Influence of Food on the Bioavailability of Drugs

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Summary

Food intake exerts a complex influence on the bioavailability of drugs. It may interfere not only with tablet disintegration, drug dissolution and drug transit through the gastrointestinal tract, but may also affect the metabolic transformation of drugs in the gastrointestinal wall and in the liver. Different food components can have different effects, and food may interact in opposite ways, even with drugs that are chemically related. Therefore, the net effect of food on drug bioavailability can be predicted only by direct clinical studies of the drug in question.

As judged mainly from single meal, single dose studies, food intake enhances the bioavailability of several different drugs, such as propranolol, metoprolol, hydralazine, hydrochlorothiazide, canrenone (from spironolactone), nitrofurantoin, erythromycin (stearate), dicoumarol, phenytoin and carbamazepine, but reduces that of drugs such as isoniazid, rifampicin, tetracycline, penicillin and ampicillin, while having no consistent effect on the bioavailability of metronidazole, oxazepam, melperone, propylthiouracil, sulphamethidine and sulphonylureas. For some drugs such as digoxin and paracetamol, the rate but not the extent of absorption is reduced.

Food may enhance bioavailability even though, or rather because, the rate of gastric emptying is reduced; this is apparently the case with hydrochlorothiazide and nitrofurantoin. The food induced enhancement of bioavailability of propranolol, metoprolol and hydralazine is probably due to reduced first pass metabolism of these drugs, while food induced improvement of drug dissolution may explain the enhanced bioavailability of carbamazepine, canrenone, dicoumarol and phenytoin. An increased gastrointestinal pH may be in part the cause of the food induced reduction of the bioavailability of drugs such as isoniazid and tetracycline.

In addition to single meal effects, repeated intake of protein-rich meals enhance, while carbohydrate-rich meals reduce, the rate of oxidation of antipyrine and theophylline. Moreover, intake of charcoal broiled meat markedly accelerates the oxidation of phenacetin and variably accelerates elimination of theophylline. Thus, food and its components and contaminants may have both short and long term effects on both the absorptive and biotransformation processes influencing systemic availability of drugs.
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In my young days, said Miss Marple, 'it was considered to be very bad manners to take medicine with one's meals. It was on a par with blowing your nose at the dinner table. It just wasn't done'.

(Agatha Christie: The Mirror Crack'd from Side to Side)

1. Food-Drug Interactions: General Considerations

In contrast to the contemporaries of Miss Marple's youth, many patients today probably ingest their drugs together with, or in close relation to, meals. However, surprisingly few data have been available as to the influence of food on the disposition of drugs.

Although this lack of data has been frequently recognised (Koch-Weser, 1974; Pierpaoli, 1972; Welling, 1977), certain opinions concerning general effects of food on drug disposition have nevertheless been made repeatedly and seem to be widely accepted. Thus, it is often taken for granted (e.g. Wagner, 1977) that food intake generally impairs the absorption of drugs. For the same reason, it has been suggested that drugs should be taken on an empty stomach whenever possible (Welling, 1977), and that variations in bioavailability could be usefully decreased if drugs were administered with food only when their irritative effects on the gastric mucosa make this necessary (Koch-Weser, 1974).

One reason for these statements seems to be the assumption that the rate, and partly also the extent, of drug absorption depends mainly on the rate of gastric emptying, and that food intake affects drug absorption negatively because of its slowing of gastric emptying rate (Chasseaud and Taylor, 1974; Heading et al., 1973; Koch-Weser, 1974; Prescott, 1974; see also editorial: British Medical Journal, 1977). These assumptions also relate to the almost axiomatic concept that, with very few exceptions, drug absorption follows the rules of passive diffusion (Binns, 1964; Katchen, 1971; Koch-Weser, 1974; Levine, 1970; Pierpaoli, 1972; Wagner, 1977).

Recent observations strongly challenge these generalisations. Thus, food intake has been found to improve the bioavailability of several common drugs (Beermann and Groschinsky-Grind, 1978a; Melander et al., 1977a,b,c, 1978; Rosenberg and Bates, 1976). Moreover, food may influence the rate of drug absorption without affecting the total amount absorbed, and both the rate and extent of absorption may be increased even though, or rather because, the rate of gastric emptying is reduced (Beermann and Groschinsky-Grind 1978a; Melander et al., 1978; Johnson et al., 1978; Rosenberg and Bates, 1976). Furthermore, active intestinal transport mechanisms may be more important than hitherto recognised (Johansson et al., 1978; Ther and Winne, 1971). In addition, food may influence not only the absorption but also the first pass metabolism of drugs in the gut and in the liver (Conney et al., 1976; Kappas et al., 1978; Melander et al., 1977a; Melander, 1978). Moreover, alterations of the carbohydrate/protein ratio of the diet may change the elimination rate of certain drugs (Kappas et al., 1976).

It follows from the above mentioned observations, that food-drug interactions are very complex, and that valid conclusions pertinent to this problem must be derived from direct studies on the specific drug in question. Thus, investigations in this field should be expanded, and information must be gathered concerning effects of food — and different kinds of food and food components — on all aspects of drug kinetics; i.e. both on bioavailability and on systemic distribution and elimination of drugs. The scope of the present review is restricted to the influence of food on drug bioavailability.

2. Concept of Bioavailability

When a drug is administered by the oral route, it goes through numerous processes before it enters the systemic circulation, from which it is eventually delivered to its site of action. Tablets must disintegrate before the drug can be dissolved from the tablet particles. After dissolution in the acid gastric juice or in the more alkaline and biliary milieu of the small intestine, the drug is absorbed; i.e. it passes through the