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Spectroscopic interaction studies of H_2 receptor antagonists with levocetirizine

Shafaque Mehboob[1]*, Moona Mehboob[2], Darakshan M Saleem[3], Mehjabeen[4], SM Tariq Rafi[5], Hurtamina Khan[6], Noor Jahan[7], Farah Owais[8], Fakhra Batool[9] and Najma Sultana[10]

[1]Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences, Jinnah Sindh Medical University, Karachi, Pakistan
[2]Department of Pharmaceutical Chemistry, School of Pharmacy, Dow University of Health Science, Karachi, Pakistan
[3]Biomedical Engineering Department, Sir Syed University of Engineering & Technology, Karachi, Karachi, Pakistan
[4,8]Department of Pharmacology, Faculty of Pharmaceutical Sciences, Federal Urdu University of Arts, Science and Technology, Karachi, Pakistan
[5,6] ENT Department, Jinnah Sindh Medical University, Karachi, Pakistan
[7]Department of Pharmacology, School of Pharmacy, Dow University of Health Science, Karachi, Pakistan
[9]Department of Pharmacy, Sardar Bhadur Khan Women's University, Quetta, Pakistan
[10](former) Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan

Abstract: Patients with allergic rhinitis may also suffer abdominal pain, gastritis or peptic ulcer. In this condition patient may use levocetirizine with famotidine or ranitidine. These drugs have potential to interact with another drug and form complex. The aim of the present study is to evaluate the possible drug drug interaction with each other which may cause increase or decrease of therapeutic effects. For this purpose, validity of Beer Lambert law was checked, lone availability of famotidine (20gm), ranitidine (150gm) and levocetirizine (5mg) were studied in pH simulated to gastric juice (pH 1), pH 4, pH 7.4 and in pH 9 and finally percent availabilities of these drugs were calculated with the help of simultaneous equation. Results showed high percentage of levocetirizine in all pH as 300.32%, 514.41%, 173.38% and 220.68% in presence of famotidine but very low availability of famotidine as 5.36%, 35.38%, 51.87% and 10.89% in presence of levocetirizine. In the case of levocetirizine and ranitidine interaction, zero percent levocetirizine was available at pH 1and 9, 56.28% in pH 4 and 191.1% in pH 7.4. On the other hand, ranitidine was available as 95.36%, 127.93%, 41.47% and 144.3%. These results showed that percentage of all drugs were altered in presence of each other due to drug-drug interaction. This may be due to the charge transfer binding capabilities of the drugs which resulted in significantly changed availability of famotidine, ranitidine as well as levocetirizine.

Keywords: Famotidine, ranitidine, levocetirizine, drug interaction.

INTRODUCTION

Famotidine and ranitidine are well known histamine H_2receptor antagonists. Famotidine is a competitive inhibitor and inhibits basal and nocturnal gastric secretion as well as the secretion stimulated by food and pentagastrin. Therefore, it is useful in duodenal and benign gastric ulcer and hyper secretions leading to pathology such as heartburn and Zollinger-Ellison syndrome. Ranitidine possesses ability to inhibit gastric secretion but on the same time few side effects due to its inhibitory effects on hepatic cytochrome p-450 mixed function oxidase system (Riley and Deruiter, 2004). levocetirizine is also an antihistamine drug but it blocks H_1 receptors. It is used as a non sedative agent in persistent and intermittent allergic conditions such as allergic rhinitis and hay fever (Jorissen *et al*, 2006).

Several studies showed that famotidine has potential to interact with the cytochrome p450 system. This interaction in turn disturbs the metabolism of different drugs such as demethylation of aminopyrine, benzphentamine and diazepam or de-ethylation of 7-ethoxycoumarin. Studies showed that famotidine has potential to interact with theophylline and phenytoin (Tripathi *et al*, 2002). Ranitidine reduce hepatic flow and can induce significant pharmacokinetic interactions with procainamide, midazolam, cobalamin (Pletz *et al*., 2003, Kubitza *et al.,* 2006). levocetirizine was also e to interact with different drugs. Altered renal clearance of dextrocetirizine was observed when given with levocetirizine (Strolin *et al.,* 2008). Sincelevocetirizine is a substrate of PgP, therefore, should be taken with caution with PgP substrate, inhibitor or inducers such as ketoconazole, cyclosporine or verapamil (PgP substrate), rifampicin (PgP inducer) or erythromycin, azithromycin and itraconazole (PgP inhibitors) (Molimard *et al.,* 2004, Hair and Scott., 2006). There is a study which showed that ranitidine potentiates the effects of levocetirizine in suppressing histamine-induced wheal (Dhanya *et al.,* 2008).

However, no study showed that levocetirizine can increase or decrease availability of famotidine or ranitidine due to any chemical reaction. Therefore, the aim of the present study is to evaluate the effect of

*Corresponding author: e-mail: shafaque.mehboob@hotmail.com

levocetirizine of percent availability of famotidine or ranitidine in pH simulated to empty gastric, full gastric, intestinal and blood.

MATERIALS AND METHODS

Solutions

Primary solutions of famotidine, ranitidine and levocetirizine were prepared by taking 0.0338, 0.0314 and 0.04254 gm of respective drugs in buffers of pH 1~9 of 1mmol concentration. Stock solutions were prepared by diluting primary solutions with corresponding buffers to get 0.1mmol concentration. Different working solutions of strength 0.01 to 0.09mmol with the help of stock solutions to study calibration curve.

Calibration curve studies

Working solutions of famotidine, ranitidine and levocetirizine were scanned (200~700nm) to observe absorbance maxima and required for calculation of epsilon. Calibration curve was plotted and validity of Beer Lambert's Law was checked.

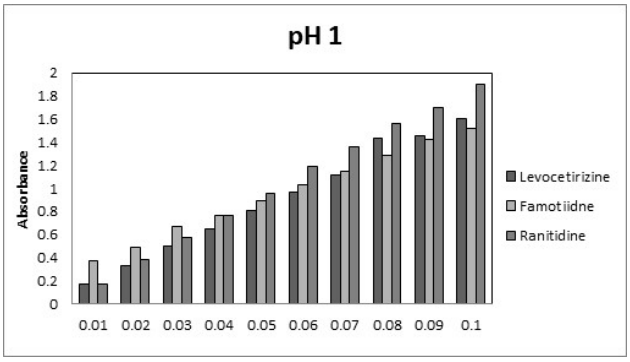

Fig. 1: Absorbance vs concentration of drugs (famotidine, ranitidine and levocetirizine) at pH 1

Availability studies

The availability of famotidine (20gm), ranitidine (150gm)and levocetirizine (5mg) were studied in pH simulated to gastric juice (pH 1), pH 4, pH 7.4 and in pH 9. Temperature was maintained at 37°C and volume was 1 liter in the dissolution apparatus. Aliquots (5ml) were withdrawn for scanning (200~700nm) to calculate the lone availability of each drug. The total volume of apparatus was maintained after every 15 minute with the same fluid. To perform drug interaction studies or availability after interaction (if any), famotidine with levocetirizine at the same time were introduced in dissolution apparatus. Same procedure was followed for ranitidine and levocetirizine. Absorbance maxima of drugs were measured at the corresponding wavelength.

RESULTS

Assay method was established under different environmental condition. For this purpose four mediums were selected in order to simulate body environment. One containing 0.1 N hydrochloric acid (simulated to gastric juice, pH of empty stomach), buffer of pH 4 (simulated to gastric juice, pH of filled stomach), buffer of pH 7.4 (simulated to blood pH) and buffer of pH 9 (simulated to intestinal pH).

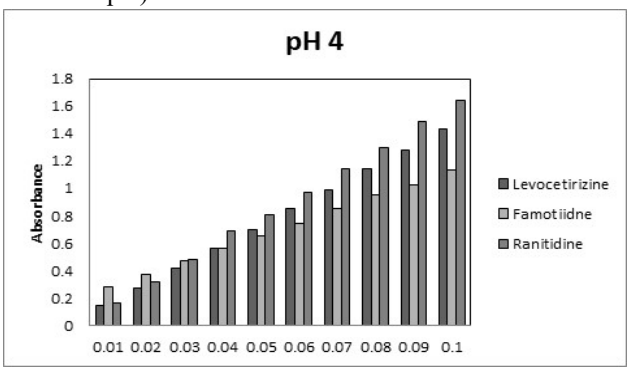

Fig. 2: Absorbance vs concentration of drugs (famotidine, ranitidine and levocetirizine) at pH 4

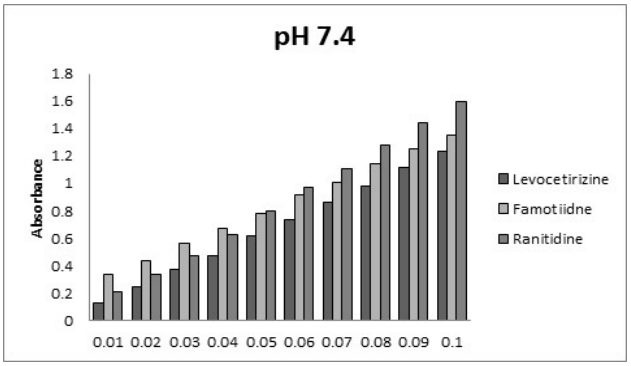

Fig. 3: Absorbance vs concentration of drugs (famotidine, ranitidine and levocetirizine) at pH 7.4

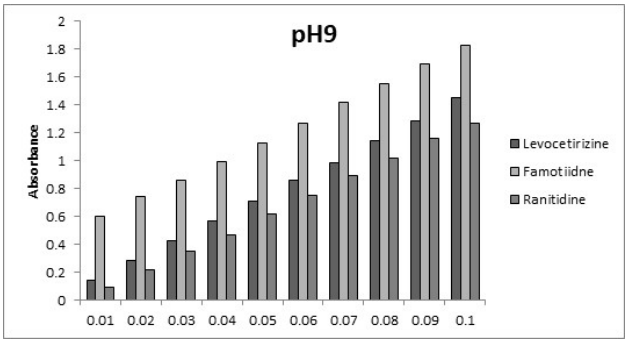

Fig. 4: Absorbance vs concentration of drugs (famotidine, ranitidine and levocetirizine) at pH 9

Figs. 1-4 showed that if concentration of the drugs (famotidine, ranitidine and levocetirizine) increased absorbance will also increase. This also indicated that Beer Lambert's Law was followed.

Epsilon values of famotidine, ranitidine and levocetirizine at pH 1, 4, 7.4 and 9 were calculated in mediums maintained at 37°C (table 1).

Table 1: Epsilon values of famotidine, ranitidine and levocetirizine at different pH

Drugs	pH	Λ max	ϵ ($moles^{-1}Lcm^{-1}$)
Famotidine	1	265	12793
Ranitidine	1	225	19474
Levocetirizine	1	231	16199
Famotidine	4	265	9422
Ranitidine	4	225	16434
Levocetirizine	4	231	14219
Famotidine	7.4	284	15695
Ranitidine	7.4	225	16587
Levocetirizine	7.4	231	12383
Famotidine	9	284	11333
Ranitidine	9	225	12012
Levocetirizine	9	231	14252

Lone availability (percentage) of famotidine, ranitidine and levocetirizine was not less than 90% and more than 115% in all concerned buffers for 120 minutes. At pH 1 when levocetirizine was allowed to interact with famotidine, 300.32% of levocetirizine and only 5.36% of famotidine was available at the end of the experiment (at 120 minute). At pH 4, 514.41% of levocetirizine and 35.38% of famotidine was available. At pH 7.4 and 9 high percentage of levocetirizine which were 173.38% and 220.68% respectively and lower percentage of famotidine which were 51.87% and 10.89% respectively were obtained (fig. 5).

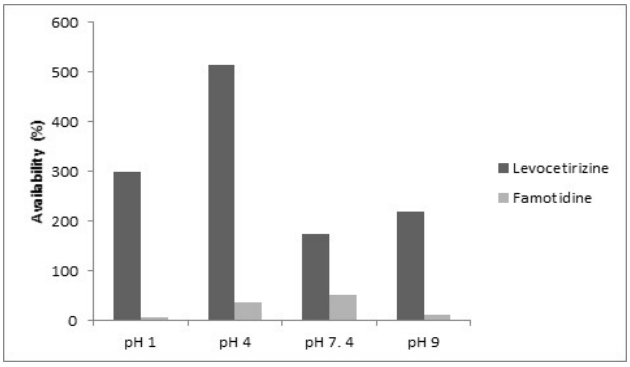

Fig. 5: percent availabilities of famotidine and levocetirizine after interaction

On the other hand, availability of levocetirizine in the presence of ranitidine was 0.0%, 56.28%, 191.1% and 0.0% in pH 1, 4, 7.4 and 9 but ranitidine was available 95.36%, 127.93%, 41.47% and 144.3% in pH 1, 4, 7.4 and 9 at the end of the experiment (fig. 6).

DISCUSSION

Patients with allergic rhinitis may also suffer abdominal pain, gastritis or peptic ulcer (Olen *et al*, 2014). Therefore, a patient may maintain on levocetirizine with famotidine or ranitidine (Jorissen *et al.,* 2006, Riley and Deruiter, 2002). However, reported studies showed that all these drugs have capability to interact with other drugs.

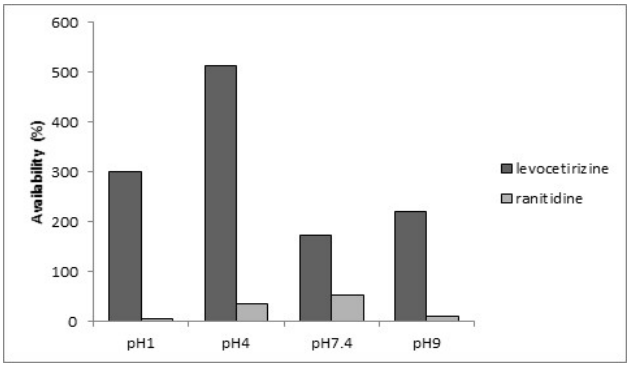

Fig. 6: percent availabilities of ranitidine and levocetirizine after interaction

Animal study showed that famotidine can affect the sleeping time induced by hexobarbital. Famotidine can also interact with diazepam, warfarin and propranolol and can disturb their plasma concentration. It can also change the kinetic of antipyrine and warfarin prothrombin complex activity. Clinical investigations also showed that famotidine can interact with theophylline and phenytoin (Tripathi *et al*, 2002). Ranitidine can also interact withABT-773(a ketolide with high protein binding ratio) (Humphries; 1987). Pletz (2003) showed the interaction between ranitidine and sucralfate (Pletz *et al.,* 2003). Levocetirizine can interact with different drugs because it's a PgP substrate. It is reported to interact with ketoconazole, cyclosporine, verapamil, rifampicin, erythromycin, azithromycin and itraconazole (Molimard *et al.,* 2004, Hair and Scott; 2006). Studies showed that it can alter percent availability of atenolol, losartan potassium, kinetics of fexofenadine and cimetidine (Mehboob *et al.,* 2017, Aftab *et al*., 2017, Devillier *et al.,* 2008, Mehboob *et al.,* 2019)

The aim of the study was to detect drug interaction by measuring percentage of two drugs without separating in dissolution apparatus (Mehboob *et al.,* 2019). For this purpose, simultaneous equation was used because both H2 antagonist (famotidine and ranitidine) and levocetirizine interfere at each other wavelength.

The interaction study of levocetirizine with famotidine resulted in significantly high percent availability of levocetirizine in all pH as 300.32%, 514.41%, 173.38% and 220.68% but very low availability of famotidine as 5.36%, 35.38%, 51.87% and 10.89%. This showed that both drugs affect each other percent availability in pH 1, 4, 7.4 and 9. In the case of levocetirizine and ranitidine interaction, zero percent levocetirizine was available at pH 1and 9, 56.28% in pH 4 and 191.1% in pH 7.4. On the other hand, ranitidine was available as 95.36%, 127.93%, 41.47% and 144.3%.

These results showed that availability of all drugs were altered in presence of each other due to drug-drug interaction. In most of the cases, percent availability of levocetirizine was significantly increased due to famotidine but ranitidine decreased its availability in simulated gastric juice and pH 9. Moreover, availability of famotidine decreased in all pH and availability of ranitidine increased in pH 9.This may be due to the charge transfer binding capabilities of the drugs which resulted in significantly changed availability of famotidine, ranitidine as well as levocetirizine (Abu-Eittah *et al*, 1976). Reported literature suggested that co-administration of two interacting drugs should be avoided (Kaleem*et al*, 2018). Recommendations for patient management also suggested that possible drug interactions should be avoided for any risk issues (Plasencia-García *et al*., 2012).

CONCLUSION

Famotidine and ranitidine interact with levocetirizine, therefore, co-administration of these drugs should be avoided and time adjustment of drug intake should be managed. Further investigations at clinical level should also be done.

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