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Drug interactions in gastrointestinal disorders therapy

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ABSTRACT

Drug-drug interactions are a major cause of adverse reactions in polypharmacy, the incidence being directly proportional to the number of associated drugs. In this work, we highlighted the main drug-drug interactions that occurred in the treatment of gastrointestinal symptoms with proton pump inhibitors and histamine H2-receptor antagonists. The two groups of agents, used in gastroesophageal reflux and ulcer disease, can be released and without a prescription on the recommendation of the pharmacist, contributing to the risk of emergence of drug-drug interactions. Drug-drug interactions can occur due to the reduction of the gastric acidity, altering the biotransformation or excretion reducing of the drug coadministrated. pH increased may affect the absorption of some drugs decreasing (e.g. ketoconazole, itraconazole, atazanavir, vitamin B12, magnesium) or increasing the absorption of others (e.g. triazolam, midazolam). Furthermore, an attention to the interaction with narrow therapeutic index drugs (e.g. warfarin, phenytoin, theophylline) is required because of the risk of the toxic or side effects by the accumulation of these drugs.

Keywords: drug-drug interactions, proton pump inhibitors, histamine H2-receptor antagonists

INTRODUCTION

Drug interaction is defined as changes in the patient's response to the drug caused by the administration or co-exposure to another drug or substance. It is reported that 20-30% of all adverse drug reactions are caused by drug interactions. This incidence is increasing among the elderly and patients taking 2 or more medicines. Modern therapy has changed the way diseases are controlled and brought benefits to significant life expectancy, resulting in reduced morbidity and mortality. Despite everyone's benefits, the possibility of adverse reactions due to drug interactions is a common cause, often preventable, of disease, disability and even death. Apart from the associated inherent danger drug, patients may have a particular and unpredictable sensitivity to certain drugs. In addition, if more than one medication is prescribed, there is always the risk of drug interactions with negative effects [1, 2].

The pharmacist has an important role in drugs, to be further identifying problems related to the use and interactions between evaluated by pharmaco-epide-

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TABLE 1. Most frequently interactions of PPIs and H2 antagonists

Drugs	Major drug interactions	Moderate drug interactions	Minor drug interactions
Proton pump inhibitors: omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole	atazanavir clopidogrel citalopram erlotinib methotrexate nelfinavir tacrolimus	alprazolam atorvastatin cisplatin diazepam digoxin ketoconazole itraconazole phenytoin simvastatin levothyroxine naproxen warfarin voriconazole theophylline rifampicin	aspirin ciprofloxacin clarithromycin cannabidiol cyanocobalamin glipizide phenobarbital rosuvastatin duloxetine valdecoxib tolbutamide
H2 receptor antagonists: cimetidine, ranitidine, famotidine	atazanavir astemizole cisapride citalopram eliglustat loperamide hydrocodone tamoxifen terfenadine	aminophylline amiodarone codeine cefpodoxime donepezil glipizide ivabradine ketoconazole metformin phenytoin quinidine warfarin zolpidem	acetaminophen caffeine cyclosporine diclofenac digoxin estradiol ketoprofen nicotine nifedipine piroxicam phenobarbital zidovudine

miological studies. An example would be the reporting of adverse reactions to medicines, with doctors and pharmacists being the health professionals who report the most frequently. Monitoring and reporting of adverse drug reactions remain essential after the authorization of the drugs and their use in real life conditions.

CLASSIFICATION OF DRUG INTERACTIONS

Drug interactions may be the result of mechanisms pharmacokinetics, pharmacodynamics or combined. Knowledge of the mechanism of occurrence of interactions drug is clinically useful because the mechanism, can influence the evolution of the results over time therapeutic, but on the other hand can also offer the possibility of avoidance interaction or even its use in order to increase the effectiveness of therapy. Drug interactions may occur throughout the mood drug as a result of endogenous and exogenous factors [3]. There are several types of drug interactions: (i) pharmaceutical drug interactions, *in vitro* interactions or incompatibilities; (ii) pharmacokinetic drug interactions (related to absorption process, distribution level, metabolism, excretion); (iii) pharmacodynamic drug interactions (molecular or cellular level; anatomical-physiological systems); (iv) interaction of drugs with food, beverages, medicinal plants.

The most frequently interactions encountered in the treatment of gastrointestinal symptoms using proton pump inhibitors (PPIs) and histamine H2 receptor antagonists are presented in Table 1 [4].

DRUG INTERACTIONS INDUCED BY PPIS

PPIs are considered drugs of choice in the therapy of gastroesophageal reflux disease and ulcers, representing a class of therapeutic agents that can be released without a prescription, on the recommendation of the pharmacist. Statistics show that worldwide sales of omeprazole are among the highest in the entire pharmaceutical industry. The advantage of these compounds is the high therapeutic potential, as well as the high compliance for the patient due to the administration in a single dose per day [5].

Omeprazole. Reduced gastric acidity during treatment with omeprazole may increase or decrease the absorption of various active substances characterized by gastric pH-dependent absorption. Because omeprazole is predominantly metabolised by CYP2C19, substances that are biotransformed in this way, such as warfarin, diazepam, or phenytoin, will accumulate in the body and may cause specific side effects. Also, drugs that inhibit this liver enzyme (clarithromycin, voriconazole) will increase the serum concentration of omeprazole with decreasing therapeutic effect. In turn rifampicin, a hepatic inducer, may reduce the plasma levels of omeprazole by stimulating its metabolic process. The results of studies in healthy subjects demonstrated a pharmacokinetic/pharmacodynamic interaction between clopidogrel and omeprazole which led to a decrease in exposure to the active metabolite of clopidogrel by 46% and a decrease in maximal inhibition of platelet aggregation (ADP-induced) by an average of 16% [6].

Pantoprazole. Patients treated with pantoprazole and warfarin or fenprocoumon should be monitored for increases in INR value and prothrombin time. Clinical studies have shown various pharmacokinetic interactions with oral contraceptives containing levonorgestrel and ethinyl estradiol, but to date there are no reliable data to strongly contraindicate their combination. Due to the strong and lasting inhibition of gastric acid secretion, pantoprazole may interfere with absorption of other drugs where gastric pH is an important factor in oral availability, such as azole antifungals (ketoconazole, itraconazole, posaconazole) and erlotinib. The results of studies targeting the interactions of pantoprazole have shown that it does not affect the metabolism of biotransformed active substances by CYP1A2 (caffeine, theophylline), CYP2C9 (piroxicam, diclofenac, naproxen) and CYP2D6 (metoprolol) [7].

Esomeprazole. Specialists should be careful when combining this compound with protease inhibitors. Concomitant administration of tacrolimus and esomeprazole increased plasma concentrations of tacrolimus. It is necessary to establish intensive monitoring of tacrolimus plasma concentrations, as well as renal function (creatinine clearance) and the dose of tacrolimus should be adjusted as needed. In contrast, esomeprazole has been shown to interfere with laboratory tests. Increased Chromatogranin A levels may interfere with investigations for neuroendocrine tumors, so it is recommended that treatment with esomeprazole be stopped temporarily for at least 5 days prior to evaluation of this parameter [7, 8].

Lansoprazole. Daily treatment with drugs that reduce the gastric acid secretion over an extended period (several years) may lead to malabsorption of cyanocobalamin (vitamin B12). Cyanocobalamin deficiency should be considered in patients with the syndrome Zollinger-Ellison and other hypersecretory pathological conditions requiring long-term treatment. In addition, lansoprazole has been shown to inhibit P-glycoprotein in vitro. Because sucralfate/antacids decrease the bioavailability of lansoprazole, it should be administered at least one hour after the administration of these drugs [7].

Rabeprazole. The combination of rabeprazole with protease inhibitors, ketoconazole or itraconazole should be performed with caution. Severe hypomagnesaemia has been reported in patients treated with rabeprazole for at least 3 months. In the case of hypomagnesaemia can appear severe symptoms such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia, but these can start insidiously and can be overlooked [7, 9].

H2-RECEPTOR ANTAGONISTS

Through competitive inhibition of the histamine H2 receptors of the gastric parietal cell, H2-receptor antagonists decrease volume and content of gastric acid secretion. They are used for the treatment of gastric and duodenal ulcers, gastroesophageal reflux and Zollinger Ellison syndrome [10]. Available H2-receptor antagonists are cimetidine, famotidine and ranitidine. They are generally given orally, but for acute suppression of gastric acid secretion are available parenteral forms (famotidine and ranitidine). Oral dosage may be given once or twice-daily, at the onset of symptoms or at least 30 min to 1 h before symptoms arise [11]. In many cases it prefers to give these drugs as a single dose at bedtime to block nocturnal gastric acid secretion because of the evidence that peptic ulcer healing is the best. The main side effects induced by H2-receptor antagonists are [12, 13]: central nervous system effects (headache, somnolence, confusion), cardiac effects (bradycardia, hypotension, heart block), hyperprolactinemia, acute pancreatitis, increased hepatic transaminase levels, increased alcohol dehydrogenase, thrombocytopenia, agranulocytosis, interstitial nephritis. interference with drug metabolism by cytochrome P450.

In this class of drugs, interactions occur especially due to the alteration of absorption or inhibition of the hepatic microsomal enzyme cytochrome P450 or reducing the urinary excretion of other drugs. The frequency of interactions is higher for cimetidine and lower in case of ranitidine and famotidine [14].

Cimetidine is the first H2-receptor antagonist used in therapy and the drug's database indicates that are a total of 422 drugs knew to interact with cimetidine of which 29 are considered to give major interactions [15]. Just like PPIs, cimetidine, and other H2-receptor antagonists used for a long period and in high doses may affect significantly the absorption of vitamin B_{12} [16]. Even if the vitamin B_{12} deficiency was observed, especially, in patients who have low body stores (e.g. vegetarian), it's important to note that vitamin B12 supplements may be useful in preventing the cimetidine antiandrogenic effects [27]..

The pH raised after administration of cimetidine or other gastric acid-reducing agents may affect the absorption of calcium, iron, zinc, folic acid, vitamin D and reduces the bioavailability of some drugs that are weak bases. Well documented in the literature are antifungal drugs, ketoconazole and itraconazole whose solubility and absorption at the gastric level is affected by a pH increased [8]. For attenuate the effect of increased pH, the antifungal drugs should be administered 2h before H2-receptor antagonists or 10-12h after the H2-receptor antagonists [19, 20].

By far the most important interactions of cimetidine, are due the inhibition of hepatic P450 isoenzymes, including CYP1A2, CP2C19, CYP2D6, and CYP3A4 [21].. The plasma concentration of therapeutic agents with a low therapeutic index and a liver metabolism may increase up to a toxic concentration, e.g. warfarin, theophylline, phenytoin. Other clinically important interactions occurred due to the cimetidine CYP isoenzymes inhibitory effect, are: beta-blockers (metoprolol or propranolol), lidocaine, quinidine or nifedipine [13, 22]. Co-administration of cimetidine with metoprolol or propranolol results in important sinus bradycardia and hypotension, no interaction effects were observed with the beta-blockers atenolol or nadolol [14].

At the renal level, which is the main route of excretion of H2-receptor antagonists, cimetidine can affect the active tubular secretion by a competitive inhibition of renal transporters. These types of interactions are considered minor or moderate, and may be considered clinically important in case of the narrow[therapeutic]index medications (e.g. antiarrhythmic, oncology medications) or in case of the populations where polypharmacy is common (e.g. the elderly, diabetics) [24]. Also, the systemic concentration of cimetidine, after i.v administration, is increased by renal P-glycoprotein inhibitor drugs such as itraconazole [25].

Ranitidine is an H2-receptor antagonist with a lower affinity for the CYP enzymes, and reduced side effects compared with cimetidine. However, ranitidine is not recommended in acute porphyria [26].. Due to the narrow therapeutic index of coumarin anticoagulants (e.g. warfarin), the close monitoring of prothrombin time is necessary during concurrent treatment with ranitidine, an increased risk of bleeding or blood clot has been reported [23]. Also, ranitidine increased the serum concentration of metoprolol and nifedipine, however these interactions appear to be with minimal clinical significance. Ranitidine may increase the plasma levels of midazolam, triazolam or glipizide by increasing the absorption and in high doses may affect the renal clearance of procainamide, rising the risk of side effects for the associated drugs.

Actually ranitidine has been withdrawn, due of N-nitrosodimethylamine, with carcinogenic potential, which is formed in long-time and at higher room temperature stored.

Famotidine is considered an extremely safe drug with a negligible effect on the isoenzymes [27]. However, a recent review, suggests that famotidine compared with other H2-receptor antagonists have been associated with increased delirium. The main drug-drug interactions are due the gastric pH increased which reduces the efficiency of drugs such as atazanavir, delaviridine, ketoconazole [8]..

CONCLUSIONS

The therapy of gastrointestinal diseases with PPIs or histamine H2-receptor antagonists may be the source for many drug-drug interactions especially in polypharmacy and sensitive patients (e.g. elderly, cancerous, etc). Special attention is required in order to prevent the toxic and side effects or to prevent the decrease of effectiveness by administering subtherapeutic doses. A thorough understanding of the mechanisms by which these agents may interact will provide better identification, prevention and a better management of the drug interactions.

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