FACTORS AFFECTING PHARMACOKINETIC DISPOSITION OF DRUGS

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ABSTRACT
Absorption of drugs from the gastrointestinal tract is a complex process the variability of which is influenced by many physicochemical and physiologic factors. The two most important physicochemical factors that affect both the extent and the rate of absorption are lipophilicity and solubility. The rate and extent of absorption are governed by the solubility, permeability and stability of the drug, with solubility being a pH-dependent parameter for weak acids and bases. The gastrointestinal tract can be viewed as discrete sections with a variety of differential local pH environments ranging from the acidic stomach to the more basic small intestine. The multiple peaking, double peaking or secondary peaking phenomena can occur in the disposition of a variety of xenobiotics during drug development (the pre-clinical phase) and in subsequent clinical studies and use. The physicochemical and physiological mechanisms underlying the occurrence of this phenomenon are often multi factorial and include but are not limited to solubility-limited absorption, modified-release formulations, complexation, enterohepatic recirculation, gastric emptying and the intestinal transit time, site-specific absorption, gastric secretion-enteral reabsorption. Double peak absorption has been described with several orally administered drugs such as cimetidine furosemide, piroxicam, ranitidine, talinolol, alprazolam and phenazopyridine.
KEY WORDS: Double peak; Pharmacokinetics; Oral; Single dose

INTRODUCTION

Absorption of drugs from the gastrointestinal tract is a complex process the variability of which is influenced by many physicochemical and physiologic factors. [1] The multiple peaking, double peaking or secondary peaking phenomena can occur in the disposition of a variety of xenobiotics during drug development (the pre-clinical phase) and in subsequent clinical studies and use. [2]

The physicochemical and physiological mechanisms underlying the occurrence of this phenomenon are often multi factorial and include but are not limited to solubility-limited absorption, modified-release formulations, complexation, enterohepatic recirculation, gastric emptying and the intestinal transit time, site-specific absorption, gastric secretion-enteral reabsorption.[1]

Double peak absorption has been described with several orally administered drugs such as cimetidine furosemide, piroxicam, ranitidine, talinolol, alprazolam and phenazopyridine.[1]Several possible explanations are stated for double peak phenomena; some of the double or multiple peak phenomena can be explained sufficiently by a parallel first order absorption model or a multi segment absorption model.[2]

PHYSICOCHEMICAL AND FORMULATION FACTORS
SOLUBILITY-LIMITED ABSORPTION

Drugs are most frequently administered extra vascularly as oral, intramuscular or subcutaneous injections, sublingually, transdermally, topically or via inhalation formulations, with the oral route being the most prevalent because of its ease of administration and reliability. For a drug that is administered extra vascularly to exert a pharmacological effect, it must first be absorbed from the site of administration. Furthermore, for systemic effects, the drug must gain access to the vascular blood where it can be transported to sites of action that are not immediately local to the site of administration.[3]

Drug absorption is influenced by many biological and physicochemical factors. The two most important physicochemical factors that affect both the extent and the rate of absorption are lipophilicity and solubility.[1,3] The membrane of the gastro intestinal epithelial cells is composed of tightly packed phospholipids interspersed with proteins. Thus, the transcellular passage of drugs depends on their permeability characteristics to penetrate the lipid bilayer of the epithelial cell membrane, which is in turn dependent on the lipophilicity of the drugs. As in the example of bisphosphonates, drugs with poor

lipophilicity will be poorly absorbed after oral administration. The effect of lipophilicity on oral absorption is best exemplified by the classical study of barbiturates conducted. In one study, the absorption of these compounds increased with increasing lipophilicity as a result of increased membrane permeability.[3]

The rate and extent of absorption are governed by the solubility, permeability and stability of the drug, with solubility being a pH-dependent parameter for weak acids and bases.[3]The gastrointestinal tract can be viewed as discrete sections with a variety of differential local pH environments ranging from the acidic stomach to the more basic small intestine. A multitude of patho physiological etiologies can also induce changes in gastric acidity and therefore alterations in the oral concentration-time profiles of drugs with pH-sensitive dissolution characteristics. Because of the pH-specific differences between segments along the length of the gastrointestinal tract, some drugs may behave not as a single entity, but rather as several discrete fractions within the gastrointestinal tract. The Biopharmaceutics Classification System (BCS) classifies oral drug absorption characteristics according to their solubility and permeability characteristics. According to the BCS, drug substances are classified into four groups: class I – high permeability, high solubility; class II – high permeability, low solubility; class III – low permeability, high solubility; class IV – low permeability, low solubility.[4]

This classification system identifies that the fundamental parameters governing the rate and extent of drug absorption are solubility and permeability. For instance, class I compounds are generally very well absorbed, often like an aqueous solution; however, gastric emptying can be the rate-limiting absorption step. Class II compounds exhibit dissolution-rate-limited absorption, and their bioavailability is very difficult to predict because of the large variability in the absorption and/or dissolution kinetics. Class III compounds exhibit permeability-rate limited absorption. Class IV compounds tend to have very poor oral bioavailability.[4,5]

This classification is widely recognized by regulatory agencies, including – but not limited to – the US FDA, the WHO, the European Medicines Agency, Health Canada, the Division of Drugs of the National Institutes of Health Services and the International Conference on Harmonization.

Sometimes erratic nature of the oral absorption of drugs is often recognizable within the early absorption phase following drug administration. A classical example is provided by allopurinol, which is known to have low solubility at an acidic pH but high solubility at an alkaline pH. The slow initial increase in plasma allopurinol concentrations that is initially observed after dosing appears to be a consequence of its low solubility in the acidic environment of the stomach. This is followed by a phase with a much higher rate of absorption, representing intestinal absorption, leading to a two-phase absorption profile.[6] These two sequential processes explain the rapid increase in plasma concentrations in the latter phase of the absorption profile. Consequently, this absorption complexity leads to multiple peaking profiles, which cannot be fitted using typical compartmental pharmacokinetic modeling.

For this drug, more complex absorption models are needed to render an adequate prediction of the concentration-time profiles during the absorption phase. A lag time is evident in the absorption of allopurinol, where concentrations of the drug remain low until 2 hours post-dose. In the case of allopurinol, because of its pH-dependent solubility, absorption can be subdivided into two or more discrete fractions within the gastrointestinal tract. These discrete fractions may have similar or very different rate constants of absorption and hence differential rates of input into the systemic circulation.[6]

COMPLEXATION: FORMATION OF POORLY ABSORBABLE BILE SALT MICELLES

A variety of orally administered drugs, including some β-adrenoceptor antagonists (β-blockers), are known to interact with poorly absorbable bile salt micelles in the small intestine, thus leading to multiple peaks. One such β-blocker is pafenolol, which demonstrates discontinuous oral absorption properties in both animals and humans. The plasma concentration time profile of pafenolol exhibits two distinct maximum concentration (C_{max}) values, with truncated and dose-dependent bioavailability that suggests incomplete and non-linear intestinal uptake and absorption.[7,8]

Binding to bile acids is assumed to cause double-peaks in the plasma curves of pafenolol in rats. Accordingly, pafenolol forms rapidly micellar complexes with bile acids in the proximal small intestine, which terminates the initial absorption. Dissociation of these micelles in the distal ileum leads to the major second pafenolol peak in plasma. In presence of food, the binding to bile acids is less significant, leading to non restricted absorption in the jejunum. In man, the second peak disappeared when a solution of the drug was co-administered with food.[1] The formation of micellar complexes involving pafenolol and bile acids within the lumen reduces intestinal uptake and absorption, leading to its low, dose-dependent, variable absorption, and the associated multiple peaks that are evident in its plasma concentration-time profile.[7]

Experimental investigations in rats after intra-duodenal administration have suggested that this double peaking phenomenon of pafenolol is not present in bile-diverted rats, demonstrating the significance of bile salts in the process.[7] Furthermore, the double peaking phenomenon was observed in fed and non-fed rats; however, food lowered the degree of bioavailability and increased the first time to reach the C_{max} (t_{max}) to 1 hour compared with 30 minutes in non-fed rats, indicating differences in the absorption rate with the intake of meals.[9] It is important to note that there was an increase in bioavailability and the fraction absorbed from the gut in both the fasted and fed rats in this same study, which reflects the impact of poor intestinal uptake. Some other β-blockers, including acebutolol and nadolol, have also demonstrated erratic fluctuations in plasma pharmacokinetics after oral administration to human subjects and rats. Acebutolol is a chiral β-blocker prescribed for hypertension, which demonstrates stereo selectivity in first-pass metabolism and renal excretion.[10] Interestingly, the multiple peaking phenomenon observed with acebutolol after oral dosing is present during the fasted and fed states, making it independent of food intake, which suggests gastrointestinal involvement.[11]

Further experimental investigation in rats has determined that food reduces its bioavailability by 60% and that saturable absorption, intestinal metabolism or enterohepatic recycling are not determinant factors for the appearance of multiple peaks in its plasma concentration.[11]

MODIFIED-RELEASE FORMULATION

Sustained-release (SR) preparations can be designed to have both a fast- and a slow-release component.[6] These discrete components may exhibit different input and behaviour in the gastrointestinal tract during oral absorption, inducing subsequent differences in absorption rate profiles. Different approaches have been undertaken to model modified-release formulations, which behave as several fractions in the gastrointestinal tract because of the different pH environments in the different gastrointestinal compartments. For instance, the mean plasma concentration of pindolol (a non-selective β-blocker), after oral administration of an SR dosage formulation to eight healthy subjects, was analyzed using both a two- and a three-fraction absorption model. These models assume one compartment with two or three first-order absorption processes from two or three discrete fractions of the drug, one first-order metabolic process and one first-order urinary excretion process. Modeled plasma data demonstrate simulation curves with all of

these various models, allowing for adequate characterization of the multiple peaking phenomenon.[6]

A two-fraction absorption model has also been applied to SR preparations of the calcium channel antagonist diltiazem.[6] An oral dose of diltiazem 60 mg in an SR formulation was administered to healthy male subjects. It was observed that diltiazem presents an irregular absorption profile, which was adequately fitted to a two-fraction absorption model, indicating differential absorption rates in at least two gastrointestinal sites.

Therefore, the release and dissolution of the drug from the SR formulation may have commenced in the stomach and continued distally in the intestine. Interestingly, large inter-individual variability was observed in the C_{max} and, in some instances, in the t_{max}.[4] Mean diltiazem plasma concentration- time profiles in dogs and humans after oral administration of an SR diltiazem preparation (HER-SR) showed a prolonged plasma concentration and double peaks.[12] The plasma diltiazem concentrations with a double peak were analyzed using multi-fraction absorption models. The HER-SR preparation was apparently divided into two fast- and slow release fraction components in the gastrointestinal tract; each fraction was absorbed at a different rate constant, and a lag time in the absorption was apparent.[13]

In dogs, the absorption site of the slow-release component of an SR diltiazem preparation in the gastrointestinal tract was examined, and 60% of the initial amount reached the colon within 5 hours of administration. Thus SR preparations can have specific absorption characteristics that result in the large bowel being a segment of the gastrointestinal tract that is available for release and absorption of the drug.[14]

PHYSIOLOGICAL FACTORS AFFECTING ORAL BIOAVAILABILITY

CONCENTRATION-TIME PROFILES

The importance of the gastrointestinal tract in the appearance of multiple secondary peaks in pharmacokinetic disposition is often apparent. Enterohepatic recycling, gastric emptying, small intestinal transit and site-specific absorption are the main mechanisms known to be involved in this phenomenon – either as individual processes or often being collectively responsible for the aberrant disposition – and are discussed in detail below. There are other theoretical possibilities for multiple peaking for which data are not available but which may be worthy of mention. One possibility lies in renal tubular reabsorption, for which changes in the urinary pH could conceivably lead to fluctuations in the concentration-time profiles of weak acids or bases secondary to percentage ionization differences and luminal membrane permeability at

various pH values. The contribution of entero-salivary recirculation, with salivary secretion and subsequent swallowing and availability for new reabsorption of the drug from the gastrointestinal tract, could also potentially lead to secondary peaks.[15]

ENTEROHEPATIC RECYCLING

Enterohepatic recycling, or enterohepatic recirculation, is often associated with a longer plasma mean residence time and multiple peaking occurrences in drug plasma concentrations over time. [16]Enterohepatic recycling is related to the physiological processes involved in bile salt and bile acid removal and retention. These components are transported from the liver to the small intestine via the bile duct, where they are largely subsequently reabsorbed back through the lumen of the gastrointestinal tract into the portal blood circulation. In some species, bile contents are transported to the gall bladder for temporary storage and, in response to hormonal responses, are subsequently transported to the duodenum via the common bile duct. Cholecystokinin, an important choleretic regulatory hormone, is secreted post-prandially to facilitate the process of digestion.[16] Bile acids, which are delivered to the duodenum, are extensively recycled by enterohepatic circulation, as are certain drugs. It is in the distal regions of the small intestine (ileum) that drugs and bile salts can be reabsorbed by the enterocytes. Bacteria present in the gastrointestinal tract can deconjugate certain xenobiotics – most notably, glucuronidated and sulphated compounds – back to the absorbable, more lipid soluble, and parent compounds. The overall effect of enterohepatic recirculation is extension of the mean residence time of drugs in the body.[16] The process has been referred to in the literature as representing a 'futile cycle', in the sense that biliary excreted drug is reabsorbed into the bloodstream. Unless the drug has been completely cleared by biliary secretion, with complete intestinal reabsorption of the drug, it is not truly futile in the sense that biotransformation within the intestinal tract, enterocytes, hepatocytes or other clearance pathways (e.g. renal) would eventually lead to drug removal from the systemic circulation.[16]

As previously discussed, enterohepatic recirculation is critical in preserving the homeostasis of bile acids. A large variety of agents from numerous drug classes can undergo enterohepatic recirculation, including NSAIDs, analgesics, cardiac glycosides, antibacterials, estrogen regulators, opioids and synthetic derivatives of bioactive compounds including retinoic acid, antihypertensives, antimicrobials, immune suppressants, immune modulators, antiarrhythmics, antineoplastics, anticonvulsants and antiretroviral agents. Additional examples can be drawn from drugs for treatment of pneumonia, anxiety, vascular disorders, gout and gastrointestinal disorders. First order absorption processes are commonly used to characterize drug absorption processes; however, for xenobiotics that undergo enterohepatic recirculation, first-order absorption processes are unable to correctly depict the disposition of the drug into the systemic circulation. A hallmark of the involvement of enterohepatic recycling in drug disposition is the presence of multiple peaks in the plasma concentration-time profile, especially after intravenous dosing. Drugs that undergo enterohepatic recycling cannot be fitted to regular pharmacokinetic models because they have a secondary absorption process leading to secondary peaks. Indeed, this secondary peaking presents itself after intravenous dosing and well beyond the absorption phase of orally administered drugs, and can make it difficult to obtain a reliable estimate of the terminal phase half-life.

Thus various modeling approaches – incorporating features such as a time-lag two compartment model;[17] a two-compartment model with a body compartment and a gastrointestinal tract compartment;[18] a four-compartment model with a gastrointestinal, central, peripheral and gallbladder compartment; [19] and a more complex five-compartment model including a sampling compartment, liver, storage compartment (gallbladder), absorption compartment from the dose, and an absorption compartment from the secreted bile[20] have been used to characterize the pharmacokinetics of such drugs.

It is clear that enterohepatic recycling occurs in a wide array of drugs, most of which undergo extensive conjugation and exhibit poor bioavailability. Enterohepatic recycling often correlates to longer than expected half-lives of drugs after oral administration compared with intravenous administration.[21] It is important to note that multiple factors affect biliary excretion, such as drug characteristics (molecular size, polarity and chemical structure), biotransformation and possible reabsorption from intra hepatic bile ductules, and transport across sinusoidal plasma membranes and caniculae membranes. Furthermore, bioavailability is also affected by gut-wall P-glycoprotein efflux, gut-wall metabolism and hepatic canalicular multidrug resistance-associated protein-2. Nevertheless, the absorption processes and enterohepatic recycling are also affected by physiological factors such as genetic abnormalities and disease states, as well as co-administration of orally absorbent or other drugs.[16] Enterohepatic cycling is known to be responsible for secondary peaks in piroxicam.[2]

GASTRIC EMPTYING AND INTESTINAL TRANSIT TIME

The rate of gastric emptying strongly impacts the rate and extent of intestinal drug metabolism and drug absorption. Various disease conditions and food intake affect stomach emptying and/or intestinal transit. Double peak absorption has been correlated with antral gastric motility as well as other factors including the presence of adjuvants or bile salts. The data showing double peaks during absorption have been modeled as the discontinuous oral absorption model. Inevitably, a delay in stomach emptying reduces the rate of drug absorption since the rate of delivery to the site of absorption, the small intestine, is prolonged. [22]

Factors affecting the rate and extent of drug absorption after oral administration may contribute to the multiple peaking phenomenons. The residence time can be particularly important for class I BCS drugs, which have high solubility and high permeability, and class III BCS drugs, which have high solubility and low permeability. Moreover, the residence time in a gastrointestinal region is dictated to a large extent by gastric emptying and gastrointestinal motility. The gastric emptying rate at which a drug moves from the stomach to the more distal duodenum is an important determinant of the overall ka of the drug. Gastric motility is known to be regulated by the migrating motor complex under fasted conditions. [23] The duodenal lumen regulates gastric motility through a feedback mechanism, depending on the contents of the duodenum, which lead to irregular contractions of the gastric antrum. [23] The duration of the gastrointestinal motility cycle has high intra- and inter-individual variability ranging from 15 minutes to more than 3 hours in duration, and is characterized by four phases. Phase I is a quiescent period lasting between 15 and 90 minutes, and phase II consists of both intermittent and irregular contractions, with a duration of ~2 hours. These gastrointestinal contractions can increase in intensity, culminating in an interval of contractions known as phase III, which is the activity phase or the housekeeping wave, lasting for 3-25 minutes. Phase IV is a brief transition period from phase III back to phase I. As very little absorption of most drugs occurs from the stomach relative to the small intestine, because of both the shorter residence time and the substantially smaller surface area, the drug is retained in the stomach until it is ultimately delivered to the intestine, where the majority of the drug is subsequently absorbed. For drugs with high water solubility, dissolution is rapid and is most likely not a rate-limiting step for absorption to occur. Under these circumstances, gastric emptying may be a critical determining factor in drug absorption. Because gastrointestinal motility, gastric empting and intestinal transit rates are discontinuous in nature, and most drug studies occur in the fasted state, plasma concentration-time courses of orally administered drugs can exhibit multiple peaks, reflecting gastrointestinal physiological variability. [24]

Gastric emptying can also have different patterns. Type I has a mono-exponential emptying pattern, which begins just after ingestion of the drug, typically when preceded by a period in which no gastric emptying has occurred. Type II has a biphasic gastric emptying pattern in which part of the drug is rapidly emptied, typically within 10–15 minutes, which is then followed by a mono-exponential emptying pattern put forth by the remaining fraction of the drug. The type III pattern is characteristic of a biphasic gastric emptying pattern, consisting of two mono-exponential emptying patterns, which are interrupted by a period of no gastric emptying. The histamineH2-receptor antagonist ranitidine also demonstrates multiple peaking in pre-clinical and clinical studies. [25] In an attempt to understand this complex phenomenon, ranitidine gastrointestinal distribution was examined in the rat small intestine after oral administration, to determine the influence of intestinal transit on secondary peaks in ranitidine serum concentration-time profiles. Ranitidine absorption from the lower ileum contributes significantly to systemic ranitidine concentrations before and during the time of the first C_{max}. Separation of the drug mass into multiple boluses may contribute to secondary peaks in ranitidine concentration-time profiles. [26]

Further clinical studies of ranitidine were examined in the presence and absence of pancreatico-biliary secretions. The extent of ranitidine systemic exposure and the C_{max} were not altered significantly by treatments; treatment effects on the small bowel transit time varied. Secondary peaks were observed in some subjects during the control treatment and other subjects during cholecystokinin treatment (0.04 mg/kg intravenously, sufficient to cause gallbladder emptying into the duodenum). Interestingly, no secondary peaks were observed in any subject during the balloon treatment, although the t_{max} was prolonged. These results support the concept that pancreaticobiliary secretions within the intestinal lumen during control or cholecystokinin treatment, as well as the gastrointestinal transit time, may influence the occurrence of secondary peaks in ranitidine concentration-time profiles. [27]

Pharmaceutical non-functional excipients are often thought to be inert and without appreciable effects within the gastrointestinal tract; however, functional excipients serve a variety of functions, including – but not limited

to – suspension, preservation, stabilization and flavouring of these delivery systems. Another important role of functional excipients in bioavailability is primarily one of solubilization. The presence of excipients such as polyethylene glycol molecular weight 400 (PEG400) can invoke an increase in small intestinal transit and consequently may affect drugs, such as ranitidine, that have a site-specific absorption window, while other excipients such as propylene glycol, vitamin E TPGS and Capmul MCM may not.[28]

In one study, the concentration-dependent effects of PEG 400 on liquid transit, ranitidine absorption and gastrointestinal transit were investigated using healthy male subjects. It was determined that there were no significant changes in gastrointestinal emptying with or without PEG 400. However, it was noted that in the presence of PEG 400, as compared with the control, the mean small intestinal transit times were reduced by 9%, 20% and 23%, respectively. Collectively, the results indicated that PEG 400 in low concentrations enhanced the absorption of ranitidine; however, high concentrations of PEG 400 decreased the absorption of ranitidine. [29] A separate study assessed the absolute bioavailability of ranitidine in different formulations administered to healthy subjects. Ranitidine was either encapsulated in a hard gelatin capsule as an immediate-release (IR) pellet formulation or solubilized as a liquid preparation in orange juice (control) or orange juice containing PEG 400 (test). It was observed that co-administration of PEG 400 reduced the absolute bioavailability by 31% and the small intestinal transit time was shortened by 37%. Interestingly, the appearance of secondary multiple peaks were less evident in the presence of the excipient PEG 400. Furthermore, it was observed that sodium acid pyrophosphate, an excipient used in effervescent formulations, resulted in reductions in the small intestinal transit time and the bioavailability of ranitidine. It has also been hypothesized that PEG 400 and other excipients that are thought to be inert have other indirect and direct effects, such as osmotic effects, on the gastrointestinal tract, which could potentially alter oral concentration-time profiles and lead to the appearance [28] and disappearance of secondary multiple peaking phenomena.

Mannitol may also decrease bioavailability because of solvent drag, and it can osmotically hold water in the small intestine, which may lead to a net flux of water into the lumen of the small intestine rather than a normal flux into plasma.[30]

SITE-SPECIFIC ABSORPTION

Orally administered drugs are primarily absorbed into the systemic circulation from the small intestine because of its large surface area and the residence time of the drug in the small intestine. It is apparent that drugs can be absorbed from other segments of the gastrointestinal tract, including – but not limited to the stomach and colon. Multiple peaking in oral plasma concentration-time profiles can ensue, and site-dependent absorption of drugs may be an underlying mechanism. Ranitidine provides an oral concentration-time profile with an initial peak and a pronounced secondary C_{max}, with high inter-subject variability in bioavailability. It has been proposed that because of this, there has been a marked discrepancy between research groups in reporting the secondary phenomena of ranitidine.[25, 31]

For instance, single peaks in the plasma concentration profiles were observed in healthy subjects, patients with liver cirrhosis and patients with renal failure with no significant differences in the pharmacokinetic parameters compared with the control group. These differences have been explained by protocol differences between studies (fasting conditions, post-dose feeding regimens and/or blood sample intervals) and averaging of mean data that might have obscured the second peak. [32] To assess the mechanism of the secondary peaks in the plasma concentration profile of ranitidine, the delivery of ranitidine to three separate locations in the gastrointestinal tract and the absorption characteristics of ranitidine were studied in healthy subjects. These subjects received ranitidine 150 mg for injection via a nasoenteric tube directly placed into their stomach, jejunum or caecum sequentially on three separate occasions. [32] The ranitidine concentrations following caecal dosing were significantly lower than those attained following both gastric and jejunal administration. The occurrences of multiple plasma concentration-time peaks were observed in several subjects after both gastric and jejunal input. The observed phenomenon of multiple local maximum concentrations appears to be further pronounced in the fasting state and is augmented by the presence of food. Together, the data suggest the possibility of site-specific absorption of ranitidine in the stomach and jejunum.

The occurrence of multiple peaking after direct administration of ranitidine within the jejunum suggested that this phenomenon is not related to variability in gastric emptying. [33] These results appear to agree with those of a separate study of healthy subjects given 150 mg ranitidine, where multiple peaking was observed in the absence of enterohepatic recycling as a major contributing factor; less than 0.2% of the dose was

recovered in bile. The absorption kinetics of ranitidine from the gastrointestinal tract were altered in the bile flow-intact rats,[34] although secondary peaks were still evident in some of the bile duct cannulated rats in whom the bile flow was interrupted; the influence of gastrointestinal transit was not reported.[35] demonstrated that the duodenal-jejunal junction is the preferential site of absorption of ranitidine. In rats given oral ranitidine, absorption was examined in the small intestine in the hope of understanding the mechanism behind the absorption of ranitidine. Of particular interest in this study were the roles of intestinal transit and secretion (exsorption). The investigators observed a bimodal distribution of ranitidine absorption, apparently caused by multiple boluses of drug mass, which led the investigators to believe that exsorption was a minor contributing factor to ranitidine distribution to the gastrointestinal tract. Duodenal absorption and a second ileal absorption phase, with decreased mid-small bowel absorption, were supported by high absorption rates in the duodenal-jejunal and distal jejuna-ileal junctional regions. [35]

GASTRIC SECRETION-ENTERAL REABSORPTION

Transporters may be involved in drug intestinal secretion, e.g. P-glycoprotein. Differences in the distribution of a transporter such as P-glycoprotein within the gastrointestinal tract may cause site-dependent absorption to occur. P-glycoprotein is more predominant in the upper parts of the gastrointestinal tract than in the ileum and colon.[36] Site dependence of oral absorption seems to be a common property of the substrates of P-glycoprotein (P-gp), a multidrug transporter of the ABC-family. P-glycoprotein is more predominant in the upper parts of the gastrointestinal tract than in the ileum and colon.[36]Several authors have measured increased expression and/or function of P-gp longitudinally along the small intestine (stomach < jejunum/ ileum). Others, however, could not verify regional differences in MDR1mRNA expression. Nevertheless, the substantial variability of talinolol absorption from modified release capsules is in line with our conception on regional differences in intestinal P-gp expression because talinolol is a non metabolized substrate of P-gp. [1] Talinolol is a β1-adrenoreceptor antagonist used in the treatment of arterial hypertension, coronary heart disease and tachyarrhythmia. [36]

The double-peak phenomenon of talinolol likely results from processing via a presystemic storage compartment within or behind the intestinal absorption barrier.[1]The evaluation of the double-peak phenomenon during absorption of the β1-selective blocker talinolol relative to paracetamol, which is well absorbed from all parts of the gut, for that one study carried out in eight white healthy human subjects. Talinolol undergoes only minor enterohepatic recirculation. Furthermore, talinolol is increasingly less absorbed along the small intestine as caused obviously by increasing expression of P-glycoprotein, that is, the second peaks after 4–6 h cannot be the results of absorption from the proximal intestine. Evaluation of the double-peak phenomenon during absorption of the β1-selective blocker talinolol relative to paracetamol, which is well absorbed from all parts of the gut, and relative to vitamin A, which is absorbed via the lymphatic pathway. For same single dose bioavailability study in eight healthy subjects were conducted in different conditions. Talinolol was given with paracetamol and retinyl palmitate in fast-disintegrating, enteric coated, and rectal soft capsules to 8 fasting male healthy subjects (21–29 years, 68–86 kg). To evaluate whether the talinolol double-peak is associated with processes of food absorption, a breakfast was served 1 h after administration of a fast disintegrating capsule. Bioavailability of talinolol in enteric-coated and rectal capsules was significantly reduced by about 50% and 80%, respectively, despite unchanged bioavailability of paracetamol. Double-peaks appeared after 2–3 h and 4–6 h with talinolol given as fast-liberating capsules. Food increased the maximum concentrations significantly (223 ± 76 g/ml vs. 315 ± 122 g/ml, $p < 0.05$) and shifted the second peak of talinolol to shorter t_{max} values (3.8 ± 1.2 h vs. 2.1 ± 0.6 h, $p < 0.05$), which was associated with faster absorption of retinyl palmitate. Pharmacokinetic model fits showed that about half of the oral talinolol dose given with and without meal is drained from the intestine via a pre systemic storage compartment. The double-peak phenomenon of talinolol is likely caused by a pre systemic storage compartment, which represents the complex interplay of heterogeneous uptake and kick-back transport processes along the intestinal-hepatic absorption pathway.[1] P-glycoprotein distribution has also been suggested to be a major contributing factor to the site specific absorption of talinolol.[36] Understandably, it is important to consider drug transporter localization, including substrates and inhibitors, in the double peaking phenomenon.

CONCLUSION

Multiple peaking in the blood fluid concentration-time curve profiles can complicate the determination and interpretation of pharmacokinetic parameters. Mechanistically, the causality of this phenomenon can be divided into physicochemical and formulation factors and physiological factors. The physicochemical and physiological mechanisms underlying the occurrence of

multiple peak and include limited to solubility-limited absorption, modified-release formulations, complexation, enterohepatic recirculation, gastric emptying and the intestinal transit time, site-specific absorption, gastric secretion-enteral reabsorption.

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