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Evaluation of the Influence of Hyoscine Butylbromide on the Oral Bioavailability of Lansoprazole in Healthy Adult Volunteers

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Abstract

The gastroesophageal reflux and/or peptic ulcer diseases are clinical conditions that occur usually accompanied of symptomatic pain. Lansoprazole, a proton pump inhibitor class drug is widely used in clinical practice for treatment of these diseases. However, its efficacy can be improved by combining with spasmolytic and/or visceral analgesic such as hyoscine butylbromide. Since hyoscine butylbromide is barely absorbed and exerts some local effects at gastrointestinal tract which may modify the absorption of lansoprazole, it is important to establish if there is a pharmacokinetic interaction after the oral concomitant administration of both drugs. For this objective, twenty-five subjects received under a crossover design an oral administration of lansoprazole (15 mg) plus placebo or a fixed-dose combination with hyoscine butiylbromide (15 mg + 10 mg, respectively). Plasma samples were obtained at different times during 10 hours. Lansoprazole plasma concentrations were determined by a high performance liquid chromatography method coupled to tandem mass spectrometry. Fixed-dose combination was well tolerated. Lansoprazole pharmacokinetic parameters were: C_{max} 621.81 ± 212.79 and 450.38 ± 192.14 ng/mL; AUC_{0-t} 1941.36 ± 845.57 and 1454.66 ± 757.28 ng·h/mL; t_{max} 2.83 ± 0.99 and 3.40 ± 1.82h; $t_{1/2}$ 1.35 ± 0.39 and 1.45 ± 0.51 h, for alone and combined fixed-dose formulation, respectively. Pharmacokinetic parameters were compared by analysis of variance and ratios of AUC_{0-t}, C_{max} and 90% confidence intervals

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obtained. Since confidence intervals exceed the 80% - 125% limits for these parameters, we conclude that there is a significantly pharmacokinetic interaction of lansoprazole when it is administered concomitantly with hyoscine butylbromide.

Keywords

Lansoprazole, Hyoscine Butylbromide, Fixed-Dose Formulation, Pharmacokinetic Interaction

1. Introduction

The acid-related disorders (ARD) include gastroesophageal reflux disease, peptic ulcer disease and stress-related erosive syndrome [1]. The typical symptoms of these disorders include primarily heartburn and acid regurgitation, whereas dispepsia, motility disorders, chest and epigastric pain are symptoms that appear in majority of cases [2]. It has been established that for a major control of ARD symptoms, the effective suppression of gastric acid production must be achievable [1] [3]. Under this scenario, the administration of anti-secretory agents for the treatment for patients with ARD is the basis of medical treatment [4]. The proton pump inhibitors (PPI) are a class of prodrugs widely used to treat ARD symptoms [1]. Lansoprazole is a PPI that has demonstrated efficacy and tolerability in the treatment of gastroesophageal reflux disease and hypersecretory disorders [5]. Its mechanism of acid suppression occurred in the final step of the gastric acid secretion by the inactivation of the H^+/K^+ ATPase enzyme [5] [6]. The conversion to its active form (a sulphenamide derivative) occurs after absorption into circulation at the gastric parietal cells especially when they are actively secreting acid [1] [7]. Lansoprazole is well absorbed after an oral administration. The peak plasma concentration occurs at 1.5 - 2.2 hours and the maximal concentration (C_{max}) is ranged from 0.75 to 1.15 mg/L, additionally it has been established that this parameter is dose proportional from 15 to 60 mg [5] [7]. Lansoprazole is metabolized in the liver to 5-hydroxylansoprazole and lansoprazole sulfone by CYP2C9 and CYP3A4, respectively [8]. Additionally, it has a short elimination half-life ($t_{1/2}$) ≈ 1 hour, however, this value is not related with the duration of gastric acid suppression [3] [9] [10] which is a pharmacological aspect that promotes the use of lansoprazole in the therapeutic field.

However, under some situations patients have a poor therapeutic response for ARD symptoms with the use of a PPI like lansoprazol. For these situations, the medical treatment can be improved trough the concomitant administration of drugs with therapeutic effects focused to reduce transient lower esophageal sphincter relaxation rate or decrease esophageal pain perception by using visceral analgesics [11]. Hyoscine butylbromide is an older antispasmodic drug related to atropine and derivative of hyoscine indicated for the symptomatic treatment of pain and discomfort associated with functional abdominal disorders [12]. In comparison with hyoscine molecule, this drug has a quaternary ammonium structure that enables to have anticholinergic activity and a limited systemic absorption, additionally, no central action is observed with this drug due hyoscine butylbromide do not pass across the blood brain barrier. Regarding the elimination of this drug, after an oral administration is mainly excreted unaltered via faecal with minor participation of renal excretion [13]. The gastrointestinal therapeutic effect of hyoscine butylbromide is due to its high affinity for muscarinic receptors located on the smooth muscle cells of the gastrointestinal tract. The inhibition of acetylcholine action at these sites is essential for the spamolytic effect and abdominal pain relief. Considering these pharmacodynamic characteristics and the low systemic availability, hyoscine butylbromide exerts a local effect [13]. Thus, hyoscine butylbromide possesses pharmacological properties that confer a suitable efficacy/safety profile. However, as another anticholinergic drug its use in ARD is controversial [14].

Owing to above described, it is important to have alternatives in the treatment of ARD disorders mainly in cases where the fixed-dose drugs combination can improve the treatment. However, it is important to understand the pharmacokinetic behavior of the designed formulation for that purpose before to evaluate its potential therapeutic use. Since the possible influence of hyoscine butylbromide on lansoprazole pharmacokinetics has not yet been determined, in this study we evaluate the possible pharmacokinetic interaction between these drugs when are administered concomitantly in a fixed-dose combination in comparison with an equal formulation of lansoprazole plus placebo.

2. Subjects and Methods

2.1. Subjects

A total of twenty-five (17 males, 8 females) young Mexican healthy volunteers of 33.0 ± 11.21 years of age (mean ± standard deviation), 162.2 ± 1.1 cm in height and weighing 64.4 ± 10.5 kg, were included in this study. They were in good health as assessed by medical history, clinical examination and suitable laboratory tests. The volunteers gave written informed consent for participation in the study, according to the protocol approved by the Institutional Ethics Committee.

2.2. Study Design and Drug Administration

A single-dose, open-label, two randomized-sequence, two-period crossover design was used in this study. Demographic data of healthy volunteers are given in **Table 1**. Volunteers arrived to the clinical facilities the day before the study began and were randomly assigned through a table random numbers to each of the two-sequences in a 1:1 ratio. After at least 10 hours fasted, an indwelling cannula was inserted in a suitable forearm vein. As result of the drug-sequence order assigned by randomization, the subjects received a single oral dose of 15 mg of lansoprazol plus placebo or the fixed-dose tablet containing 15 + 10 mg of lansoprazol and hysocine butylbromide, respectively, with 250 ml of water. Heparinized blood samples (6 mL) were obtained before

Table 1. Demographic data and sequence of administration of the healthy volunteers that participated in the study. A corresponds to lansoprazole alone and B to the fixed-dose combination.

Subject	Gender	Age (years)	Height (m)	Weight (kg)	BMI (kg/m^2)	Sequence
1	Male	21	1.747	88.05	29.10	B-A
2	Female	55	1.469	52.55	24.70	A-B
3	Male	26	1.700	77.30	26.70	B-A
4	Male	43	1.677	63.00	22.60	B-A
5	Male	43	1.627	70.05	26.70	B-A
6	Female	31	1.646	59.00	21.90	A-B
7	Male	55	1.698	78.30	27.40	B-A
8	Male	24	1.818	70.85	21.60	B-A
9	Male	32	1.697	67.00	23.50	A-B
10	Male	34	1.708	65.00	22.50	A-B
11	Male	33	1.728	72.40	24.50	A-B
12	Female	47	1.454	49.10	23.40	B-A
13	Male	49	1.628	65.85	25.10	A-B
14	Female	40	1.476	56.45	26.10	A-B
15	Male	26	1.716	77.00	26.30	B-A
16	Male	22	1.685	77.00	27.30	A-B
17	Female	26	1.389	48.60	25.50	A-B
18	Female	25	1.551	53.30	22.20	A-B
19	Male	29	1.620	59.20	22.50	B-A
20	Male	18	1.704	60.40	20.90	A-B
21	Female	35	1.522	55.35	24.00	A-B
22	Male	50	1.578	67.50	27.40	B-A
23	Male	20	1.585	68.65	27.50	B-A
24	Male	22	1.684	60.85	21.60	A-B
25	Female	36	1.454	48.10	22.90	B-A

(predose) and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 6, 8 and 10 hours after drug administration. Plasma was obtained by centrifugation of blood samples and stored frozen at temperature below −50˚C until analyzed for drug concentration determination.

2.3. Determination of Lansoprazole in Plasma

Plasma levels of lansoprazole was determined by a high performance liquid chromatography coupled to tandem mass spectrometry method previously validated and all tests were carried out in accordance to the Mexican Official Norm [15]. The extraction procedure consisted in a liquid-liquid extraction using a mixture of eter: dichloromethane. Pantoprazole was added as internal standard. The separation of the compounds was carried out using an Agilent Zorbax Eclipse Plus C18 eluted with a mixture of ammonium formate and acetonitrile as mobile phase. The detection of the compounds was made by a API 3200 mass/mass spectrometer (Applied Biosystems, Inc). The samples were subsequntly analyzed with an ESI source and then quantified by multiple reaction monitoring. No interferences were observed at the retention times of the compounds. The method was linear in the range of 5 to 2000 ng/ml, with intra- and inter-day accuracy (measured as absolute deviation) between 3.25 - 11.25%, whereas the precision of the method (coefficient of variation) was lower than 5.78%.

2.4. Pharmacokinetic and Statistical Analysis

Individual plasma-level time curves were constructed for each formulation. The maximal concentration (C_{max}) and time to reach this maximum (t_{max}) were directly obtained from these curves. The area under the plasma concentration versus time curve (AUC_{0-t}) was obtained by the trapezoidal rule up to the last measurable time [16]. Extrapolation to infinite (AUC_{∞}) was determined by dividing the last concentration by the elimination rate constant. The elimination half-life ($t_{1/2}$) was obtained by log-linear regression of the terminal decay phase.

The bioavailability parameters (C_{max} and AUC_{0-t}) were log transformed and compared by analysis of variance for a cross-over design. Ratios and 90% confidence limits for C_{max} and AUC_{0-t} with both formulations were calculated and two-one sided tests were employed to evaluate if the confidence limits were within the acceptance criteria (80% - 125%) [17]. All pharmacokinetic analysis was carried out using WinNonlin Professional software (Pharsight, Palo Alto, CA, USA).

3. Results and Discussion

Lansoprazole oral pharmacokinetics was characterized in all subjects enrolled and no important adverse events were observed. **Figure 1** depicts the plasma level-time course after administration of an oral dose of 15 mg of

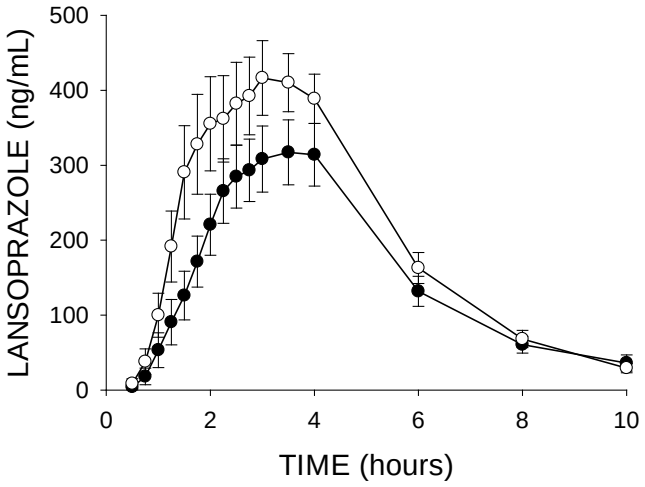

Figure 1. Lansoprazole plasma concentration against time curves after administration of an oral dose of 15 mg in two pharmaceutical formulations, lansoprazole + placebo (white circles) and lansoprazole + hyoscine butylbromide 10 mg (black circles) to 25 healthy volunteers. Data are expressed as mean ±s.e.m.

lansoprazole plus placebo and the fixed-dose combination of 15 mg + 10 mg of lansoprazole plus hyoscine butylbromide. It can be observed that after administration of formulations lansoprazole plasma levels increased reaching a maximum of around 2.5 to 3.5 hours. Thereafter, levels decayed with a half-life of about 1.4 hours. Pharmacokinetic parameters obtained by non-compartmental analysis are shown in **Table 2**. In order to establish if formulations tested are bioequivalent, ratios of AUC_{0-t} and C_{max} for both formulations, as well as 90% confidence intervals were obtained. The results of these ratios and confidence intervals, probability of exceeding limits of acceptance and the power test are shown in **Table 3**.

It is well recognized that previous to evaluate the clinical effects of a fixed dose combination of drugs in a new formulation, is necessary to verify the safety of its administration for a possible drug-drug interaction between the drugs in study, especially when at least one of them exerts a local effect on the site of administration as is the case of hyoscine butylbromide. It has been established that pharmacokinetic drug-drug interaction refers to an alteration of the concentration of one drug caused by the presence of a second drug through effects on absorption, distribution, metabolism or excretion [18] [19]. Since hyoscine butylbromide is not significantly absorbed by oral route, in this study we evaluated the oral pharmacokinetics of lansoprazole after the administration of a single dose from fixed-dose combination tablets containing 15 mg of lansoprazole and 10 mg of hyoscine butylbromide in healthy volunteers under fasted conditions. The formulation studied contains two drugs widely used for gastrointestinal disorders and there are no previous reports about the evaluation of the possible pharmacokinetic interaction between lansoprazole and hyoscine butylbromide. In terms of tolerability, no important adverse events were observed with the formulations evaluated. In order to examine if the coadministration influences on the pharmacokinetic parameters of lansoprazole, similarly the oral pharmacokinetics of this drug was studied when it was administered alone. The results obtained demonstrated that hyoscine butylbromide significantly affects the oral bioavailability of lansoprazole. It was observed a decrease in the C_{max} and AUC values with differences statistically significantly, as well as a delay in the time to reach the C_{max}, although no differences for $t_{1/2}$ values were observed, the results indicate a pharmacokinetic interaction between hyoscine butylbromide and lansoprazole. In that sense, we discarded a possible interaction at distribution or metabolism processes, since hyoscine butylbromide is barely absorbed and is not a CYP2C19 or CYP3A4 inductor which is enzymes responsibles of the metabolism of lansoprazole. Due hyoscine butylbromide acts locally on gastrointestinal system, this allow to suggest that the mechanism of this drug-drug interaction occurs during the process of absorption of lansoprazole.

Few previous reports have studied the effect of the coadministration of hyoscyne butylbromide on the oral bioavailability parameters of some drugs or on the swallowing of oral pharmaceutical forms. Channer *et al*., [20] evaluated the effect of previous administration of intravenous hyoscine butylbromide (20 mg) on the oesophageal transit of hard gelatin capsules in healthy subjects. The drug treated groups exhibit a significantly reduced

Table 2. Pharmacokinetic parameters of lansoprazole after administration of an oral single dose of the formulations in study to 25 healthy volunteers. Data are expressed as mean ± s.e.m.

Parameter	Lansoprazole 15 mg + placebo	Lansoprazole 15 mg + hyoscine butylbromide 10 mg
C_{max} (ng/mL)	621.81 ± 212.79	450.39 ± 192.14
t_{max} (h)	2.83 ± 0.99	3.40 ± 1.82
AUC_{0-t} (ng·h/L)	1941.39 ± 845.57	1454.66 ± 757.28
AUC_{∞} (ng·h/L)	2011.47 ± 915.67	1555.67 ± 837.70
$t_{1/2}$ (h)	1.35 ± 0.39	1.46 ± 0.51

Table 3. Comparison of 90% confidence limits of C_{max} and AUC_{0-t} and probability of exceeding the limits of acceptance for bioequivalence of two formulations of lansoprazole tested. Limits were fixed at 80% - 125% for C_{max} and AUC_{0-t}.

Parameter	Geometric mean ratio (Test/Reference)	90% Confidence Interval (%)	Probability of exceeding limits of acceptance		Power $(1-\beta)$
			P < 80%	P > 125%	
C_{max}	70.18	62.06 - 79.37	0.959	0.000	0.845
AUC_{0-t}	72.97	66.68 - 79.86	0.953	0.000	0.980

transit may explained by the anticholinergic oesophageal effects by hyoscine butylbromide. El-Bahie *et al*., [21] experimentally used intramuscular hyoscine butylbromide to simulate the delay in the gastric emptying observed after an overdose of mefenamic acid. The effect of hyoscine butylbromide produced a significantly delay to achieve maximal concentrations of mefenamic acid but without modifications on area under the plasma-concentration-time curve. For its part, Carrasco-Portugal *et al*., [22] demonstrated a lack influence of hyoscine butylbromide (20 mg) on the oral pharmacokinetics of ketorolac (10 mg) when were administered in an oral fixed dose formulation. Similarly to our results, Ajima *et al*., [23] demonstrated a significantly effect of hyoscine butylbromide on the bioavailability of paracetamol (which has been demonstrated to be a marker of gastric emptying/motility [24]). Previous to the administration of an oral dose of parecetamol (1 g), an oral dose of hyoscine butylbromide (10 mg) was administered. The results showed a significantly decrease in C_{max} value (≈50%) as well as the AUC values in comparison to those that received paracetamol alone. Additionally, the t_{max} value was 1 hr delayed, whereas the $t_{1/2}$ value was similar between the groups studied.

An important issue with potential to affect the oral bioavailability of drugs is the gastric emptying rate which depends of some factors including the pH of the stomach and the intake of other drugs [25]. In that sense, it has been established an active participation of acetylcholine in the generation of H^+ ions by the parietal cells of the gastric mucosa by stimulation of the muscarinic M3 receptors on these cells, which supposses that an inhibition of M3 receptors may cause a decrease of H^+ ions [1]. Therefore, the participation of an anticholinergic agent such hyoscine butylbromide could decrease the generation of H^+ and modify the pH of the stomach. Moreover, one of the most studied effects of hyoscin butylbromide is its ability to decrease the gastric motility and/or emptying rate which is in a dose-dependent manner [13] [20] [21] [23] [26]-[29]. By knowing the solubility and permeability of lansoprazole after an oral administration it belongs to class II of the Biopharmaceutical Classification System (BCS) since has a low solubility and high permeability [30]. By this, lansoprazole exhibits a dissolution rate-limited absorption will have a significant impact in the blood concentration-time profile, therefore, its bioavailability could be more susceptible to reduce when the gastric emptying/motility decrease.

4. Conclusion

Our results indicate that the concomitant oral administration of hyoscine butylbromide alter significantly the pharmacokinetics of oral lansoprazole. Further studies are necessary in order to evaluate the clinical outcomes in the symptomatology of ART that can be obtained by administering of this new formulation.

References

[1] Fock, K., Ang, T., Bee, L. and Lee, J. (2008) Proton Pump Inhibitors: Do Differences in Pharmacokinetics Translate into Differences in Clinical Outcomes? *Clinical Pharmacokinetics*, **47**, 1-6. http://dx.doi.org/10.2165/00003088-200847010-00001

[2] Katz, P., Gerson, L. and Vela, M. (2013) Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. *American Journal of Gastroenterology*, **108**, 308-328. http://dx.doi.org/10.1038/ajg.2012.444

[3] Blum, R., Hunt, R., Kidd, S., Shi, H., Jennings, D. and Greski-Rose, P. (1998) Dose-Response Relationship of Lansoprazole to Gastric Acid Antisecretory Effects. *Alimentary Pharmacology & Therapeutics*, **12**, 321-327. http://dx.doi.org/10.1046/j.1365-2036.1998.00306.x

[4] Huang, J. and Hunt, R. (2001) Pharmacological and Pharmacodynamic Essentials of H(2)-Receptor Antagonists and Proton pump Inhibitors for the Practising Physician. *Best Practice & Research. Clinical Gastroenterology*, **15**, 355-370. http://dx.doi.org/10.1053/bega.2001.0184

[5] Langtry, H. and Wilde, M. (1997) Lansoprazole. An Update of Its Pharmacological Properties and Clinical Efficacy in the Management of Acid-Related Disorders. *Drugs*, **54**, 473-500. http://dx.doi.org/10.2165/00003495-199754030-00010

[6] Matheson, A. and Jarvis, B. (2001) Lansoprazole. An Update of Its Place in the Management of Acid-Related Disorders. *Drugs*, **61**, 1801-1833. http://dx.doi.org/10.2165/00003495-200161120-00011

[7] Spencer, C. and Faulds, D. (1994) Lansoprazole. A Reappraisal of Its Pharmacodynamic and Pharmacokinetic Properties, and Its Therapeutic Efficacy in Acid-Related Disorders. *Drugs*, **48**, 404-430.

[8] Pichard, L., Curi-Pedrosa, R., Bonfils, C., Jacqz-Aigrain, E., Domergue, J., Joyeux, H., Cosme, J., Guengerich, F.P. and Maurel, P. (1995) Oxidative Metabolism of Lansoprazole by Human Liver Cytochromes P450. *Molecular Pharmacology*, **47**, 410-418. http://dx.doi.org/10.2165/00003495-199448030-00007

[9] Gerloff, J., Mignot, A., Barth, H. and Heintze, K. (1996) Pharmacokinetics and Absolute Bioavailability of Lansopra-

zole. *European Journal of Clinical Pharmacology*, **50**, 293-297. http://dx.doi.org/10.1007/s002280050111

[10] Howden, C., Metz, D., Hunt, B., Vakily, M., Kukulka, M., Amer, F. and Samra, N. (2006) Dose-Response Evaluation of the Antisecretory Effect of Continuous Infusion Intravenous Lansoprazole Regimens over 48 h. *Alimentary Pharmacology & Therapeutics*, **23**, 975-984. http://dx.doi.org/10.1111/j.1365-2036.2006.02849.x

[11] Fass, R. (2012) Therapeutic Options for Refractory Gastroesophageal Reflux Disease. *Journal of Gastroenterology and Hepatology*, **27**, 3-7. http://dx.doi.org/10.1111/j.1440-1746.2012.07064.x

[12] Mueller-Lissner, S., Tytgat, G., Paulo, L., Quigleys, E., Bubeck, J., Peil, H. and Schaefer, E. (2006) Placebo- and Paracetamol-Controlled Study on the Efficacy and Tolerability of Hyoscine Butylbromide in the Treatment of Patients with Recurrent Crampy Abdominal Pain. *Alimentary Pharmacology & Therapeutics*, **23**, 1741-1748. http://dx.doi.org/10.1111/j.1365-2036.2006.02818.x

[13] Tytgat, G. (2007) Hyoscine Butylbromide. A Review of Its Use in the Treatment of Abdominal Cramping and Pain. *Drugs*, 67, 1343-1357. http://dx.doi.org/10.2165/00003495-200767090-00007

[14] Koerselman, J., Pursnani, K., Peghini, P., Mohiuddin, M., Katzka, D., Akkermans, L. and Castell, D. (1999) Different Effects of an Oral Anticholinergic Drug on Gastroesophageal Reflux in Upright and Supine Position in Normal, Ambulant Subjects: A Pilot Study. *American Journal of Gastroenterology*, **94**, 925-930. http://dx.doi.org/10.1016/s0002-9270(99)00043-x

[15] Mexican Official Norm (1999) Tests and Procedures to Prove That a Medication Is Interchangeable. Mexican Official Norm, NOM-177-SSA1-1998. Requirement 9.1. Official Journal of the Federation, México City, México.

[16] Rowland, M. and Tozer, T. (1989) Clinical Pharmacokinetics. Concepts and Applications. 3rd Edition, Lea and Febiger, Philadelphia.

[17] Schuirmann, D. (1987) A comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics*, **15**, 657-680. http://dx.doi.org/10.1007/BF01068419

[18] Grasela Jr., T.H., Antal, E.J., Ereshefsky, L., Wells, B.G., Evans, R.L. and Smith, R.B. (1987) An Evaluation of Population Pharmacokinetics in Therapeutic Trials. Part II. Detection of a Drug-Drug Interaction. *Clinical Pharmacology and Therapeutics*, **42**, 433-441. http://dx.doi.org/10.1038/clpt.1987.174

[19] Fleisher, D., Li, C., Zhou, Y., Pao, L.H. and Karim, A. (1999) Drug, Meal and Formulation Interactions Influencing Drug Absorption after Oral Administration. Clinical Implications. *Clinical Pharmacokinetics*, **36**, 233-254. http://dx.doi.org/10.2165/00003088-199936030-00004

[20] Channer, K.S., Wolinski, A. and Virjee, J. (1983) The Effect of Hyoscine Butylbromide on the Swallowing of Capsules. *British Journal of Clinical Pharmacology*, **15**, 560-563. http://dx.doi.org/10.1111/j.1365-2125.1983.tb02091.x

[21] El-Bahie, N., Allen, E.M., Williams, J. and Routledge, P.A. (1985) The Effect of Activated Charcoal and Hyoscine Butylbromide Alone and in Combination on the Absorption of Mefenamic Acid. *British Journal of Clinical Pharmacology*, **19**, 836-838. http://dx.doi.org/10.1111/j.1365-2125.1985.tb02724.x

[22] Carrasco-Portugal, M.C., Fernández del Valle, C., Aguilar-Carrasco, J.C., Patiño-Camacho, S., Reyes-García, J.G. and Flores-Murrieta, F.J. (2012) Evaluation of the Possible Pharmacokinetic Interaction between Ketorolac and Hyoscine Butylbromide in Healthy Volunteers. *Clinical Pharmacology in Drug Development*, **1**, 208.

[23] Ajima, U., Garba, M. and Yakasai, I. (2012) Comparison of the Effects of Cimetidine and Hyoscine-N-Butyl Bromide on Paracetamol Pharmacokinetics in Healthy Volunteers. *Der Pharma Chemica*, **4**, 872-881.

[24] Ayalasomayajula, S., Meyers, D., Koo, P., Salunke, A., Majumdar, T., Rebello, S., Sunkara, G. and Chen, J. (2015) Assessment of Pharmacokinetic Drug-Drug Interaction between Pradigastat and Acetaminophen in Healthy Subjects. *European Journal of Clinical Pharmacology*, **71**, 425-432. http://dx.doi.org/10.1007/s00228-015-1822-2

[25] Tandon, V. (2002) Bioavailability and Bioequivalence. In: Schoenwald, R.C., Ed., *Pharmacokinetics in Drug Discovery and Development*, CRC Press, Boca Ratón, 98-112. http://dx.doi.org/10.1201/9781420010084.ch5

[26] Schmid, E., Bleichert, A., Uberla, K., Ritter, U. and Fehlhaber, E. (1968) Testing of Orally Administered Spasmolytics Demonstrated by the Effect of Hyoscine-N-Butylbromide on Gastric Motility. *Arzneimittel-Forschung*, **18**, 1449-1453.

[27] Schmid, E., Bleichert, A., Kitzing, J. and Ritter, U. (1969) Inhibition of Small Intestine Motility by Orally Administered Hyoscine-N-Butylbromide. *Arzneimittel-Forschung*, **19**, 998-999.

[28] Schmid, E., Wagner, T. and Ritter, U. (1971) Inhibition of Gastric Motility by Rectal Administration of Hyoscine-N-Butylbromide. *Arzneimittel-Forschung*, **21**, 813-815.

[29] Stacher, G., Bergmann, H., Havlik, E., Schmierer, G. and Schneider, C. (1984) Effects of Oral Cyclotropium Bromide, Hyoscine N-Butylbromide and Placebo on Gastric Emptying and Antral Motor Activity in Healthy Man. *Gut*, **25**, 485-490. http://dx.doi.org/10.1136/gut.25.5.485

[30] Wu, C., Sun, L., Yang, Y., Ren, C., Ai, X., Lian, H. and He, Z. (2013) Profiling Biopharmaceutical Deciding Properties of Absorption of Lansoprazole Enteric-Coated Tablets Using Gastrointestinal Simulation Technology. *International Journal of Pharmaceutics*, **453**, 300-306. http://dx.doi.org/10.1016/j.ijpharm.2013.06.034