1. INTRODUCTION

Medications and food are often taken together. Linking drug administration to a regular event like a meal can improve the patient’s adherence to the treatment regimen, especially in the elderly (1). However, concomitant drug and food intake create the opportunity for an interaction that may change (increase or decrease) drug benefit or toxicity.

The response to a drug is largely dependent on its concentration at the cellular site of action (drug receptor). Increased drug concentration generally causes enhanced magnitude and duration of effect, whereas decreased drug concentration produces the opposite result. The concentration at the drug receptor of an orally administered medication is determined by the net result of oral bioavailability (rate and fraction of the oral dose of drug absorbed into the systemic blood circulation), distribution from the circulation to the drug receptor, and removal from the drug receptor.

For most medications, absorption from the gastrointestinal (GI) tract occurs in the proximal portion of the small intestines (duodenum). This is mainly owing to much greater surface area and blood flow compared to the stomach. Before gaining access into the systemic circulation, drugs must pass through the gut wall, enter the portal blood circulation, and pass through the liver (Fig. 1). Mechanisms in both the gut wall and the liver are capable of reducing drug bioavailability. This can occur by enzymatic conversion of drug to derivatives (metabolites) at these sites, a process known as presystemic or first-pass drug metabolism. Oral drug bioavailability is commonly determined by measuring the systemic plasma drug concentration–time profile. A change in its rate (as indicated by peak drug concentration \(C_{\text{max}}\) and time to \(C_{\text{max}}\) \(t_{\text{max}}\)), or extent (as determined by the area under the drug concentration–time curve \(\text{AUC}\)), can have important implications for pharmacotherapy.

More than 10 years ago, our group observed that grapefruit juice markedly increased the rate and extent of oral bioavailability of the dihydropyridine calcium channel antagonist, felodipine. It was originally suggested from a secondary finding in an ethanol–drug interaction study (2). In this investigation, grapefruit juice had been chosen to mask the taste of the ethanol. Results showed that plasma drug concentrations were not different.
between felodipine plus ethanol (in grapefruit juice) or felodipine alone (with grapefruit juice). However, both groups had concentrations that were several-fold higher than those observed in other pharmacokinetic investigations in which the same dose of felodipine was given with water. A systematic examination for obvious possible causes, such as incorrect dose or drug assay problems, did not resolve this discrepancy. This eventually resulted in a pilot project in a single volunteer to judge the possible role of the juice. Plasma felodipine concentrations were more than fivefold higher with grapefruit juice compared to those with water (3). Subsequently, the interaction was established in a formal clinical study involving patients with untreated borderline hypertension (4). This finding represented a new type of food–drug interaction and critically illustrated the importance of unexpected observations in research.