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Is the clinical relevance of drug-food and drug-herb interactions limited to grapefruit juice and Saint-John's Wort?

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ABSTRACT

An interaction of drug with food, herbs, and dietary supplements is usually the consequence of a physical, chemical or physiologic relationship between a drug and a product consumed as food, nutritional supplement or over-the-counter medicinal plant. The current educational review aims at reminding to the prescribing physicians that the most clinically relevant drug-food interactions may not be strictly limited to those with grapefruit juice and with the Saint John's Wort herbal extract and may be responsible for changes in drug plasma concentrations, which in turn decrease efficacy or led to sometimes life-threatening toxicity. Common situations handled in clinical practice such as aging, concomitant medications, transplant recipients, patients with cancer, malnutrition, HIV infection and those receiving enteral or parenteral feeding may be at increased risk of drug-food or drug-herb interactions. Medications with narrow therapeutic index or potential life-threatening toxicity, e.g., the non-steroidal anti-inflammatory drugs, opioid analgesics, cardiovascular medications, warfarin, anticancer drugs and immunosuppressants may be at risk of significant drug-food interactions to occur. Despite the fact that considerable effort has been achieved to increase patient' and doctor's information and ability to anticipate their occurrence and consequences in clinical practice, a thorough and detailed health history and dietary recall are essential for identifying potential problems in order to optimize patient prescriptions and drug dosing on an individual basis as well as to increase the treatment risk/benefit ratio.

1. The clinical significance of drug–drug & drug-food interactions

Dietary substances can alter drug absorption, distribution, metabolism and/or elimination via physiologic and physicochemical mechanisms. For more than 15 years, the clinical relevance of drug–drug and drug-food interaction has been focused and limited to the modulation of drug metabolism and, to a lesser extent transport, within the cells of the liver and the proximal small intestine where the largest quantity of drug-metabolizing enzymes and transporters are located [1]. The clinical relevance of pharmacokinetic or pharmacodynamic drug–drug or drug-food interactions is questioned when enhanced toxicity and/or therapeutic failure might occur at clinically relevant dosing regimen [2]. While some drug–drug or drug-food interactions may be used to improve dosing regimen and clinical outcome (e.g., using ritonavir or grapefruit juice to increase human immunodeficiency virus (HIV) protease inhibitors bioavailability), most of them will have unpredicted and sometimes life-threatening consequences (e.g., erythromycin plus cisapride increases the risk of torsades de pointes). Age, malnutrition, malabsorption, chronic liver disease, kidney failure, polymedication, long-term drug dosing, and pharmacogenetics are well-known risk factors for drug–drug and drug-food interactions. In a study of 205 consecutive patients admitted to an emergency room, the prevalence of potential drug interactions was 13% with two drugs during long-term treatment and increased up to 82% with 7 or more [3].

There are three major categories of drug interactions: pharmacodynamics (associations of antihypertensive drugs, pain killers and anticoagulants), pharmaceutical (physicochemical incompatibility between two different drugs such as for instance the

Abbreviations: HIV, Human Immunodeficiency Virus; CYP, Cytochrome P450; TKI, tyrosine kinase inhibitor; P-gp, P-glycoprotein; OATP, Organic Anion Transporting Polypeptide; INR, International Normalized Ratio.

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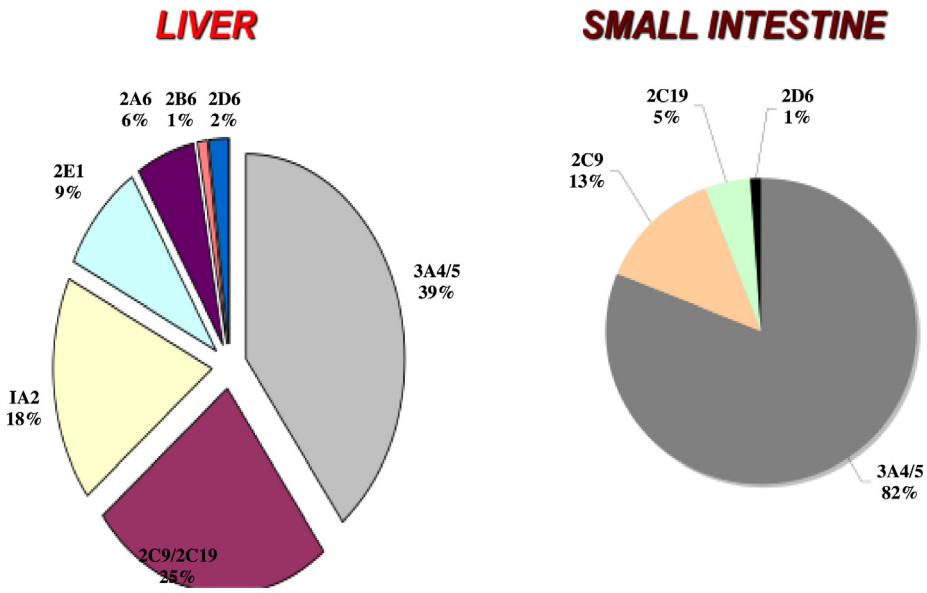

Fig. 1. Human liver and small intestinal CYP distribution [5,6].

administration of ciprofloxacin with calcium carbonate), and pharmacokinetics [4]. Drug interactions that affect a drug's absorption, distribution (or protein binding), metabolism or excretion are considered pharmacokinetic interactions. By understanding the mechanism by which drugs are normally metabolized, many pharmacokinetic drug interactions can be better understood, increasing the ability to predict and prevent potentially serious interactions.

Changes in drug systemic exposure and oral bioavailability may be related to the induction of metabolism and transport, a rapid source of elimination and underdosing or, conversely, to an inhibition leading to overdosing and toxicity. For drugs taken orally, the small intestine expresses high amounts of numerous active cytochrome P450 (CYP) isoforms and is the first step of the first-pass effect of drugs [5,6]. The expression of CYP is variable from one individual to another, explaining in part the differences in bioavailability of certain drugs. CYP3A4, the main metabolic pathway of over 60% of currently marketed drugs, represents 35% and 80% of CYPs expressed in the liver and the small intestine, respectively (Fig. 1) [5,6].

In the Western world, functional foods, health foods and food supplements deliver the necessary macro- and micronutrients to enhance health [7]. Hence, a growing number of patients are using over-the-counter products with bioactive ingredients together with prescribed medications, thus increasing the risk of serious adverse reactions due to interactions between prescribed medication and potentially bioactive compounds.

Drug-food interactions occur more often than thought. They are defined by any food, herbal medicines, or dietary supplements-induced changes in oral bioavailability leading to changes in drug concentrations that may affect efficacy and/or toxicity [8]. Despite, the critical importance of drug-food interaction clinical studies, including during the clinical phases of new drug candidate development, robust methodological guidelines for such clinical pharmacology studies are lacking in order to make definitive clinical & regulatory recommendations [9]. Indeed, examination of the effects of food consumption on the pharmacokinetics of drugs should not be limited to basic recommendations such as "take with or without food" since prescribing physicians are willing to understand the mechanisms by which food, dietary supplements and medicinal plants may alter systemic drug availability [9].

The current manuscript describes the most common drug-food interactions the prescribing physicians may encounter in primary care practice. As this review rather stands for an educational review rather than a systematic literature review and in order to better understand how food, beverages, dietary supplements or herbal medicines may interact with orally administered medications, we have tried to summarize the major mechanisms underlying these interactions.

2. Underlying mechanisms of food, herbs, micronutrients or dietary supplements effect on drug exposure & response

Underlying mechanisms by which food, herbs, micronutrients or dietary supplements exert interactions with drugs generally physiologic, physicochemical and/or biochemical processes [9]. Dietary substances can alter drug absorption, distribution, metabolism and/or excretion via physiologic and physicochemical mechanisms. Drug-food interactions have long been thought to be limited to the influence of the type or timing of meals on the absorption of a drug. Food does indeed delay gastric emptying, raise the pH of the proximal small intestine, increase hepatic blood flow and extend the time of gastrointestinal transit, in comparison with fasting [8,10]. A meal reduces by up to 70% the plasma concentrations of isoniazid, rifampicin, ethambutol, valsartan, furosemide and hydralazine, requiring fasting conditions and spacing between meals to maintain the effectiveness of these drugs [11,12]. The peak plasma concentration of quinidine was significantly decreased by concomitant salt intake, without altering the metabolic activity of 17 healthy volunteers [13]. High-fat meals decrease the intestinal absorption and plasma concentrations of alkylating agents (melphalan, chlorambucil, busulfant), antimetabolites agents (methotrexate, 5-fluorouracil, 6-mercaptopurine), vinorelbine, topotecan, rubitecan, and some tyrosine kinase inhibitors (TKIs), e.g., gefitinib and ionafamib [10]. Based on the recent recommendations published by Singh et al., the majority of cytotoxic agents must be taken with or immediately after meals, in order to optimize their intestinal absorption and reduce variability [10]. Likewise, the systemic exposure of daclatasvir, a direct acting antiviral agent recently marketed in the treatment of hepatitis C was decreased by almost 30% with a high-fat meal but this reduction was not considered clinically significant [14].

Conversely, a high-fat, high-calorie breakfast increased by 61% and up to 211% the systemic exposure of simeprevir and pari-