Effects of Food on Clinical Pharmacokinetics

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Abstract

Food-drug interactions can be associated with alterations in the pharmacokinetic and pharmacodynamic profile of various drugs that may have clinical implications. The various phases in which food may interact with a coadministered drug are: (i) before and during gastrointestinal absorption; (ii) during distribution; (iii) during metabolism; and (iv) during elimination. Absorption and metabolism are the phases where food has most effect, and this review will focus on those areas. It will also review the variable and complex effects of antacids and metal ions on drug absorption.

Mechanisms related to food effects on drug absorption have been described under 5 categories: those causing decreased, delayed, increased or accelerated...
absorption, and those in which food has no significant effect. Among the major variables that interface between differential effects of food and postprandial bioavailability are: (i) the physicochemical characteristics and enantiomorphomic composition of the drug; (ii) timing of meals in relation to time of drug administration; (iii) size and composition of meals (especially fat, protein and fibre); and (iv) dose size. However, the influence of food is largely a matter of the design of the pharmaceutical formulation. In addition, the mechanism of ‘food effect’ may involve physiological and sensory responses to food, such as changes in gastrointestinal milieu and gastric emptying rate, reflex action, and may also involve the site and route (either portal or lymphatic) of drug absorption.

Mixing drugs with fruit juice, such as grapefruit and orange juice, and acidic beverages, such as commercial soft drinks, may affect absorption because of decreases in gastric pH, which could offer a therapeutic advantage in certain clinical conditions, such as patients with HIV disease and cancer. The increased bioavailability caused by the concomitant intake of grapefruit juice results from the inhibition of intestinal cytochrome P450 (CYP) 3A4, but not hepatic CYP3A4 or colon CYP3A5, which probably involves the bioflavonoid naringenin and furanocoumarins.

Although there is a vast amount of literature, there is still no rational scientific basis to predict the effect of food for a particular chemical entity or a chemical class of therapeutic agents. A mechanistic understanding of the effects of food may serve as a key to the pharmacokinetic optimisation of patient therapy, both in outpatients and hospitalised patients of various age groups.

1. Effects of Food on Drug Absorption

It is important to consider drug-food interactions because the pharmacokinetics of a prescribed drug may be affected when coadministered with food. Recently, Welling[1] classified drug-food interactions into 5 categories: those causing reduced, delayed, increased and accelerated absorption, and those in which food has no effect. The variable, but clinically important, effects of food have long been recognised. Some of the drug-food interactions reported in the literature during the past decade are listed in table I. Some drugs belong to more than one category: for example, aspirin (acetylsalicylic acid), avitriptan, libenzapril, cilazapril and pidoti-mod, whose absorption may be both reduced and delayed in presence of food. On the other hand, the absorption of midazolam and triazolam is delayed and the extent of bioavailability is increased when ingested with grapefruit juice. There are other instances in which the rate of absorption [measured as peak plasma drug concentration (Cmax) and time to Cmax (tmax) values] may be decreased or delayed but the overall bioavailability remains unchanged. Also there are few interactions in which the rate of drug absorption is slightly enhanced or accelerated, but the bioavailability is not significantly modified by food.[24,76,133,134,179]

1.1 Delayed Absorption

Food can affect both the rate and extent [measured as area under the concentration-time curve (AUC)] of drug absorption from the gastrointestinal (GI) tract. However, the extent of absorption is not usually affected. The delayed absorption or decreased rate of absorption usually results from a slower gastric emptying rate and/or increased gastric pH resulting from the ingestion of food. Pharmacokinetically, this is manifested as a decreased Cmax and a corresponding longer tmax and/or lag time (tlag). The delayed absorption may also be expressed in terms of a larger mean residence time (MRT). In fact, the slow rate of gastric emptying delays the onset of drug absorption, which usually occurs in the proximal region of the small intesti-