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INFLUENCE OF PIPERINE ON PHARMACOKINETICS OF ZOLMITRIPTAN IN RATS: INVOLVEMENT OF CYP3A METABOLISM

Ravi Prakash Degala[1*], Govinda Rao Kamala[2], N. Suvarna Jyothi[3], P. Anusha[4] and D. Surya Tejaswini[5]

[1-5]Department of Pharmacology, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh-533461.

***Corresponding Author: Ravi Prakash Degala**
Department of Pharmacology, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh-533461.

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ABSTRACT
Zolmitriptan is a second generation triptan effective medicine used in the treatment of migraine headaches. Piperine (1-piperoylpiperidine) is the world's first reported bio enhancer alkaloid was found to enhance bioavailability of structurally and therapeutically diverse drugs. It was main pungency principle in both black and long pepper. In this study the pharmacokinetic profile of zolmitriptan after oral administration of zolmitriptan (0.5mg/kg) alone and in combination with piperine (10mg/kg) to rats were investigated via validated HPLC method. The blood samples were collected at various time points such as 0(predose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12, 24 hours post treatment. As the *Invivo* pharmacokinetic studies had indicated, the Cmax, Tmax, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, AUC%, $AUMC_{0\text{-}24}$, $AUMC_{0\text{-}\infty}$, $t_{1/2}$, $MRT_{0\text{-}24}$and $MRT_{0\text{-}\infty}$ were increased by approximately 77.63%, 24%, 66%, 77.86%, 44.51%, 77.40%, 114.64%, 21.90%, 6.82% and 21.98% respectively, where as clearance and volume of distribution decreased by 50% and 32% when zolmitriptan co-administered with piperine. In conclusion, our study demonstrated that piperine significantly improved the *Invivo* bioavailability of zolmitriptan and the influence of piperine on the pharmacokinetics of zolmitriptan may be attributed to the inhibition of CYP3A and P-gp in rats. Further research needed to investigate detailed mechanism of improved bioavailability of zolmitriptan via its combination with piperine. This observation suggests the possibility that the combination of piperine with other CYP3A and P-gp dual substrates may also improve bioavailability.

KEYWORDS: Zolmitriptan, Piperine, Bioavailability, Pharmacokinetics, P-glycoprotein, Cytochrome P-450.

INTRODUCTION
Migraine is a neurovascular disorder which involved dilatation of cerebral arteries and is commonly associated with symptom such as nausea, sensitivity to light or sound, vomiting, and urinary frequency. Approximately 20% of women and 8% of men suffer from periodic episodes of migraine headaches. Migraine is the most common disease in patients between 30 and 50 years of age.[1, 2]

Triptans are serotonin 5-hydroxytryptamine receptor agonists. They are generally effective and are used to treat migraine pain and certain other headaches. They can be taken as tablets, capsules, quick-dissolving wafers, or intranasal spray.[3] Zolmitriptan is one of most common type of Triptans which inhibits the peripheral trigeminovasular system and able to access central sites in the brain stem. Zolmitriptan occurs at low blood levels after therapeutic administration. It has low bioavailability (approximately 40%) when administered orally due to hepatic first pass metabolism.[4]

Piperine (PIP) is a dietary alkaloid, major component of black pepper (Piper nigrum Linn) and has been used as spice and nutrient enhancer.[2] Piperine exhibits a numberof health-promoting effects, such as antioxidant, antimutagenic, anti-ulcer, anti-inflammatory and antitumoractivities.[5,6] Previous studies have demonstrated that piperine enhances the bioavailability of many structurallyand therapeutically diverse drugs, such as phenytoin[7-9] carbamazepine[10], midazolam[11], propranalol and theophylline.[12] Piperine has been reported to act as an inhibitor of pathways mediated by P-glycoprotein (P-gp), an efflux membrane transporter, and several cytochrome P450 enzymes (CYP) as wellas of phase II metabolism.[13-16] Results of in vitro studies also indicate that piperine inhibits CYP3A4, CYP2C9 and UDP glucuronyl transferase dependent metabolism.[17] It also has been shown to alter the pharmacokinetics of the P-gp and CYP substrates domperidone[18] and fexofenadine (FEX)[19] in rats through inhibition of P-gp-mediated drug efflux.

In this study, we hypothesized that if Piperine acts as an inhibitor of CYP3A and P-gp mediated drug efflux,

possibly in the intestine and liver, it will enhance the bioavailability of zolmitriptan, a CYP3A and P-gp substrate. To our knowledge, there are no published studies regarding to interaction between Piperine and zolmitriptan. Therefore, we investigated the pharmacokinetic profile of zolmitriptan after oral administration of zolmitriptanalone and in combination with piperine in rat model.

MATERIALS AND METHODS

Drugs and chemicals

Zolmitriptan was obtained as a gift sample from NATCO Pharma; Hyderabad (India). Piperine was purchased from Sigma-Aldrich Chemical Co., St. Louis, MO, USA. All HPLC grade solvents (acetonitrile, Sodium Lauryl Sulfate, Ortho Phosphoric Acid, and water) were procured from MERCK. All other chemicals used were of analytical grade and purchased from local chemical agencies.

Animals

Albino Wistar rats (National Institute of Nutrition, Hyderabad, India), of either sex, weighing 200–250 g, were selected. Animals were maintained under standard laboratory conditions at 25 ± 2ºC, relative humidity 50 ± 15% and normal photoperiod (12 h dark/12 h light). Commercial pellet diet (Rayon's Biotechnology Pvt Ltd, India) and water were provided *ad libitum*. The studies were carried out for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India.

Pharmacokinetic study in rats

Preparation of drugs

Zolmitriptan was dissolved in distilled water where as piperine (10mg) was accurately weighed before being triturated in a dry clean mortar with an addition of 30µL of tween 80 and then, required volume of 0.9% sodium CMC was added and triturated again to suspend the drug in it. Then, suspension was transferred to plastic vials. Piperine suspension was administered concomitantly with zolmitriptan solution to the animals within 10 minutes of the preparation of the suspension**.**

Experimental procedure

Wistar rats were randomly distributed into two groups of six animals in each group. Before doing, all experimental animals were fasted for 18 h and but water was given *ad libitum.* Experimental design was as follows.

Group I: Zolmitriptan (0.5 mg/kg; p.o.),

Group II: Zolmitriptan (0.5 mg/kg; p.o.), + Piperine (10 mg/kg; p.o.).

Blood sample collection from rats

In this study, blood samples were collected from retro-orbital sinuses using 2 ml eppendorf tubes containing sodium citrate as an anticoagulant at time points 0(predose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12, 24 hours post treatment. Plasma was separated by centrifugation at 5000 RPM/10 min and stored at −20°C until further analysis. Plasma concentration of zolmitriptan was estimated by a validated HPLC method.

Estimation of Zolmitriptan in plasma by a sensitive HPLC method

The zolmitriptan in plasma samples was estimated by HPLC using internal standard method. For this purpose a calibration curve was constructed by analyzing plasma samples containing different concentrations of zolmitriptan.

Standard solutions

Primary stock solution of 1mg/ml of zolmitriptan was prepared in methanol. Appropriate dilutions of zolmitriptan from stock solution were made in mobile phase to produce working stock solutions of 0.05, 0.10, 0.25, 0.50, 1, 2 and 4 µg/ml. these dilutions were used to spike plasma in the preparation of calibration of curve. Zolmitriptan spiked plasma samples were prepared by mixing 1 ml blank plasma with appropriate volumes of the standard zolmitriptan solutions (100µL) on the day of the analysis. A blank was also prepared containing 1 mL blank plasma.

Extraction procedure

Plasma was spiked with varying quantities of zolmitriptan stock solution was prepared, so as to give a series of drug concentrations ranging from 0.05 to 4 µg/ml. 100µL of spiked plasma was taken and to this 25µL of internal standard (Diphenhydramine stock solution 10µg/mL in methanol) was added and then vortexed (Vortex mixer, Genei, Mumbai) for 60 seconds. Then 500µL of methanol was added to precipitate proteins and vortexed for 5 min and centrifuged at 5000 rpm in a micro centrifuge (REMI Scientifics, India) for 10 min. supernatant was taken and dried in vacuum oven at 40^{o}C. Dried samples were then redispersed in 100µL methanol and vortexed. The supernatant was transferred in to a microcentrifuge tube and from this 20µL was injected for HPLC analysis.

Chromatographic conditions

A quaternary gradient HPLC (Waters Delta prep HPLC system, USA) with a rheodyne manual injector (Rheodyne, Cotati, CA, USA) attached with a 100µL sample loop was used for loading the sample. A variable wavelength programmable photo diode array (PDA) detector (Waters 2999 PDA, USA) and reversed phase C-18 column {(250mm×4.63mm ID; particle size (5µm) (waters associates)} was used. The HPLC system which was equipped with the EMPOWER 2 software (Waters, Milford, MA, USA) was used for data acquisition and processing.

The mobile phase consisted of Phosphate buffer and Acetonitrile (15mM) {(80:20, v/v)}. The pH of the mobile phase was adjusted to 4±0.1 with orthophosphoric acid. The filtered mobile phase components were pumped from the respective reservoirs at the flow rate of 1ml/min. the column temperature was

maintained at room temperature (30°C). The eluent was detected by a PDA detector at a wavelength of 248 nm.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using the Try-kinetica software trial version 5.0. When "NCA assistant-non-compartmental-extra vascular" page was opened. Units of time points and concentrations were given. Then, various time points and corresponding concentrations (for which PK parameters to be determined) were entered into the page of "NCA assistant-non-compartmental-extra vascular". Once the data was entered, analyze button was clicked and then a graph was appeared. Study button was pressed to see few PK parameters. For getting complete PK parameters, dose of zolmitriptan 0.5 mg/kg was entered in the dose option. Then, data was again analyzed by clicking on analyze. Then, two line graphs were appeared. Then, study option was clicked to see the complete PK parameters of zolmitriptan. Each animal data was given and PK parameters were calculated for each animal data. Then, average of one PK parameter for the all the animals of a same group was taken. This data was subjected to statistical analysis.

Statistical Analysis

The results were expressed as mean ± S.D. Comparisons of plasma concentration vs. time profiles of zolmitriptan alone group and zolmitriptan with the piperine combination group were analyzed using two-way ANOVA followed by Bonferroni post hoc test whereas comparisons of pharmacokinetic parameters of these two groups were analyzed using unpaired student's *t* test. *P<0.05, **P<0.01, ***P<0.001 were considered as statistically significant.

RESULTS

Calibration curve

The run time was set at 10min and zolmitriptan and internal standard appeared on the chromatogram at 8.425 min and 5.372 respectively as shown in fig.no.2 to 4. There was no interference of any other peak with drug peak. When the same sample containing drug was injected six times, the retention time of the drug was almost same for all the six injection samples. The mean peak area of eletriptan and its respective peak areas were subjected to regression analysis by least square method, and high correlation coefficient was observed (r=0.999) in the range of 0.05-4µg/mL. The regression of zolmitriptan concentration over its peak area was found to be Y = 1.766x + 0.077 with a high correlation coefficient, where Y is peak area and X is plasma concentration of zolmitriptan. This regression equation was used to estimate the amount of zolmitriptan in plasma. Calibration values were shown in table 1 and Linearity graph was shown in Figure 1.

Table 1: Calibration of the HPLC method for the estimation of Zolmitriptan in plasma by using Diphenhydramine as internal standard.

SI. No	Plasma concentration of Zolmitriptan (µg/ml)	Mean peak area of Zolmitriptan	Mean peak area of internal standard	Mean peak area ratio
1.	0.05	56903.25	405612.58	0.140
2.	0.10	101259.38	403909.02	0.251
3.	0.25	229856.27	410815.38	0.560
4.	0.50	407206.86	399057.59	1.020
5.	1	754964.13	404718.94	1.865
6.	2	1419508.75	411076.27	3.453
7.	4	2913084.08	404209.73	7.207

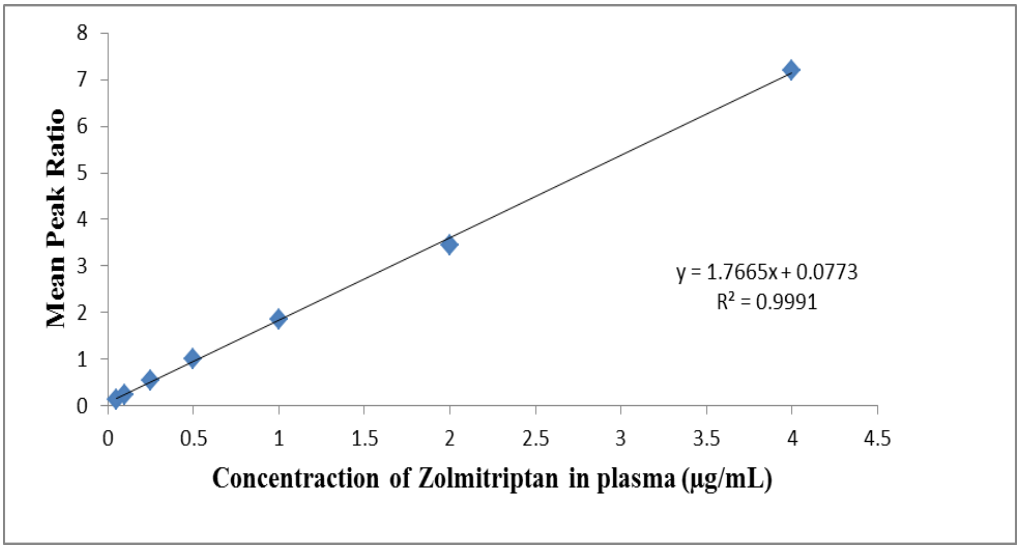


Figure 1: Calibration curve for the estimation of eletriptan in plasma.

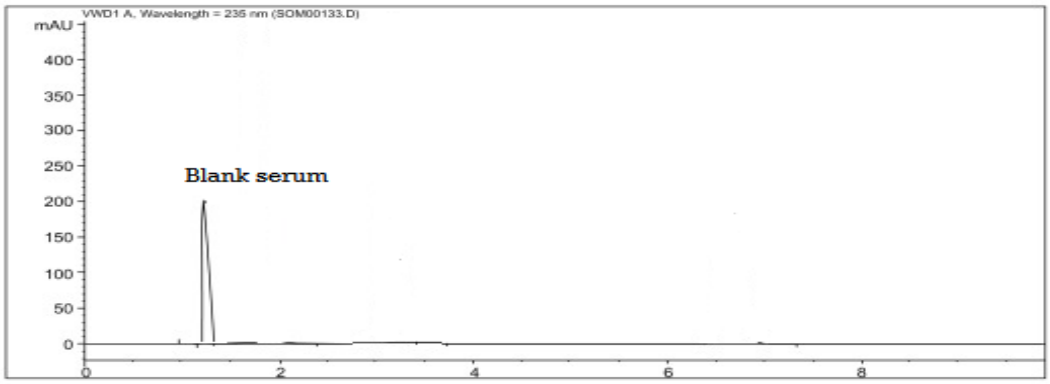


Figure 2: HPLC chromatogram of blank plasma.

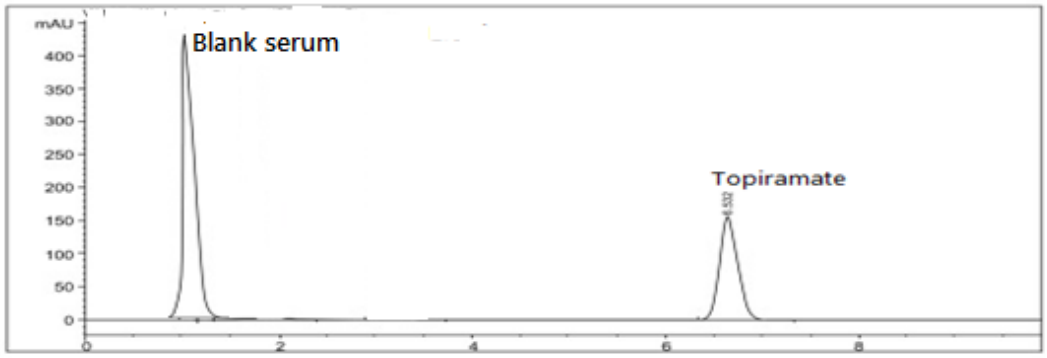


Figure.3: HPLC chromatogram of blank plasma with internal standard (Diphenhydramine).

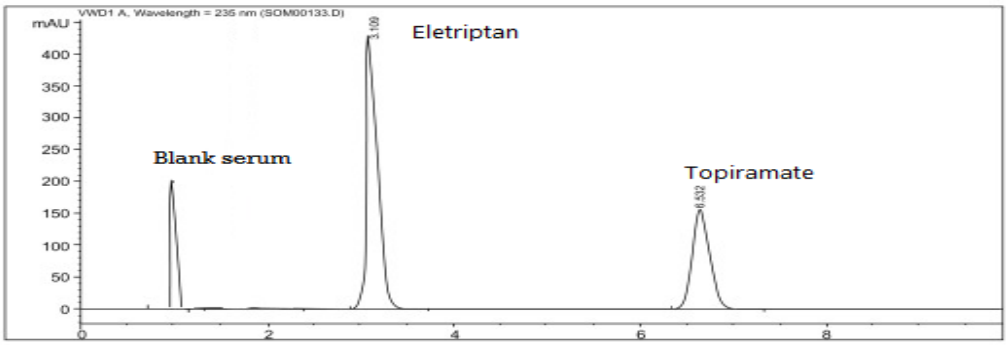


Figure 4: HPLC chromatogram of spiked plasma with Zolmitriptan.

Effect of Piperine on plasma concentration time profiles of Zolmitriptan

The plasma concentration vs time profiles of zolmitriptan in rats following oral treatment of zolmitriptan with and without piperine were shown in table no.2 and figure no 5. From the comparison of plasma concentration profiles of zolmitriptan in the absence and presence of piperine, it is clear that there was a significant increase in the plasma drug exposure of zolmitriptan in the combination group at following time points 0.5hr (^{ns}P> 0.05), 1.0 hr(^{ns}P> 0.05), 1.5 hr (^{ns}P> 0.05), 2.0 hr (***P<0.001), 2.5 hr (***P<0.001), 3.0 hr (***P<0.001), 3.5 hr (**P<0.01), 4th hr (***P<0.001), 6.0 hr(**P<0.01), 8.0 hr (**P<0.01), 12.0 hr (^{ns}P>0.05) and 24.0 hr (^{ns}P>0.05).

Table 2: Summary of mean plasma concentrations of zolmitriptan treated group and zolmitriptan with piperine treated group – single dose study.

Time Points (hr)	ZOLMITRIPTAN (2mg/kg)		ZOLMITRIPTAN (0.5mg/kg) + PIPERINE (10 mg/kg)			
	MEAN	S.E.M	MEAN	S.E.M	P value	Summary
0	0.00	0	0.00	0	P > 0.05	Ns
0.5	51.88	6.38	62.68	4.73	P > 0.05	Ns
1	85.44	7.68	106.31	3.16	P > 0.05	Ns
1.5	125.66	7.63	168.18	4.54	P<0.001	***

2	137.19	6.22	208.03	3.35	P<0.001	***
2.5	134.01	8.95	268.38	5.02	P<0.001	***
3	113.07	6.22	220.94	8.52	P<0.001	**
3.5	99.82	5.92	172.94	7.66	P<0.001	***
4	86.28	6.07	144.86	10.60	P<0.001	***
6	71.08	5.11	101.81	9.28	P<0.01	**
8	44.67	5.25	77.97	4.56	P<0.01	**
12	28.40	3.68	48.75	3.15	P > 0.05	Ns
24	12.45	1.31	25.91	1.15	P > 0.05	Ns

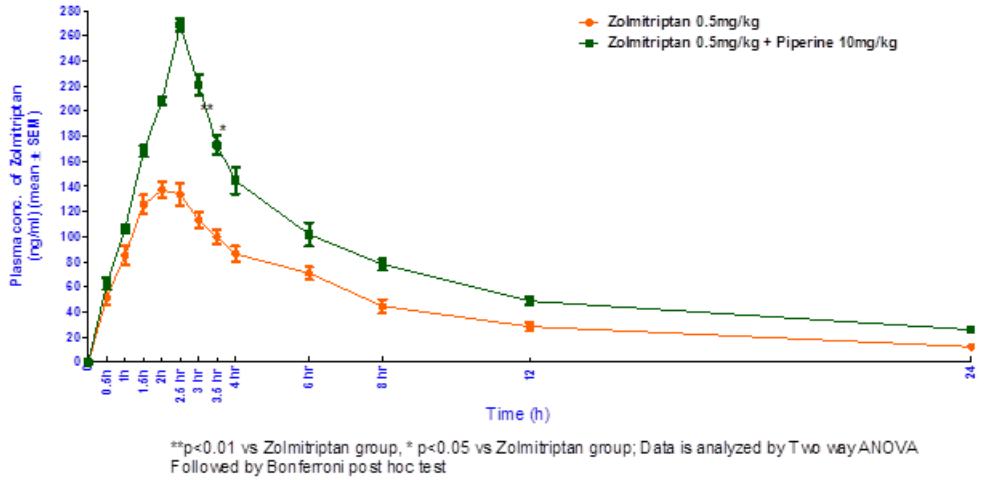


Figure 5: Comparison of mean plasma concentrations of Zolmitriptan treated group and zolmitriptan with Piperine treated group – single dose study.

Effect of Piperine on pharmacokinetic parameters of Zolmitriptan

The calculated pharmacokinetic parameters of zolmitriptan alone and zolmitriptan with piperine in rats were shown in Table 3. The AUC_{0-24} of zolmitriptan has significantly (p<0.001) increased in the combination group (1743.06 ± 68.97**) than AUC_{0-24} of zolmitriptan of zolmitriptan alone treated group (1050.00±72.48). This increase is almost 1.6 times. In similar manner, the $C_{max}$of zolmitriptan has significantly (p<0.01) increased in the combination group (268.4±5.01***) than $C_{max}$of zolmitriptan of zolmitriptan alone treated group (151.1±3.05). This increase is almost 1.7 times. Compared with the zolmitriptan alone group, the AUMC, MRT, $t_{1/2}$significantly (p<0.001) increased when zolmitriptan combined with piperine (combination group). In contrast, the clearance of combined group (0.0002±0.000008***) significantly (p<0.001) decreased when compared with zolmitriptan alone group (0.0004±0.00002). The T_{max} and volume of distribution of combined group not significantly altered when compared with alone group. The pharmacokinetic parameters were represented in table.no.3 and expressed in histogram no.1.

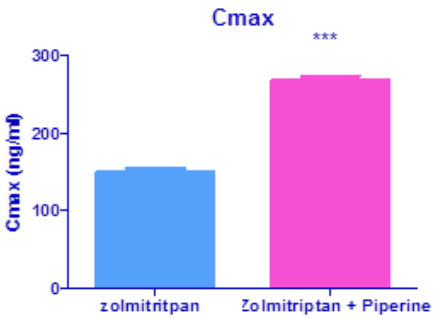
The percentage change of various pharmacokinetic parameters like Cmax, Tmax, AUC_{0-24}, $AUC_{0-\infty}$, AUC%, $AUMC_{0-24}$, $AUMC_{0-\infty}$, $t_{1/2}$, MRT_{0-24} and$MRT_{0-\infty}$ were increased by approximately 77.63%, 24%, 66%, 77.86%, 44.51%, 77.40%, 114.64%, 21.90%, 6.82% and 21.98% respectively, where as clearance and volume of distribution decreased by 50% and 32% after treatment with piperine (table.no.3).

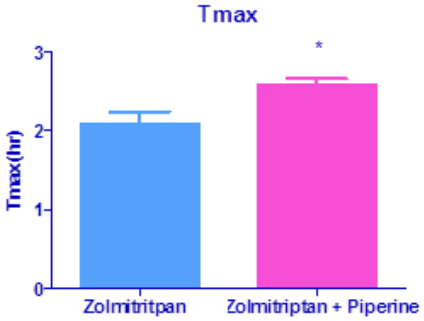
Table 3: Summary of pharmacokinetic parameters estimated following the oral administration of zolmitriptan alone group and zolmitriptan with Piperine combination group – single dose study.

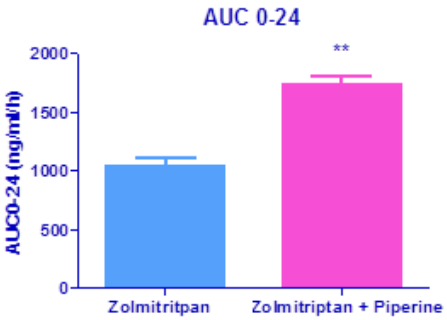
Pharmacokinetic Parameters	Zolmitriptan alone	Zolmitriptan with Piperine	% Change after treatment with Piperine
C_{max}(ng/mL)	151.1±3.053	268.4±5.019***	77.63
T_{max}(hr)	2.083±0.153	2.583±0.083*	24
AUC_{0-24} (ng.hr/ml)	1050.00±72.48	1743.06±68.97**	66
$AUC_{0-\infty}$(ng.hr/ml)	1188.06±89.20	2113.14±76.01***	77.86
AUC%	12.22±0.87	17.66±0.95**	44.51
$AUMC_{0-24}$ (ng/ml/h*h)	7852.72±781.3	13930.13±622.2***	77.40
$AUMC_{0-\infty}$ (ng/ml/h*h)	13180±1438	28290±1307***	114.64
$t_{1/2}$ (h)	8.172±0.53	9.961±0.31*	21.90
MRT_{0-24} (hr)	7.47±0.21	7.98±0.06*	6.82

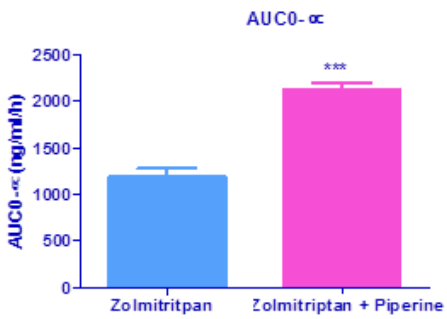
$MRT_{0-\infty}$ (hr)	10.96±0.47	13.37±0.36**	21.98
Clearance (L/h)	0.0004±0.00002	0.0002±0.000008**	-50
Volume of distribution (V_d) (L)	0.005±0.0003	0.0034±0.0001*	-32

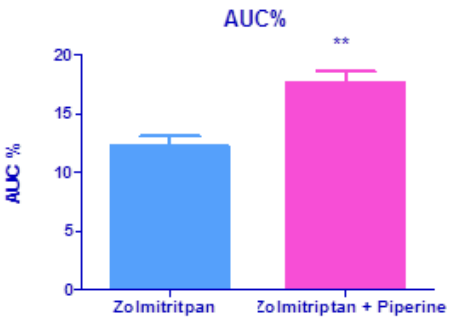
Values are the Mean± S.E.M. of six rats.***p<0.001 vs Zolmitriptan group, **p<0.01 vs Zolmitriptan group, * p<0.05 vs Zolmitriptan group; Data is analyzed by unpaired student's *t* test.

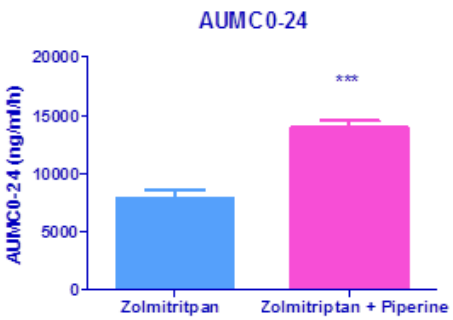


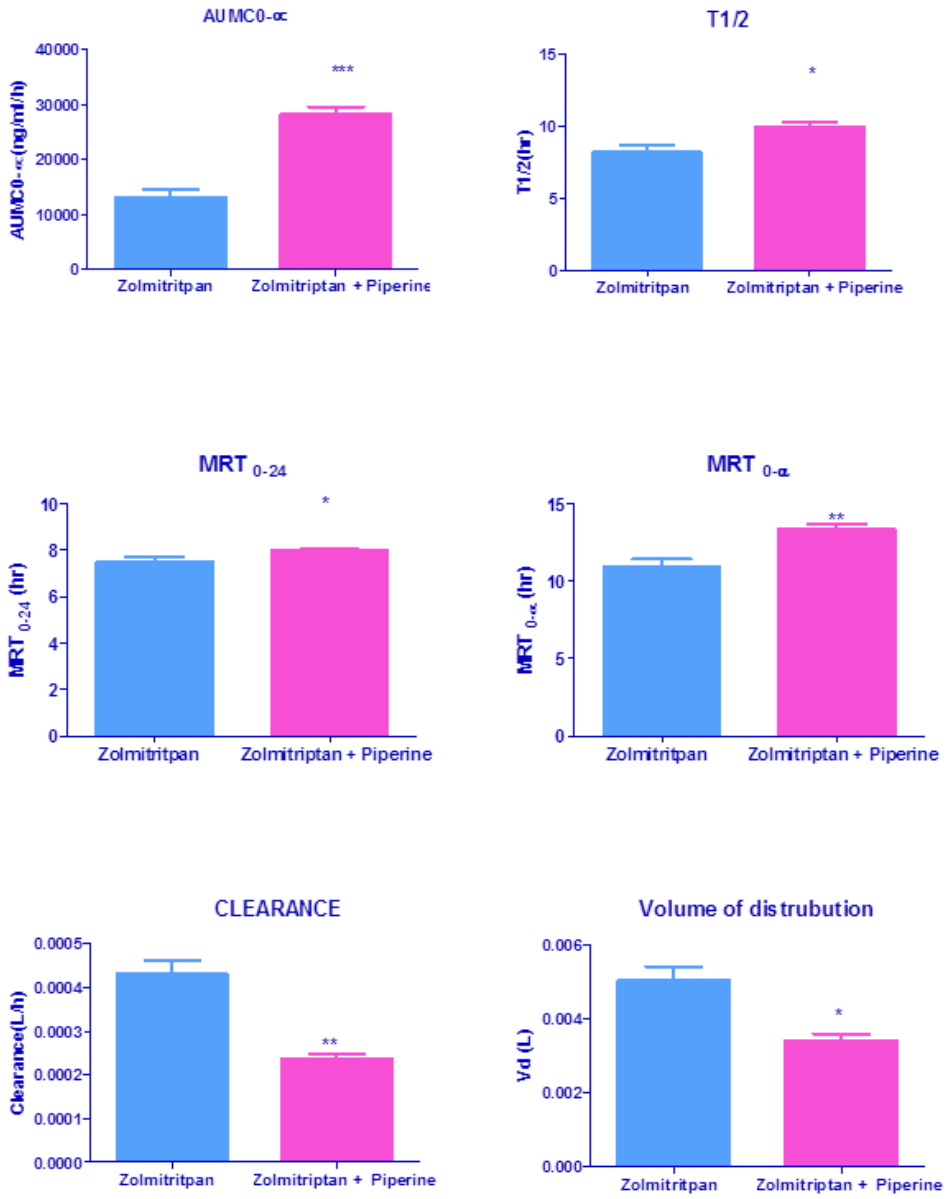












Histogram 1: **Summary of pharmacokinetic parameters of zolmitriptan alone group and zolmitriptan with Piperine combination group – single dose study.**

DISCUSSION

The results of the study showed piperine pretreatment can significant enhance bioavailability and decrease clearance of zolmitriptan when compared to control. Our results can demonstrate a possible relation between zolmitriptan concentration and CYP3A activity. This enzyme has an important role in microsomal drug metabolisms. Thirty percent of cytochrome P450 enzymes of liver are made of CY3A4.[20] It has been estimated that CYP3A4 is responsible for 50 percent of the metabolism of all drugs that being eliminated via hepatic microsomal enzymatic system.[21] In addition to having an active role in hepatic metabolism of drugs, CYP3A4 is sufficiently active in the small intestine.[22, 23] CYP3A4 is active in the metabolism of lipophilic substrates such as fentanyl, alfentanil, oxycodone, and methadone.[24] CYP3A4 inhibitors that have been well studied include: azole antifungal agents and a number of the macrolide antibodies. There are clinically important examples such as midazolam, alprozolam, atorvastatin, simvastatin, felodipine, nifedipine, and cyclosporine that are affected by this system.[25] Among the CYP3A substrates, zolmitriptan was one of the substrate of CYP3A. The metabolism of zolmitriptan can reflect to the rate of hepatic CYP3A activity in both intestine and liver. Any changes in CYP3A enzymatic pathway, may affect zolmitriptan metabolism.

In the present study piperine the main alkaloid of black pepper, could significantly prolong life time of zolmitriptan in rats. This may increase the pharmacologic activity and can induce and prolong anti-

migraine properties of the drug. These effects of piperine may be the result of inhibition of CYP3A4 activity. Previous animal studies have demonstrated that piperine inhibits several CYP450 mediated pathways.[26] Piperine is a selective non-competitive inhibitor of CYP3A but has lower activity on the other microsomal enzymes. It can inhibit activity UDP-glucuronosyltransferase as well.[27] In the present study administration of piperine can change the important pharmacokinetic parameters of zolmitriptan. It means that piperine's direct effect on zolmitriptan elimination is not assumed and it can increase the half-life of zolmitriptan via inhibition of its hepatic microsomal elimination. The inhibition or induction of enteral CYP3A4 and p-glycoprotein can mediate considerable drug interactions. These of interactions may be due to a considerable variation in drug action from no effect to toxic effect of drugs.[28]

The genes of CYP3A4 and p-glycoprotein are expressed in enterocytes and the bioavailability of many drugs such as cyclosporine A, midazolam, verapamil, HIV protease inhibitors and digoxin could be affected by the enzyme and transporter.[28, 29] The Metabolism of zolmitriptan can show the activity of both hepatic and intestinal CYP3A. Piperine inhibits p-glycoprotein and CYP3A activity. Since, these proteins become expressed in enterocytes and hepatocytes; they have an effective role in first-pass metabolism of subject drugs. Piperine content of nutritional regimen can change the levels of p-glycoprotein and CYP3A substrates in blood. However more researches are needed to prove intestinal or hepatic effects of piperine, especially to justify their mechanism in the present study.

CONCLUSION

The improvement in absorption of zolmitriptan may be due to the inhibition of P-gp and CYP3A inthe intestine and liver by piperine. Piperine enhanced the oral pharmacokinetics of eletriptan, suggesting that combined use ofpiperine and zolmitriptan may be useful inreducing the dose of zolmitriptan and require closemonitoring of potential drug interactions in migrainepatients. The combination of piperine with anyother CYP3A enzyme series and P-gp dual substrate may improve absorption of drugs which have poor oralbioavailability. Further studies are recommended toverify their influence in humans.

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