

Oral Bioavailability in Special Populations

Abstract

The extent of absorption following oral administration of drugs may vary among patients. There are several factors that can contribute to this variability including age, gender, disease state, genetic variability, and body weight. The impact of these factors on the extent of absorption is not the same. As body exposure to the administered dose will potentially affect the therapeutic effect of the drug, it is important to understand the impact of each of these factors on the extent of absorption to be able to adjust the dosing regimen and achieve a therapeutic outcome.

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Introduction

To achieve a desired systemic effect, drug molecules have to be absorbed to the systemic circulation after extra vascular administration. The fraction of the administered dose that reaches intact to the systemic circulation is called "bioavailability, F". Therefore, drug's bioavailability is a measure of the extent of

absorption to the systemic circulation. Several drug-, formulation-, and patient-related factors can alter the extent of absorption (Table 1). A comprehensive understanding these factors is a key to improve drug's bioavailability, and hence its therapeutic effect. For example, bioavailability of acid-labile drugs can be enhanced by using an enteric coated formulation to bypass the effect of the gastric acid.

Table 1: A summary of patient's and drug's related factors that may affect Bioavailability.

Drug-related	Formulation-related	Patient-related
Physicochemical properties e.g. Molecular weight, lipophilicity, acidity	Route of administration e.g. only intravenous route guarantees 100% bioavailability	Physiological properties of the site of administration e.g. surface area, pH, blood flow, thickness
Chemical and enzymatic stability e.g. Effect of acidic pH on acid-labile drugs	Non-active ingredients (excipients) e.g. Calcium-containing excipients are known to form insoluble complexes with Tetracycline antibiotics and may impact their bioavailability	Extent of first-pass effect (Pre-systemic elimination)

The extent of absorption, bioavailability, may vary among patients after extra vascular administration of the same dose of the same drug. This inter-patient variability in bioavailability may be attributed to several factors such as age, disease state, weight, genetic factors, gender, and concomitant drug administration (drug interactions). Understanding how these factors may impact bioavailability in these patient populations can guide pharmacists and other healthcare professionals in adjusting the dose and dosing regimens to maintain plasma concentrations in the desired therapeutic range.

Obesity

There is only limited information regarding the effect of obesity on the bioavailability of drugs, and therefore, no guidelines are currently available to optimize bioavailability in this patient population. A study aimed to evaluate the bioavailability of midazolam, a Cytochrome P450 (CYP) 3A4 substrate, in morbidly obese patients (mean body weight of 144±22kg) reported a substantially higher bioavailability (60%) compared to healthy

control volunteers (28%) [1]. In contrast, another study that included obese patients (mean body weight of 117±8kg) did not find any significant difference in midazolam oral bioavailability in obese patients compared to lean controls [2].

This increase in bioavailability in morbidly obese individuals may be explained by one or more of the following:

- i. Reduced expression and metabolizing activity of CYP3A4 in the intestine of morbidly obese patient may inhibit the first-pass effect, and hence improve bioavailability of drugs that are major substrates for this CYP isoform [3].
- ii. The greater splanchnic blood flow due to increased cardiac output in morbidly obese patients may enhance drug absorption across intestinal membrane and reduce the transit time and exposure to intestinal drug metabolizing enzymes [4].
- iii. Altered membrane permeability and increased paracellular absorption in obese patients [5].

Very little information is available to examine the potential effect of gastric or jejunoileal bypass surgery on drug bioavailability. A single study examining the pharmacokinetics of phenazone in 17 obese patients reported that the rate and extent of drug absorption and hepatic drug metabolizing capacity appear to be unaffected 12-57 months after intestinal shunting [1].

In conclusion, predicting bioavailability in obese patients remains a challenge, and therefore close therapeutic drug monitoring is required.

Pediatric Patients

During early development, several complex physiological processes occur and significantly alter drug absorption and impact the bioavailability of drugs. Those factors that have been extensively studied include gastric pH, gastric motility, gastric transit time, intestinal motility, and activity of various intestinal enzymes and bacterial colonization.

In general and due to immaturity of the parietal cells, the secretion of gastric acid may not reach the adult level until 1-2 years of age. Therefore early neonates have a higher intra-gastric pH (3.1-3.7) compared to the more mature infants (1.6-1.8). This age-dependent changes in gastric pH may explain the observed higher bioavailability of acid-labile drugs such as penicillin and ampicillin in neonates when compared to older children and adults. Consistent with the pH partition hypothesis, the absorption of weak acids such as phenytoin and barbiturates will be delayed and/or incomplete in neonates.

The reduced gastric motility and hence prolonged gastric emptying time during the neonatal period relative to that of the adult may partially explain the delayed absorption for orally administered phenobarbital, digoxin, and sulfonamides [6]. The prolonged exposure of drug molecules to the gastric acid in neonates may or may not impact the extent of absorption depending on the physicochemical properties and the formulation of the drug. On the other hand, the reduced intestinal motility in the newborns and young children may prolong intestinal transit time and contact with the small intestine, the major site for drug absorption, and therefore enhances bioavailability.

Activity and function of various enzymes responsible for the first-pass effect are generally poorly developed in neonates and young children compared to adults [7]. Therefore drugs such as midazolam that normally undergo extensive first-pass effect in adults have higher bioavailability in neonates. On the other hand, bioavailability and activity of drugs that are administered as prodrugs may be reduced in young children secondary to the lack of enzymes that are required to generate the active drug.

Although affected mostly by diet than developmental maturation, the composition and rate of gastrointestinal colonization may have an impact on intestinal motility and drug metabolism. For example, the intestinal colonization by anaerobic bacteria that hydrolyze oral digoxin reaches adult level by 2 years of age. Therefore, digoxin oral bioavailability is expected to be higher in children below 2 years of age compared to older children and adults.

The overall impact of the aforementioned developmental factors on bioavailability may or may not be clinically significant and other factors, such as drug's physicochemical properties, should be also considered.

Renal Dysfunction

The impact of renal dysfunction on drug bioavailability has not been well-studied, and therefore the available data are inconsistent. For example, although the bioavailability of some drugs (e.g. furosemide and pindolol) has been reduced in renal impairment, other drugs (e.g. erythromycin, propranolol, and tacrolimus) have shown improved bioavailability. Renal injury is normally associated with accumulation of endogenous inhibitors known as uremic toxins that may influence the transport and metabolism system in the small intestine. Reduced functional expression of several efflux transporters (e.g. pgp) in the gastrointestinal tract can increase bioavailability of specific substrates for these transporters [8]. Similarly, drugs with high first-pass extraction ratio have an increased bioavailability during renal impairment secondary to down regulation of phase I enzymes such as CYP3A. In contradiction to these findings, the oral bioavailability of cyclosporine, a CYP3A4 and pgp substrate, was reduced by 65% in renally-impaired patients compared to control subjects. This reduction in bioavailability was explained by the depressed bile excretion and increased transport of cyclosporine by pgp out of the cells back to the GI tract [9]. Finally it should be noted that, although several studies have shown a correlation between renal impairment and alteration in oral bioavailability, several of these changes were due to drug-drug interactions rather than an effect of the renal dysfunction. For example, patients with renal disease are frequently treated with calcium-containing phosphate binders that may interfere with the absorption of some drugs such as digoxin and fluoroquinolone antibiotics.

Geriatric Patients

The major physiological changes that may impact drug absorption and bioavailability in geriatric patients include reduced gastric acid production (elevated gastric pH), reduced gastric motility, reduced splanchnic blood flow, reduced intestinal absorptive surface area and reduced function of intestinal drug metabolism and transporters. Although changes in drug absorption tend to be clinically insignificant for most drugs, the next section gives some examples of how these changes may affect extent of absorption for selected drugs.

An optimal absorption of calcium carbonate, commonly used in this patient population, requires an acidic environment. Age-related reduction in gastric acid secretion reduces the extent of calcium absorption and increase the risk of constipation. Therefore, healthcare professionals usually consult elderly patients to either use this salt with an acidic fluid or use a calcium salt that dissolves more easily in a less acidic environment (e.g. citrate). Additionally, the higher gastric pH in geriatric patients may result in early release of enteric-coated dosage forms that are intended to dissolve in the small intestine.

The bioavailability of levodopa, a commonly used agent for Parkinson's, was reported to be significantly lower in the elderly

secondary to reduced gastric emptying and longer gastric transit time, and therefore degradation of levodopa by gastric hydrolytic enzymes such as dopa-decarboxylase [10].

The use of more medications than are clinically indicated, i.e. polypharmacy, is common among the elderly. Several studies have shown significant drug-drug interactions involving changes in drugs' bioavailability and were associated with negative health outcomes [11].

Hepatic Dysfunction

The liver does not only play a central role in drug's biotransformation, but parameters such as hepatic blood flow, amount and function of binding plasma proteins, and biliary excretion may significantly impact other pharmacokinetics properties, including drug absorption and bioavailability. Due to its unique anatomical position, any drug absorbed from the gastrointestinal tract will be exposed to the first-pass effect of the liver secondary to its drug metabolizing enzymes and biliary excretion transport systems. Therefore the oral bioavailability of drug with high to intermediate hepatic extraction ratio, that normally undergo extensive first-pass effect, is significantly higher in patients with hepatic diseases. Examples of drugs that show a significant increase in bioavailability in patients with liver cirrhosis are Carvedilol, Labetalol, Metoprolol, Morphine, Propranolol, and Verapamil [12]. Such increase in drug's bioavailability may necessitate dose adjustment to avoid toxicity. For example, initial Carvedilol dose in cirrhotic patients is normally 20% of the normal dosage.

Drugs with low extraction ratio do not undergo extensive first-pass effect, and liver dysfunction does not significantly affect their oral bioavailability.

Pregnancy

The major physiological changes that may affect drug absorption during pregnancy are diminished gastric and intestinal motility and increased gastric pH. These changes may only affect drug dissolution and rate of drug absorption, without any significant effect on extent of absorption. Theoretically, an increase in gastric pH may increase the ionization of weak acids, and reduce their absorption more than that of weak bases. However, there are no clinical reports to support this hypothesis, and therefore there are no current guidelines to adjust dose based on these expected changes in drug absorption during pregnancy [13].

Conclusion

Several physiological and pathological factors may affect drug's bioavailability after oral administration and may cause inter-individual variations in patients' response to even equal doses. Understanding the mechanisms by which these factors can impact bioavailability can help in predicting the bioavailability behavior in different patient populations. It may be important also to design specific pharmacokinetics studies in these special populations to assess the impact on bioavailability and create accurate guidance on the appropriate dosing regimens in these special populations. Table 2 gives a summary of the aforementioned factors and how they may impact oral bioavailability.

Table 2: A summary of factors that may affect bioavailability in special population.

Special Population	Factors that May Increase Bioavailability	Factors that May Decrease Bioavailability
Obesity	Reduced expression and functional activity of the gastric drug metabolizing enzymes. The greater splanchnic blood flow. Altered membrane permeability and increased paracellular absorption	No data available
Pediatric Patients	Higher intra-gastric pH (for acid-labile drugs) Immature development of the gastric drug metabolizing enzymes	Higher intra-gastric pH (for weak acidic drugs) Longer gastric transit time (for acid-labile drugs)
Geriatric Patients	Reduction in gastric acid secretion. Reduced gastric emptying and longer gastric transit time Polypharmacy	Polypharmacy
Renal Impairment	Impaired first-pass elimination. Drug-drug interactions	Reduced bile acid excretion. Drug-drug interactions
Hepatic Impairment	Impaired first-pass elimination	No data available
Pregnancy	Increased gastric pH (Basic drugs). Diminished intestinal motility	Increased gastric pH (Acidic drugs). Diminished gastric motility (acid-labile drugs)

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