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Multiple Peaking Phenomena in Pharmacokinetic Disposition

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Contents

Abstract . . . 351
1. Physicochemical and Formulation Factors . . . 352
   1.1 Solubility-Limited Absorption . . . 352
   1.2 Complexation: Formation of Poorly Absorbable Bile Salt Micelles . . . 356
   1.3 Modified-Release Formulation . . . 357
2. Physiological Factors Affecting Oral Concentration-Time Profiles . . . 359
   2.1 Enterohepatic Recycling . . . 359
   2.2 Gastric Emptying and Intestinal Transit Time . . . 362
   2.3 Site-Specific Absorption . . . 367
   2.4 Gastric Secretion-Enteral Reabsorption . . . 369
   2.5 Anaesthesia and Surgery . . . 370
3. Conclusions . . . 371

Abstract

Multiple peaking in the blood fluid concentration-time curve is a phenomenon occasionally encountered in pharmacokinetics. When it occurs, it can create difficulties in the determination and interpretation of pharmacokinetic parameters. Multiple peaking can occur as a consequence of a number of different mechanisms. These include, in addition to others, factors related to the formulation, be it the drug chemical entity itself or other formulation-related factors such as the excipients incorporated into the product design. Another contributing factor that can work in concert with the formulation is the physiological makeup of the gastrointestinal tract itself. This includes the pH and components of bile such as bile salts and phospholipids, the secretion of which is regulated by hormonal and dietary factors. In some cases, biochemical differences in the regional areas of the gastrointestinal tract, such as regiospecificity in bile concentrations and/or transport proteins, could contribute to windows for absorption that result in multiple peaking of xenobiotics. One of the most common sources of multiple peaking is contributed by biliary secretion followed by intestinal reabsorption of a drug, a process for which the term 'enterohepatic recycling' has been coined. This cause of multiple peaking is associated with special consideration in the calculation and interpretation of the drug clearance and volume of distribution. In this review, each of these various causes of multiple peaking is discussed, with incorporation of relevant examples for illustrative purposes.

A review of the biomedical literature clearly demonstrates that 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 multifactorial 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, and effects of surgery and anaesthesia (table I). The aim of this review is to present and discuss pertinent examples from the literature that highlight the mechanistic circumstances surrounding multiple peaking in pharmacokinetic disposition.

1. Physicochemical and Formulation Factors

1.1 Solubility-Limited Absorption

Drugs are most frequently administered extravascularly 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 extravascularly 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.

The process of absorption is associated with considerations of rate and extent, both of which represent key determinants of the ultimate bioavailability of a drug. 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. A multitude of pathophysiological aetiologies 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:[146] class I – high permeability, high solubility; class II – high permeability, low solubility; class III – low permeability, high solubility; class IV – low permeability, low solubility.

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.[146] 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.

The 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.[105] 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 modelling. 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.[105]

Another classical example of this multiple peaking phenomenon is provided by the antibacterial doxycycline. Doxycycline exhibits secondary peaks in the serum profile of pigs after intravenous administration (20 mg/kg) via an indwelling cannula (figure 1).[139] The secondary peaking phenomenon has also been observed in healthy subjects[140,141,147] and has been attributed to the phenomenon of enterohepatic recycling,[147] based on the observation that doxycycline has a high affinity

Table I. Summary table of drugs exhibiting multiple peaking phenomena

Mechanism and drug	Indication/drug class	Routes of administration	Species (condition or disease)[a]	References
Anaesthesia and surgery				
Fentanyl	μ Opioid agonist	Intravenous	Human	1-4
		Infusion	Human	5
Alfentanil	Opioid analgesic/anaesthetic	Intravenous	Rat	6
		Infusion	Human	7
		Intravenous	Human	8
		Infusion, intravenous	Rat	6,9-11
Sufentanil	Opioid analgesic	Intravenous	Human (tourniquet release)	12
Propofol	Sedative	Intravenous	Human	13
Thiopental sodium	Barbiturate general anaesthetic	Intravenous	Human	14,15
Diazepam	Benzodiazepine	Intravenous	Human	16
Complexation				
Pafenolol	β-Adrenoceptor antagonist (β-blocker)	Intraduodenal	Rat (non- and bile duct cannulated)	17
		Oral	Rat, human	18
			Rat (fasted, fed)	19,20
			Human	21,22
		Intra-intestinal	Rat	23
Acebutolol	β-Blocker	Oral	Rat (normal/arthritis)	24
			Rat	25,26
Nadolol	β-Blocker	Intravenous	Rat (fasted)	27,28
Enterohepatic recycling				
4-ene-valproic acid	Anti-epileptic	Intravenous	Rat	29
17α-ethynylestradiol	Contraceptive	Intra-arterial	Rainbow trout	30
17β-estradiol	Sex hormone	Oral	Human	31
Amprenavir	Protease inhibitor	Oral	Human	32-34
Cosalane	Anti-HIV agent (HIV to cell-binding inhibitor)	Intravenous	Rat	35
Digoxin	Cardiac glycoside	Intravenous	Dog and human (predicted via physiologically based pharmacokinetic model)	36
Dihydrocosalane	HIV (antiretroviral)	Intravenous	Rat	35
Doxycycline	Antibacterial	Oral	Human	37
Epristeride	5α-reductase inhibitor	Intravenous, oral	Human	38
Ethinylestradiol	Contraceptive	Oral	Human	31
Etodolac	NSAID	Intravenous	Rat	39
Isotretinoin	Acne (retinoid)	Intravenous	Monkey	40
		Oral	Human	41
Methotrexate	Chemotherapeutic	Oral	Human, dog, rat, mouse	42
Mycophenolate mofetil	Immunosuppressant	Intravenous	Human (renal transplant)	43-45

Continued next page

Table I. Contd

Mechanism and drug	Indication/drug class	Routes of administration	Species (condition or disease)[a]	References
Nevirapine	Reverse transcriptase inhibitor	Oral	Human	46
		Oral	Rat	47
N^G-nitro-L-arginine	Nitric oxide synthase inhibitor	Intravenous	Rat	48 49
Otilonium bromide	Spasmolytic	Intravenous, oral	Rat (normal, bile-cannulated)	50
Oxazepam	Benzodiazepine	Oral	Human (uraemic)	51
		Intravenous infusion, oral	Human, dog	52
Oxytetracycline	Antibacterial	Intravenous, oral	Pig	53
Roquinimex	Immunostimulant	Oral	Human	54,55
Tetracycline	Antibacterial	Oral	Rat	56
Moxisylyte (thymoxamine)	α_2-Adrenoceptor antagonist	Intravenous, oral	Rat	57
Tiagabine	GABA uptake inhibitor	Oral	Human	58
XK 469	Anti-tumour agent	Intravenous infusion	Human	59
Zeranol (zearalenone)	Mycotoxin	Intravenous, oral	Pig	60
Entero-salivary recirculation				
Paracetamol (acetaminophen)	Analgesic, antipyretic	Oral	Human	61
Benzathine + procaine benzylpenicillin	Antibacterial	Intravenous	Pig	62
Gastric emptying				
Ranitidine	Histamine H_2-receptor antagonist	Oral	Human	63
				64
			Rat (GI tract clamped)	65
			Human	66
Ranitidine/PEG 400	H_2-receptor antagonist/excipient	Oral	Human	67 68
Mannitol	Excipient	Oral	Human	69,70
Sucrose	Excipient	Oral	Human	69
Cimetidine	H_2-receptor antagonist	Oral	Human (duodenal ulcer)	71 72
			Human (fasted, fed)	73-75
		Duodenal infusion, oral	Dog	76
Paracetamol	Analgesic, antipyretic	Oral	Human	77
Alprazolam	Benzodiazepine	Oral	Rat	78,79
Epinastine	H_1-receptor antagonist	Oral	Rat	80
Carbon tetrachloride	Hepatotoxin	Oral	Rat	81
Levodopa	Parkinson's disease	Oral	Human	82
Piretanide	Loop diurectic	Oral (via gastroscope)	Human	83
Sampatrilat (UK 81252)	ACE inhibitor, neural peptide	Oral	Dog	84

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Table I. Contd

Mechanism and drug	Indication/drug class	Routes of administration	Species (condition or disease)[a]	References
Danazol	Endometriosis	Intra-intestinal, oral	Human	85,86
Penicillamine	Chelator	Oral	Human (fasted, fed)	87
			Dog	88
Pranlukast	Peptidoleukotriene antagonist	Oral	Human	89
Avitriptan	Serotonin 5-HT_1-receptor agonist	Oral	Human (fasting, high-fat fed)	89
Saquinavir	Viral protease inhibitor	Oral	Human (fed)	90
Sumatriptan	5-$HT_{1B/D}$-receptor agonist	Oral	Human	91
		Intranasal	Human	92
Furosemide (frusemide)	Loop diuretic	Oral	Human	93,94
Gastric secretion-enteral reabsorption				
Phenoperidine	Anaesthetic	Intravenous	Human	95-97
Fentanyl	μ Opioid receptor agonist	Intravenous	Human	98 99-102
		Infusion	Rat	9
Modified-release formulation				
Valproic acid	Anticonvulsant/mood-stabilizer	Oral	Human	103
		Oral, intraduodenal	Rat (fasted)	104
Diltiazem	Calcium-channel antagonist	Oral	Human	105,106
			Dog	106-108
Site-specific absorption				
Ranitidine	H_2-receptor antagonist	Nasoenterically to sites of gastrointestinal tract	Human	109
		Oral	Human, rat	110
			Rat (bile duct intact, cannulated)	111
			Human	112
			Rat	113
			Human	114-117
		Intravenous, oral	Human	118
		Intestinal perfusion	Human	119
Glibenclamide (glyburide)	Sulfonylurea	Gastroscope to sites of GI tract	Human	120
Cimetidine	H_2-receptor antagonist	Oral	Human	121
			Rat	113
			Human (modelling)	122 115
Veralipride	Benzamide antipsychotic	Oral	Human	123-125 126
			Human (modelling)	127

Continued next page

Table I. Contd

Mechanism and drug	Indication/drug class	Routes of administration	Species (condition or disease)[a]	References
1-(2-fluoro-5-methyl-β-L-arabinofuranosyl)uracil	Hepatitis B, Epstein-Barr virus	Oral	Rat	128
Biriperone (centbutindole)	Dopamine receptor antagonist	Oral	Rat	129
Talinolol	β_1-Adrenoceptor antagonist	Oral	Human	130-132
		Intravenous	Human (T-tube drainage after cholecystectomy)	133
		Intestinal perfusion	Human	134
Dichloroacetate	Lactic acidosis	Oral	Rat (naïve, GST-zeta depleted)	135,136
			Rat (naïve, bile duct cannulated)	137
Cimetropium bromide	Antispasmodic	Oral	Human	138
Solubility-limited absorption				
Allopurinol	Anti-hyperuricemic	Oral	Dog	105
Pindolol	β-Blocker	Oral	Human	105
Doxycycline	Antibacterial	Intravenous	Pigs	139-141
Tourniquet release				
Fentanyl + midazolam	μ Opioid receptor agonist, benzodiazepine	Intramuscular, intravenous,	Human (tourniquet release)	142
Cefazolin	Antibacterial	Infusion	Human (tourniquet inflation)	143
Vecuronium bromide	Muscle relaxant	Intravenous	Human (tourniquet release)	144
Sufentanil	Opioid analgesic	Infused	Human (tourniquet release)	145

a If no condition or disease is specified, the subjects were healthy.

GI = gastrointestinal; **GST** = glutathione transferase.

for bile (10- to 15-fold higher than for serum)[148] and that physiologically, cyclic discontinuous biliary excretion occurs.[56,149,150] Doxycycline passively diffuses across the intestinal wall, subsequently forming stable complexes in the lumen, and this process represents a major contributor to total body clearance.[151,152] Therefore, the mechanism responsible for the secondary peaks in serum may be discontinuous reabsorption due to local changes in the gastric pH, coupled with changes in the content of the intestinal lumen, processes related to peristalsis and digestion.[139] As for allopurinol, classical compartmental pharmacokinetic models are unable to appropriately model this phenomenon, and alternative models, including elements of discontinuous cyclic transfer[150] or physiological models,[153] are more suitable for modelling of doxycycline.

1.2 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

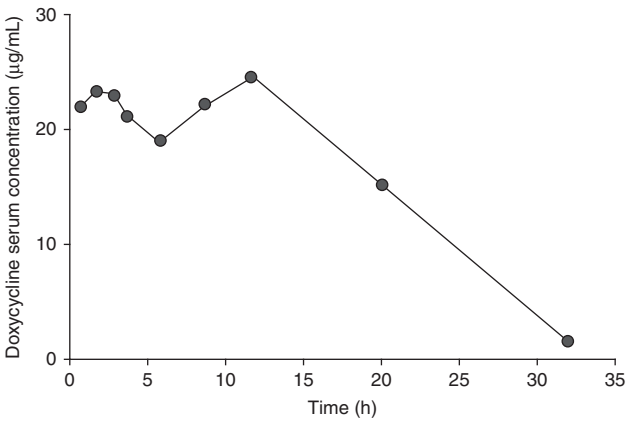

Fig. 1. Secondary peaks in the doxycycline serum concentration-time profile in one pig after a single intravenous administration of 20 mg/kg of bodyweight (reproduced from Riond and Riviere,[139] with permission).

bioavailability that suggests incomplete and non-linear intestinal uptake and absorption.[17,18]

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.[17] Experimental investigations in rats after intraduodenal 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.[17] 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.[19]

Pafenolol has been extensively studied in the rat model because it has interesting absorption properties and routes of elimination similar to those in humans.[20-22,154] Further investigation has revealed that pafenolol has specific absorption in the ileocolonic region,[23] that its dose-dependent increase in bioavailability is caused by an increase in intestinal uptake[20] and that its predominant mechanism for excretion into faeces is intestinal excretion (exsorption) from blood into the gut lumen, since only 3% of a given intravenous dose was recovered as pafenolol in bile.[20] 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,[24] which demonstrates stereoselectivity in first-pass metabolism[155] and renal excretion.[155,156] The double peaking phenomenon in the pharmacokinetics of acebutalol is not affected by intragastric elevation of the pH with cimetidine.[157] 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.[25] 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.[25,26,156] Since multiple peaks were also apparent in bile duct-ligated rats administered the drug, bile salts do not appear to have a significant effect on the absorption of acebutolol, which parallels predictions using a thermodynamic 1 : 1 interaction model with dihydroxy bile salts.[158]

Nadolol is another β-blocker that also presents multiple peaks in its plasma concentration-time profiles, and this has been correlated primarily with hydrophobic and electrostatic aggregates with dihydroxy bile salts,[158] such as sodium cholate, inhibiting its intestinal absorption.[27] Furthermore, the inhibition in intestinal absorption has been attributed to stable micelle formation with bile salts (sodium cholate and its taurine and glycine conjugates), which causes a loss of thermodynamic activity, decreasing the intestinal uptake into the membrane without affecting its membrane permeability.[28] However, other β-blockers such as atenolol, carteolol, pindolol and propranolol do not appear to have their absorption inhibited by formation of micelles with bile salts.[27,28]

In summary, there are several examples of drugs that can form unabsorbable micelles with bile salts in the gastrointestinal tract. The reduction in drug absorption after oral administration occurs rapidly and is consistent with micelle formation in the proximal part of the small intestine due to high concentrations of bile acids in the ileum. In the distal ileum, where no intact micelles are taken up because of dissociation of micelles, bile acids are actively reabsorbed by the enterocytes. This occurs coincidentally with enhanced intestinal absorption of the micelle-free drug in solution and a secondary peak in the plasma concentration-time profile.

1.3 Modified-Release Formulation

Sustained-release (SR) preparations can be designed to have both a fast- and a slow-release component.[105] 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 analysed 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. Modelled plasma data demonstrate simulation curves with all of these various models, allowing for adequate characterization of the multiple peaking phenomenon.[105]

Another example can be observed in the absorption of an SR oral formulation of the anticonvulsant valproic acid (sodium valproate), where double peaks in its concentration-time profile are apparent. Because of the complexity of the input process, the data are best fitted using a zero-order absorption rate, a first-order absorption rate and the Weibull absorption model with double absorption rate constants. In this case, the Weibull model was used as an approximation of the overall input process since it fitted the data more successfully than a single first-order absorption rate constant (k_a) or a single zero-order absorption rate constant (k_0).[103] This double peaking phenomenon is consistent with absorption involving two sites (see section 2.3).

This large interindividual variability was also observed after administration of an SR formulation of valproic acid to healthy subjects. Figure 2 depicts the relevant differences in valproic acid concentrations in subject 9, where its t_{max} of 12 hours represented the secondary peak, opposite to the earlier t_{max} (6 hours) and the lower C_{max} in subject 6.[103] One possible explanation for these differences in absorption could be the differences in the rate of absorption in each of the two anatomical compartments (the stomach and intestine) between individuals. In the case of valproic acid, it is absorbed from the stomach at a slower rate than from the intestine in rats.[104] This difference in the rate of absorption can also be coupled with plausible transient rate alterations secondary to meal times.[103] Therefore, it can be observed that modifying the release of a drug in formulation will not only alter the release and dissolution rate in the different gastrointestinal sites but will also alter the rates of absorption, which could lead to the appearance or increase of multiple peaking phenomena.

A two-fraction absorption model has also been applied to SR preparations of the calcium channel antagonist diltiazem.[105] 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 interindividual variability was observed in the C_{max} and, in some instances, in the t_{max}.[105] The 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. The plasma diltiazem concentrations with a double peak were analysed using multi-fraction absorption models. The two-fraction absorption model and the two-step discontinuous absorption model have been utilized, identifying that the two-fraction absorption model was useful for the comparison of *in vitro* and *in vivo* release profiles and for the evaluation of the food effect on the absorption behaviour of HER-SR.[106] 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.[107] In dogs, the absorption site of the slow-release component of an SR diltiazem

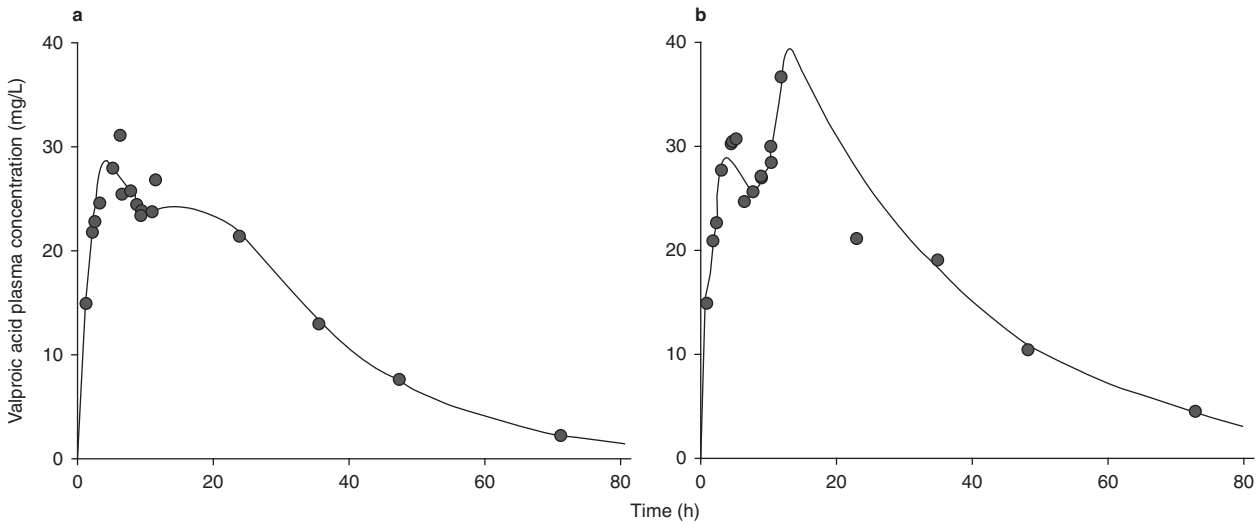

Fig. 2. Plasma concentration-time profiles for valproic acid in (**a**) subject 6 and (**b**) subject 9 following oral administration of a valproic acid 500 mg sustained-release tablet. The lines were obtained when the data were fitted to a double Weibull input function (reproduced from Bressolle et al.,[103] with permission of John Wiley & Sons, Inc. © 2006 Wiley-Liss, Inc., a Wiley Company).

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.[106,108,159]

2. Physiological Factors Affecting Oral 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.[61] Furthermore, secondary peaks could also result from local irritation and inflammation at injections sites that alter diffusion and hence the input rate of the drug from the site to the systemic circulation, as has been suggested for benzathine benzylpenicillin and procaine benzylpenicillin in piglets.[62]

2.1 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.[160] 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. 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, parent compounds. The overall effect of enterohepatic recirculation is extension of the mean residence time of drugs in the body.[160] 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.[160] 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.[160]

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, immunosuppressants, immunomodulators, 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 modelling

approaches – incorporating features such as a time-lag two-compartment model;[161] a two-compartment model with a body compartment and a gastrointestinal tract compartment;[162] a four-compartment model with a gastrointestinal, central, peripheral and gallbladder compartment;[163] 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[164] – have been used to characterize the pharmacokinetics of such drugs. Many of these pharmacokinetic models have exhibited good measures of fit and prediction for enterohepatic recycling. Thus the choice of model depends on the available input information to feed the model and the complexity of the study design required to accommodate the model.

Furthermore, for drugs with a sizable contribution of biliary secretion to their clearance, a proper understanding of the degree of enterohepatic recycling is essential because it may significantly affect the pharmacokinetic parameter estimation. Once the drug is extruded from the liver into the bile flow, it can be considered to be cleared from the systemic circulation. The reabsorption process effectively represents an additional dose of the drug into the system. Mathematical methods and study design considerations have been developed to deal with the needed correction of the dose in the estimation of the pharmacokinetic parameters.[165] Even when using non-compartmental methods, secondary peaks may complicate estimation of secondary pharmacokinetic parameters of the area under the concentration-time curve (AUC) and terminal phase half-life (as mentioned above). To optimally assess enterohepatic recycling, the rates of intestinal absorption, biliary excretion and biliary re-excretion are needed, coupled with determination of the major route of elimination, as well as a mass balance for the parent drug and metabolites.[160,166]

For example, one of the classical drugs that undergo enterohepatic recirculation is the opioid morphine. After oral administration of a 7.6 mg/kg morphine dose to the rat, a relatively rapid initial absorption phase with a t_{max} of around 40 minutes was achieved, followed by an exponential decrease in the concentration, having the appearance of a second peak (second t_{max}) at around 6 hours.[167] It has been established that morphine undergoes enterohepatic recirculation in both rats and dogs.[167,168] In the liver, morphine is mainly metabolized to glucuronides as morphine-6-glucuronide and morphine-3-glucuronide,[169] which are eliminated via bile, as observed in humans.[170] In the small intestine, morphine glucuronides are hydrolysed by bacteria liberating morphine while making it available for reabsorption, and the enterohepatic recirculation circle is complete. The release of the drug may occur spontaneously but can also be triggered by circadian variations in gallbladder emptying and by intake of food. Furthermore, because of the high first-pass metabolism, low bioavailability and short half-life of morphine, formulation efforts such as a controlled-release (CR) tablet of morphine have been pursued to decrease the dosing frequency and increase patient compliance.[171] The CR formulation prolonged the t_{max} and lowered the C_{max} with no differences in bioavailability, and high interindividual variability was observed regardless of the route of administration. However, enterohepatic recycling was still observed regardless of the delivery system of the CR formulation.[171]

Another drug that undergoes enterohepatic recycling is ezetimibe, which is a selective cholesterol absorption inhibitor. Not only the parent drug (ezetimibe) but also its phenolic glucuronide exhibit multiple peaks in their plasma concentration profiles, and this phenomenon has been correlated with enterohepatic recycling.[172] Ezetimibe undergoes extensive glucuronidation in the intestine to a phenolic glucuronide excreted in bile. It has been suggested that ezetimibe is reabsorbed in the ileum to be repeatedly delivered back to the lumen of the intestinal tract (the site of action) via enterohepatic recycling, enhancing its residence time and therapeutic effect.[173] Furthermore, Ezzet et al.[172] explored the effect of enterohepatic recycling on the pharmacokinetics by incorporating ezetimibe as a secondary input into the intestinal tract of a two-compartment population pharmacokinetic model. For this, the gallbladder emptying time was set as the meal time because food stimulated bile secretion, which was assumed to deliver a fraction of ezetimibe into the intestinal tract. The model adequately fitted the media concentrations of ezetimibe, allowing for good prediction of the pharmacokinetic parameters of a compound with enterohepatic recycling.[172]

Certain NSAIDs and analgesics undergo enterohepatic recycling. For instance, when the anti-inflammatory agent piroxicam (20 mg) was administered to individual subjects, multiple peaks were observed; however, variability was observed in the C_{max} and the minimum concentration (C_{min}). The multiple peaks were correlated with the gallbladder emptying time; because this varies between individuals, it was described as the factor accounting for the high interindividual variability. Furthermore, the enterohepatic recycling of piroxicam was correlated with its long plasma half-life (~45 hours).[174] Rofecoxib – a selective COX-2 inhibitor, which has been voluntarily removed from the market – exhibited the multiple peaking phenomenon in children with sickle cell haemoglobinopathy,[175] in healthy adults and cholecystectomy patients,[176]

and in rats.[177] In rats, it was determined that the double peaks in rofecoxib plasma concentration-time profiles were related to the biliary secretion of a glucuronidated metabolite that subsequently deconjugates in the gastrointestinal tract and is reabsorbed.[177] Similarly, enterohepatic recycling was observed in mice, rats and dogs after administration of the analgesic AY-30 068 (a tetrahydrocarbazole-1-acetic acid derivative), which was confirmed by comparing the serum concentration of the radiolabelled AY-30 068 in bile-cannulated and sham-operated rats. It was reported that the rapid decrease in serum radioactivity in the bile-cannulated rats indicated that enterohepatic recycling is responsible for the high concentrations in plasma and longer half-lives.[178] Furthermore, enterohepatic recycling in rats of other anti-inflammatory drugs such as ketoprofen,[179] isoxepac[180] and sulindac[181] accounts for the sustained concentrations and long half-lives of the active drugs.

The multiple peaking phenomenon was also observed after intravenous administration of etodolac in rats. In this study, it was observed that the *S*-etodolac (active enantiomer) plasma concentration profile exhibited secondary peaks, which were related to extensive enterohepatic recycling (figure 3). This was confirmed by a significant reduction in the AUC of *S*-etodolac but not *R*-etodolac, and the disappearance of secondary peaks in the *S*-etodolac plasma profile in bile duct-cannulated rats. Furthermore, the stereoselective differences between enantiomers were attributed to a greater extent to plasma protein binding of *R*-etodolac, and to preferential conjugation and biliary excretion of *S*-etodolac.[39] In humans, multiple peaking was not apparent, because the glucuroconjugated enantiomers were excreted in urine rather than in bile.[182] Multiple peaking was also observed after intravenous administration of buprenorphine 0.002 mg/kg to healthy subjects. A secondary peak was observed around 90 minutes post-dose,[183] and it was correlated with enterohepatic recycling based on evidence in rats[184] and in humans.[185,186]

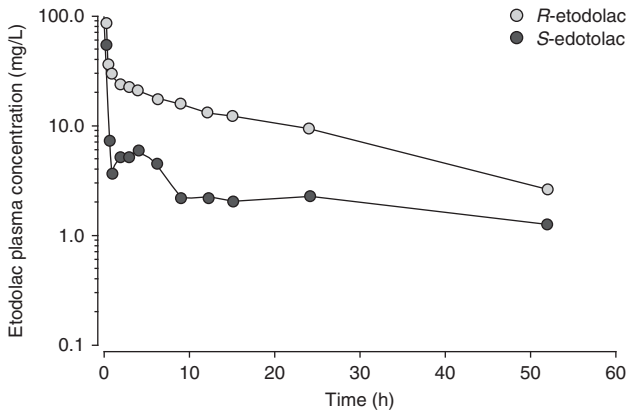

Fig. 3. Plasma concentration-time profiles of representative rats given etodolac enantiomers intravenously as 5 mg/kg of racemate, showing the enantiomer profiles of *R*-etodolac and *S*-etodolac (reproduced from Brocks and Jamali,[39] with permission).

Episteride, a selective and uncompetitive inhibitor of human steroid 5α-reductase isoform 2, was administered orally (a 5 mg tablet) or intravenously (a 4.5 mg infusion over 30 minutes) to healthy male subjects. Secondary peaks were observed at around 24 hours in the majority of subjects following administration via both routes.[38] Because secondary peaks were observed after administration via both routes, discontinuous absorption was not the mechanism underlying this phenomenon. It was concluded that enterohepatic recycling occurred because of the high degree of biliary excretion of the predominant metabolite in rats (acyl glucuronide).[187] Similarly, the phyto-estrogen 8-prenylnaringenin, a chiral synthetic derivative of the flavonoid naringenin with estrogenic activity, has demonstrated that it undergoes enterohepatic recycling. It was administered orally at different doses (50, 250 or 750 mg) to postmenopausal women, and rapid absorption and secondary peaks were observed, suggestive of enterohepatic recycling. It was observed that secondary maximal peaks occurred at 7–10 hours post-dose at all doses, with higher predominance in the higher-dose group. Furthermore, it was suggested that the first meal (4 hours post-dose) would have started the enterohepatic recycling process, because it allowed for gallbladder emptying, and that broader secondary peaks were observed in the higher-dose groups because primary absorption occurred at the same time as enterohepatic recycling (secondary absorption).[188]

Similar to 8-prenylnaringenin, a wide array of natural and synthetic phyto-bioactive compounds have been tested clinically, and multiple peaking phenomena due to enterohepatic recycling have been observed. For instance, glycyrrhizin – an active ingredient of licorice that is customarily used for treatment of inflammation, allergic disorders, and liver and gastrointestinal ailments – was observed to exhibit enterohepatic recycling in rats,[189] which was predicted to occur in humans, based on physiologically based pharmacokinetic modelling, using compartmental modelling with a gallbladder compartment.[190] Another example is the isoflavone derivative ipriflavone, which has been shown to inhibit bone resorption in osteoporosis animal models and was administered to healthy subjects and subjects with mild to moderate renal impairment (200 mg three times daily for 9 days). Secondary peaks were observed in the plasma profiles of the patient group but not in healthy subjects,[191] which was suggested to be due to enterohepatic recycling of the parent compound (ipriflavone) and the M1, M2 and M5 metabolites, as was observed in rats and

dogs.[192] The presence of secondary peaks in patients with renal impairment could be explained by impaired urinary excretion in these patients, causing the biliary pathway to become more important and significant for elimination.[191] Also, the isoflavone genistein exhibited enterohepatic recycling after single-dose administration of a standardized soy extract capsule containing 64.12 mg of total isoflavones (genistin 38.42 mg, genistein 7.73 mg, daidzin 15.09 mg and daidzein 2.88 mg) to healthy women. However, only genistein plasma concentrations were measured, and secondary peaks were observed in 30% of the patients at 4–6 hours.[193] Isoflavones (such as genistein) undergo extensive phase II glucuronidation and sulphation. Once they reach the lower intestine, they are cleaved by intestinal microflora, allowing them to be reabsorbed and leading to secondary peaks, as has been observed in other similar clinical studies.[194-196] Other classes of bioactive compounds that demonstrate enterohepatic recycling include dithiolethiones, indoles and isothiocyanates such as the compounds found in cruciferous vegetables. A synthetic dithiolethione oltipraz that has been identified to have chemoprotective effects was orally administered (20 mg) to fasted healthy subjects. Secondary peaks were observed for oltipraz and its inactive metabolite M3 (pyrrolopyrazine rearrangement) in numerous patients.[197] It was observed that the secondary peaks of the parent compound (oltipraz) were due to its poor solubility in water and its erratic and pulsatile absorption. M13 (the glucuronidated conjugate of M3)[198] is cleaved by the intestinal microflora to M3, causing enterohepatic recycling of M3 and explaining its secondary peaks in plasma concentration-time profiles. However, this process does not account for enterohepatic recycling of oltipraz, because the necessary chemical rearrangement with an intermediate allows inter-conversion from the M3 metabolite to the parent, oltipraz.[197] Thus secondary peaks of oltipraz are due to erratic and pulsatile absorption in fasted subjects, which was correlated with an observed food effect (disappearance of secondary peaks in fed subjects) in a phase I trial.[199] Enterohepatic recycling has also been reported in a number of flavonoids and gingko flavonoids.[200]

α-Methyldopa was observed to exhibit enterohepatic recycling in dogs after intra-arterial and oral administration, where secondary peaks were observed at around 1 hour and 4 hours, respectively. Enterohepatic recycling was concluded after intra-arterial administration because the time of the secondary peak corresponded to the time of feeding of the dogs, allowing for gallbladder bile release facilitating a secondary absorption process. After oral administration of α-methyldopa to dogs, continued absorption and an extended half-life were observed in the plasma profile of several dogs despite the short t_{max}.[201] Similar results were observed in humans, where it was concluded that enterohepatic recycling contributed to the prolonged absorption of α-methyldopa.[202] Similarly, enterohepatic recycling was observed after oral administration of the anti-hypertensive ripisartan (UP 2696) [a single oral dose of 160 mg as a capsule] to healthy subjects. It was observed that at least two secondary peaks were present in the plasma profile, indicating the possibility of two cycles of recirculation, which were model fitted to a compartmental model with a gallbladder and peripheral compartment.[203] Furthermore, it has been proposed that the secondary peaks observed after intravenous and intramuscular administration of the anxiolytic benzodiazepine clonazepam were due to enterohepatic recycling,[204] because the glucuronide of clonazepam may be deconjugated by intestinal flora and reabsorbed from the intestine in the form of the parent drug.[205,206] Also, clonazepam exhibited a longer half-life (~39 hours) than other benzodiazepines such as alprazolam and lorazepam, which had half-lives of 9 hours and 11 hours, respectively.[207]

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.[208] 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 intrahepatic 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 coadministration of orally absorbent or other drugs.[160]

2.2 Gastric Emptying and Intestinal Transit Time

Factors affecting the rate and extent of drug absorption after oral administration may contribute to the multiple peaking phenomenon. 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 k_a of the drug. Gastric motility is known to be regulated by the migrating motor complex under fasted conditions.[78,209,210] 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.[78,211] 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.[212] Gastric emptying can also have different patterns.[77] Type I has a monoexponential 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 monoexponential 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 monoexponential emptying patterns, which are interrupted by a period of no gastric emptying.

The histamine H_2-receptor antagonist ranitidine also demonstrates multiple peaking in pre-clinical and clinical studies.[63,64] 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.[65] 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 μg/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.[66]

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 (PEG 400) 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.[68,213-215] 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.[67] 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 coadministration 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 was 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[68] and disappearance of secondary multiple peaking phenomena.[213-215]

Solid oral formulations of drug excipients, including carbohydrates and polyethylene glycol, are commonplace. The incorporation of excipients that may not be simply inert in a formulation has the *ab initio* potential to affect the intestinal transit of a dosage form.[216] For instance, the use of mannitol as an excipient in a formulation of cimetidine led to significantly reduced bioavailability of this drug, which is primarily absorbed from the small intestine, compared with the same drug formulated with sucrose. The small intestinal transit times were significantly shortened after administration of the mannitol solution containing cimetidine and the tablet, with the transit time of the mannitol solution containing cimetidine being 23% of the transit time of the sucrose solution containing cimetidine.[69] Curiously, the sucrose formulation exhibited a double peaking phenomenon to a greater degree than the mannitol preparations, which may suggest that the residence time available for absorption was affected by the excipient. 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.[70]

Double peaks in the plasma concentration-time curve frequently occur after administration of cimetidine as a liquid or tablet in the fasted state.[71-74] However, double peaking does not occur if cimetidine is administered intravenously or concomitantly with food.[212] The multiple peaking of cimetidine has been hypothesized to mechanistically occur for several reasons such as enterohepatic recycling, site-specific absorption and gastric emptying. Although enterohepatic recycling has been ruled out because of the low amounts present in bile,[212,217-220] gastric emptying[212] and an adequate pH[110] appear to be of particular mechanistic interest and appear to increase the variability of double peaking seen in concentration-time profiles of cimetidine.

Thus it is evident that the optimum pH,[110] feeding/fasting[109] and gastric emptying rates in different phases[212] – as well as any other factors affecting gastric motility – all play an integral role in observation and understanding of multiple peaking in pharmacokinetic profiles of cimetidine.[76]

Another example is carbon tetrachloride (CCl_4), which was orally administered with either oil or various aqueous dosage vehicles to determine the pharmacokinetic consequences in terms of the incidence of multiple peaking phenomenon.[81] In the dosage forms made with aqueous vehicles, no secondary peaks were observed. However, formulations made with Mazola® corn oil produced observable secondary peaks. It was apparent in this study that the corn oil substantially delayed but did not diminish the absorption of CCl_4 in the gastrointestinal tract. It was concluded that the k_a was much lower in the oil formulation than in the aqueous formulation. In this study, it was evident that corn oil affected the intragastric motility and gastric emptying, as could be clearly seen from the delay in absorption. As suggested by the plasma concentration-time curve profile, the CCl_4 dose was broken up into absorbable fractions enclosed in lipid globules, resulting in the early initial and subsequent multiple peaks.[81]

For most narcotic analgesics, gastric emptying patterns follow either a type I profile (a monoexponential gastric emptying pattern upon ingestion), a type II profile (a biphasic gastric emptying pattern where a fraction of the total dose is rapidly emptied followed by a monoexponential decrease of the remaining fraction, or a type III profile (a biphasic gastric emptying pattern with two intervals of monoexponential emptying interrupted by a period with no emptying).[77] For the commonly used pain reliever paracetamol (acetaminophen), it has been suggested that gastric emptying is rate limiting in the absorption of the drug. Variability in stomach emptying rates and intestinal blood flow rates over the course of the entire absorption process after a single dose would likely result in variable rates of appearance of drug concentrations in plasma. For instance, paracetamol (20 mg/kg) in an aqueous solution was coadministered with a non-absorbable isotopic marker to human subjects ($n = 8$).[77] When administered with the anticholinergic propantheline, which delays gastric emptying, the absorption of paracetamol was reduced (figure 4). Conversely, the absorption of paracetamol was increased by the gastrointestinal motility modifier metoclopramide, which is known to stimulate gastric emptying by increasing gastric peristalsis and relaxing the pyloric sphincter, thus shortening the overall gastric emptying rate. There was no change in the extent of absorption, as measured by urinary excretion.[221]

An interesting double peaking phenomenon has been reported in the pharmacokinetics of the benzodiazepine alprazolam and

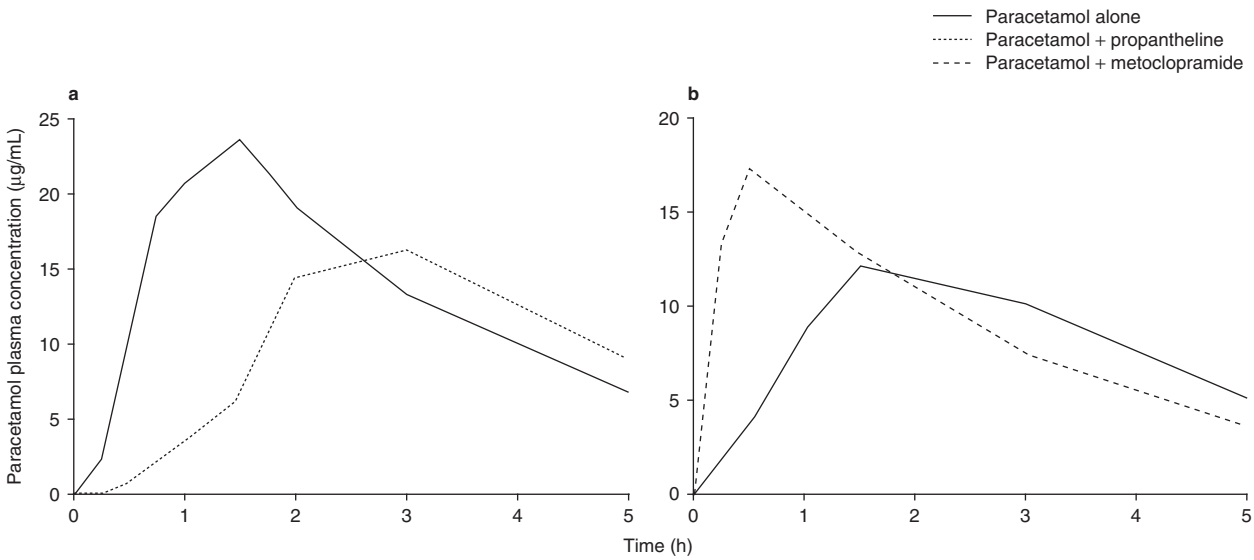

Fig. 4. (**a**) Inhibitory effect of propantheline on paracetamol (acetaminophen) absorption in six patients. (**b**) Increased rate of paracetamol absorption after administration of metoclopramide in five healthy subjects (reproduced from Nimmo et al.,[221] with permission from the BMJ Publishing Group).

its metabolites after oral administration in rats. Alprazolam is an anxiolytic agent, which demonstrates multiple peaking in serum concentration data as well as secondary peaks for its metabolites. It is hypothesized that this multiple peaking is due to a reduction in gastric motility caused by the muscle relaxant effects of alprazolam, which leads to biphasic gastric emptying and hence a local maximum in concentration-time profiles.[78,79] Alprazolam has also been studied when coadministered with theophylline to rats.[78] In this study, it became apparent that the double peaking of the plasma concentration-time profiles was dependent on changes in the elimination rate of the drug. The k_a and the rate of elimination (k_e) are of particular importance because the decline in the plasma concentration-time profile is dependent on the lower of the two rate constants. In this study, the smaller or slower value was the k_e, which is likely to account for the double peaking phenomenon in plasma concentration-time profiles. A similar oral pharmacokinetic profile was observed for epinastine, a non-sedating H_1-receptor antagonist.[80]

A double peaking phenomenon can also be observed with levodopa, which is used to manage Parkinson's disease and dopa-responsive dystonia. In one study, levodopa was coadministered with paracetamol and ^{99}Tc-DTPA (diethyl triamine pentaacetic acid). Seventy-five percent of patients presented double peaking in their plasma concentration-time profiles.[82] A plausible explanation for the appearance of double peaking is that levodopa is rapidly absorbed in the small intestine, with its absorption being dependent on the gastric emptying rate. Similar gastric emptying effects can be observed in elderly patients and young subjects because of the absorption profile of levodopa; however, the actual mechanisms involved in the resulting secondary peaks in concentration-time profiles are not entirely understood but may account for the pharmacodynamic variability of this agent in Parkinson's therapy.

The kinetics of absorption of piretanide, a loop diuretic, in solution was assessed in humans after instillation into the stomach via a gastroscope, direct administration to the duodenum, and instillation into the ascending colon with and without intravenous coadministration of hyoscine-*N*-butylbromide (HNB), an agent that immobilizes the stomach,[83] in order to assess if piretanide is absorbed directly from the stomach or is rapidly released into the intestine. It was observed that piretanide is directly absorbed from the stomach, based on the increase in the rate of absorption after the stomach-immobilizing effect of HNB disappeared. Piretanide exhibits a double peaking phenomenon in serum concentrations with and without coadministration of HNB, where it can be observed that coadministration of HNB enhances the initial phase of absorption by inhibiting the spontaneous emptying of the stomach, indicating direct absorption of piretanide from the stomach.[83]

Danazol is a derivative of the synthetic steroid ethisterone, which is a modified testosterone used in the treatment of endometriosis. After oral administration, danazol was found to produce a double peaking phenomenon, whereas only single peaks were present after intra-intestinal administration to the proximal jejunum or the proximal ileum. The multiple peaking may have been related to a combination of inhibition of gastric

emptying and regulated absorption due to the presence of lipid monoglyceride in the emulsifying formulation; however, as danazol solubility is dependent on bile salt solubilization within the upper intestine, the secondary peaks were characteristically higher than the initial peaks. Furthermore, it was observed that danazol absorption is dependent on bile salt solubilization, with similar C_{max} values being attained after jejunal or oral administration, and double peaks were present regardless of administration of food.[85,86,222] However, in the case of penicillamine, secondary peaks were only observed in fasted healthy subjects, while single peaks were observed in fed subjects.[87] Enterohepatic recycling was ruled out as an explanation for this multiple peaking phenomenon, as double peaks should be prevalent regardless of the route of administration, in view of the secondary peaks observed after oral administration of penicillamine to dogs and humans, while single peaks were observed after intravenous administration to a female mongrel dog.[88] These results indicated that the multiple peaking phenomenon must be related to the route of administration (oral) of penicillamine under fasting conditions, which has been attributed to the gastrointestinal transit time or an 'absorption window' effect due to a process that is interrupted by the presence of food.

The selective peptidoleukotriene antagonist pranlukast, used in the treatment of asthma, was studied in healthy subjects. Pranlukast was orally administered to fed subjects for 7 days in doses of 112.5–675 mg. Blood samples were obtained at predetermined intervals. The plasma concentration-time profiles after all doses presented with secondary peaks, which were still evident after accumulation on day 8. It was observed that the secondary peaks after multiple dosing were prolonged and greater in magnitude than the secondary peaks observed after single dosing. It was also observed that there was evidence of an absorption lag-time (~2 hours). It was proposed that the pharmacokinetics of pranlukast are influenced by the diurnal variations in absorption (chronopharmacokinetics), based on the observed differences between plasma concentrations after morning and evening dosing, which were actually found to be pharmacologically advantageous, based on the diurnal patterns of asthma attacks.[89] Later, it was confirmed that there was a diurnal variation in absorption, with higher AUC values of the drug being present after evening dosing and a longer lag-time for absorption being visible after evening dosing. The diurnal variation in pranlukast absorption, and possibly the secondary peaking, were attributed to regiospecific intestinal absorption[223] (section 2.3). Pranlukast serves as an example wherein viewing overall mean plasma concentration-time curves, the multiple peaking phenomenon can be shrouded; when individual profiles are used, double peaking is readily seen in all subjects given the drug.

The effects of migraines on gastric emptying, gastrointestinal stasis and alterations in gastrointestinal motility are well documented in the literature.[224] For instance, a significant delay in gastric emptying induced by the antimigraine agent sumatriptan (a serotonin 5-$HT_{1B/D}$ receptor agonist) and avitriptan (a 5-HT_1-like agonist) has been reported, and this is also likely to occur with second-generation triptans (i.e. rizatriptan, zolmitriptan, naratriptan, eletriptan, almotriptan and frovatriptan).[225] Sumatriptan has displayed multiple peaks in plasma oral and nasal concentration-time profiles.[91,92] Furthermore, some patients with an unsatisfactory response to oral sumatriptan appear to have a slower rate and a lower extent of absorption during the first 2 hours post-dose, compared with patients with a satisfactory response who have significantly faster absorption and higher earlier plasma concentrations.[226] Similarly, saquinavir, a viral protease inhibitor of HIV-1, exhibited secondary peaks that were correlated with the gastrocolonic response because of an increase in drug dissolution upon food consumption, coupled with an increase in gastric motility and secretions.[90]

Finally, the relationship between gastric motor activity, gastric emptying of caffeine pellets and their absorption was investigated in the fed state in healthy humans by monitoring antral motility and plasma concentrations, and a pharmacokinetic model for gastric emptying-dependent absorption was developed.[227] Gastric emptying appeared to occur following a 'quiescent' phase of 1–2 hours. Fifty percent of the dose was emptied in the initial 'active' phase and 90% within 3.5 hours following dosing, and there were one or more 'quiescent' phases when no emptying occurred. Double peaking phenomena in absorption rates appear to relate to gastric motor activity and gastric emptying. An alternative hypothesis has suggested that a 'Magenstrasse' or 'stomach highway' exists, with antral contractile waves and fundic contractions working in unison. Some drug particles released in 'Magenstrasse' are more rapidly emptied into the small intestine, while 'non-Magenstrasse' particles would be gradually emptied from the stomach, giving rise to double peaking phenomena with certain drugs.[228]

It was observed that gastric emptying and the intestinal transit time play a critical role in the absorption of a variety of drugs. It has to be noted that feeding conditions are a key determinant, as they alter these two parameters. Furthermore, coadministration of co-solvents, solubilizers and/or motility modifiers can significantly change the absorption and the onset of drugs in the gastrointestinal tract, which may ultimately affect the bioavailability of the drugs.

2.3 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 intersubject variability in bioavailability.[64,118,229-232] It has been proposed that because of this, there has been a marked discrepancy between research groups in reporting the secondary phenomena of ranitidine.[64,118] For instance, single peaks in the plasma concentration profiles were observed in healthy subjects, patients with liver cirrhosis[233] and patients with renal failure,[234,235] 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.[109] 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 (figure 5). 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.[109] 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.[109] 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.[110] The absorption kinetics of ranitidine from the gastrointestinal tract were altered in the bile flow-intact rats,[111] 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.

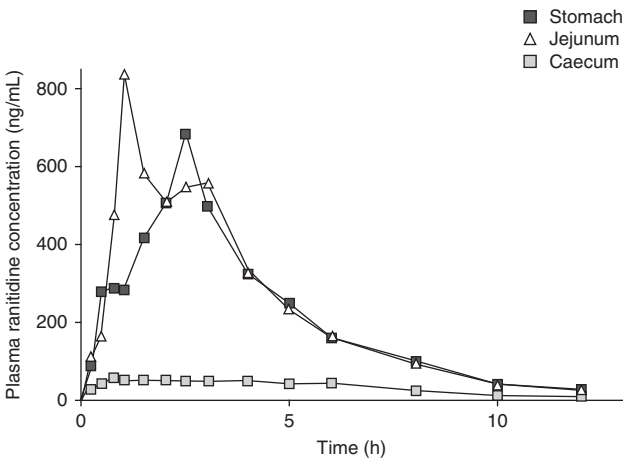

Fig. 5. Typical subject's plasma ranitidine concentration-time profiles following bolus administration of ranitidine 150 mg into the stomach, jejunum and caecum. Note the double concentration peaks after jejunal administration (reproduced from Williams et al.,[109] with kind permission from Springer Science + Business Media).

Gramatte et al.[119] 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.[119] 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.[119] In an analogous study, glibenclamide (glyburide) was administered to healthy subjects and patients at different sites in the gastrointestinal tract (the stomach, duodenum or colon) under visual control.[120] The observed concentration-time profiles were related to the site of administration, the differences in rates of absorption and anatomical differences based on their biological purposes.[120]

Not only ranitidine, but also cimetidine has demonstrated multiple peaking in its human plasma concentration-time profiles.[113,114,121] However, these profiles were variable with co-ingestion of food and antacids. Mummaneni and Dressman[113]

investigated cimetidine and ranitidine in rats, and determined that the uptake of these antagonists was linear over concentration ranges of 0.0005–40 mmol/L and 0.0005–5 mmol/L, respectively. It was determined that absorption occurred as a passive process and that there were site-specific differences in the absorption of these two antagonists, which competition studies found were mutually independent of one another and famotidine. The sites of absorption, ranked from highest to lowest, were the ileum, duodenum, jejunum and colon.[113] The serum concentrations of cimetidine and ranitidine have been well described using a discontinuous oral absorption model[115,116] and a compartmental model with fractional absorption from the absorption compartment for ranitidine.[118] Both approaches exhibited good concentration simulations and agreement with pharmacokinetic parameters in the literature.

Another possible example of a drug with site-specific absorption was demonstrated by a study of veralipride administered orally to healthy subjects. The plasma concentration-time profiles exhibited double peaks when administered as a solution but not when administered intravenously or in a capsule, and these findings were attributed to two different mechanisms.[123] Rapid absorption appeared to occur in the proximal part of the gastrointestinal tract, followed by a second absorption phase in more distal regions.[123,124] After administration of multiple doses of veralipride, site-specific absorption was suggested to be the major mechanism responsible for the multiple peaking phenomenon, with the end of the stomach or the upper part of the small intestine being the plausible major site of absorption.[124]

Absorption of veralipride in the small intestine was evaluated using a new drug delivery telemetric shuttle, because the presence of multiple peaking suggested a secondary absorption site.[125] The telemetric shuttle was employed to co-administer both veralipride and veralipride D_3 in order to study multiple sites of absorption in the small intestine. The telemetric capsule delivered the drug in solution into the small intestine at predetermined time intervals after oral administration at an anatomical location between the jejunum and the ileum. Based on this new drug delivery system, it was suggested that the secondary absorption site may reside within the small intestine (figure 6). The intestinal transit and residence time at this site, coupled with the k_a, may be the main factors responsible for the appearance of multiple peaking in the absorption of this drug. Importantly, a telemetric capsule appears to be a useful adjunctive method that facilitates site-specific administration of drug and is a non-invasive means of investigating sites of drug absorption in the gastrointestinal tract.[125] Subsequently, veralipride plasma concentration-time profiles have been simulated using compartmental modelling with a double site of

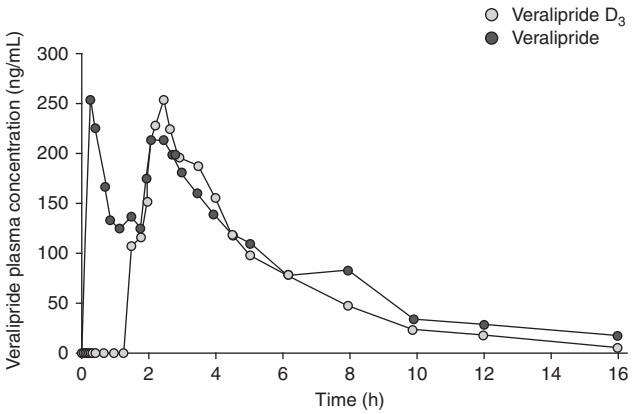

Fig. 6. Mean plasma concentration-time profile of veralipride and veralipride D_3 from five subjects. Delivery of veralipride D_3 was done 1.5 h after time zero (reproduced from Staveris et al.,[125] with permission).

absorption, to characterize the absorption window.[126] This model was further modified and generalized to more than two successive absorption sites, and data were successfully simulated to describe a hypothetical three-site multiple peaking model.[127] These models have evolved to account for non-absorptive sites and simultaneous absorption.[116] Discontinuous absorption models have been developed with two absorption sites and various non-absorbing sites.[115,236] These models can be a useful tool in characterizing the disposition of drugs exhibiting two absorption peaks following oral administration.

Moreover, 1-(2-fluoro-5-methyl-β-L-arabinofuranosyl)uracil (L-FMAU) has activity against hepatitis B virus and Epstein-Barr virus. L-FMAU exhibited double peaks in its plasma concentration-time profiles after oral administration to rats, which indicated discontinuous oral absorption. Enterohepatic recycling was discounted as being the mechanism responsible for secondary peaks, as they were only seen after oral administration but not after intravenous administration. The pattern of L-FMAU absorption incorporated two separate absorption processes following oral administration of the nucleoside in rats, with significantly different absorption rate constants. A discontinuous oral absorption model incorporating two separate absorption processes was successfully employed to describe the absorption profile of L-FMAU, which was observed to occur in two distinct phases or sites.[128] Variable absorption rates in different gastrointestinal tract regions have also been observed for the dopamine receptor antagonist biriperone (centbutindole) after intravenous (2 mg/kg) and oral administration (4 mg/kg) to rats. Both biriperone and its hydroxy metabolite displayed multiple peaks in their serum concentration-time profiles. It is possible that PEG 600 (a co-solvent employed in the oral administration arm to improve solubility) may have altered the absorption of the parent compound and the

metabolite, thereby suggesting that solubility of the parent compound played a role in the dissolution and absorption of biriperone. The possibility of site-specific absorption in the gastrointestinal tract was also suggested, as well as storage and release from a post-absorptive depot site, with variable absorption rates. It is unlikely that enterohepatic recycling was the mechanism responsible for multiple peaking, as multiple peaks were not observed after intravenous administration.[129]

Dichloroacetate (DCA) is a drinking water disinfectant by-product commonly found in municipal water supplies. Its disposition and absorption were studied in glutathione transferase zeta 1 (GSTζ)-depleted male F344 rats and in naïve rats after both intravenous and oral administration.[135,136] It was observed that DCA resulted in secondary peaks in plasma concentration-time profiles. However, it is worthy of note that these secondary peaks occurred temporally long after the initial absorption phase of the drug. Further studies indicated a dose-related relationship between the appearance of those secondary peaks and the intensity of those peaks. Enterohepatic recirculation was initially hypothesized to be the cause of the peaks; although the low amount of biliary excretion of DCA[137] and the absence of secondary peaks after intravenous administration[136] ruled out enterohepatic recirculation as the cause. Gastric emptying was not felt to be responsible for the multiple peaks. The authors speculated that the multiple peaking was a consequence of region-dependent absorption. DCA is rapidly absorbed from the stomach and upper regions of the small intestine. This is followed by phases of reduced absorption in the ileum and then increased absorption in the colorectal region, with the absorption increase in the lower gastrointestinal tract leading to a secondary plasma peak.[135]

Cimetropium bromide is a quaternary ammonium antispasmodic drug, which was assessed after intravenous and oral administration to healthy subjects.[138] The concentration-time profile showed multiple peaking, which was attributed to two distinct absorption phases. The absorption was poor and discontinuous, and abruptly ended during the second phase. It is thought that the low concentrations that are absorbed are able to still produce therapeutic effects, and that there are accumulation sites along the gastrointestinal tract, which may lead to multiple peaks that can account for the interesting concentration-time profile of cimetropium bromide.[138]

2.4 Gastric Secretion-Enteral Reabsorption

After intravenous administration of phenoperidine as an adjuvant during general anaesthesia, a small increase in the plasma concentration was observed 40–60 minutes post-dose. It was suggested that phenoperidine may be eliminated gastrically and subsequently reabsorbed from the gastrointestinal tract and, as such, its reabsorption and disposition may be related to the pH gradient between plasma (pH 7.4) and the stomach (pH 2.3).[95,96] In a study with healthy subjects, three sets of experiments were conducted.[97] In the first experiment, subjects were given phenoperidine intravenously. In the second experiment, subjects were orally administered the antacid Andursil® before and after intravenous phenoperidine. In the third experiment, subjects were orally administered phenoperidine dissolved in water. The purpose of these experiments was to determine if there were effects of an antacid on phenoperidine disposition. In experiment one, secondary peaks were observed in the phenoperidine plasma concentration-time profiles between 20 and 50 minutes. When Andursil® was administered with phenoperidine, a dramatic change in the plasma concentration-time profiles was observed, with a reduction or disappearance of the secondary peaks. The bioavailability of the orally administered phenoperidine was significantly decreased to less than 15% and below the lower limit of detection after 60 minutes. Collectively, these results indicate that phenoperidine is eliminated via the enteric system and reabsorbed in the small intestine. Under the influence of the antacid, it is evident that the typical gastric elimination of phenoperidine is slowed, hence the reduction or elimination of the secondary peaks.[97]

Studies of fentanyl have also demonstrated secondary peaks in fentanyl plasma concentrations.[98-100] Sixteen percent of the dose was contained within the stomach 10 minutes after administration, which suggested that entero-systemic recirculation might lead to the observed secondary peaks.[101] Excretion of both alfentanil and fentanyl into the stomach of rats has been shown.[9] Afentanil is known to have a smaller volume of distribution and lower total clearance, a shorter plasma half-life and greater plasma protein binding than fentanyl.[102] Combination of fentanyl with prophylactic cimetidine was shown to reduce the secondary peaks of fentanyl that are seen when fentanyl is administered alone.[237] The concavity in the serum concentration-time curve in subjects at 10–60 minutes has been attributed to enteric recirculation or redistribution from tissues.[100]

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. A study investigated the influence of the release rate of talinolol and P-glycoprotein-mediated efflux and bioavailability in humans.[130] Talinolol is

a β_1-adrenoreceptor antagonist used in the treatment of arterial hypertension, coronary heart disease and tachyarrhythmia. This drug has a broad therapeutic range, low plasma protein binding, minor enterohepatic recirculation[130] and very low metabolic clearance.[130,238] In this study, fasting healthy subjects were orally administered either a 100 mg IR tablet or a CR tablet and were put on a strict diet for the duration of the study. A washout period of 7 days was allotted between treatment periods. *In vitro* studies determined that the solubility of the IR tablet of basic talinolol is pH dependent. The dose is completely dissolved in less than 15 minutes in the low pH of the stomach, whereas at pH 6.8, the dissolution is slower (BCS class II). The release of CR talinolol was sustained without being affected by the pH. This multiple peaking phenomenon was observed in plasma concentration-time curves after oral administration.[130-132] Enterohepatic recirculation was ruled out as the cause of the double peaks, because of the low biliary elimination after an intravenous dose of talinolol.[133] *In vitro* tests with surfactants and talinolol demonstrated a reduction in the dissolution rate, which led the researchers to believe that bile salt, cholesterol, phospholipid, steroid and small intestinal peptide interactions in the proximal part of the small intestine are contributing factors to the decreased bioavailability and double peaking phenomenon. Furthermore, it has been observed that talinolol in healthy subjects exhibits incomplete absorption due to the site-dependent absorption rate in the small intestine, with an inversely proportional relationship between the absorption rate of talinolol and the distance between the stomach and the absorption site in the small intestine.[239] Dissolution of both IR and CR formulations of talinolol was determined to be pH dependent, permitting regiospecific absorption within different parts of the small intestine. P-glycoprotein distribution has also been suggested to be a major contributing factor to the site-specific absorption of talinolol.[130,240] Understandably, it is important to consider drug transporter localization, including substrates and inhibitors, in the double peaking phenomenon.

2.5 Anaesthesia and Surgery

Anaesthesia and surgery may influence a variety of physiological factors, including cardiac output; local, regional and peripheral blood flow; and gastrointestinal, renal and hepatic function – all of which may affect the pharmacokinetic disposition of drugs. It is therefore not surprising that secondary or multiple peaks in plasma concentration-time profiles can ensue.

For instance, some orthopaedic surgery is performed with a pneumatic tourniquet to ensure a bloodless operative area. When drugs are administered before inflation of the tourniquet, appreciable amounts of the drug can be sequestered in tissues and subsequently released when the tourniquet is eventually deflated, leading to multiple peaking in plasma concentration-time curves.[142,241] This phenomenon was first demonstrated with fentanyl and midazolam with and without release of a thigh tourniquet.[1,99,142] Cefazolin administration before tourniquet administration resulted in a secondary increase in plasma concentrations upon deflation of the tourniquet in 30% of patients.[143] This has also been shown to occur following vecuronium bromide administration.[144] Following cross-clamp release during aortic surgery, secondary peaks in plasma sufentanil concentrations were evident 3–18 hours post-dose.[145] These peaks appeared to be coincident with vascular clamp removal or transfer of patients to the intensive care unit, where spontaneous movement was likely. Other investigators found secondary peaks with fentanyl and midazolam at various times (1–120 minutes) after tourniquet release.[142]

Secondary peaks in the fentanyl concentration-time profiles tend to temporally occur upon recovery from anaesthesia,[2,3,5,98] along with subsequent spontaneous motor activity, suggesting elution from tissue by exercise-induced increases in blood flow, although this may also occur during surgery itself[2] and in non-anaesthetized subjects.[1,4,100] Furthermore, the effect of age on the pharmacokinetics of fentanyl has been assessed in two age groups (one comprising individuals younger than 50 years and the other comprising individuals older than 60 years). It was determined that fentanyl would be clinically effective for longer periods in patients older than 60 years because it had a significantly longer half-life and decreased clearance in this age group.[2]

Most anaesthetics are associated with a large volume of distribution and accumulation in tissues and slow redistribution from muscle and fat back to the systemic circulation. It has been postulated that drug release from muscles secondary to increased patient movement and enhanced muscle blood flow could contribute to increased plasma concentrations during anaesthesia recovery. This has been modelled using physiological pharmacokinetic model simulations for fentanyl and alfentanil, in which changes in body composition, blood flow and cardiac output play a critical role in the prediction of plasma concentrations of both drugs.[6] Similarly, an infusion model using different consecutive infusion rates has been successfully applied to simulate plasma concentrations of fentanyl after an intravenous bolus.[242] Secondary peaks in drug plasma concentrations appear to occur at a parallel chronology to passive or active limb and increase in muscle mobility. Sufentanil plasma concentrations following lower-extremity tourniquet release demonstrated a 15% elevation in plasma concentrations,

resulting in a secondary peak, with 45% of patients exhibiting such peaks.[241]

Furthermore, a study of alfentanil pharmacokinetics in patients undergoing abdominal aortic reconstruction surgery demonstrated secondary peaks 7–16 hours after administration. Aortic cross-clamping and unclamping, as well as infusion of large volumes of crystalloid, are commonplace. Haemodynamic changes could alter drug distribution and elimination; furthermore, haemodilution increased the unbound fraction and drug distribution.[7] One patient had an 8-fold increase in alfentanil concentrations at the time of aortic unclamping. Thus it has been proposed that release of the drug from skeletal muscle ensues during emergence from anaesthesia with an increase in mobility and muscle blood flow. Once again, temporally, secondary peaks appear to parallel reperfusion and recovery and could represent mobilization of tissue deposits of drugs through increased perfusion.[8]

The effect of a pneumatic tourniquet on sufentanil pharmacokinetics and multiple peaking has been examined.[12] Sufentanil was either stopped when the tourniquet was released or 15 minutes after tourniquet release, or sufentanil was started after tourniquet inflation. Exsanguination and inflation of the pneumatic tourniquet had no significant effect on pharmacokinetic disposition. Sufentanil demonstrated secondary peaks 30–60 minutes after tourniquet deflation, which appeared to temporally correlate with patient mobilization. Furthermore, McQuay et al.[98] administered fentanyl in gynaecological surgery and observed secondary peaks. This was attributed to increased muscle tone and voluntary movement associated with the return to consciousness of the patient.

In one study, the intravenous sedative propofol (Diprivan®) exhibited secondary peaks in its drug concentration-time profile after administration of 2.5 mg/kg for induction of anaesthesia, which was maintained using 1.5% halothane and 67% nitrous oxide in oxygen.[13] The presence of the secondary peaks was highly associated with the time of recovery from anaesthesia, specifically when related to the recorded times of eye opening and correct recall of date of birth. It was proposed that local changes in propofol concentrations adjacent to the sample site (drug returning from the arm muscle to the blood compartment) or whole-body changes in blood flow may contribute to the secondary peaks. An extrahepatic component of the metabolism of the drug was proposed because of the high clearance (higher than hepatic blood flow) of propofol. The extrahepatic component that was related to occurrence of the secondary peaks could include the lungs, gastrointestinal tract and kidney.[13]

Several other drugs, including thiopental sodium[14,15] and diazepam,[16] also appear to exhibit secondary peaks during the recovery period after anaesthesia. In the case of thiopental sodium, blood samples were collected from pregnant women at the time of caesarean section. A small, transient, 5-minute increase in the plasma concentration of thiopental sodium was observed at the time of delivery of the child. The precise mechanism underlying these secondary peaks is not known. Nevertheless, fluctuations in pressure on blood vessels is known to occur during removal of the fetus at delivery, and disruption of normal blood flow to the uterine area may have been responsible.[14,15] For diazepam, which was administered at parturition, some women exhibited uneventful puerperia (group I) or underwent postnatal tubal ligation (group II). In both groups, small increases in diazepam plasma and blood concentrations were evident following delivery. However, in the case of group II, a second increase in the plasma concentration was evident following the tubal ligation procedure. For group I, it was proposed that the stress-induced physiological changes during labour might have resulted in an accelerated decline in plasma concentrations of diazepam prior to delivery, and that termination of the stress at delivery resulted in a redistribution of the drug from the peripheral tissues, thereby causing the secondary peaks. For group II, it was proposed that on top of the physiological changes during delivery, posture and exercise contributed to the recovery of certain parameters such as cardiac output. Patients in group II had their mobility restricted because they were scheduled to undergo tubal ligation 24–48 hours postpartum, in contrast to patients in group I, who became ambulatory after delivery.[16]

3. Conclusions

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. These mechanisms are often multifactorial and include – but are not limited to – solubility-limited absorption, modified-release formulations, complexation, enterohepatic recycling, gastric emptying and variability in the intestinal transit time, site-specific absorption, gastric secretion-enteral reabsorption, and alterations from anaesthesia and surgery. A review of the literature indicates that the most common source of multiple peaking is biliary secretion of the xenobiotic followed by intestinal reabsorption of the xenobiotic, termed 'enterohepatic recycling'. In this new millennium – and with the advent of new delivery systems, formulations, biomaterials and technologies, and a plethora of exciting therapeutic approaches – the occurrence of multiple

peaking phenomena in pharmacokinetic profiles, with additional pharmacokinetic mechanistic explanations, will undoubtedly continue to be observed and reported.

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