30 Years
BAPEN
Putting patients at the centre of good nutritional care
1992 - 2022

Predicting Drug Absorption in Patients with a Short Bowel

Uchu Meade, Richard Ng Kwet Shing, Jeremy Nightingale and the BIFA Committee

The absorption of drugs in patients with a short bowel (SB) can be hard to predict. It may be affected by the remaining length and type of functioning gut, gastric emptying and small bowel transit rates, gastric secretion, bowel perfusion and the physicochemical properties of the drug.

Key points

1. A knowledge of how much functioning small and large bowel remains helps predict absorption.
2. The time to the blood maximum drug concentration (Tmax) and oral bioavailability help predict absorption.
3. The biopharmaceutical classification system (BCS) is based upon drug solubility and permeability and helps predict the drug absorption.
4. Lipid soluble drugs need a long length of bowel to be absorbed so are likely to be poorly absorbed in patients with a SB.
5. Caution should be used with drugs that are efficacious within a narrow therapeutic range.
6. Due to malabsorption, a drug that readily forms a solution may be given in higher than normal doses. However, a formulation that bypasses the gastrointestinal tract (GIT) may be better (e.g., by injection or infusion, topical, buccal or rectal application).
7. Prolonged released drug formulations should be avoided in patients with a SB.
8. Careful monitoring of drug blood levels or of an effect (e.g., INR for warfarin) may be needed to achieve the desired clinical outcome and avoid an adverse reaction.
9. Absorption may improve over time due to intestinal adaptation (especially in patients with a colon in continuity) or to drugs that slow gut transit.

Explanations

1. A patient with a duodenostomy is unlikely to absorb much of any oral preparation, while a patient with a metre of small bowel in continuity with more than half their colon may absorb most of a medication. The majority of drugs given orally are absorbed from the jejunum due to its large surface area. There needs to be a good understanding of the patient's gastrointestinal in-circuit anatomy (and out of circuit anatomy if a chyme reinfusion is being considered).
2. The highest blood concentration (Cmax) and the time that the maximum concentration is reached (Tmax) are dependent on the rate at which the drug enters and is removed from the body. Drugs that reach their Cmax quickly (less than two hours) tend to be absorbed higher in the gastro-intestinal tract so are more likely to be absorbed in patients with SB (e.g. fluconazole Tmax 0.5 -1.5 hours) while those that are absorbed slowly (e.g. amlodipine Tmax 6-12 hours) are not. Oral bioavailability is the amount of active drug that reaches the systemic circulation after oral administration. It ranges from 1 (100% of the drug reaches the systemic circulation) to 0, (none of the drug reaches the systemic circulation). Oral bioavailability of medicines can also change when switching from one formulation to another. For example, digoxin tablets and liquid are not bioequivalent therefore a dose adjustment may be required. The most quickly absorbed drug in each class (e.g., lacipine in preference to amlodipine) should be used. The Tmax, Cmax and oral bioavailability (in normal subjects) can be found in the manufacture's information.

Continued over page...

3. The BCS classifies drugs into four categories based upon solubility and permeability. A drug with high solubility and high permeability (Class I) is absorbed quickly and therefore achieves a fast Tmax and a higher Cmax so there is likely to be some absorption even in patients with a very short bowel (**see table**).

Table: Examples of drugs that have a Tmax of two hours or less and are BCS class I

- Paracetamol
- Codeine phosphate
- Pregabalin
- Bisoprolol and Metoprolol
- Ramipril and Enalapril
- Levetiracetam
- Levofloxacin
- Metronidazole
- Lorazepam, zopiclone and midazolam
- Mirtazepine
- Venlafaxine
- Cyclizine
- Ondansetron
- Lansoprazole*

* Omeprazole T max is 0.5 hr but is BCS class II

4. The un-ionized form of a drug is usually lipid soluble and can diffuse readily across the phospholipid cell membrane. However, the proportion of ionised and un-ionised forms present at any specific region is influenced by the pH of the solution and the pKa of the drug. Drugs that are weak acids are better absorbed in an acidic environment (e.g., aspirin, penicillins and L-dopa) and weak bases in a more alkaline one (e.g., pethidine), where their un-ionised forms predominate (e.g., a drug with a pKa of 4 will have increased solubility with increased pH and a drug with a pKa of 7 will have increased solubility with lower pH).

5. The therapeutic range is the concentration range in which the drug is eliciting a therapeutic response. If the amount of drug absorbed is too low then the concentration will fall below the minimum needed to elicit the desired pharmaceutical response and so result in treatment failure, if too high it may result in toxic adverse effects. Drugs with a narrow therapeutic range include warfarin, digoxin, phenytoin and need to be used with caution as increasing their dose can suddenly result in toxic levels. Their effect (e.g., INR for warfarin) or drug levels will need to be monitored.

6. A higher dose than recommended by the manufacturer, off label/ off licensed, is often needed to compensate for malabsorption of a drug in patients with a SB. Drugs with a wide therapeutic range are most desirable for SB patients as these have a wider margin of safety. Adverse effects of a drug can be obtained from its Summary of Product Characteristics (SPC).

   When absorption is uncertain or if there are difficulties in obtaining good oral absorption, alternative routes or methods need to be considered. These include:
   • intravenous • intramuscular • subcutaneous • transdermal
   • oro-mucosal • rectal.

7. Solid drug formulations (e.g. tablets and capsules) have been developed with a variety of different release profiles to target specific areas of the gut. These different protective coatings or casings (which mainly aim to give protection from gastric juices), or modified release casings (which allow for targeting of specific sections of the gut) must first be broken down to allow liberation of the drug (disintegration). Once disintegration has occurred, the drug can form a solution (dissolution) for absorption. Some are designed to remain intact for several hours and/or only to disintegrate at a specified pH (modified- release/sustained-release preparations), others have mixed profiles, and some have the liberated drugs separately coated for targetting purposes. For this reason, prolonged or modified release preparations (e.g., morphine) are best avoided in patients with a SB as they are likely to pass through unabsorbed. Ghost tablets are those that have released the active drug but appear intact in the stoma output. Drugs with artificial sweeteners may increase stool output and thus reduce absorption.

8. Therapeutic drug monitoring is available for a range of drugs in the UK from local and more specialised laboratories (e.g., rivaroxaban). Many drugs levels can be measured from blood samples that are taken at a specific time relating to when taken (e.g., before a dose for carbamazepine (trough level) or six hours after a dose for digoxin [peak level]).

9. With time, absorption of a drug may improve as intestinal adaptations occurs (e.g., in patients with a jejunum in continuity with a colon). As stoma output reduces there may be improved absorption of salt, water, nutrients and drugs, therefore drug doses may need to be reduced.

More research is needed in all aspects of drug absorption in patients with a short bowel.

Suggested reading:

- Meade U et al. Drug absorption in short bowel. In Intestinal Failure Second edition (in press by Springer)
- Hong WB, Tan WK, Law LS, Ong DE, Lo EA. Changes of drug pharmacokinetics in patients with short bowel syndrome: a systematic review. European Journal of Drug Metabolism and Pharmacokinetics. 2021 Jul;46(4):465-78.
- Ward N. The impact of intestinal failure on oral drug absorption: a review. Journal of Gastrointestinal Surgery. 2010 Jun;14(6):1045-51.
- Papich MG, Martinez MN. Applying biopharmaceutical classification system (BCS) criteria to predict oral absorption of drugs in dogs: challenges and pitfalls. The AAPS journal. 2015 Jul;17(4):948-64.
- BCS Database via http://www.ddfint.org/