centrifugation to isolate plasma. Isolated plasma was stored in two different aliquots of 100 µL each. Estimation of glucose concentration was carried out using ERBA kits containing glucose oxidase, peroxidase, chomogen L-amino antipyrine, and phenol. Standard and blank plasma were added in respective tubes containing glucose reagent and mixed well. After an incubation period of 15 min, blood glucose concentrations were measured using a semi auto-analyzer. The percentage blood glucose reduction was calculated as follows:

$$\%\,Blood\ glucose\ change = \frac{(FBS - Blood\ sugar\ at\ time\ 't'\ ) \times 100}{FBS}$$

Where FBS is fasting blood sugar.

### Estimation of plasma concentration of metformin

A simple reverse phase high-performance liquid chromatographic method reported by Wanjari *et al*. was adopted for the estimation of metformin concentration in rabbit plasma. Acetonitrile was added to the aliquot to deproteinize the rabbit plasma and extract metformin. A C18 column (300 mm × 2.4 mm) was employed with ammonium acetate (0.15 M) and acetonitrile (90: 10; pH–5.5; 1.0 mL/min) as mobile phase and ultraviolet detection at 236 nm.

### Pharmacokinetic modeling

Non-compartmental analysis was used to compute primary and secondary pharmacokinetic parameters. Peak plasma concentration ($C_{max}$) and time taken to reach $C_{max}$ ($t_{max}$) were read directly from the plasma time versus concentration data. $AUC_{0-t}$ and $AUC_{0-\infty}$ were computed by linear trapezoidal method. Pharmacokinetic modeling was carried out using PKSOLVER add-in for Microsoft Excel.

### Statistical analysis

All statistical analyses were performed using Graphpad Prism 9.4.0. Data normality was determined using Shapiro–Wilk test. Numeric variables were summarized as mean ±

**Table 1:** Study design and dosing

| Study group | Number of animals | Pre-treatment medication | Study drug |
|---|---|---|---|
| Group I | 5 | - | Metformin (30 mg/kg) in aqueous |
| Group II | 5 | - | Ranitidine (5 mg/kg) |
| Group III | 5 | Ranitidine (5 mg/kg) 30 min before administration of study drug | Metformin (30 mg/kg) |

All animals received 100 mg/kg of streptozotocin intravenously via marginal ear vein 48 h before administration of the study drug

**Table 2:** Comparison of plasma metformin concentrations between study groups

| Time (hours) | Group I (ng/mL) | | | | | Group III (ng/mL) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | I | II | III | IV | V |
| Fasting | - | - | - | - | - | - | - | - | - | - |
| 0.5 | 374.0 | 299.4 | 272.9 | 302.3 | 342.9 | 432.8 | 514.8 | 435.1 | 378.5 | 512.6 |
| 1 | 1217.3 | 1258.0 | 1330.2 | 1178.7 | 1291.9 | 2465.1 | 2230.7 | 2852.0 | 2383.7 | 2840.4 |
| 2 | 2562.1 | 2739.4 | 2406.8 | 1886.9 | 2470.4 | 3054.3 | 2999.7 | 2482.8 | 3162.4 | 2519.3 |
| 3 | 1700.3 | 2002.5 | 1872.7 | 2792.1 | 1905.1 | 2798.3 | 2670.1 | 2002.5 | 2732.7 | 2131.7 |
| 4 | 1304.4 | 1177.0 | 1145.2 | 1916.3 | 1218.5 | 2058.0 | 1981.2 | 1681.3 | 2086.2 | 1567.1 |
| 6 | 242.5 | 260.2 | 288.9 | 491.4 | 246.4 | 1310.6 | 1001.3 | 820.6 | 1060.6 | 778.6 |
| 8 | BLQ | BLQ | BLQ | BLQ | BLQ | 353.2 | 242.5 | BLQ | 307.5 | BLQ |

Group I animals received metformin alone (30 mg/kg); Group III animals were pre-treated with ranitidine (5 mg/kg) followed by metformin (30 mg/kg) after 30 min; BLQ: Below limit of quantification

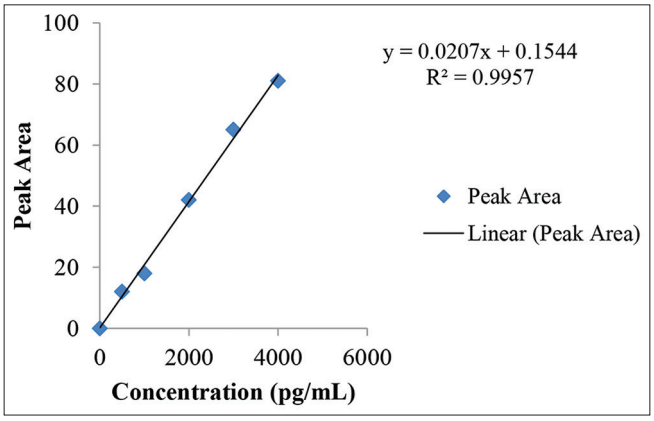


**Figure 1:** HPLC calibration curve for metformin

SD or median (minimum and maximum) depending on data normality while categorical variables were summarized as number (proportion). Statistical significance of difference in blood glucose levels between study groups was determined using Analysis of variance ordinary measures and *post hoc* analysis-Bonferroni corrections. Statistical significance of difference in $C_{Met}$ was determined through unpaired t-test.

## RESULTS

### Bioanalytical parameters

Metformin had a mean ± SD retention time of around 4.2 ± 0.8. The total run time for the chromatography was 6.5 min. The percentage coefficient of variation (percent CV) for the quality control samples of metformin ranged from 10.34% to 14.10%, with a total accuracy of 98.20–101.02%. The assay was linear with the correlation coefficient of calibration curve being 0.995. The HPLC calibration curve of metformin is shown in Figure 1.

$C_{Met}$ at intervals on 0.5, 1, 2, 3, 4, 6, and 8 h are shown in Table 2. It is significant that $C_{Met}$ was below the limit of quantification at 8 h in rabbits dosed only with metformin (30 mg/kg) suggesting a near complete elimination of the drug from systemic circulation. However, quantifiable levels of metformin were observed at 8 h in rabbits dosed with metformin (30 mg/kg) and ranitidine (5 mg/kg) suggesting an significant increase in the mean residence time of the molecule caused by decrease in metformin elimination.

Statistically significant difference in $C_{Met}$ was observed between study groups at 0.5, 1, 4, 6, and 8 h only. Significant differences in $C_{Met}$ were not observed at 2 and 3 h. The initial phase of elimination after rapid distribution may theoretically be reduced in rabbits pre-treated with ranitidine causing difference in $C_{Met}$ at 0.5 h and 1 h. OCT inhibition by ranitidine increases the $C_{Met}$ during 4, 6, and 8 h. Biological half-life and mean residence time of metformin were extended by 120 min by concomitant administration of ranitidine. While statistically significant difference was not observed in the time taken to reach peak plasma concentration, $C_{max}$ significantly differed between study groups. Area under the curve of metformin was significantly increased by ranitidine pre-treatment in rabbits suggesting an increase in systemic exposure to metformin. While the apparent volume of distribution of metformin was did not significantly differ in rabbits pre-treated with ranitidine (5 mg/kg), statistically significant difference in metformin clearance was observed between rabbits with and without ranitidine pre-treatment. It is evident that ranitidine decreases the elimination of metformin thereby decreasing the systemic clearance. Decrease in clearance increases the systemic bioavailability and duration of action of metformin as observed in our study. Pharmacokinetic profile of metformin in rabbits that received metformin (30 mg/kg) and those that received metformin (30 mg/kg) and ranitidine (5 mg/kg) is shown in Table 3. Time versus plasma concentration plot of metformin in rabbits with and without ranitidine pre-treatment is shown in Figure 2.

The pharmacokinetic profile of metformin is altered by concomitant administration of ranitidine as evident from the time versus plasma concentration plot. While $T_{max}$ has occurred at almost similar intervals, $C_{max}$ of metformin lies higher in rabbits pre-treated with ranitidine. The phase of elimination of metformin is prolonged significantly by ranitidine and hence the systemic bioavailability.

**Table 3:** Comparison of pharmacokinetic profile of metformin between study groups

| S. No. | Parameter | Study group | | Difference | *P*-value |
|---|---|---|---|---|---|
| | | Group I | Group III | | |
| 1 | $X_{0.5}$ | 318.3±17.9 | 454.8±26.1 | 136.5±31.6 (63.5 to 209.4) | 0.003** |
| 2 | $X_1$ | 1255.0±26.7 | 2554±125.0 | 1299±127.8 (1005 to 1594) | 0.000**** |
| 3 | $X_2$ | 2413.0±143.0 | 2843.7±142.4 | 430.6±201.8 (−34.8 to 896.0) | 0.0654 |
| 4 | $X_3$ | 2055.0±190.7 | 2467±165.8 | 412.5±252.7 | 0.1413 |
| 5 | $X_4$ | 1352.3±143.5 | 1874.7±105.3 | 522.5±178.0 (112.0 to 932.9) | 0.0188* |
| 6 | $X_6$ | 305.9±47.1 | 994.3±95.2 | 688.5±106.2 (443.6 to 933.3) | 0.000*** |
| 7 | $X_8$ | 0.0±0.0 | 180.6±75.8 | 180.6±75.8 (5.8 to 355.5) | 0.044* |
| 8 | $t_{1/2}$ | 1.1±0.0 | 1.9±0.2 | 0.8±0.2 (0.3 to 1.2) | 0.003** |
| 9 | $T_{max}$ | 2.2±0.2 | 1.6±0.2 | −0.6±0.3 (−1.3 to 0.1) | 0.0943 |
| 10 | $C_{max}$ | 2594.2±74.7 | 2981.8±61.3 | 387.6±96.6 (164.8 to 610.4) | 0.0039** |
| 11 | $AUC_{0-8}$ | 7902.5±302.9 | 12115.5±813.0 | 4213±867.6 (2212 to 6214) | 0.0013** |
| 12 | $AUC_{0-inf}$ | 8387.5±385.0 | 13590.6±415.2 | 5203±566.2 (3897 to 6509) | 0.000*** |
| 13 | $AUMC_{0-inf}$ | 25642.2±2073.0 | 52009.1±2038.0 | 26367±2907 (19664 to 33070) | 0.000**** |
| 14 | $MRT_{0-inf}$ | 3.0±0.1 | 3.8±0.1 | 0.8±0.1 (0.4 to 1.2) | 0.0015** |
| 15 | $V_d$ | 0.6±0.0 | 0.6±0.1 | 0.0±0.1 (−0.13 to 0.21) | 0.2397 |
| 16 | Cl | 0.36±0.0 | 0.23±0.0 | 0.13±0.0 (0.10 to 0.17) | 0.000**** |

Where $X_{0.5}$, $X_1$, $X_2$, $X_3$, $X_4$, $X_6$, and $X_8$ represent average $C_{Met}$ at time 0.5h, 1 h, 2 h, 3 h, 4 h, 6 h, and 8 h respectively. Average $C_{Met}$ are given in units of ng/mL. $t_{1/2}$: Biological half-life in hours; $T_{max}$: Time taken to reach peak plasma concentration in hours; $C_{max}$: Peak plasma concentration in ng/mL; $AUC_{0-8}$: Area under the curve from 0 h to 8 h in ng/mL*h; $AUC_{0-inf}$: Sum of area under the curve from 0 h to 8 h and area under the curve from 8 h to time infinity in ng/mL*h. $AUMC_{0-inf}$: Total area under the first moment curve from 0 h to time infinity in ng/mL*$h^2$. MRT: Mean residence time in hours. V/F: Volume of distribution in (mg/kg)/(ng/mL); Cl/F: Apparent clearance in (mg/kg)/(ng/mL)/h

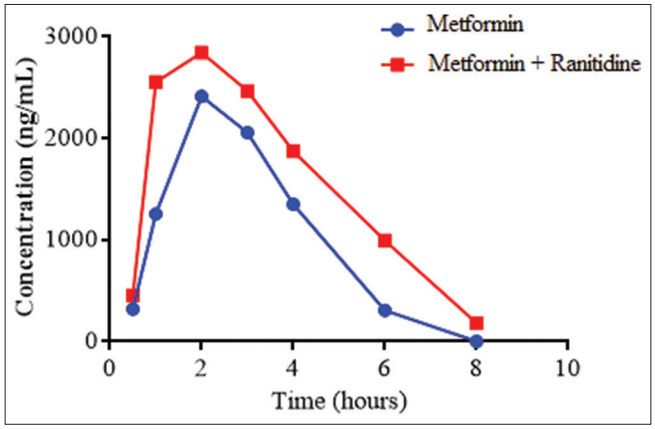


**Figure 2:** Time versus plasma concentration plot of metformin and metformin with ranitidine

Effect of metformin (30 mg/kg), ranitidine (5 mg/kg), and metformin (30 mg/kg) + ranitidine (5 mg/kg) on the blood glucose profile of rabbits was studied. Percentage blood glucose reduction was relatively increased in rabbits dosed with metformin (30 mg/kg) + ranitidine (5 mg/kg) than rabbits that received only metformin (30 mg/kg). No changes from the basal blood glucose levels were observed in rabbits that only received ranitidine (5 mg/kg) as shown in Figure 3.

Oral hypoglycemic actions of metformin as observed through reduction in basal blood glucose levels are more pronounced in presence of ranitidine. However, reduction in basal blood glucose levels was not evident in rabbits dosed only with ranitidine (5 mg/kg) due to lack of hypoglycemic properties. Thus, ranitidine increases the hypoglycemic actions of metformin by decreasing the clearance and increasing systemic exposure. Average blood glucose levels and average reduction from basal blood glucose levels are shown in Table 4.

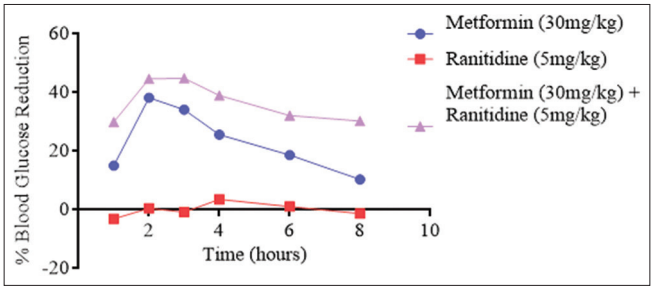


**Figure 3:** Percentage blood glucose reduction in study groups

Significant reduction in basal blood glucose levels was observed in rabbits dosed with metformin (30 mg/kg) as shown in Figure 4. Percentage reduction from basal blood glucose levels correlated with $C_{Met}$ suggesting a linear concentration-response relationship. However, no changes in blood glucose levels were observed in rabbits dosed only with ranitidine (5 mg/kg) as shown in Figure 5. Pre-treatment with ranitidine has increased percentage blood glucose reduction from basal values significantly with a linear concentration-response relationship as shown in Figure 6.

**Table 4:** Effect of metformin (30 mg/kg), ranitidine (5 mg/kg), and metformin (30 mg/kg) + ranitidine (5 mg/kg) on the blood glucose profile of rabbits

| Time (hours) | Blood glucose levels (mg%) | | | *P*-value | % Blood glucose change | | | *P*-value |
|---|---|---|---|---|---|---|---|---|
| | Group I | Group II | Group III | | Group I | Group II | Group III | |
| Fasting | 105.7±4.4 | 96.5±3.2 | 104.8±3.6 | 0.0060** | - | - | - | 0.000**** |
| 1 | 89.9±5.6 | 99.3±2.4 | 73.5±4.7 | | 15.1±3.6 | −3.1±2.4 | 30.0±3.7 | |
| 2 | 65.6±5.2 | 95.8±2.0 | 58.1±2.9 | | 38.2±3.2 | 0.5±2.6 | 44.7±1.0 | |
| 3 | 69.9±4.8 | 97.0±2.0 | 57.9±3.2 | | 34.2±1.9 | −0.8±2.4 | 44.9±1.4 | |
| 4 | 78.7±4.2 | 92.9±2.6 | 63.9±2.4 | | 25.7±1.9 | 3.5±2.3 | 39.1±0.7 | |
| 6 | 85.9±3.6 | 95.3±3.6 | 71.2±3.4 | | 18.7±1.5 | 1.1±3.7 | 32.2±1.5 | |
| 8 | 94.7±3.7 | 97.5±2.0 | 73.3±4.7 | | 10.4±1.7 | −1.3±2.3 | 30.3±2.2 | |

Data represented as Mean±SEM; *P* values retrieved through one-way analysis of variance ordinary measures; 95% CI

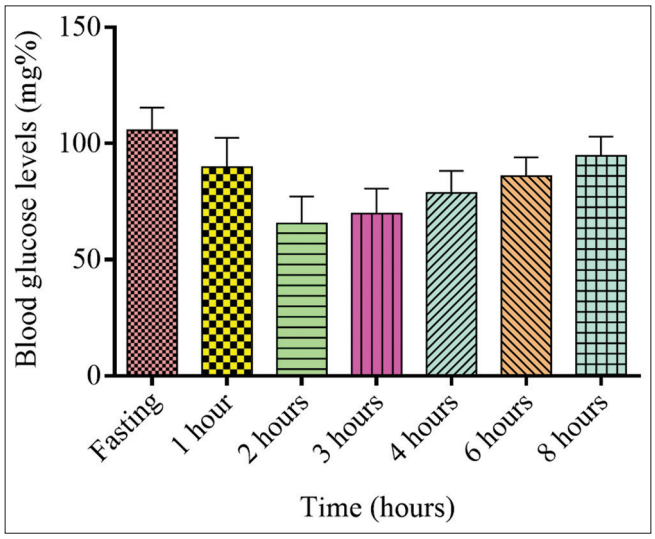


**Figure 4:** Effect of metformin (30 mg/kg) on blood glucose levels of rabbits. *P* = 0.000****, Total degrees of freedom = 34, F =9.554, 95% CI; *P*-value retrieved through one-way analysis of variance (ANOVA) repeated measures

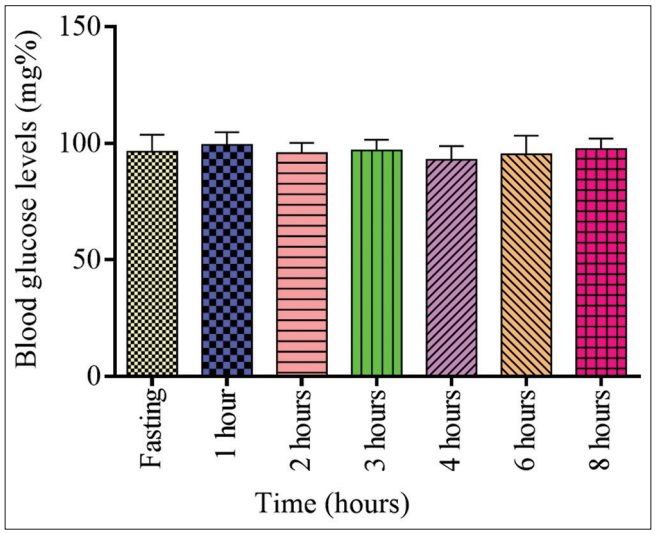


**Figure 5:** Effect of ranitidine (5 mg/kg) on blood glucose levels of rabbits. *P* = 0.1806, Total degrees of freedom = 34, F =1.971, 95% CI; *P* value retrieved through one-way ANOVA repeated measures

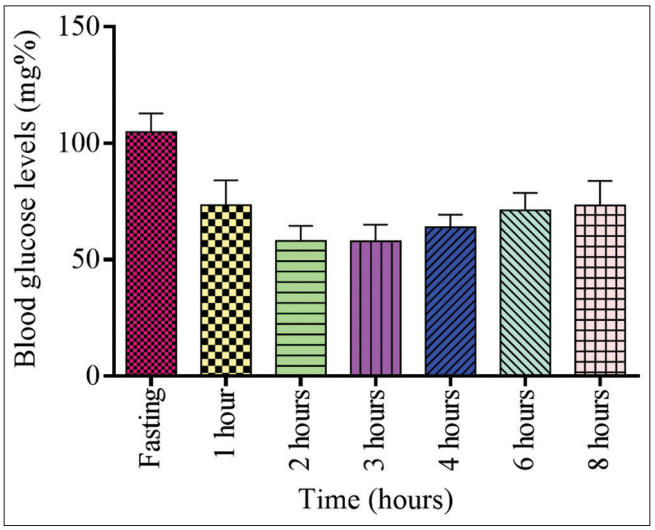


**Figure 6:** Effect of metformin (30 mg/kg) + ranitidine (5 mg/kg) on blood glucose Levels of rabbits. *P* = 0.1806, Total degrees of freedom = 34, F =1.971, 95% CI; *P* value retrieved through one-way ANOVA repeated measures

## DISCUSSION

Metformin, the first line agent for treatment of Type II diabetes mellitus is commonly prescribed with acid suppressing agents including $H_2$ receptor antagonists including ranitidine.[16] Being a cation at physiological pH, metformin depends on the solute lipid carrier system of transporters including OCT1.[17] $H_2$ receptor antagonists on the other hand are inhibitors of transporters drug transporters including multidrug and toxin extruders (MATE), OCTs and plasma membrane monoamine transporters.[18] Hence, concomitant administration of metformin and ranitidine together is postulated to decrease the renal elimination of metformin.[19] Although decreased renal clearance of metformin might increase its systemic bioavailability and more pronounced hypoglycemic effects, toxic plasma levels of metformin would be achieved in patients with underlying renal dysfunction. Metformin has been reported to cause lactic acidosis in patients with renal dysfunction and the risk of lactic acidosis is significantly increased in patients who are coadministered $H_2$ receptor

antagonists. Significant increase in the AUC of metformin was observed when animals were pre-treated with ranitidine. Famotidine, a selective inhibitor of MATE1 has been shown to increase metformin systemic bioavailability and a transient increase in the pharmcodynamic response to metformin.

## CONCLUSION

This study aimed to investigate the potential interaction between ranitidine and metformin. The results of the study showed that ranitidine decreased the clearance of metformin by inhibiting the organic cation transporter 1 (OCT1), which is responsible for the uptake of metformin into the liver. This inhibition resulted in increased exposure to metformin, and subsequently, a greater percent reduction in glucose levels. While the study demonstrated the potential for ranitidine to enhance the therapeutic effect of metformin, it also highlighted a significant safety concern. The increased exposure to metformin may increase the risk of developing lactic acidosis, a serious complication of metformin therapy. This is particularly relevant as lactic acidosis is already a rare but life-threatening side effect of metformin, and the increased risk associated with this drug interaction may make it a serious concern for patients. In summary, the study provided valuable insight into the potential interaction between ranitidine and metformin, however, it also highlighted the need for further research to confirm the safety and efficacy of this drug interaction in human subjects. Clinicians should be aware of this potential interaction and monitor their patients closely when both drugs are being used concomitantly.

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