Original article

A study of in-vitro interaction of Ketotifen Fumarate with Domperidone at different gastric and intestinal pH

Mohammad Aktar Sayeed [1], Fuad Mohammed Farhad [1], Syed Mohammed Tareq [2], Md. Ikram [1], Md. Nurul Islam [1], Saiful Alam Siddique [1], Dipesh Das [3]

[1] International Islamic University Chittagong, Bangladesh
[2] Southern University Bangladesh
[3] University of Chittagong, Bangladesh

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Abstract: *Aim* — The main focus of the project was to identify whether there is any interaction between Ketotifen Fumarate (antihistamine) and domperidone (Antiemetic/dopaminergic antagonist) present or not at simulated gastric and intestinal solutions of different pH. *Methods* — Using Job's continuous-variation analysis the possible drug-drug interaction was determined at a fixed temperature (37ºC) at the studied pH. From Job's continuous-variation analysis the views of drug-drug interaction at different concentration ratio at all pH (0.4, 1.2, 2.0, 2.8, 6.8, and 7.4) except 6.0 were noted. *Results* — Data obtained from spectroscopic analysis showed decrease in free-drug concentration of both of the drugs analyzed when they were within the same gastric simulated solution. *Conclusion* — Concurrent administration of Ketotifen Fumarate and domperidone would result in the formation of a stable complex and this is likely to reduce the the rapeutic activities of both drugs.

Keywords: drug interaction, Domperidone, job's plot, Ketotifen fumarate, pH, spectral pattern

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Correspondence to Fuad Mohammed Farhad. Address: Department of Pharmacy, International Islamic University Chittagong, Bangladesh.
Tel: +88 01920555598. E-mail: fuadekushe_52@yahoo.com

Introduction

The drug ketotifen is a benzocycloheptathiophene derivative which has been reported to have anti- histaminic and anti-anaphylactic properties [1]. Ketotifen antagonizes histamine at H1 receptors at mast cells, inhibits calcium uptake, blocks passive cutaneous anaphylactic reaction, reverses isoprenaline induced beta-adrenoceptor tachyphylaxis, and inhibits both allergen-induced and drug-induced asthma [2]. Through a number of clinical trials, this drug has been shown to have a beneficial effect in the treatment of asthma [3-4]. Domperidone is an antidopaminergic drug used to suppress nausea and vomiting, as a prokinetic agent and for promoting lactation. It is a specific blocker of dopamine receptors. It speeds gastrointestinal peristalsis, causes prolactin release, and is used as antiemetic and tool in the study of dopaminergic mechanisms. There is some evidence that domperidone has antiemetic activity [5]. Domperidone is used, along with metoclopramide, cyclizine, and 5HT3 receptor antagonists to treat nausea and vomiting. Domperidone can be used in patients with Parkinson's disease [6] because, unlike metoclopramide [7], domperidone does not cross the blood–brain barrier. Domperidone has also been found effective in the treatment of gastroparesis [8], and for paediatric gastroesophageal reflux. The major goal of the present study was to find out whether two drugs-ketotifen and domperidone might undergo drug-drug interaction at simulated gastric fluid having various pH. The absorbance of drugs at those solutions was taken and analyzed using Job's plot [9].

Material and methods

Materials

All the chemicals and reagents used in this study were of analytical grade and were stored under optimum storage conditions. The experimental mixtures and solutions were prepared in standard volumetric flasks about one hour prior to recording the data.

Drugs used in the study: Ketotifen fumarate and Domperidone.

The λmax value of drug used in the study: 300nm (The λmax Ketotifen fumarate).

Instrument used: pH Meter, UV/VIS Spectrophotometer, Electronic balance, Water bath.

Solvents: i) Distilled water, ii) Hydrochloric acid, iii) Ethanol.

Preparation of Hydrochloric acid

In order to prepare Hydrochloride acid of 0.1 M concentration, 9.1 ml of hydrochloric acid (Molecular weight 36.5 gm/mol, 37% concentrated) was taken in a liter volumetric flask and the volume made up with distilled water to the mark. Similarly 18.18 ml of HCl

acid was diluted in a liter volumetric flask up to the mark with distilled water to make the solution of 0.2 M concentration.

Preparation of Potassium chloride

In order to prepare Potassium chloride of 0.2 M concentration, Potassium chloride (14.9 gm), (Molecular weight 74.55 gm/mol) was dissolved in distilled water in a liter flask and the volume made up to the mark with same solvent.

Preparation of potassium dihydrogen phosphate

In order to prepare potassium dihydrogen phosphate of 0.1 M concentration, Potassium chloride (13.609 gm), (Molecular weight 136.09 gm/mol) was dissolved in distilled water in a liter flask and the volume made up to the mark with same solvent.

Preparation of Sodium hydroxide

In order to prepare of 0.1 M concentration, sodium hydroxide pellets (20 gms), (Molecular weight 40 gm/mol) were taken in a 500 ml volumetric flask, dissolved in little distilled water and volume was made up to the mark with the same solvent. 100 ml of this solution (1 M concentration) was further diluted in 500 ml volumetric flask with distilled water, resulting concentration was 0.2 M.

Preparation of acidic buffer (pH 0.4, 1.2, 2.0, and 2.8)

These buffers are prepared by using sodium chloride, potassium chloride, sodium hydroxide and hydrochloric acid with the help of pH meter.

Preparation of Basic buffer (pH 6.0, 6.8, and 7.4)

These buffers are prepared by using Potassium dihydrogen phosphate (KH_2PO_4), potassium chloride, sodium hydroxide and hydrochloric acid with the help of pH meter.

Preparation of Ketotifen Fumarate solution

100 ml of $1*10^{-3}$ M solution of Ketotifen Fumarate was prepared as the stock solution by dissolving 0.425 gm of Ketotifen Fumarate in 100 ml of distilled water in a 100 ml Volumetric flask. To prepare $1*10^{-5}$ M solution of Ketotifen Fumarate, 1 ml of $1*10^{-3}$ M solution was taken in another 100 ml volumetric flask and the volume was adjusted by distilled water up to the mark.

Preparation of Domperidone solution

100 ml of $1*10^{-4}$ M solution of Domperidone was prepared as the stock solution by dissolving 0.425 gm of Domperidone in 100ml of distilled water in a 100 ml Volumetric flask. To prepare $1*10^{-5}$ M solution of Domperidone, 1ml of $1*10^{-4}$ M solution was taken in another 10 ml volumetric flask and the volume was adjusted by distilled water up to the mark.

Methods

Job plot ,also known as the method of continuous variation or Job's method was used to analyze the free drug concentration after concurrent administration using the observed spectroscopic data. According to Job's method (Job, 1971) a series of solutions were prepared in which the analytical concentration of one reactant (usually the cation) was held constant while that of the other was varied. The absorbance of a series of Ketotifen Fumarate with domperidone in different molar ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) was measured by keeping the total molar concentration constant. The observed absorbance of the mixtures at various molar fractions was subtracted from the sum of the values for the free drugs (Ketotifen Fumarate and domperidone). The absorbance difference (D) was then plotted against the molar fractions of the drug in the mixtures. If the formation constant is reasonably favourable, two straight lines with different slopes that intersect at a molar ratio that corresponds to the ratio of drugs in the complex are obtained.

Results

In the present investigation, the interaction of Ketotifen Fumarate and Domperidone has been studied by different methods of analysis under different pH (0.4, 1.2, 2.0, 2.8, 6.0, 6.8 and 7.4) at different concentrations. The spectral characteristics and spectrophotometric analysis of the complexation process have been evaluated. The results obtained from various methods are discussed below.

Spectral studies of interaction of Ketotifen Fumarate & Domperidone

In spectral observation analysis, each of the drugs studied showed absorption in UV-VIS region. The molecular species of Ketotifen Fumarate & Domperidone when separately mixed showed some changes in absorption characteristics of this drug molecule including some shifts in the absorption maxima. Initial detection of complexation of Ketotifen Fumarate with Domperidone was done from the nature of spectra of pure compounds as well as their 1:1, 1:2 and 2:1 mixtures in buffer solution of pH 0.4, 1.2, 2.0, 2.8, 6.0, 6.8 and 7.4 at a fixed concentration ($1*10^{-5}$ M). It is obvious that each compound has its unique molecular structure or electronic configuration which is responsible for absorption of light in the form of ultraviolet or visible form. For this reason the spectrum of any pure compound obtained from UV-spectrum will be of one kind that will be totally different from the other compound or the complex of that compound with other compounds. It is because interaction between two compounds may lead to form complex which has different light absorption capacity (due to change in physicochemical and optical properties) and the spectral pattern is altered. Thus alteration in spectral pattern may be regarded as an indicator for the primary interaction of drugs. The spectra of target molecules alone and mixture of Ketotifen Fumarate with Domperidone showed significant changes in their absorption intensities. This may be due to the interaction of Ketotifen Fumarate with Domperidone that alter the absorption intensities as complexation occurs.

Effect of Domperidone on Ketotifen Fumarate by Job's method of continuous variation at different pH

The molar ratios of the complexes of Ketotifen Fumarate with Domperidone were estimated by Job's spectrophotometric method of continuous variation. The observed absorbance values measured in pH 0.4, 1.2, 2.0, 2.8, 6.0, 6.8 and 7.4 at various concentrations $1*10^{-5}$ M to $9*10^{-5}$ M Ketotifen Fumarate with Domperidone at 300nm is given in *Tables* 1-7. In this method, solutions of different concentrations of Ketotifen fumarate and Domperidone were prepared by plotting corrected absorbance against the volume fraction of one reactant. It may be mentioned that drug solutions with identical analytical concentrations are

mixed in such a way that total volume and the total moles of reactant in each mixture is constant but the mole ratio of the reactants varies systematically. At pH 0.4, 1.2, 2.0, 2.8, 6.0, 6.8 and 7.4 Ketotifen Fumarate forms strong 1:1 complex with Domperidone.

Table 1. Values of job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 0.4

Conc. of Ketotifen	Absorb. of Ketotifen	Conc. of Domperidone	Absorb. of Domperidone	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M×10^{-5}	B	C	D=(A+B)-C
1	0.160	9	1.028	0.297	0.891
2	0.268	8	0.918	0.302	0.884
3	0.419	7	0.8	0.317	0.902
4	0.543	6	0.689	0.347	0.885
5	0.687	5	0.575	0.424	0.838
6	0.826	4	0.441	0.538	0.729
7	0.971	3	0.334	0.679	0.626
8	1.129	2	0.193	0.910	0.466
9	1.229	1	0.116	1.015	0.330

Table 2. Values of job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 1.2

Conc. of Ketotifen	Absorb. of Ketotifen	Conc. of Domperidone	Absorb. of Domperidone	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.14	9	0.927	0.230	0.837
2	0.300	8	0.817	0.239	0.878
3	0.403	7	0.711	0.258	0.856
4	0.556	6	0.603	0.308	0.851
5	0.670	5	0.501	0.395	0.776
6	0.820	4	0.386	0.524	0.682
7	0.970	3	0.277	0.679	0.568
8	1.093	2	0.192	0.860	0.376
9	1.234	1	0.143	1.256	0.121

Table 3. Values of job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 2.0

Conc. of Ketotifen	Absorb. of Ketotifen	Conc. of Domperidone	Absorb. of Domperidone	Absorb. of mixture	Absorb. Difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.167	9	1.071	0.270	0.968
2	0.318	8	0.935	0.280	0.973
3	0.446	7	0.813	0.307	0.952
4	0.608	6	0.696	0.353	0.951
5	0.773	5	0.56	0.463	0.870
6	0.915	4	0.464	0.588	0.791
7	1.059	3	0.324	0.742	0.641
8	1.118	2	0.221	0.967	0.362
9	1.349	1	0.112	1.261	0.200

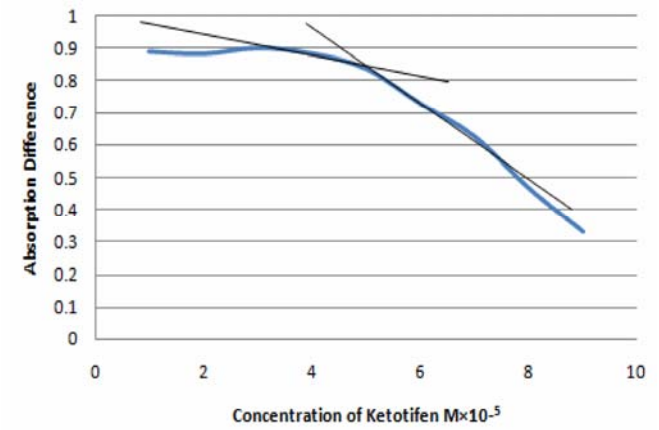

Figure 1. Job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 0.4

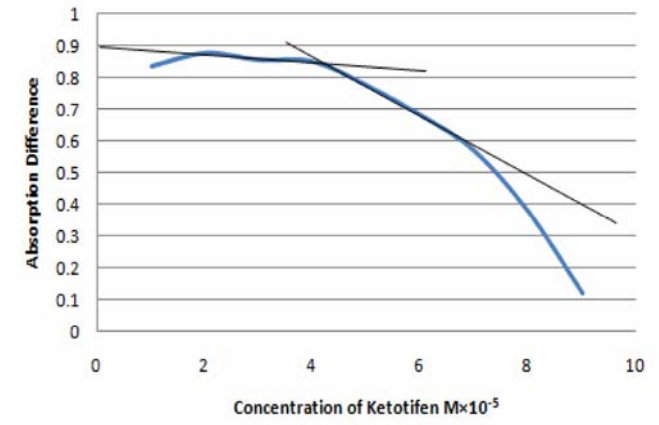

Figure 2. Job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 1.2

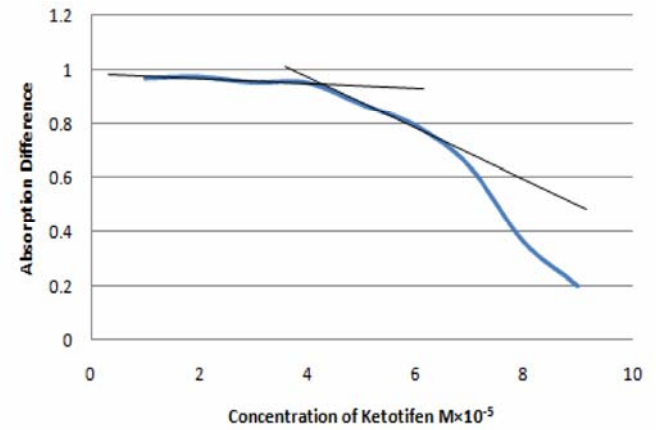

Figure 3. Job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 2.0

Table 4. Values of job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 2.8

Conc. of Ketotifen	Absorb. of Ketotifen	Conc. of Domperidone	Absorb. of Domperidone	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.137	9	1.019	0.264	0.892
2	0.275	8	0.901	0.268	0.908
3	0.426	7	0.768	0.286	0.908
4	0.588	6	0.651	0.321	0.918
5	0.722	5	0.54	0.408	0.854
6	0.868	4	0.433	0.557	0.744
7	0.993	3	0.303	0.696	0.600
8	1.126	2	0.193	0.923	0.396
9	1.271	1	0.103	1.104	0.270

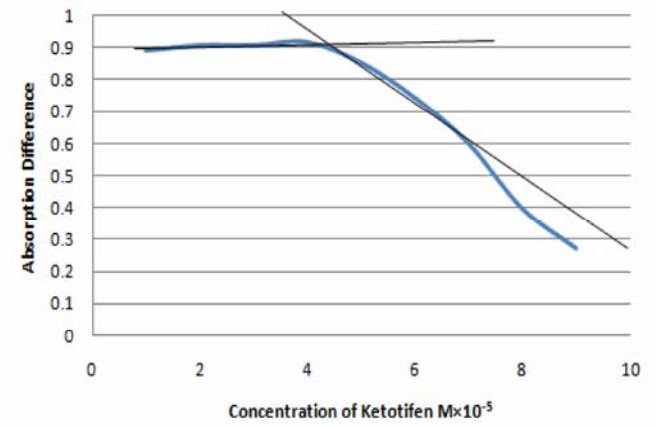

Figure 4. Job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 2.8

Table 5. Values of job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 6.0

Conc. of Ketotifen	Absorb. of Ketotifen	Conc. of Domperidone	Absorb. of Domperidone	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.161	9	0.350	0.100	0.411
2	0.340	8	0.317	0.132	0.525
3	0.471	7	0.285	0.201	0.555
4	0.623	6	0.225	0.260	0.588
5	0.702	5	0.220	0.372	0.55
6	0.880	4	0.172	0.532	0.52
7	0.973	3	0.111	0.620	0.464
8	1.271	2	0.082	0.921	0.432
9	1.190	1	0.040	1.031	0.199

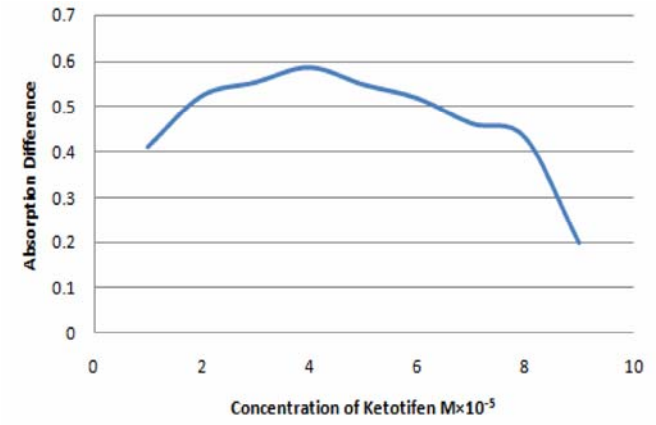

Figure 5. Job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 6.0

Table 6. Values of job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 6.8

Conc. of Ketotifen	Absorb. of Ketotifen	Conc. of Domperidone	Absorb. of Domperidone	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.123	9	0.947	0.206	0.864
2	0.259	8	0.841	0.234	0.866
3	0.420	7	0.657	0.242	0.835
4	0.528	6	0.550	0.292	0.786
5	0.676	5	0.452	0.388	0.74
6	0.811	4	0.362	0.513	0.66
7	0.931	3	0.274	0.660	0.545
8	1.076	2	0.175	0.858	0.393
9	1.174	1	0.102	1.020	0.256

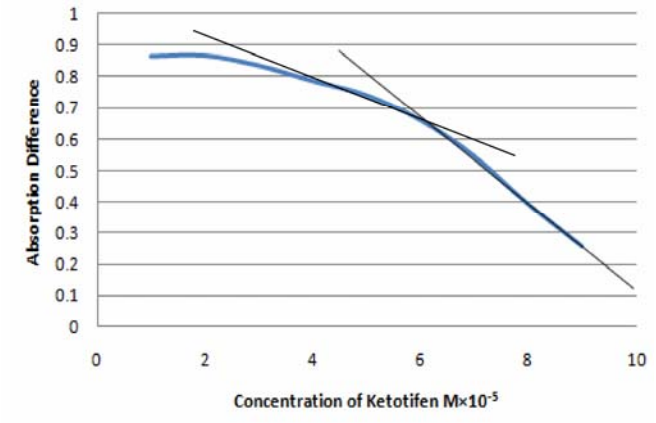

Figure 6. Job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 6.8

Table 7. Values of job's plot for complexation of complexation of Ketotifen Fumarate with Domperidone at pH 7.4

Conc. of Ketotifen	Absorb. of Ketotifen	Conc. of Domperidone	Absorb. of Domperidone	Absorb. of mixture	Absorb. difference
$M \times 10^{-5}$	A	$M \times 10^{-5}$	B	C	D=(A+B)-C
1	0.125	9	0.678	0.026	0.777
2	0.254	8	0.566	0.052	0.787
3	0.380	7	0.527	0.099	0.808
4	0.527	6	0.431	0.208	0.750
5	0.661	5	0.366	0.331	0.696
6	0.782	4	0.286	0.474	0.594
7	0.902	3	0.225	0.625	0.502
8	1.031	2	0.138	0.826	0.343
9	1.132	1	0.084	0.998	0.218

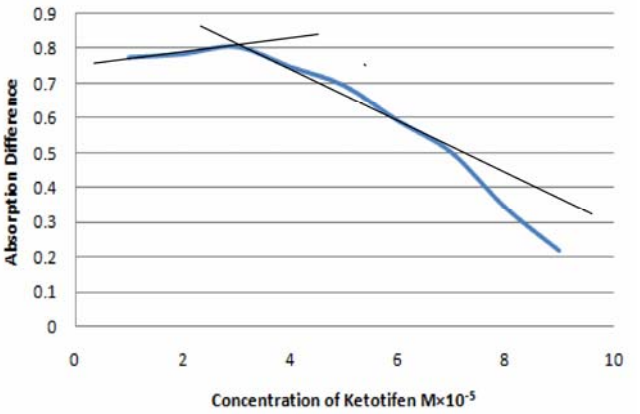

Figure 7. Job's plot for complexation of Ketotifen Fumarate with Domperidone at pH 7.4

Discussion

Previous works on human subjects as well as animal models suggest that Domperidone goes into a number of drug-drug interactions [10-12]. As Ketotifen Fumerarate and Domperidone are often prescribed together, this study investigates the possible interaction between these two drugs through *in vitro* study. The two drugs under investigation were interacted together at different pH. Different concentrations comprising $1*10^{-5}$ M to $9*10^{-5}$ M of ketotifen were interacted with domperidone. The breakdowns in the curves of ketotifen were found at $5*10^{-5}$, $4*10^{-5}$, $4*10^{-5}$, $4*10^{-5}$, $6*10^{-5}$ and $3*10^{-5}$ at the pH of 0.4, 1.2, 2.0, 2.8, 6.8 and 7.4 respectively. However, no break in the curve at pH 6 was observed. So it was assumed that there was no interaction at pH 6.

Conclusion

The experimental results indicate that interaction of ketotifen with domperidone decreases the free drug concentration of both drugs which may result in decreased affinity towards the receptors. Consequently one or both drugs may show diminished pharmacological activity in the system. However, further study using animal model is required to estimate the bioavailability of these drugs when administered into the system.

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Conflict of interest

No conflict of interest has been declared by the authors.

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Authors:
Mohammad Aktar Sayeed – Associate professor, Department of Pharmacy, International Islamic University Chittagong, Bangladesh;
Fuad Mohammed Farhad – B.Pharm, International Islamic University Chittagong, Bangladesh;
Syed Mohammed Tareq – Assistant professor, Department of Pharmacy, Faculty of Science and Engineering, Southern University Bangladesh;
Md. Ikram – B.Pharm, International Islamic University Chittagong, Bangladesh;

Md. Nurul Islam – B.Pharm, International Islamic University Chittagong, Bangladesh;
Saiful Alam Siddique – B.Pharm, International Islamic University Chittagong, Bangladesh;
Dipesh Das – Bachelor of Science in Genetics, University of Chittagong, Bangladesh.

