INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Drug-Drug-Dietary interactions in pharmacotherapy of GIT medication: A review

Akula sowjanya[*1,2], Abhisek Pal[1]

[1]Department of Pharmacology, GITAM School of Pharmacy (GITAM Deemed to be University), Rudraram, Hyderabad, Telangana-502329, India
[2]Department of pharmacology, Marri Laxman Reddy Institute of pharmacy, Dundigal, Hyderabad, Telangana-500043, India

ABSTRACT

Successful drug therapy depends on the interaction between drug-drug and drug-diet. Drug interactions are a vital reason for causing adverse drug reactions and modify one drug effect by another drug and these kinds of interactions can increase or decrease the effectiveness of the drug. Polypharmacy could be a major risk for Drug-Drug and Drug-food interactions. Food Consumption can alter the effect of drugs by interfering either with their pharmacokinetics or pharmacodynamics processes. Anti-ulcer drugs are used to treat different types of ulcer and that may interact with another drug showing undesirable effects. GIT medications interfere with another type of medication either with at the pharmacokinetic and pharmacodynamic level. The main objective of this article is to review data regarding common Drug-drug & Drug-food interactions related to GIT medications. Data was collected from Google Scholar, PubMed, and Scopus databases, and they were reviewed for publication on drug-drug & drug-food interactions related to GIT medications. This data is very helpful for pharmacists while reviewing and analyzing prescribed medication, especially in geriatrics prescriptions.

*Corresponding Author

Name: Akula sowjanya
Phone: 8106445852
Email: akula.sowjuu@gmail.com

INTRODUCTION

Drug interactions are an important, anonymous root of medication errors, which express a notable risk of harm to patients and opportunities for health-care systems (Kapadia *et al.*, 2013). Polypharmacy is a major risk of causing drug-drug and Drug-food interactions. Polypharmacy is a term used to define the administration of more than 5 drugs at a time. "Potential Drug-Drug Interaction" refers to the drug must alter the effect of another drug, when both drugs are simultaneously administered. This review aims to summarize the Drug-drug & food-drug interactions related to GIT medications. Gastrointestinal drugs are classified as Antiulcer drugs cimetidine, ranitidine, omeprazole, misoprostol and sucralfate. Antiemetics are ondansetron, domperidone, metoclopramide. Antidiarrhoeal agents are Ispaghula, atropine, codeine, loperamide, sulfasalazine, etc. Drug interactions are classified into 3 main types - Drug-drug, Drug-diet and Drug-herb interactions.

Drug-Food interactions

Numerous individuals have the mixed up idea that being common all types of food and herbs are protected but a few herbs and food may interact with prescription drugs regularly taken bring about gen-

uine side effects. Specialist recommend that natural does not mean it is safe. Medicine that is taken by mouth goes through the stomach related framework similarly as food and herbs taken orally do. At the point when drugs and certain food are taken simultaneously, they can interact so that diminishes the adequacy of ingested tranquilize or decrease the absorption of food nutrients. Furthermore, nutrient and herbal supplements are taken with recommended medicine that can bring about adverse reactions. Drug-food cooperation occurs due to food influences the substances in medication that the patient is taking influencing the viability of medication being regulated. Old age patients taking at least 3 medications for chronic conditions such as diabetes, hypertension, elevated cholesterol and congestive heart failure that kind patients should be specially observed for such drug-food interactions.

Drug-Drug interaction

Drug interactions are comprehensively split into pharmacokinetic and pharmacodynamics interactions.

Pharmacokinetic Interaction

Pharmacokinetic interactions occurs when the absorption, distribution, metabolism, elimination process of the one drug is altered by another drug and hence such interactions are also called as ADME interactions.

Pharmacodynamics Interactions

Pharmacodynamics interactions happen because of alteration of the activity of one drug by another drug. This may bring about an improved response (synergism) a constricted response (antagonism) or an abnormal response (Niu *et al.*, 2019).

Drug-Drug interactions

Proton-pump inhibitors and clopidogrel

Combination of clopidogrel and aspirin was utilized for treatment of coronary heart diseases and diminishing the threat of new coronary ischemic occasions. Some adverse gastrointestinal symptoms associated with clopiodogrel and aspirin. PPIs are used to prevent the gastrointestinal symptoms. Clopidogrel is a pro drug that should be utilized an intrahepatic two advance oxidative cycle. Cytochrome P450 enzymes (CYP1A2, CYP2B6 and CYP2C19) are required for activation and metabolism of clopiodogrel. CYP1A2, CYP2B6 and CYP2C19 enzymes are required to convert the clopidogrel to 2-oxo-clopidogrel, which is then once more oxidized to convert the clopidogrel active metabolite with the help of CYP2B6, CYP2C19, and CYP3A4. CYP2C19 is by all accounts vital in metabolization and activation of clopidogrel. PPIs are

inhibiting CYP2C19 enzyme so, activation of clopidogrel is inhibited. *Invitro* investigations indicated that Lansoprazole, omeprazole drugs are significantly inhibiting the CYP2C19 while pantoprazole and rabeprazole drugs are not significantly inhibit CYP2C19. A few pharmacodynamics studies concluded a potential clopidogrel PPI interaction. As a result of this interaction there is a reduction of the clopidogrel platelet anti-aggregation effect. So, cardiovascular risk increases with concurrent administration of clopidogrel and PPIs (Chen *et al.*, 2013).

Cimetidine with benzodiazepines

Cimetidine is H2 receptor antagonist, neutralizes the gastric juices in gastrointestinal tract and rise the pH in GIT. Cimetidine elevates the diazepam and lorazepam absorption because elevated gastric pH may increase the weekly basic benzo diazepines absorption. Plasma levels of benzo diazepines were increases. Drowsiness elevated in patients who are attending utilize the cimetidine with diazepam and Lorazepam (McGowan and Dundee, 1982).

Cimetidine with cardiovascular drugs

Mechanism for cimetidine interaction with another drug is hindrance of hepatic metabolism. Cimetidine inhibits the hepatic microsomal enzymes that enzymes required for metabolism of beta blockers. Cimetidine increases the blood concentration of beta blockers and potentiate the actions of beta blockers. Concomitant administration of cimetidine and nifedipine could alter the pulse rate and blood pressure due to the hindrance of liver oxidative metabolism. Cimetidine used along with lidocaine may increases lidocaine concentration and increases the toxicity of lidocaine because of a lessening in oxidative liver metabolism or liver blood stream. Cimetidine increases the plasma levels of quinidine and leads to toxicity of quinidine. Besides, redesigned arrhythmic effects might be observed. Association probably achieved by an obstacle of hepatic drug metabolism of quinidine by cimetidine. As per literature, vital pharmacokinetic clinical effects on cardiovascular medication have been noted with cimetidine, while ranitidine may not have significant kinetics impacts on propranolol, nifedipine, lidocaine, quinidine, procainamide (Saltissi *et al.*, 1981).

Proton-pump, Histamine 2 receptor blockers with vitamin B12

Gastric acid is produced by parietal cells and that gastric acid is used to split vitamin B12 from ingested food. Parietal cells also produce the intrinsic factor and this factor required to absorb the vitamin B12. Gastric acid production decreased by PPIs and histamine receptor blockers and it may lead to

malabsorption of vitamin B12 (Miller, 2018).

Magnesium-Aluminium Hydroxide Antacid with Rufloxacin

Rufloxacin is an oral fluoroquinolone active against the gram negative and gram positive oxygen consuming microbes. Magnesium and aluminium salts present in the acid neutralizers can decrease the extent to which rufloxacin is absorbed. Mechanism of interaction between antacid and quinolones is by all accounts the formation of chelate complexes between the 3-carboxyl and the 4-oxo substituents of quinolones and metal ions. Aluminium along with quinolones forms a stable complex. Reduction in amount of rufloxacin absorbed is a result of concomitant administration of antacid and possibility of this interaction is dependent on the time gap between administrations of the 2 drugs. To avoid this interaction between antacid and rufloxacin, they should be administered with a time gap of at least 4 hr (Lazzaroni *et al.*, 1993).

Methotrexate with PPIs

Methotrexate poison levels are prompted when this drug is used at high dosages with PPIs for example, omeprazole, esomeprazole, and pantoprazole which diminishes methotrexate clearance resulting in raised serum levels of methotrexate and also its metabolite hydroxyl methotrexate. There are two proposed mechanisms for this obstruction of methotrexate elimination induced by PPIs. The first mechanism is the presence of H+/K+ ATPase in the renal epithelium just as gastric parietal cells. PPIs inhibit renal H+/K+ ATPase which is required for tubular secretion of methotrexate, bringing about an expanded half-life of methotrexate. Another mechanism includes conceivable PPIs inhibits ATP-subordinate efflux of methotrexate by BCRP in human kidney proximal tubules. Even though it was shown that PPIs inhibit BCRP mediated transport of methotrexate *Invitro,* the uncertainty of the clinical importance of this interaction is due to the higher half-maximal inhibitory concentration of PPIs when compared to the therapeutic unbound plasma concentration (Chioukh *et al.*, 2014).

Ketoconazole with sucralfate, H2-receptor blockers, PPIs

Ketoconazole, a drug used to treat the fungal infections is decreasingly absorbed with an increasing gastric pH. Gastric pH increases due to administration of antacids, H2-receptor antagonists and proton pump inhibitors. In contrast, in low gastric pH, Ketoconazole is absorbed easily. Bioavailability of ketoconazole decreases due to concurrent administration of ketoconazole with sucralfate, H2 receptor blockers, PPIs. Concurrent administration of keto-conazole with sucralfate, H2 receptor blockers, PPIs should be avoided. If these agents were to be administered concurrently, there should be a time gap of at least 2 hr between the doses (Hoeschele *et al.*, 1994).

Aluminium hydroxide, famotidine with tos-floxacin

Tosufloxacin acts against gram positive and gram negative bacteria, including anaerobic microscopic organisms. Between fasting and non fasting conditions, tosufloxacin is absorbed about 1.4 times higher under non fasting conditions. Area under curve of tosufloxacin was diminished essentially 68.4% by concurrent administration of aluminium hydroxide, while an immaterial impact of simultaneous co-organization of famotidine. Absorption of tosfloxacin is not diminished by bivalent cations like Fe^{+2}, Mg^{+2} and Ca^{+2} co-organization of different fluoroquinolones with metal containing acid neutralizers that may diminish the bioavailability of fluoroquinolones is ascribed to cooperation with metal particles, delivering chelated mixes which are less ready to permeate membranes (Granneman *et al.*, 1992). Urinary recovery values are diminished essentially 66% by the simultaneous organization of aluminium hydroxide yet were not influenced by the co-organization of famotidine. The degree of the communication may shift and retention can be quite diminished, synchronous organization of aluminium hydroxide and tosufloxacin should be avoided. Famotidine may give an option in contrast to acid neutralizers to patients who require oral fluoroquinolone treatment.

Sonidegib with esomeprazole

Sonidegib, a drug that was recently promoted widely is used for treating locally progressed basal cell carcinoma, a condition that can't be treated with surgery or radiation treatment. Sonidegib is taken by an oral route and it is a weak base. The solubility of sonidegib depends on pH, lower solubility at pH > 4.5 but PPIs are raises the gastric pH because it inhibits gastric acid production. The bioavailability of sonidegib is decreases due to high gastric pH. Sonidegib plasma concentration is diminished by 32–38% when co-administered with esomeprazole. Some adverse reactions revealed in the combination of sonidegib and esomeprazole i.e. abdominal distension, stomach pain, loose bowels, flatulence and regurgitation (Jain *et al.*, 2017).

Pantoprazole with vecuronium

Pantoprazole at low doses has potentiated basal contractile jerk reactions and this was followed by paralysis at higher dosages response to stimulation

Table 1: List of GIT associated Drug-food interactions

Drug name	Food	Drug-food interactions
Esomeprazole	High-fat meal	Reduces the bioavailability (Morcos *et al.*, 2017).
Cimetidine	Any type of food	Bioavailability increases (Hansten, 1992).
Cimetidine	caffeine	Caffeine effects increased due to decreases the metabolism of caffeine by cimetidine (Feely and Wood, 1982).
Cimetidine	ethanol	Metabolism of ethanol is decreased by cimetidine. There is an increase concentration of ethanol (Hansten, 1992).
H2 receptor antagonists	Nicotine	H2 receptor antagonists may reduce the clearance of nicotine. Patients should be noticing the expanded nicotine impacts when utilizing the patches or gum for smoking discontinuance (Bendayan *et al.*, 1990).
Esomeprazole	Any type of food	Any kind of food alter the absorption of esomeprazole. One-hour time gap necessary between consumption of meals and esomeprazole (Jain *et al.*, 2017).
Misoprostol	Any kind of food	Food reduces the early high peak plasma concentration of misoprostol acid (Jain *et al.*, 2017).
Calcium carbonate	Oxalic acid rich containing foods (spinach or rhubarb), phytic acid (bran and whole grains).	Oxalic acid and phytic acid decrease calcium absorption. Require minimum 2 hours time gap between calcium intake and foods rich in oxalic acid or phytic acid (Wohlt *et al.*, 2009).
sucralfate	Food	Obstruction of feeding tubes due to precipitation and formation of bezoars. Insoluble aluminium-protein complex formed between aluminium in the sucralfate and the protein in the enteral feeding (Tait *et al.*, 1994).
sucralfate	Orange juice	Orange juice upgrades sucralfate absorption (Tait *et al.*, 1994).

of rat phrenic nerve, indicating a double activity. It might happen because of weak anticholinesterase activity of pantoprazole. Pantoprazole potentiated the vecuronium induced neuromuscular blockade and it is reversed by neostigmine. Pantoprazole reduces the time for neuromuscular blockade in the cumulative dose response curve of vecuronium, proposing an expected interaction between them. Patel *et al.* (2010) concluded that the Acute and chronic administration of pantoprazole significantly reduced the time for the head drop (rabbit head drop method) by vecuronium infusion. This gives additional proof that pantoprazole produces a neuromuscular blockade. A proposal was made that patients receiving pantoprazole as a treatment for peptic ulcer or pre-sedative medication should be screened, to prevent prolonged paralysis.

Clopidogrel is co-administered with atorvastatin and lansoprazole

Clopidogrel is used for cardiovascular and cerebro vascular diseases. 2 cytochrome enzymes CYP3A4, CYP2C19 is required for activation of clopidogrel.

Fat soluble statin example atorvastatin is mainly metabolized by CYP3A4 which is required to activate clopidogrel. Drug interaction occurs between clopidogrel and atorvastatin due to binding site competition and this coadministration may inhibit clopidogrel activation and decreases the antiplatelet effect. Lansoprazole also a competitive inhibitor due to it is metabolized by CYP3A4 and CYP2C19.

Zhang *et al.* (2015) concluded that coadministration of clopidogrel, atorvastatin and lansoprazole is safe. Effect of clopidogrel is not decreased due to clopidogrel is metabolized by many CYP450 (CYP1A2, CYP2C9, CYP2D6, CYP3A5). The different combined use of CYP3A4, CYP2C19 inhibitors may not enough to inhibit the metabolism of clopidogrel and fat-soluble statins, lansoprazole. The conclusion of his study is a patient diagnosed with Non-ST-elevation acute coronary syndrome and patients who are simultaneously administered clopidogrel, atorvastatin and lansoprazole, the anti platelet effect of clopidogrel did not decreases and adverse effects did not increase over 6 months.

Lansoprazole with fluvoxamine

Gastric acid secretion decreased by lansoprazole due to inhibiting the (H +/K +) - ATPase in gastric parietal cells. Lansoprazole is widely metabolized by CYP2C19 and CYP3A4 to two significant metabolites, 5-hydroxylansoprazole and lansoprazole sulphone, respectively. Clinically administered as a racemic mixture of the (R) - and (S) - enantiomers, the plasma concentration of (R) - lansoprazole is considerably higher than those of the (S) - lansoprazole enantiomer in both broad metabolizers (EMs) and poor metabolizers (PMs). Fluvoxamine is a specific serotonin reuptake inhibitor (SSRI), and it is powerful CYP1A2, CYP2C19 inhibitor. At the point when lansoprazole is Co-administered with fluvoxamine, there is increases in the plasma concentration of (S) lansoprazole compared with that of the (R) - enantiomer. Fluvoxamine inhibits the metabolism of lansoprazole and it may lead to significantly decreases elimination in extensive metabolizers. As an exception, Lansoprazole when metabolized in extensive metabolizers by CYP3A4, Lansoprazole sulphone is the resulting metabolite because CYP2C19 activity is obstructed by fluvoxamine, while in the Poor Metabolizers of CYP2C19, fluvoxamine somewhat inhibit the development of lansoprazole sulphone but not significantly (Yasui et al., 2004).

Ondansetron with droperidol

Droperidol and ondansetron are the first line drugs used for the treatment of postoperative nausea and vomiting (PONV). Separately the two medications give rise to the delayed QT interval, the clinical impact of combined treatment might be adjusted by drug interactions and result in increases in the risk of arrhythmia. The collaboration among ondansetron and droperidol was shown the additive effect, the two medications act freely of one another through their particular mechanism of action (Miura et al., 2005).

Lansoprazole and clarithromycin

Clarithromycin a drug used to treat bacterial infections when co-administered with proton pump inhibitors including lansoprazole proves to be highly effective in the eradication of H. pylori. Lansoprazole is metabolized with the help of cytochrome P450 enzymes (CYP2C19, CYP3A4). At higher concentration sulfoxidation of lansoprazole catalysed by CYP3A4 and hydroxylation is catalysed by CYP2C19 at lower concentrations. Potentially clarithromycin inhibits CYP3A4 for this reason potent drug interactions occur with those agents that are metabolized by CYP3A4. Clarithromycin significantly expanded the Cmax of lansoprazole in all genotype gatherings and significantly delayed the half-life of lansoprazole in Poor metabolizers. CYP2C19 is overwhelmingly engaged with lansoprazole metabolism in extensive metabolizers and CYP3A4 is in Poor metabolizers. The bioavailability of lansoprazole is increased by Clarithromycin and a further study of the mechanism behind it showed the P-glycoprotein mediated transport of Clarithromycin back to the intestinal lumen after absorption was inhibited. Clarithromycin alters the lansoprazole pharmacokinetics due to inhibition of both CYP3A4 and P-glycoprotein in poor metabolizers, only P-glycoprotein inhibition in extensive metabolizers (Dabbous et al., 2001).

Domperidone with ketoconazole

Domperidone is an anti-emetic and prokinetic drug. The high portion intravenous domperidone was related to QTc prolongation and arrhythmias. Domperidone is metabolized by CYP3A4 and a substrate of P-glycoprotein. Ketoconazole is a powerful inhibitor of CYP3A and P-glycoprotein, so a pharmacokinetic interaction occurs between ketoconazole and domperidone. The plasma concentrations of domperidone are increasing three-fold when given with ketoconazole because domperidone metabolism inhibited by ketoconazole. The higher concentration of domperidone rises the QT interval. Domperidone impact alone on QTc prolongation is very less and clinically not significant. So, Concurrent administration of dompridone and ketoconazole should be avoided (Saito et al., 2005).

Ondansetron and cisplatin

Cisplatin drug (cationic) excretion requires Human natural cation carrier 2 and multidrug and poison expulsion proteins (MATEs). Cisplatin is an anti-cancer medication used for the treatment of malignant solid tumours. The major significant adverse effect of cisplatin is nephrotoxicity. Excretion transporter's like OCT2 and MATE1 (rodents) and MATE2 (humans) are required for the secretion of cisplatin into the urine and they are present in the apical layer of proximal tubular cells. Ondansetron (5HT-3 receptor antagonist) is active against chemotherapy induced nausea and vomiting especially patients who are taking emetogenic cisplatin-based regimens. Ondansteron is strongly inhibits MATEs than OCTs. The risk of cisplatin induced nephrotoxicity increased due to the powerful restraint of MATEs by ondansetron (Boyce et al., 2012).

Ondansetron and metformin

Metformin is utilized to diminish the glucose level in diabetes patients. Metformin pharmacokinetic parameter values are significantly altered

by ondansetron. Metformin excretion requires some specialized transporters like OCTs and MATEs. Ondansetron is an inhibitor of MATEs transporters. Around 75% Ondanseteron bound to plasma proteins and remaining 25% unbound drug concentration adequate to inhibit the apical MATEs. The unbound ondansetron has decreased the secretion of metformin into the urine, causing the accumulation of metformin in the plasma. The co-administration of Ondansetron and metformin reliably upgraded the glucose-bringing down impact by metformin (Li *et al.*, 2016).

Antacids and aspirin

Chronic use of antacids may potentially reduce serum salicylate concentration in peoples who are taking large doses of aspirin. The mechanism involved in between these two drugs is the reduction in aspirin renal tubular reabsorption due to urinary alkalinization by antacids, bringing about increases the renal salicylate clearance. Antacids should be administered before two hours of aspirin dose because this time gap may decrease the retention of aspirin in uremic patients (D'arcy and Mcelnay, 1987).

Sucralfate and digoxin

Sucralfate is an ulcer defensive, it is an aluminum salt of sulfated sucrose. Digitalis is a cardiac glycoside that is utilized to treat certain heart conditions like a congestive cardiovascular failure (CHF) and atrial arrhythmias. Digitalis can expand blood flow all through the body and diminish swelling in the upper and lower limbs. Digoxin absorption and therapeutic effectiveness decreased by sucralfate. There is a time gap required between the administration of sucralfate and digitalis. Digitalis must be administered two hours before (or) 6 hours after sucralfate. Here patients should be advised to notify their doctor if they experience worsening of their heart symptoms (Rey and Gums, 1991).

Food and GIT drugs interactions

Food and drug interactions may diminish or expand the drug effect. Some normally utilized spices, natural products just as alcohol might because the failure (or) decreases the drug therapeutic effect and serious modifications of the patient's well-being. Some clinically applicable food-GIT drug interactions are brought about by food-instigated changes in the bioavailability of the drug Table 1.

CONCLUSIONS

The drug-drug, drug-food interaction should be notable and recognized. Antacids change the absorption of numerous medications resulting in a decreased therapeutic effect. The impact of food on drugs brings about a decrease in the drug bioavailability and change in drug clearance. The interaction may bring about genuine hazardous results. Hence pharmacist becomes aware of the need for monitoring of potential Drug-Drug & Drug-Food interactions and educate patients regarding drugs and foods to be avoided when taking certain medication.

REFERENCES

Bendayan, R., Sullivan, J. T., Shaw, C. 1990. Effect of cimetidine and ranitidine on the hepatic and renal elimination of nicotine in humans. *European Journal of Clinical Pharmacology*, 38(2):165–169.

Boyce, M. J., Baisley, K. J., Warrington, S. J. 2012. Pharmacokinetic interaction between domperidone and ketoconazole leads to QT prolongation in healthy volunteers: a randomized, placebo-controlled, double-blind, crossover study. *British Journal of Clinical Pharmacology*, 73(3):411–421.

Chen, J., Chen, S., Lian, J. 2013. Pharmacodynamic impacts of proton pump inhibitors on the efficacy of clopidogrel in vivo–a systematic review. *Clinical cardiology*, 36(4):184–189.

Chioukh, R., Hudson, M., Ribes, S. 2014. Proton pump inhibitors inhibit methotrexate transport by renal basolateral organic anion transporter hOAT3. *Drug Metabolism and Disposition*, 42(12):2041–2048.

Dabbous, A., Khoury, S. J., Chehab, I. R. 2001. Ondansetron versus dehydrobenzoperidol and metoclopramide for management of postoperative nausea in laparoscopic surgery patients. *Journal of the Society of Laparoendoscopic Surgeons*, 5(2):139–142.

D'arcy, P. F., Mcelnay, J. C. 1987. Drug antacid interactions assessment of clinical importance. *Drug*

Intelligence & Clinical Pharmacy, 21(7-8):607–617.

Feely, J., Wood, A. J. 1982. Effects of cimetidine on the elimination and actions of ethanol. *JAMA*, 247(20):2819–2821.

Granneman, G. R., Stephan, U., Birner, B. 1992. Effect of antacid medication on the pharmacokinetics of temafloxacin. *Clinical Pharmacokinetics*, 22(1):83–89.

Hansten, P. D. 1992. Effects of H2-receptor antagonists on blood alcohol levels. *JAMA*, 267(18):2469–2470.

Hoeschele, J. D., Roy, A. K., Pecoraro, V. L. 1994. In vitro analysis of the interaction between sucralfate and ketoconazole. *Antimicrobial Agents and Chemotherapy*, 38(2):319–325.

Jain, S., Song, R., Xie, J. 2017. Sonidegib: mechanism of action, pharmacology, and clinical utility for advanced basal cell carcinomas. *OncoTargets and Therapy*, 10:1645–1653.

Kapadia, J., Thakor, D., Desai, C. 2013. A study of potential drug-drug interactions in indoor patients of medicine department at a tertiary care hospital. *Journal of Applied Pharmaceutical Science*, 3(10):89–96.

Lazzaroni, M., Imbimbo, B., Bargiggia, S. 1993. Effects of magnesium-aluminum hydroxide antacid on absorption of rufloxacin. *Antimicrobial Agents and Chemotherapy*, 37(10):2212–2216.

Li, Q., Yang, H., Guo, D. 2016. Effect of ondansetron on metformin pharmacokinetics and response in healthy subjects. *Drug Metabolism and Disposition*, 44(4):489–494.

McGowan, W. A., Dundee, J. W. 1982. The effect of intravenous cimetidine on the absorption of orally administered diazepam and lorazepam. *British Journal of Clinical Pharmacology*, 14(2):207–211.

Miller, J. W. 2018. Proton pump inhibitors, h2-receptor antagonists, metformin, and vitamin b-12 deficiency: clinical implications. *Advances in nutrition*, 9:511–518.

Miura, M., Tada, H., Yasui-Furukori, N. 2005. Enantioselective disposition of lansoprazole in relation to CYP2C19 genotypes in the presence of fluvoxamine. *British Journal of Clinical Pharmacology*, 60(1):61–68.

Morcos, P. N., Guerini, E., Parrott, N. 2017. Effect of food and esomeprazole on the pharmacokinetics of alectinib, a highly selective ALK inhibitor, in healthy subjects. *Clinical Pharmacology in Drug Development*, 6(4):388–397.

Niu, J., Straubinger, R. M., Mager, D. E. 2019. Pharma-codynamic drug–drug interactions. *Clinical Pharmacology & Therapeutics*, 105(6):1395–1406.

Patel, T. K., Patel, P. B., Tripathi, C. B. 2010. Effect of pantoprazole and its interactions with vecuronium on the neuromuscular junction. *Indian journal of pharmacology*, 42(1):36–39.

Rey, A. M., Gums, J. G. 1991. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *DICP: the annals of pharmacotherapy*, 25(7-8):745–746.

Saito, M., Yasui, N. F., Takahata, T. 2005. Effects of clarithromycin on lansoprazole pharmacokinetics between CYP2C19 genotypes. *British Journal of Clinical Pharmacology*, 59(3):302–309.

Saltissi, S., Crowther, A., Byrne, C. 1981. The effects of chronic oral cimetidine therapy on the cardiovascular system in man. *British Journal of Clinical Pharmacology*, 11(5):497–503.

Tait, S. F., Hickson, K., McGaw, B. 1994. Orange juice enhances aluminium absorption from antacid preparation. *European journal of clinical nutrition*, 48(1):71–73.

Wohlt, P. D., Zheng, L., Gunderson, S. 2009. Recommendations for the use of medications with continuous enteral nutrition. *American Journal of Health-System Pharmacy*, 66(16):1458–1467.

Yasui, N. F., Saito, M., Uno, T. 2004. Effects of fluvoxamine on lansoprazole pharmacokinetics in relation to CYP2C19 genotypes. *Journal of clinical pharmacology*, 44(11):1223–1229.

Zhang, J. R., Wang, D. Q., SBDeng 2015. Efficacy of clopidogrel and clinical outcome when clopidogrel is coadministered with atorvastatin and lansoprazole: a prospective, randomized, controlled trial. *Medicine*, 94(50):2262.