Original Article

Food-Drug Interactions - A Short Review of the Particularities of Pharmacokinetics and Pharmacodynamics Molecular Stage Correlations

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Abstract

The purpose of this article is to revise the main types of food and orally administered drugs. Food-drug interactions are biunivocal, meaning that food influences pharmacokinetics and that certain pharmacodynamic actions of drugs and the drugs themselves both directly (by interactions) and indirectly (by modifying food behaviour) influence the ingested quantity and the food profile. The medical term for interaction describes situations where food accelerates, delays or prevents the absorption of a drug; where food modifies the distribution of a drug within tissue or interferes with metabolization, transport and removal of substances from the organism; where food blocks drugs' effects by modifying the pharmacodynamic actions; where food intensifies or inhibits the secondary or natural effects of certain drugs; and where drugs modify the taste of or appetite for certain aliments. Some foods and drugs might have similar chemical structures which, when consumed simultaneously, cause confusion within the body and determine the absorption of one at the expense of the other.

Conclusions: Pharmacokinetic interactions are the most frequent and, in most cases, the most difficult to predict. Anticipation of the potential for decreased or increased effects of particular drugs due to their associations with certain food classes will lead to better monitoring of the anticipated clinical effects.

Keywords: drug, food, pharmacokinetics, pharmacodynamics, metabolism, absorption, effect.

1. INTRODUCTION

Food-drug interactions represent a major threat to the safety and efficiency of oral pharmacotherapy. In order to avoid these as much as possible, greater understanding of the basic mechanisms is essential.1 Various research groups have studied a variety of mechanisms that might lead to food-drug interactions.2-3 Food intake may impact upon the pharmacokinetic profile due to specific or non-specific reasons. The most important example of food-drug pharmacokinetics is the interaction between grapefruit juice and drugs such as cyclosporine and felodipine.4 Interaction may occur through different mechanisms, including inhibition of CYP3A4 metabolism, as well as inhibition of membrane and efflux transporters. This type of food-drug interaction can easily be avoided by omitting certain foods. Non-specific food-drug pharmacokinetic interactions are caused by functional modifications of the gastrointestinal tract, induced by food intake. These include modification of gastric emptying kinetics, high concentrations of bile salts or increased hepatic perfusion.1-2,5 Food-drug pharmacodynamic interactions are caused by a specific interaction between a drug and a component of food, which then has a certain pharmacological effect. However, due to the increasing number of nutrients and supplements, pharmacodynamic interactions may remain undetected.6-8 It should also be noted that this type of food-drug pharmacological interaction is not only limited to orally administered drugs.

2. Material and method

Various specialized e-platforms have been researched (PubMed, Scopus and Web of Science) with regard to the various interactions that might occur between food and drugs. By analogy with drug-drug interactions, food-drug interactions can be classified into the following: pharmacokinetic interactions that might occur at the level of drug absorption; at the level of drug metabolization; at the level of drug transportation; and at the level of drug elimination and pharmacodynamic interactions relating to the main effects of the drug or the drug's side effects and adverse effects.

3. Results

3.1. Pharmacokinetic interactions – absorption

Because a pharmaceutical form does not remain within the oral cavity for very long, during this stationing, poor absorption might occur, uninfluenced by the presence of food. Along the oesophagus, transit of a solid substance takes 10 seconds. The oesophagus is not an absorption area due to generally quick transit times. At gastric level, a drug comes into direct contact with ingested food, and the intensity of this contact depends on the content of gastric liquid. The pharmaceutical form dissolves at this level. Drug dissolution depends on its solubility. Gastric liquid has an acid pH, containing hydrochloric acid at a concentration of 0.160 N, pepsin and gastric mucus; it also contains a small quantity of little active lipase, cathepsin, urea, aminoacids, aminated acids and mineral salts. The intensity of this contact depends on when the drug is administered (before or after a meal).9 Liquid availability within the gastrointestinal tract is a necessary condition for the release and absorption of an orally administered drug. The presence of a concentration gradient between the intestinal lumen and blood is the driving force of passive absorption of drugs.10 The small intestine is the most important place where drugs are absorbed; at this level, most of the active principles remain until absorbability is sufficiently high, provided that the drug is mandatorily stable within the intestinal environment and does not react with endogenous substances, thus forming insoluble compounds. If intestinal motility is high, transit time will be short and, consequently, the dissolution and absorption processes will be incomplete. The normal intestine flora also has an important role in biotransformation of active principles. Since intestinal juices contain all the enzymes required for food digestion, such enzymes are expected to be responsible for the metabolization or inactivation of certain substances.11 If the intestinal motility is high, the transit shall be short and consequently, the dissolution and absorption processes shall be incomplete. In the medical literature many studies are reported on the potential therapeutic effect of probiotics12 and the normal intestine flora has an important role as well in the biotransformation of active principles.

Colon absorption is quantitatively reduced. Small-intestine absorption modulates absorption within the colon (substances that are not retained in the jejunum and ileum are absorbed). At this level, one cannot speak of food-drug interactions. Drug absorption within the gastrointestinal tract is achieved in certain areas specific to each drug due to different solubility, permeability and stability along the gastrointestinal tract and the pH modifications along the lumen, enzymatic degradation and active transport; pH levels are known to vary along the intestine.13-14

3.2. Pharmacokinetic interactions – transport and distribution

Albumin is responsible for binding long chains, fatty acids and acid drugs, e.g., warfarin, phenylbutazone, diazepam and ibuprofen, α1-acid glycoprotein is an acute phase reactant which is selective for basic drugs, such as verapamil, disopyramide and propranolol.15-16 Lipoproteins, which are responsible for transporting lipids, can bind with certain hydrophobic drugs such as amiodarone, clozapine and cyclosporine.17 Therefore, if a food component binds at the same places on the protein as drugs, they may be dislodged from the binding site.18 Despite all this, few clinical studies indicate the effects of plasmatic protein-binding modifications in the case of most orally administered drugs.19

3.3. Pharmacokinetic Interactions – drug metabolization

Most pharmacokinetic interactions occur during the drug metabolization stage. The enzymes involved in the first stage of drug metabolization belong to an enzymatic complex generically known as P450 cytochrome. The most important of these enzymes are the CYP1A, CYP2C and CYP3A sub-families. Each of these enzymes metabolizes certain drugs and may be both induced and inhibited by certain chemical substances.20 The CYP1A sub-family is responsible for metabolizing certain drugs such as paracetamol, oral anticoagulants and caffeine. Clinical studies have reported up to 36% inhibition of CYP1A2 by food supplements containing Echinacea (21). The CYP3A sub-family is responsible for metabolization of approximately 70% of

drugs, e.g., benzodiazepine, cardiotonic glycosides, antivirals and oral anticoagulants. Hypericum perforatum (St. John's wort) is a vegetal product that causes the most interactions when associated with various classes of drugs. The enzymatic-inhibiting activity of grapefruit juice was discovered in 1980, when felodipine bioavailability was noticed. Flavones (naringenin) and furanocoumarins (components of grapefruit juice) are inhibitors of the CYP3A4 isoform. A subsequent study proved that it decreases the concentration of intestinal CYP3A4 (but not the enzyme's hepatic form).21

3.4. Pharmacokinetic interactions – excretion

Plasmatic concentration and urinary excretion of active principles may also be affected by food. Certain foods may influence elimination of certain active principles or metabolites through their effect on the urinary pH. Among the foods that have acid potential, the following must be mentioned: meat, meat preparations, blueberries, bread, plums and dried plums; foods that have alkaline potential include milk, fruits (except the above) and all vegetables (excluding corn and lentils). For instance, salicylic acid may be absorbed at an alkaline urinary pH but is excreted at an acid pH; the same goes for ascorbic acid or theophylline.21

3.5. Pharmacodynamic interactions

Pharmacodynamic interactions are the least frequent. Variations in the proteic binding of drugs are a key factor in modification of substances' actions. Most drugs found in the blood are in equilibrium between the free active form and the inactive bound form. The most important blood element involved in binding a drug is albumin.22 A significant drop in albumin serum concentration will lead to an increase in a drug's free fraction and, therefore, an increase in its active form. Hypoalbuminemia after eating will have important pharmacological implications, especially for drugs that have a tendency to bind to albumins (phenylbutazone and valproic acid).23 In the case of such drugs, the free fraction will increase in the event of hypoalbuminemia (the pharmacological effects having been modified), and this sometimes reaches toxic doses. For these substances, the apparent distribution volume is sensibly proportional to their free fraction. Reduction of proteic binding may have important clinical consequences for drugs with significant proteic-binding properties and a low therapeutic index. These substances include digoxin, diphenylhydantoin, K antivitamins and antidiabetics. By reducing binding of the active principles to proteins, the plasmatic concentration of the free-form active principle is increased, which leads to faster elimination. Thus, the toxic effects at renal level are enhanced due to excretion of the active form of the drug principle (with the process of transformation into inactive metabolites being reduced).24

4. Conclusions

Interpretation of food-drug interactions is, in most cases, difficult, and the question arises as to whether the results might be attributed to a particular interaction or whether they are the consequence of a nutritional issue. At molecular level, food is a variability factor in terms of the activity of drugs. Interactions occur depending on the drug type, its pharmacological particularities and the food type. Foods can exert effects at any pharmacokinetic stage. Sometimes, food-drug associations are beneficial (e.g., enhancement of liposoluble drugs if a lipid-rich meal is administered). Although interactions between drugs and specific foods have been identified, they do not necessarily occur in all patients and will not necessarily be significant from a clinical viewpoint. Therefore, it is important to estimate the potential reduction or enhancement of drugs' effects when associated with a certain class of food. A better understanding of potential food-drug interactions will lead to optimal monitoring of the expected clinical effects.

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6. Disclosure

The authors report no conflicts of interest in this work.

6.1. Author Contributions

PAM he had the idea of the study, RRO,CG, LA he collected the data, MN,ALT he followed the interpretation of the data. All authors read and approved the final version of the manuscript.

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6.3. Competing interests

The authors declare that they have no competing interests.

6.4. Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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