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A Study on the Effect of Pantoprazole on Pharmacokinetic and Antidepressant Activity of Fluoxetine

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ABSTRACT

Peptic ulcer and Depression are managed by co-administering number of drugs for long duration. Hence, drug-drug interactions which are important cause of antagonistic drug reaction and may lead to amplified risk of hospitalization and amplified care cost. The study was piloted to find the impact of pantoprazole which is generally used for primary peptic ulcer disease in humans on the pharmacokinetic and antidepressant activity of fluoxetine. The influence of pantoprazole on pharmacokinetic parameters of fluoxetine was studied in healthy male albino rabbits. The effect of pantoprazole on antidepressant activity was studied using four animal models. The serum concentration of fluoxetine was estimated by HPLC. And the antidepressant activity was studied using despair swim test, compulsive gnawing test, serotonin syndrome and tail suspension test. After treating with pantoprazole for 7 days the concentration of serum fluoxetine was significantly decreased at 2nd, 4th, 8th, 16th and 24th hour. Pantoprazole treatment for one week exhibited significantly changes in the pharmacokinetic parameters like AUC, AUMC, t1/2 and Cmax of fluoxetine in healthy albino rabbits. The immobility time significantly decreases after pantoprazole treatment for one week by despair swim and tail suspension test in rats and mice respectively. Compulsive gnawing test and serotonin syndrome also shows decrease in the effect after pantoprazole treatment. When both drugs are co-administered together dose of fluoxetine should be increased.

Key words: Depression; Fluoxetine; Pantoprazole; Drug-drug interaction; Tail Suspension test; Despair Swim Test.

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INTRODUCTION

Drug-drug interactions may occur when more than one therapeutic agent are administered in a patient to treat a single ailment or multiple ailments. The concomitant use of multiple drugs is often desired to obtain a therapeutic objective or to treat co-existing ailments. Simultaneous use of several therapeutic agents may lead to drug-drug interactions, results in altered patient's response to therapy which may be seen by enhanced or diminished effects of one or both of the drugs or the appearance of a new effect which is not seen with either drug alone. There are several diseases which require lifetime treatment for their management such as hypertension and diabetes. Patients with such diseases are often prescribed with multiple drugs for the treatment of other coexisting diseases, which might be either for a short period of time or lifelong. So, while prescribing medication it is important to determine the incidence and frequency of occurrence of drug interactions, which shows serious implications in hospitalized patients. In addition, it is also important to find out agents that are most likely to produce hazardous interactions. In this present study, an attempted has been made to find out the possibilities of occurrences of interactions between simultaneously used drugs prescribed for treatment of the two diseases namely; Peptic ulcer and depression which may co-exist and require chronic treatment [1-5].

Peptic ulcer is the gastro intestinal disorder which occurs due to an imbalance factor like acid pepsin, helicobacter pylori and defensive factors like gastric mucus and bicarbonate secretion, prostaglandins, and innate resistance of the mucosal cells factors. Development of ulcer disease and death from it has been associated with the birth of urbanization and was interpreted as a birth-cohort event with the peak of disease in those born during thelate19th century [6-8].

According to the latest WHO data published in 2011, PUD deaths in India reached one lakh eight thousand three hundred and ninety three or 1.20% of total deaths, being ranked 5th position in the world [9].

Depression is an extremely common psychiatric condition, about which a variety of neurochemical theories exist and for which a corresponding variety of drug are used in treatment. At any given moment, about 5 to 6% of the population is depressed (point prevalence), and an estimated 10% of population may become depressed during their lives (life time prevalence).The symptoms of depression are often subtle and unrecognized both by patient and physicians. Major depressive disorder has a lifetime prevalence of approximately 9.15% and perhaps as high as 20% in women. The mean age of onset is 35-40 years, although onset can be at any age. There are specific

correlations with socioeconomic stress. In this present study possible interaction between an antiulcer drug (pantoprazole) and antidepressant drug (fluoxetine) was determined [10-11].

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H +, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H+, K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested [12].

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) and prescribed for the treatment of depression. Fluoxetine acts by desensitization of 5-HT1A somatodendritic receptors and 5HT1B nerve terminal auto receptors. However, there is no any literature regarding interactions between pantoprazole and fluoxetine has been reported [13].

Compounds which stimulate serotonin receptors or which increases dramatically the serotonergic transmission in the CNS cause a series of behavioral changes in rats which is called the serotonin syndrome such as head weaving, increased locomotion, forepaw treading, tremor, hind limb abduction, flat posture and lower lip retraction. With increasing knowledge about the subtypes of serotonin receptors these symptoms were defined to be associated with 5-HT receptors and their specific agonists. The behavioral motor syndrome (5-HT syndrome) can be elicited by injecting, the serotonin precursor. The serotonin syndrome in rats has been used to study the interaction of drugs with central 5-HT system of rats. It is also used for the screening of the psychoactive drugs and this method offers several advantages like this is fast, require no elaborate equipment and provide information on CNS permeability etc[14].

The main objective of the present study was to assess the effect of pantoprazole on pharmacokinetic and antidepressant activity of fluoxetine in healthy rat, mice and rabbits and also to suggest the alterations in the dose and frequency of administration of fluoxetine, if necessary. Interaction between fluoxetine and pantoprazole could be due to their strong protein binding and by similar metabolic pathway. When both of the drugs are given together fluoxetine dose should be increased.

MATERIALS AND METHOD

Chemical used: Pure sample of Fluoxetine and pantoprazole was obtained as a gift sample from Time Pharma, Nepal. Surgical spirit, Methanol, Acetonitrile were procured from S.D Fine chemicals, Mumbai, India. All the chemicals used were of analytical grade.

Animal used: Rabbits (2-2.5 kg), rats (150-200 gm), mice (18-22 gm). All animal used were male sex and albino species.

Ethical approval: The study protocol was approved by Institutional Animal Ethics Committee (IAEC), Mallige College of Pharmacy, Bangalore.

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HOUSING OF EXPERIMENTAL ANIMALS

Rabbits were housed in stainless steel cages with a fenestrated Floor to allow faeces to drop through into a pan and were provided with regular rabbit chow. Rats are housed in separate clean cages. The bedding material of the cages rats were removed and replaced thrice a week with fresh materials as often as necessary to keep the animals clean and dry. The animals were provided with distilled water ad libitum throughout the experiment. The rats were fed with standard pelleted diet. The animals were acclimatized to standard laboratory conditions of temperature (25 ± 3°) and maintained on 12:12 h natural light: dark cycle. The animals were maintained under standard conditions in an animal house approved by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

EXPERIMENTAL PROCEDURE

Effect of Pantoprazole treatment on pharmacokinetic parameters of Fluoxetine in Healthy albino rabbits:

Four male albino rabbits were taken and marked suitably. Rabbits were fasted for 18 h before commencing the experiment and the blood was collected (at '0' h) before the administration of fluoxetine. Later all the rabbits received fluoxetine (10 mg/kg) solution orally, the time of administration was noted. Blood samples were collected thereafter at prefixed time intervals i.e. 0, 2, 4, 8, 16 and 24 h after dosing. Blood samples were collected in tube, kept a side and centrifuge for 15-20 min at 3000 rpm to collect serum. Serum samples were stored at 2-8° for analysis. After blood collection animals were left for a washout period of 15 days with normal diet. The next part of this experiment was conducted on the same group of animals. All the rabbits received pantoprazole (10 mg/kg) orally once a day for one week. On the 7th day, 6 h after administration of the drug, the rabbits were fasted for 18 h. On the 8th day, pantoprazole (10 mg/kg) was administered orally to all the animals; the time of administration was noted. After 60 min of pantoprazole administration, fluoxetine (10 mg/kg) was given orally. Blood samples were collected in a blood collection tube at prefixed time intervals i.e. 0, 2nd, 4th, 8th, 16th and 24th h after fluoxetine dosing, serum was separated from blood and stored at 2-8° for analysis. The serum concentration of fluoxetine was estimated by High Performance Liquid Chromatography method [15-16].

Effect of pantoprazole treatment on antidepressant activity of fluoxetine in healthy albino rat by despair swim test:

Six Male albino rats were brought to the laboratory one day before the experiment and were housed separately in cages with free access to food and water. The apparatus vertical Plexiglas cylinder (height: 40 cm; diameter: 18 cm) is used, which containing 15 cm of water maintained at 25°. The rats are individually forced to swim in that cylinder for the first time are initially highly active trying to escape from by climbing the wall or diving to the bottom and vigorously swimming in circles. Activity after 2-3 min begins to subside and to be interspersed with phases of immobility or floating of increasing length. Immobility reaches a plateau after 5-6 min for approximately 80% of the time where the rats remain immobile. The rats in water for 15 min are removed and are dried for 1 h, later and the total duration of immobility is measured during a 5 min test. An animal is judged to be immobile whenever it remains floating passively in the water in a slightly hunched but upright position, its nose just above the surface. In the first part of experiment, albino rats were administered with fluoxetine (10 mg/kg) in a heated enclosure (32°) before being returned to their home cages. After 24 h they are again placed in the vertical Plexiglas cylinder and for a 5 min test the total duration of immobility is measured. In the next part of the experiment, the same group of animals after a gap of 15 days were administered with pantoprazole (10 mg/kg) once a day for one week. On the 8th day, pantoprazole (10 mg/kg) were administered to all the animals, and the time of administration was noted. After 60 min of pantoprazole administration, fluoxetine (10 mg/kg) was administered, the test was repeated and the total duration of immobility for duration of 5 min was measured at 0, 2nd, 4th, 8th, 16th and 24th h after fluoxetine administration [17].

Effect of pantoprazole treatment on antidepressant activity of fluoxetine in healthy albino mice by tail suspension test:

This experiment was carried out to find out the effect of pantoprazole (15 mg/kg) treatment on the antidepressant activity of fluoxetine (10 mg/kg) by using tail suspension test in healthy albino mice. In the first part of experiment, animals were administered with fluoxetine (10 mg/kg). The time of the drug administration was noted for all the animals. The animals were subjected to tail suspension test and the duration of immobility was measured for duration of 6 min at 0, 2nd, 4th, 8th, 16th and 24th h after drug administration. In the next part of the experiment, the same groups of animals after a gap of 15 days were administered with pantoprazole (10 mg/kg) for one week, once a day. On the 7th day, 6 h after administration of drug, the rats were fasted for 18 h. On the

8th day, pantoprazole (10mg/kg) was administered and after1 h fluoxetine (10 mg/kg) was administered, the test was repeated and the total duration of immobility for duration of 6 min was measured [18-19].

Compulsive gnawing in mice:

Male mice having a body weight between 18-20 gm were injected with 10mg/kg apomorphine S.C. 30 min, prior to apomorphine injection the animals were treated with the test drug or the vehicle. Immediately after apomorphine injection, 6 mice were placed into a cage with wired lid. The bottom of the cage was covered with corrugated paper, the corrugation facing upwards. The mice started biting into paper causing fine holes or tearing the paper. The number of bites into the corrugated paper was evaluated by placing template upon paper. The template had 10 rectangle windows divided into 10 areas of the same size. In a total of 100 areas the number of bites was checked. In this way percentage of damaged paper was calculated. Percent gnawing of the test compound was compared with that of standard antidepressant drug imipramine, considering its value as 100% [20]. The results obtained are tabulated in table 5.

SEROTONIN SYNDROME:

Forepaw Treading Test:

Six male albino rats weighing between 160-180 grams were selected and housed in cage with free access to food and water. In the first part of experiment, rats were administered with fluoxetine (10 mg/kg, p.o.). The time of the drug administration was noted for all the animals. After 30 minutes of fluoxetine administration, 5-hydroxytryptophan (5-HTP) (25mg/kg, p.o.) was administered to all the rats. Each rat was scored during 0-15, 15-30, 30-45, and 45-60, minute after the oral administration. The severity of the symptoms were scored as following scale, forepaw treading (0=absent; 1=weak; 2=continuous). All the rats were left for washout period of 15 days.

In the next part of the experiment, the same animals after a gap of 15 days were administered with pantoprazole (10 mg/kg, p.o.) once a day for one week. On the 8th day, pantoprazole (10mg/kg, p.o.) was administered to all the animals, and the time of administration was noted. After 60 minutes of pantoprazole administration, fluoxetine (10 mg/kg, p.o.) was administered. Again after 30 minutes of i.e. administration, 5-hydroxytryptophan (25mg/kg, p.o.) was administered to all the rats. Severity of symptoms was scored as mentioned earlier. The results obtained are tabulated in the table 6, depicted in figure 5.

STATISTICAL EVALUATION:

The data of methods are expressed as mean ± SEM for each treatment group. The data obtained from each response measures were subjected to student ‘t’ test using parametric statistics, Graph

Pad Prism trial version 6.01. A value of $P < 0.05$ was considered statistically significant.

RESULT AND DISCUSSION:

Serum concentration of fluoxetine before and after pantoprazole treatment in healthy albino rabbits:

As shown in table 1, the serum concentration of fluoxetine at 2 h was 0.1189 µg/ml and the peak concentration was at 4th h i.e. 0.1228 µg/ml. It started declining at 8th h. The serum concentration of fluoxetine at 2nd, 4th, 8th, 16th and 24th h was decreased after pantoprazole treatment. The peak concentration was observed at 2nd h i.e. 0.0504 µg/ml and started declining at 8th, 16th, 24th h, which was shown in fig 1. The pharmacokinetic parameters are tabulated in table 2. It revealed that AUC and AUMC of fluoxetine was changed after pantoprazole treatment. The Cmax, AUC and AUMC of fluoxetine are decreased due to pantoprazole treatment. These results revealed the absorption of fluoxetine was diminished by pantoprazole treatment, which was shown in fig 2.

Table 1: Serum concentration of fluoxetine before and after pantoprazole treatment in healthy albino rabbits.

S.N	Time (hrs)	Serum concentration of Drug in µg/ml	
		Fluoxetine(10 mg/kg)	Fluoxetine (10 mg/kg, *p.o.)* + Pantoprazole (10 mg/kg, *p.o.*) #
1	0	0	0
2	2	0.1189 ± 0.0447	0.0504± 0.0040
3	4	0.1228 ± 0.0073	0.0480 ± 0.0055***
4	8	0.0675 ± 0.0143	0.0207 ± 0.0013*
5	16	0.0511 ± 0.0014	0.0184 ± 0.0001***
6	24	0.0343 ± 0.0019	0.0162 ± 0.0066*

Number of rabbit per group is 4, Values are expressed as Mean ± SEM.
*p<0.05 , **p<0.01 , ***p<0.001

Table 2: Data showing the pharmacokinetic parameters of fluoxetine before and after Pantoprazole treatment in healthy albino rabbits.

Pharmacokinetic parameters		Fluoxetine (10 mg/k.g, p.o.)	Fluoxetine (10 mg/kg, p.o.) + Pantoprazole (10 mg/kg, p.o.)
AUC_{0-t}	(µg/ml/hr)	2.368	0.941
$AUMC_{0-t}$	(µg/ml/hr)	59.2867	25.268
$t_{1/2}$	(hr)	16.38	15.401
C_{max}	(µg/ml/hr)	0.1228	0.0504
T_{max}	(hr)	4	2
MRT	(hr)	25.038	26.852

Where, AUC_{0-t} is Area under curve, $AUMC_{0-t}$ is area under first order moment curve, t1/2 is terminal half -life, C_{max} is concentration maximum, T_{max} is time of concentration maximum, MRT is Mean residential time and p.o is per oral treatment.

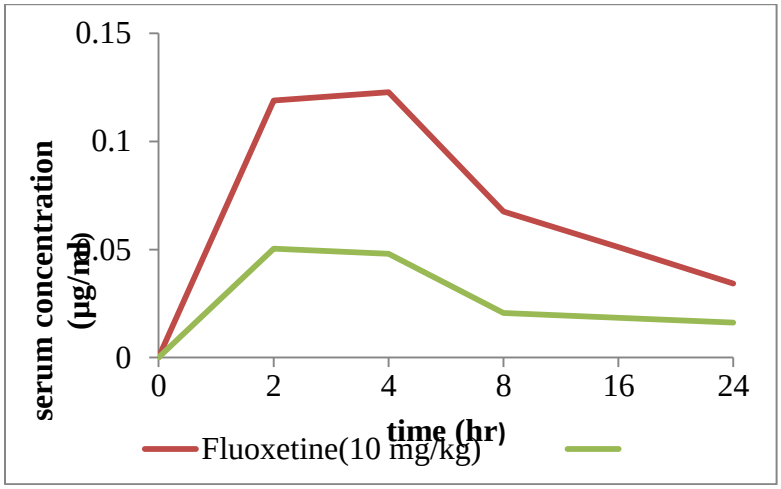

Figure 1. Graphical representation of serum concentration of Fluoxetine before and after Pantoprazole treatment in healthy albino rabbits.

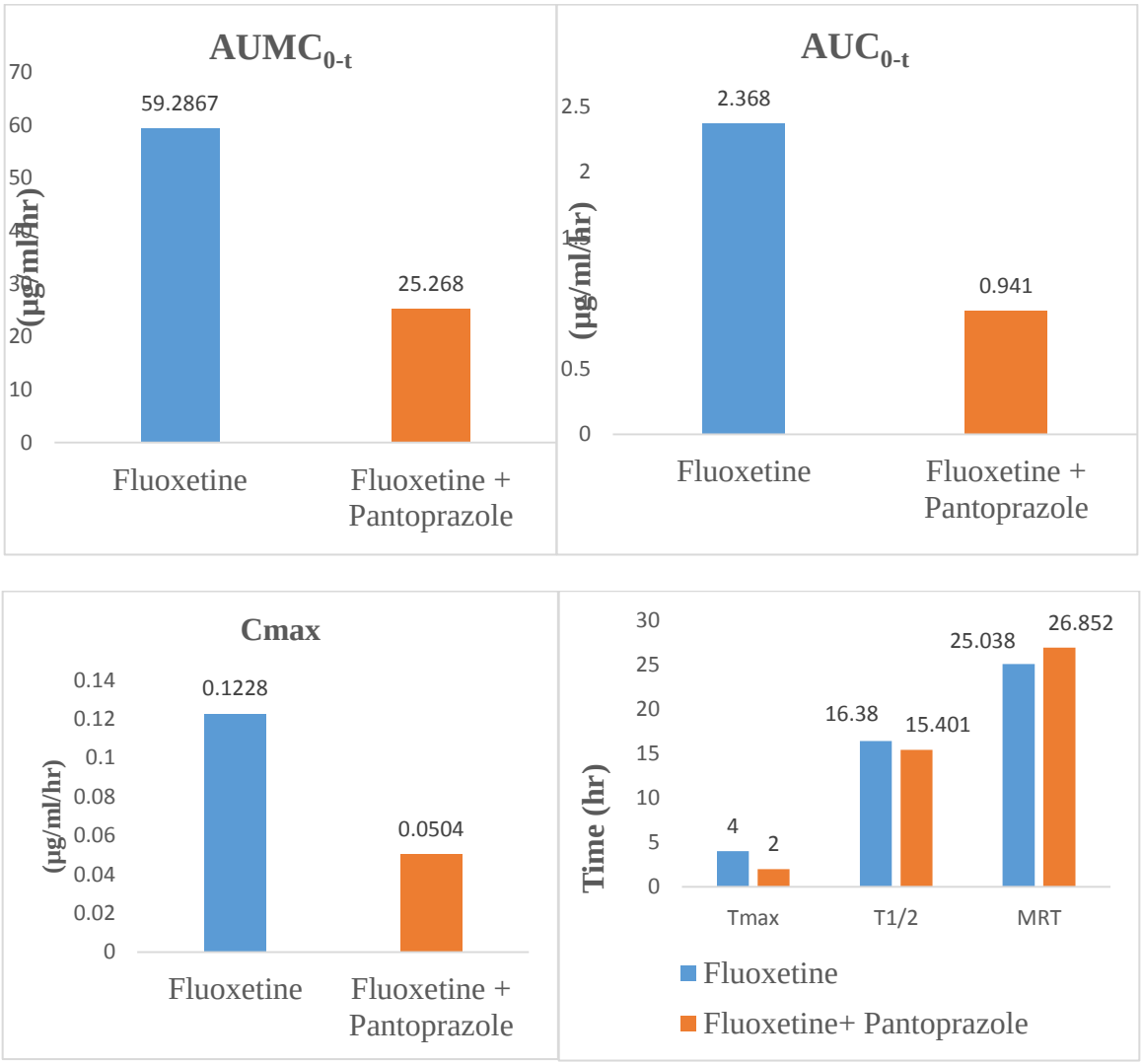

Figure 2 Graphical representation of the effect of Pantoprazole on the pharmacokinetic parameters of Fluoxetine.

Effect of pantoprazole treatment on antidepressant activity of fluoxetine by despair swim test in healthy albino rats:

As shown in table 3 , fluoxetine exhibited immobility time of 50 sec at the initial state i.e. 0 h followed by 42, 18, 23, 29 and 34 sec at 2^{nd} ,4^{th} ,8^{th} and 16^{th}, and 24^{th} h respectively. The maximum effect is shown in 4^{th} h i.e. 18 seconds after fluoxetine treatment only. Simultaneously effect was decreased after 4^{th} h i.e. 23, 29 and 34 second at 8^{th}, 16^{th}, and 24^{th} h respectively. These results confirm their antidepressant activity tested in this animal model. After a week administration of pantoprazole alone and with fluoxetine after wash out period, data showed difference in immobility time which was shown in fig 3. Pantoprazole treatment for one week increased the immobility time in healthy albino rats significantly at 2^{nd}, 4^{th}, 8^{th} and 16^{th}, and 24^{th} h. The least immobility time was seen in 4th h i.e. 33 sec. significant increase was shown in 4^{th}, 8^{th} and 16^{th} and 24^{th} h.

Table 2. Data showing the effect of pantoprazole on the antidepressant activity of fluoxetine by despair swim test.

S. No.	Time in hours	Immobility time(sec) in 5 minutes test	
		Drug treatment	
		Fluoxetine (10 mg/kg p.o.)	Fluoxetine + Pantoprazole (10 p.o. ± 30 mg/kg p.o.)
1	0	50 ± 3.41	46 ± 2.50
2	2	42 ± 1.39	43 ± 2.19
3	4	18 ± 1.15	33 ± 1.701***
4	8	23± 1.40	36 ± 1.740***
5	16	29 ± 1.97	39 ± 1.838**
6	24	34 ± 1.98	41 ± 0.763*

Number of rat per group is 6., Values are expressed as Mean ± SEM. ,
*p<0.05, **p<0.01 , ***p<0.001

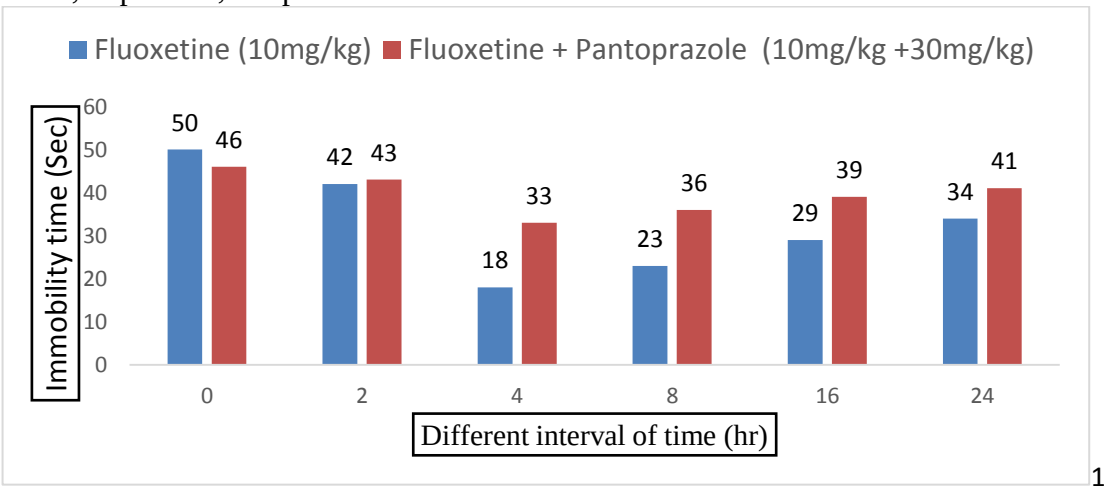

Fig 3: Graphical representation of a Pantoprazole treatment on immobility time of Fluoxetine in Despair swim test.

Table 4: Data showing the immobility time of Fluoxetine before and after Pantoprazole treatment in healthy albino mice using Tail Suspension Test.

	Average immobility time (sec) in 6mins	
	Drug treatment	
Time in hours	**Fluoxetine**	**Fluoxetine + Pantoprazole**
	(10mg/kg p.o.)	**(10mg/kg p.o. + 30mg/kgp.o.)**
0	130 ± 2.257	123 ± 1.983**
2	136 ± 1.641	103 ± 2.257
4	82 ± 0.9661	91 ± 0.97***
8	96 ± 0.7923	105 ± 0.5774***
16	100 ± 0.7638	109 ± 1.352**
24	146 ± 1.592	134 ± 4.143

Number of rat per group is 6., Values are expressed as Mean ± SEM. ,
*p<0.05, **p<0.01 , ***p<0.001

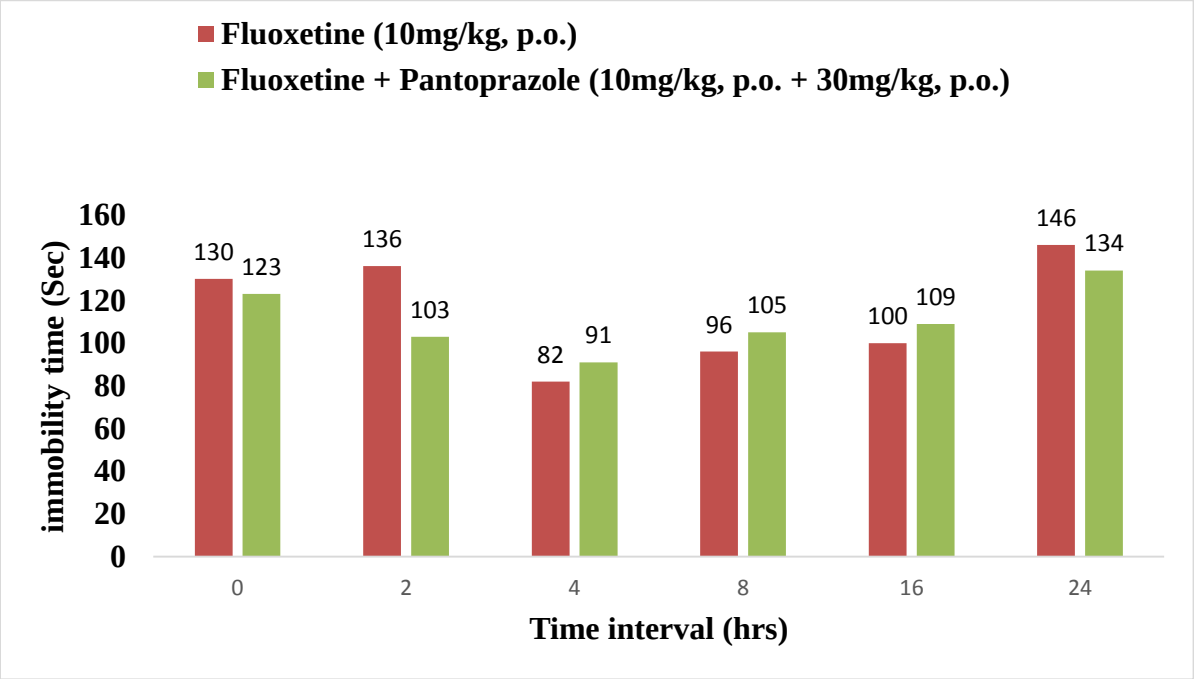

Figure 4: Graphical representation of a Pantoprazole treatment on immobility time of Fluoxetine in Tail Suspension Test.

Effect of pantoprazole treatment on antidepressant activity of fluoxetine by tail suspension test in healthy albino mice:

The results of tail suspension test are shown in figure 4, indicates that fluoxetine exhibited immobility time of 130 sec at the initial state i.e. 0 h followed by 136, 82, 96, 100 and 146 sec at 2^{nd} ,4^{th} ,8^{th} and 16^{th}, and 24^{th} h respectively. The maximum effect is shown in 4^{th} hour i.e. 82 sec after fluoxetine treatment only and the results were tabulated in table 4. Simultaneously effect was decreased after 4^{th} h i.e. 96, 100, 146 sec at 8^{th}, 16^{th} and 24^{th} h respectively. Immobility time show

significant changes during 4th, 8th and 16th h, but at 0, 2nd and at 24th h no significant change occurred. The effect of fluoxetine was maximum at 4th h. After a week administration of Pantoprazole alone and with fluoxetine after wash out period day data showed different in immobility time. This treatment for one week increased the immobility time in healthy albino mice significantly. But significant increase is shown in 4th, 8th and 16th h, i.e.91, 105 and 109 respectively. However at 0, 2 nd and 24th h did not showed significant difference. The least immobility time was seen in 4th h i.e. 91 sec.

In this present study possible interaction between fluoxetine and Pantoprazole were determined in healthy rats, where fluoxetine and Pantoprazole were used. Since both the drugs are administered for longer duration and metabolized by the common enzymes CYP3A4, CYP2C19 there was significant drug interaction. Hence the present study has been taken up to evaluate the influence of Pantoprazole on the pharmacokinetic and antidepressant activity of fluoxetine in healthy rabbits, rats and mice. The possibility of interaction between these two drugs might be due to the alteration in the absorption site, replacement at protein binding site (distribution), metabolism site and elimination site. It was found that both the drugs are metabolized by common enzymes CYP3A4 and CYP2C19 and both of them binds to the common protein i.e. albumin.

Single administration of fluoxetine in rabbits showed its maximum serum concentration i.e. 0.1228 ± 0.0073µg/ml at 4 h. Other pharmacokinetic parameters like AUC, AUMC, Cmax and MRT showed value at 2.368*(µg/ml/hr*), 59.2867(*µg/ml/hr*), 0.1228(*µg/ml*) and 25.038 hour respectively. But after co-administration of fluoxetine and Pantoprazole, serum concentration decreased to 0.0530 ± 0.0055*µg/ml* and $t_{1/2}$ decreased from 16.38 to 15.401 hrs. Other pharmacokinetic parameters have also been decreased. Similarly, Tmax decreased from 4th hour to 2nd hour. It may be due to displacement of pantoprazole from the protein binding site, so the concentration of the fluoxetine have been decreased or other possible mechanism may also be involved because both the drugs are metabolized by same enzyme i.e. CYP 3A4 and CYP2C19.

In force swim test, immobility time of experimental animal was reduced after administration of fluoxetine. This result confirms the antidepressant activity of fluoxetine in experimental animals, drugs primarily blocking noradrenaline uptake preferentially increase climbing behavior. Swimming behavior was increased when given in combination.

In test swim test, the immobility time was increased in all hours with combination therapy rather than fluoxetine alone. It may be due to the decreased concentration of fluoxetine in mice after both drug therapies.

In compulsive gnawing test, the biting into paper causing fine holes or tearing the paper decreases as apomorphine was administered along with combination of fluoxetine and pantoprazole than fluoxetine alone.

Table 5: Data showing the number of bites within 1 hour interval time of Fluoxetine before and after Pantoprazole treatment in healthy albino mice using compulsive gnawing test.

Percentage of damage corrugated paper	
Drug treatment	
Apomorphine (10mg/kg) +Fluoxetine (10mg/kg)	**Apomorphine (10mg/kg) +Fluoxetine (10mg/kg) +Pantoprazole (10mg/kg)**
28	22

In forepaw trading test, Data shown in the table 6 represent that fluoxetine treatment on rats with serotonin precursor has a significant effect on fore paw treading. Effect on Forepaw trading decreases as pantoprazole was administered along with fluoxetine than fluoxetine alone.

Table 6: Chart showing the fore paw treading of Fluoxetine before and after Pantoprazole treatment in healthy albino rats using serotonin syndrome test.

S. No.	Treatment	Dose (mg/kg)	Forepaw treading score			
			0-15 min	15-30 min	30-45 min	45-60 min
1	**Fluoxetine**	**10**	0.5±0.22	0.833±0.166	1.166±0.166	1.5±0.166
2	**Fluoxetine + Pantoprazole**	**10**	**0.4**±0.13	0.699±0.121**	1.056±0.113**	1.41±0.122*

CONCLUSION

The present study suggested that there is an interaction when pantoprazole is co-administered with fluoxetine. The interaction between pantoprazole and fluoxetine appears to be both Pharmacokinetic and pharmacodynamics interaction. The possible interactions at pharmacokinetic and Pharmacodynamics level may be due to presence of common metabolizing enzyme CYP3A4 and CYP2C19 interaction between agonist and antagonist at drug receptor respectively. So, the interfering effects of pantoprazole and fluoxetine must be considered if patient is consuming pantoprazole and fluoxetine together.

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REFERENCES:

1. Brunton LL, Lazo JS, Parker KL. The Pharmacological Basis of Therapeutics. 10th ed. Goodman and Gilman's: New York: McGraw Hill, 2006.
2. Singh J, Patel SC. Pharmacokinetics changes of Fluvoxamine and Pioglitazone by drug-drug interaction in healthy, diabetic and depressive rats. Int J Pharm Pharma Sci 2013; 5(1): 352-55.
3. Swamy VKM. A study on drug-drug interaction of Esomeprazole and anti-diabetic drugs. J Young Pham 2010; 2(4): 424-27.
4. Kohler GI. Elements of Clinical Pharmacy. 1st ed. BS Shah Prakashan: Ahmedbad, 2004.
5. Erenmemisoglu A et al. Effects of some antidepressants on glycaemia and insulin levels of normoglycaemic and alloxan-induced hyperglycemic mice. J Pharm Pharmacol 1999; 51: 741-43.
6. Joy MJ, Prathyusha S, Reddy GAK. A review on anti-ulcer plants. Andhra Pradesh, India: Sree Vidyanikethan College of Pharmacy, Tirupathi- 517102.
7. Sonnenberg A. Causes underlying the birth-cohort phenomenon of peptic ulcer: analysis of mortality data 1911-2000, England and Wales. International journal of epidemiology. 2006;35(4):1090-7.
8. Susser M, Stein Z. Civilisation and peptic ulcer. Lancet. 1962;279:116-9.
9. World Health Rankings, India: Peptic Ulcer Disease. 2013 3-10. Available on: http://www.worldlifeexpectancy.com/india-peptic-ulcer-disease/.
10. Rang HP, Dale MM, Ritter JM, Moore PK. Pharmacology. UK: Churchill livingstone; 2003.
11. Page, Curtis, Sutter, Walker, Hoffman. Integrated pharmacology. spain: Mosby publication; 1997. 109-10.
12. ME P. Pantoprazole, a new proton-pump inhibitor, has a precise and predictable profile of activity. European journal of gastroenterology & hepatology. 1996;8:15-20.
13. Seth SD. Textbook of Pharmacology. 3rd ed. New Delhi: *Elsevier A division of Reed Elsevier India Private Limited*; 2009.
14. Ortmann R. The 5-HT syndrome in rats as tool for the screening of psychoactive drugs. Drug Development Research 1984;4:593-606.
15. Caccia SM, Francasso C. Influence of dose and route of administration on the kinetics of fluoxetine and its metabolite norfluoxetine in tha rat. Psycopharmacol 1990; 100 (4): 509-14.

16. Orsulak PJ et al. Determination of the antidepressant fluoxetine and its metabolite norfluoxetine in serum by reversed-phase HPLC with ultraviolet detection. Clin Chem 1998; 34(9): 1875-78.
17. Vogel GH. Drug discovery and evaluation: Pharmacological assays. Springer-Verlag: Berlin Heidelberg, 2002.
18. Maurice E. Comparative in-vivo effects of Irbesartan and Losartan on angiotensin II receptor binding in the rat kidney following oral administration. Clin Sci 2000; 99: 331-41.
19. Tominaga M. Beta-blocker treatment of dilated cardiomyopathy: Beneficial effect of carteolol in mice. J Am Heart Asso 2013: 2021-27.
20. Sanmukhani J, Anovadiya A. Evaluation of antidepressant like activity of curcumin and its combination with Fluoxetine and Imipramine: An acute and chronic sudy. Pharmacol Rep 2011; 68(5): 769-75.