Interactions Affecting Drug Absorption

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**Summary**

The influence of drug-drug and drug-food interactions affecting the absorption of orally administered medication is reviewed. Drug-drug interactions can be classified in terms of indirect effects by one drug on gastrointestinal tract physiology influencing the absorption of other drugs, or direct interactions involving altered pH, adsorption, absorption, or chelation. Most, but not all, drug-drug interactions result in reduced or delayed systemic drug availability.

Drug-food interactions may result in reduced, delayed, or increased systemic drug availability. The absorption of only a small number of drugs is unaffected by concomitant food intake. The degree of interaction and whether it positively or negatively affects drug absorption depends on a number of factors including the physical and chemical nature of the drug, the formulation, the type of meal, and the time interval between eating and dosing.

Mechanisms of drug-food interactions are not well characterised. They clearly involve both direct and indirect factors in a similar fashion to drug-drug interactions, but indirect factors probably predominate. Reduced or delayed drug absorption is generally attributed, at least in part, to delayed stomach-emptying due to food. Increased absorption may also result from delayed stomach-emptying facilitating greater drug dissolution before it passes from the stomach into the small intestine. Increased bioavailability of some drugs, e.g. propranolol, metoprolol and labetalol, may be related to reduced presystemic clearance.

The potential clinical implications of drug-drug and drug-food interactions must be taken into account with oral medications in order to minimise variations in systemic drug availability and hence in clinical efficacy.

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The degree of clinical response to an administered drug is a function of the intrinsic pharmacological activity of the drug or its metabolites, the concentration of active substance at the site or sites of action, and the time during which therapeutic concentrations are maintained. For drugs that act systemically, the magnitude of response is usually directly or indirectly related to circulating levels of active compound, and these are in turn controlled, to a large extent, by the ease with which the drug passes from the absorption site into the systemic circulation.

The rate and efficiency with which an orally administered drug is absorbed, i.e. its bioavailability, is commonly determined in healthy individuals under controlled, and generally fasting, conditions. This type of procedure is required by regulatory agencies so that drug bioavailability can be established under controlled conditions, with minimum interference by other substances (Federal Register,
1977). However, in clinical practice, orally administered drugs are rarely administered under such ideal conditions. Patients receiving medication may receive more than one drug at the same time, and one drug may influence the absorption of another. This is particularly important in hospitals and in geriatric therapy where it is not uncommon for individuals to receive several drugs simultaneously.

Medication may also be ingested under varying situations relative to food and fluid intake. Evidence has now accumulated that food may have a marked and often unpredictable effect on the rate and extent of oral drug absorption (Toothaker and Welling, 1980; Welling, 1977b; Welling and Tse, 1982). Despite the considerable interest that has developed recently in this type of drug interaction, only a relatively small number of drugs and dosage forms have been investigated. Thus, guidelines for optimum drug dosage design relative to food and fluid intake are still in the formative stage, and much remains to be done before sufficient information is available to permit the patient to be adequately advised regarding food and fluid interactions influencing oral drug availability.

Drug absorption is influenced by many other factors in addition to those identified above, i.e. by the chemical form, degree of ionisation, type of formulation, particle size, solvent effects and dissolution. The influence of these factors on drug absorption has been discussed elsewhere (Niazi, 1979; Rowland and Tozer, 1980), and will not be considered in this review. Rather, attention will be focused on interactions with other drugs, and also changes in drug absorption due to food and fluid ingestion, as these represent 2 major factors that are likely to affect oral drug absorption in clinical practice.

1. Drug-Drug Interactions Affecting Absorption

Interactions between drugs that influence absorption from the gastrointestinal tract into the systemic circulation represent a major problem in drug therapy. While many types of interactions have been identified, many others probably have not been recognised due to the difficulty of establishing cause-effect relationships for symptomatic changes in patients receiving multiple drug therapy.

Some typical interactions that have been shown to cause altered drug absorption are summarised in table I. The results of some interactions are minor, and are unlikely to be clinically significant, while others are more profound and are likely to give rise to clinically important changes, usually in the form of reduced absorption of the affected compound. It is evident from table I that observed interactions involve a wide range of drug types. A variety of mechanisms is also likely to be involved, although in many cases these are unknown. It is nevertheless possible to separate the interactions into 3 major types: (1) those occurring indirectly as a result of the action of the affecting agent on the gastrointestinal tract; (2) those resulting from the direct action by one drug or substance on another; and (3) those whose mechanism of action remains obscure.

1.1 Interactions that Affect Drug Absorption Indirectly

One of the primary factors influencing drug absorption is gut motility, i.e. the time during which the drug or drug dosage form is retained in the stomach, the speed with which it passes from the stomach into the small intestine, and the intestinal transit time. Any drug that affects gut motility is likely to influence the absorption of other drugs, or of itself, in some way.

1.1.1 Drug-Induced Changes in Gastrointestinal Motility

Propantheline has anticholinergic activity, and reduces gastrointestinal motility and stomach emptying rate. Metoclopramide, on the other hand, increases stomach emptying rate and is used clinically to prevent gastric reflux. Both of these agents have a marked effect on drug absorption, presumably resulting from their opposing influences on stomach emptying rate. Administration of metoclopramide has been shown to increase the ab-