ELSEVIER

Intake of oral targeted anticancer agents with food or acid-reducing agents can majorly affect drug absorption and thereby potentially treatment benefit or the severity of toxicities.

Effect of food and acid-reducing agents on the absorption of oral targeted therapies in solid tumors

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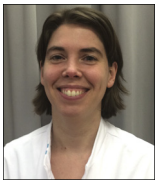
Oral targeted therapies represent an increasingly important group of drugs within modern oncology. With the shift from intravenously to orally administered drugs, drug absorption is a newly introduced factor in drug disposition. The process of absorption can have a large effect on inter- and intrasubject variability in drug exposure and thereby potentially treatment benefit or the severity of toxicities.
The intake of oral targeted therapies with food and concomitant use of acid-reducing agents (ARAs) can significantly affect drug absorption. The size and direction of the effect of food and ARAs on drug absorption varies among drugs as a result of different chemical characteristics. Therefore, an awareness and understanding of these effects for each drug is essential to optimize patient outcomes.

Introduction

The identification of molecular pathways involved in cancer cell proliferation and survival, angiogenesis, and metastasis has led to the development of numerous molecularly targeted therapies. These targeted therapies are currently used in almost every type of cancer and are an important component of modern oncological treatment. Targeted therapies are subdivided in monoclonal antibodies, administered intravenously or subcutaneously, and small molecules, administered orally. The oral targeted therapies are prescribed in a fixed dose, which frequently results in highly variable systemic drug exposure [1]. Yet, evidence is accumulating that reaching a drug concentration in a therapeutic window is important for clinical benefit and toxicity [2,3]. In addition, it is hypothesized that low concentrations can even induce drug resistance [4].

Variation in systemic drug exposure is the result of inter- and intrasubject differences in drug absorption, distribution, metabolism, elimination, and drug adherence. With intravenously



Annelieke Willemsen is in training to become an internist-medical oncologist and clinical pharmacologist at the Radboud university medical center, Nijmegen, The Netherlands. She is a PhD candidate working in the field of medical oncology and pharmacology. Her research focuses on the pharmacokinetics and toxicity of oral targeted anticancer drugs in general, and of mTOR inhibitors more specifically.

Carla van Herpen was appointed a full-time senior staff member at the Department of Medical Oncology of the Radboud university medical center, Nijmegen, The Netherlands in 2002 and, since then, she has become heavily involved in Phase I and II experimental therapy studies. In 2004, she presented her PhD thesis 'Intratumoral administration of interleukin-12 in head and neck cancer'. Since 2012, she has been an associate professor in experimental oncology, especially head and neck cancer, which has been her focus of treatment and research since 1994.

Nielka P. van Erp is a hospital pharmacist at the Radboud university medical center where she is the pharmacist responsible for oncolytic patient care. She directs a research group that focuses on the pharmacology of targeted oncolytics used in solid tumors. Her research mainly involves the unraveling of pharmacokinetic–pharmacodynamic behavior of targeted oncolytic drugs to identify early on those patients who will benefit most from an individualized dose. Additionally, her research group explores approaches to optimize the bioavailability of oral targeted drugs. She is board member of the Dutch Oncology Pharmacology Group and organizes the International Workshop on Dose Optimization strategies for Targeted Drugs.

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dosed chemotherapy, drug absorption has no role. However, for oral targeted therapies, absorption is relevant, because it is a potential major source of the large inter- and intrasubject variability in pharmacokinetics observed for oral targeted cancer drugs [5,6]. Food and acid-reducing agents (ARAs) can significantly affect drug absorption. Oral targeted therapies, such as tyrosine kinase inhibitors (TKIs), are highly lipophilic and often show pH-dependent solubility; therefore, they are especially susceptible for food–drug and pH–drug interactions [5]. As a result, the intake of these drugs with food or ARAs can result in decreased or increased systemic drug exposure. The concurrent use of ARAs is frequently encountered, because 20–55% of patients undergoing cancer treatment use ARAs [4,5].

In this review, we investigate the effect of food and ARAs on the absorption of oral targeted therapies used for solid tumors, based on the available literature.

Absorption

Oral bioavailability is determined by two processes: absorption and first-pass metabolism. The first step in drug absorption is disintegration of the formulation and dissolution of the active drug. After the drug is dissolved, it must pass through the intestinal mucosa to the portal circulation. For lipophilic molecules, such as TKIs, the most common route of drug transport is transcellular passive movement. Other routes of transport are transcellular transport by active carrier mechanisms or paracellular transport [7]. Before reaching the systemic circulation, the drug can have already been metabolized in the intestinal wall and the liver, together constituting the first-pass metabolism. The oral bioavailability is the final percentage of a drug that reaches the systemic circulation in intact form (Fig. 1) [8].

The process of absorption is influenced by a multitude of factors: chemical characteristics of the drug (e.g., lipophilicity or dissociation constant (pKa) value), intestinal physiology (e.g., absorptive surface area, transit time, pH, splanchnic blood flow, or bacteria that influence metabolism), and external influences (e.g., co-medication or food). Drug characteristics that are the major determinants of oral absorption are solubility aspects on the one hand and the permeability (i.e. the amount of drug that crosses the membrane) on the other hand [6,9,10].

Solubility and permeability are both influenced by the ionization state of a drug. Most TKIs are weak basic drugs and, as such, their ionization state depends on the pH of the environment. When drugs are ionized, aqueous solubility is higher, whereas, in the unionized state, permeability through the lipid bilayers of the intestinal mucosa is higher. Weak basic drugs, such as TKIs, will be present mostly in the ionized state in the acidic environment of the stomach, whereby their dissolution is facilitated. In the basic environment of the intestine, these drugs are predominantly in the unionized state and will thereby permeate more readily [11].

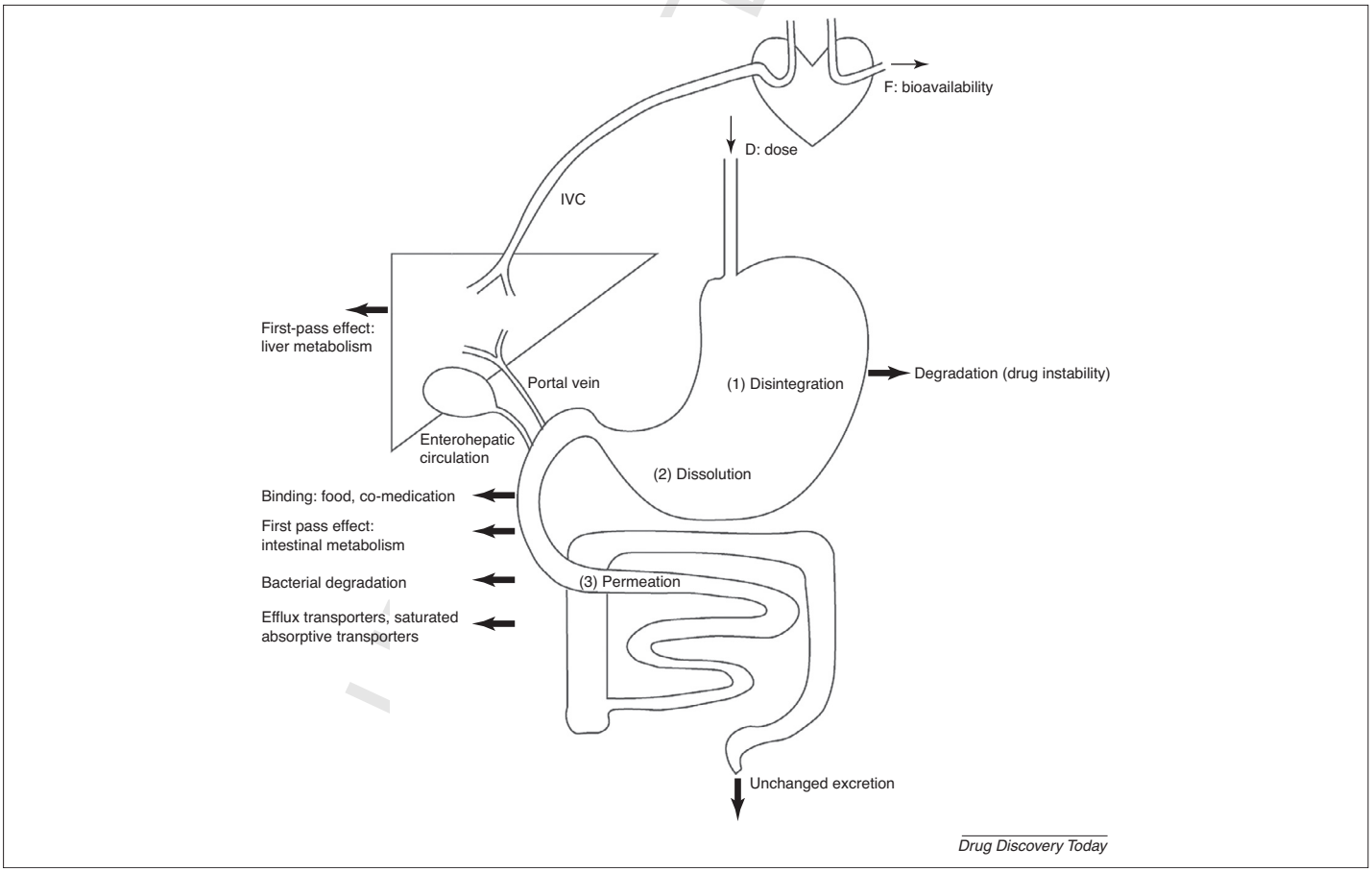

FIGURE 1

Steps in drug absorption: after intake, disintegration, dissolution, and permeation occur. The bioavailability of a drug can be decreased by degradation, binding, intestinal metabolism, efflux transporters, saturated absorptive transporters, and liver metabolism.

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