Food and Oral Antineoplastics: More Than Meets the Eye

Rajul K. Jain1, Satjit S. Brar2, and Lawrence J. Lesko2

Abstract

Food can alter the bioavailability of orally administered drugs. Description of food effects in product labels and information about administration in relation to food are influenced by a variety of factors. Because food effects can change drug efficacy and toxicity, it is important that physicians and patients be aware of them. Clin Cancer Res; 16(17); 4305–7. ©2010 AACR.

In this issue of Clinical Cancer Research, Kang and Ratain publish an intriguing article about the effects of food on the relative bioavailability of oral anticancer agents (1). In their analysis, they find that 6 of the 11 orally administered new molecular entities granted marketing indications by the U.S. Food and Drug Administration (FDA) for the treatment of cancer between 2000 and 2009 have considerably different bioavailability in the fed versus fasted states. Three of the six were designated by the authors to have a magnitude of food effect likely to result in clinical implications, defined as an area-under-the-curve (AUC) increase of at least 150% or decrease of at least 50%, in the fed versus the fasted states. Although these three medications all have greater bioavailability in the fed state, each agent's label recommends administration in the fasted state. The authors note that this recommendation is generally opposite of the labeled recommendation given for non-antineoplastic drugs, which are advised to be given with food when the bioavailability is higher in the fed state. On the basis of the labeling of these three products, the authors conclude that the labeling for oral antineoplastic agents is inconsistent with fundamental principles of pharmacology. Their claim is based on the potential for lower dose levels resulting in an equivalent AUC for each agent when given with food, which they suggest would be safe to do given that the intersubject AUC variation is not significantly different in the fed versus fasted states.

The authors are to be commended for highlighting the importance of food effects in the administration of oral medications. Although food effects are well appreciated by drug developers and regulatory agencies, clinicians and patients are often less aware of their importance (2). Food can alter bioavailability by delaying gastric emptying, stimulating bile flow, increasing splanchnic blood flow, changing gastrointestinal pH, changing luminal metabolism, and physically or chemically interacting with the drug (3). For these reasons, food-effect bioavailability studies are usually conducted for orally administered agents. These studies aim to assess the effects of food on the rate and extent of drug absorption when the drug product is administered shortly after a meal (fed conditions), as compared with administration under fasting conditions. When a food effect is found to exist (a food effect is concluded when the 90% confidence interval for the ratio of population geometric means for the area-under-the-blood-level curve, AUC, and peak blood level, Cmax, between fed and fasted treatments, is not contained in the equivalence interval of 80 to 125%), the FDA requires that the sponsor provide specific recommendations on the clinical significance of the food effect in the product label, including directions on whether the medication should be taken with or without food (4).

Although mean AUC differences in the fed versus fasted states, based on interpatient comparisons and the coefficient of variation (CV) of these AUCs, are one determinant of whether a product's label indicates the medication should be taken with or without food, the authors did not make note of several other important considerations. Differences in intrapatient bioavailability are one of the most significant and underrecognized of such considerations. Although individual patients can have a medication's dose titrated to the desired effect, it is rarely feasible for an individual patient to adjust his or her dose by administration with or without food to achieve consistent bioavailability and systemic exposure. The volume and timing of a meal, caloric content, liquid content, fat versus carbohydrate content, temperature, and physical composition can all produce unpredictable variability in the magnitude of a food effect from dose to dose (5). So, although, for example, lapatinib's AUC in the fed state is 425% of that in the fasting state, this increase is after administration with a high-fat meal. With a low-fat meal, AUC increases by 267%, about half of that with a high-fat meal (6). If patients took the drug with meals of differing content or at different times relative to a meal, the benefit and risk of the treatment is uncertain (7). Furthermore, mean population differences in exposure under fed and fasting conditions do not reflect the differences that an individual patient could expect.
These AUC differences have significant labeling implications for medications administered to cancer patients, in whom either disease or concurrent medication can induce nausea, anorexia, or other gastrointestinal (GI) symptoms that may result in variations in daily tolerance of fatty foods. The FDA’s “Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies” recommends that a high-fat meal be composed of approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat, and that the meal be consumed within 30 minutes (4). Ingesting 900 to 1,000 calories in this fashion may be doable in the setting of a clinical trial over a limited time period, but may prove to be difficult for cancer patients who often take oral antineoplastics for weeks, months, or years. So, although it is true that consistent coadministration with a high-fat meal may allow a lower-dosing level, inconsistent dietary habits could result in significant intradose variation in bioavailability.

This variation is exemplified by the simulation presented in Fig. 1 of a hypothetical, orally administered antineoplastic drug, which has an approximate twofold increase in bioavailability when taken with a high-fat versus a low-fat meal. In the simulation, the drug is prescribed at a lower dose with instructions to take with a high-fat meal rather than at a higher dose under fasting conditions, as might be recommended in the product’s label. The dashed line shows the steady-state blood concentration under fed conditions with the high-fat meal. The solid line shows the intradose variability in blood concentrations when the drug is also taken at the lower dose, but with food intake containing varying amounts of fat at different times, for example, either a high-fat meal with some doses, a low-fat meal with other doses, and, in some cases, taking a dose while fasting (equivalent to no fat) because of cancer or concurrent medication-induced food intolerance. These fluctuations in blood levels can potentially lead to intrapatient variability in effectiveness and safety of the drug.

Other considerations about the product label and food beyond AUC differences and their variability are important. Pharmacokinetic parameters that play a role in determining labeling in relation to food include peak exposure (Cmax), time to peak exposure (Tmax), lag-time, and terminal elimination half-life (8). Food may affect AUC and Cmax differently, and consideration is given to which pharmacokinetic parameter is related to effectiveness and safety. Among nonpharmacokinetic parameters, GI toxicities can be the primary driver of a product’s label. For example, it is recommended that imatinib be taken with food to minimize GI irritation (9). This recommendation exists, in part, because there have been reports of gastrointestinal perforation, including death, with the medication. Conversely, temozolomide is recommended to be taken while fasting to minimize nausea (10).

Another important determinant of the final label is the condition under which pharmacokinetic-pharmacodynamic studies and pivotal registration studies of the agent are done. In oncology, food-effect and other special

---

**Fig. 1.** An identical medication dose is given under two fed conditions and on an empty stomach: dashed line, medication taken consistently with high-fat meal; solid line, medication taken with food containing different amounts of fat. Arrows indicate those doses not given with a high-fat meal in the solid-line scenario. All other doses in both scenarios were with high-fat meals. The shaded area represents the hypothetical therapeutic range. Simulations were done using Pharsight Phoenix WinNonlin 6.1 with a one-compartment, first-order absorption and elimination pharmacokinetic model, and plotted with S-PLUS 8.1. Input parameters: apparent volume of distribution (V/F) = 1,600 L; apparent clearance (CL/F) = 83.9 L/h; absorption rate constant (Ka) = 0.98 h⁻¹. For the case of variable food intake, drug bioavailability with a low-fat meal and while on an empty stomach were 50% and 25%, respectively, of that with a high-fat meal.
population studies (for example, renal and hepatic impairment studies and concurrent medication studies) are often done after the initial trials show some evidence of efficacy and pivotal trials are already underway. This sequencing may be due to competition between sponsors producing medications with similar or identical modes of action, as well as to the desire for sponsors and regulatory agencies to make efficacious molecules available for unmet medical needs as quickly as possible. Given the interest in maximizing drug efficacy and safety, labels often carry recommendations that mirror the administration conditions under which the most safety and efficacy data were collected.

Food effects are complex, and multiple factors beyond relative AUC and C\text{max} under fed and fasting conditions determine the final labeled recommendations about dosing in relation to food. When analyzing the label given to any product or product class, all of the potential influencing factors should be considered. Additionally, sponsors are encouraged to conduct food-effect studies early in a product’s development so the results can be implemented into larger clinical trials of the product. Finally, patient and physician education about the importance of food effects should continue to be emphasized whenever such opportunities arise in clinical practice.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

Received 07/12/2010; accepted 07/12/2010; published OnlineFirst 08/24/2010.

**References**
