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Mechanisms underlying food–drug interactions: Inhibition of intestinal metabolism and transport

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ABSTRACT

Food–drug interaction studies are critical to evaluate appropriate dosing, timing, and formulation of new drug candidates. These interactions often reflect prandial-associated changes in the extent and/or rate of systemic drug exposure. Physiologic and physicochemical mechanisms underlying food effects on drug disposition are well-characterized. However, biochemical mechanisms involving drug metabolizing enzymes and transport proteins remain underexplored. Several plant-derived beverages have been shown to modulate enzymes and transporters in the intestine, leading to altered pharmacokinetic (PK) and potentially negative pharmacodynamic (PD) outcomes. Commonly consumed fruit juices, teas, and alcoholic drinks contain phytochemicals that inhibit intestinal cytochrome P450 and phase II conjugation enzymes, as well as uptake and efflux transport proteins. Whereas myriad phytochemicals have been shown to inhibit these processes in vitro, translation to the clinic has been deemed insignificant or undetermined. An overlooked prerequisite for elucidating food effects on drug PK is thorough knowledge of causative bioactive ingredients. Substantial variability in bioactive ingredient composition and activity of a given dietary substance poses a challenge in conducting robust food–drug interaction studies. This confounding factor can be addressed by identifying and characterizing specific components, which could be used as marker compounds to improve clinical trial design and quantitatively predict food effects. Interpretation and integration of data from in vitro, in vivo, and in silico studies require collaborative expertise from multiple disciplines, from botany to clinical pharmacology (i.e., plant to patient). Development of more systematic methods and guidelines is needed to address the general lack of information on examining drug–dietary substance interactions prospectively.

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Abbreviations: APAP, acetaminophen; AUC, area under the curve; BG, bergamottin; bid, two times a day; C_{max}, maximum concentration; CBJ, cranberry juice; CYP, cytochrome P450; DDI, drug–drug interaction; DHB, 6′,7′-dihydroxybergamottin; FDA, Food and Drug Administration; EGCG, epigallocatechin gallate; GI, gastrointestinal; GFJ, grapefruit juice; IC_{50}, half maximal inhibitory concentration; K_i, inhibition constant; k_{inact}, maximal inactivation rate constant; K_m, substrate concentration at which reaction rate is half of V_{max}; NC, not calculated; NS, not statistically significant; NSP, not specified; OATPs, organic anion transporting polypeptides; P-gp, P-glycoprotein; PK, pharmacokinetics; PD, pharmacodynamics; SS, statistically significant; SULTs, sulfotransferases; V_{max}, maximum rate; tid, three times a day.

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1. Introduction

The impact of food on successful delivery of promising new drug candidates via the oral route poses a major challenge during drug development. The influence of dietary substances on drug disposition depends on numerous variables, ranging from physicochemical properties of the drug to postprandial changes in the gastrointestinal (GI) tract (Charman et al., 1997; Custodio et al., 2008). Components of the diet that modulate intestinal cytochrome P450 and phase II conjugation enzymes, as well as uptake and efflux transport proteins, constitute increasingly recognized contributors to food effects on drug disposition (Rodríguez-Fragoso et al., 2011). Many dietary substances or food ingredients derived from botanical sources have been shown to inhibit these processes in vitro, but translation to the clinic has been inconclusive or considered irrelevant (Farkas & Greenblatt, 2008). Understanding the mechanisms by which these dietary substances alter drug PK and PD outcomes is critical to assess clinical significance and management.

Prediction of PK properties of new drug candidates entering clinical trials can be an arduous, sometimes elusive, task. The added complexity of food effects increases such difficulty. Robust guidelines on the evaluation of potential dietary substance–drug interactions are lacking (Abdel-Rahman et al., 2011). Clinical studies often are difficult to compare, inconclusive, and/or fail to meet strict criteria required to make definitive clinical and regulatory recommendations. Commercially available modeling and simulation software can be a valuable tool to evaluate and predict, quantitatively, potential dietary substance–drug interactions. A key contributing factor to predictive success is a thorough knowledge of the causative ingredient(s) contained in the dietary substance. Identification, characterization, and validation of specific bioactive components as marker compounds can guide appropriate clinical trial design. Such studies enable development and validation of PK–PD models describing the relationship between a given dietary substance and drug of interest. The current review provides an update on dietary substance–drug interaction research, addresses challenges and potential solutions regarding the conduct and interpretation of associated studies, and discusses in silico strategies for predicting food effects.

2. Food–drug interactions

2.1. Definition

A food–drug interaction is the consequence of a physical, chemical, or physiologic relationship between a drug and a product consumed as food or a nutrient present in a botanically-derived food or dietary supplement (Santos & Boullata, 2005; Genser, 2008). Such an interaction may manifest clinically as compromised health status due to altered PK and/or PD of the drug or dietary substance. Although dietary substances are regulated as food or dietary/herbal supplements, bioactive constituents in these substances can act like "perpetrator" drugs. That is, a dietary substance can increase systemic "victim" drug exposure (AUC), increasing the risk of adverse events and toxicity, or decrease systemic victim drug exposure, leading to therapeutic failure (Santos & Boullata, 2005). A lack of an interaction may be due to insufficient concentration(s) of causative ingredients at the enzyme or transporter active site, metabolism of causative ingredients to inactive products, or transport of causative ingredients out of target cells (e.g., enterocyte, hepatocyte). Underlying mechanisms by which food exerts such effects generally include physiologic, physicochemical, and/or biochemical processes (Fleisher et al., 1999). Elucidation of these processes in relevant organ systems is essential to resolve issues related to formulation, dosing schedule, and optimal pharmacotherapeutic strategies (Li et al., 2002; Lentz, 2008; Parrott et al., 2009).

2.2. Regulatory guidelines

Potential clinically significant implications of food–drug interactions are recognized by worldwide regulatory agencies, each with specific guidelines. A guidance issued by the United States Food and Drug Administration (FDA) in 2002 provided recommendations on the design and conduct of food effect and fasted/fed state studies (http://www.fda.gov/cder/guidance). High-calorie (~800–1000 cal) and high-fat (~50% of total caloric content) test meals represent the 'worst-case scenario' and are expected to alter maximally GI physiology and subsequent systemic drug availability. Although examination of the effects of food consumption on the PK of drugs is a standard practice, the issue has become greater than "take with or without food" since a variety of specific dietary substances has been shown to alter systemic drug availability. Evaluation of the underlying mechanism(s) can ultimately lead to firm conclusions required to make informed clinical and regulatory decisions or guidelines.

3. Underlying mechanisms of food effect on drug exposure and response

3.1. Physiologic and physicochemical mechanisms

Dietary substances can alter drug absorption, distribution, metabolism, and/or excretion (ADME) via physiologic and physicochemical mechanisms. Physiologic/mechanical mechanisms include delayed gastric emptying, stimulated/increased bile or splanchnic blood flow, and GI pH or flora changes. Alterations of such processes can lead to reduced absorption of some drugs (e.g., penicillins, angiotensin-converting enzyme inhibitors) (Singh, 1999). Physicochemical mechanisms include binding of the drug by the food. For example, enteral nutrition formulas are incompatible with the antiepileptic agent, phenytoin, which can bind to proteins and salts in enteral formulations, resulting in reduced phenytoin absorption and potentially inadequate seizure control (Lourenço, 2001). Some tetracyclines and fluoroquinolones can bind to divalent cation-containing products (e.g., calcium in dairy), resulting in reduced drug absorption (Polk, 1989; Jung et al., 1997) and potential therapeutic failure. High fat meals can increase drug absorption by improving solubility, such as with some antiretroviral protease inhibitors (e.g., saquinavir, atazanavir) (Plosker & Scott, 2003; Le Tiec et al., 2005). Other examples are discussed comprehensively in several sources (Wolinsky & Williams, 2002; McCabe et al., 2003; Boullata & Armenti, 2004; Meckling, 2007; Stargrove et al., 2008).

3.2. Biochemical mechanisms

Biochemical mechanisms include interference with co-factor formation or function, potentiation of drug PD, and modification of drug metabolizing enzyme/transporter function by the dietary substance (Chan, 2002). For example, vitamin K-rich foods interfere with co-factor function and should be consumed cautiously with the anticoagulant, warfarin, as they can disrupt vitamin K metabolism and increase risk of bleeding or clot formation (Holbrook et al., 2005). Isoniazid and monoamine oxidase inhibitors, used to treat tuberculosis and depression, respectively, inhibit the breakdown of endogenous and dietary amines; a tyramine-rich diet can potentiate a hypertensive crisis (Brown et al., 1989; Self et al., 1999). Foods consumed as beverages account for a very high proportion of dietary antioxidant intake (Pulido et al., 2003). Growing evidence supporting cardioprotective benefits promotes moderate consumption as part of a healthy lifestyle (Kaplan & Palmer, 2000; Guilford & Pezzuto, 2011). However, certain beverages contain substances that can influence drug disposition via modulation of drug metabolizing enzymes and transporters in the intestine.

Several studies have assessed the effect of wine, beer, fruit juices, tea, and specific constituents therein on CYP activity in vitro, but clinical studies are limited. These beverages have become highly recommended supplements to routinely prescribed and over-the-counter drugs and/