First Pass Metabolism

Abstract

In this article in the series of 'bite sized' pharmacology, we will look at the concept of first pass metabolism. All drugs given by the oral route undergo a degree of first pass metabolism either in the gut or the liver, with some drugs being destroyed before they reach the systemic circulation. This pharmacokinetic process affects the bioavailability of drugs administered by this route and is an important consideration for the prescriber.

Knowledge of first pass metabolism can assist the prescriber when deciding on doses and dose schedules to ensure that patients receive their medications at the correct dosing, by the correct route for optimum therapeutic effect. It also helps the prescriber understand why dose adjustments are made for some drugs when switching the route of administration from oral and why some drugs cannot be given by the oral route.

Drug Metabolism

The process of drug metabolism is part of the body's normal response to removal of drugs and chemicals from the system. Hepatic metabolism, or biotransformation is the main site and method of the process of elimination. This is followed by excretion of the drug and its metabolites from the body. The liver plays an extremely important role in drug removal. When drug molecules are distributed in the blood stream the plasma flow through the functional units of the liver present these molecules for biotransformation. This occurs after administration by any route. This article will only look at the oral route and the process of first pass metabolism.

The oral route of drug administration is by far the most common used route of giving medication to patients. It is accessible, least invasive for many patients and well tolerated and convenient. Many common drugs are available in oral formulations as well as in

presentations suitable for administration by other routes. There are very few drugs in the BNF that have no oral formulation.

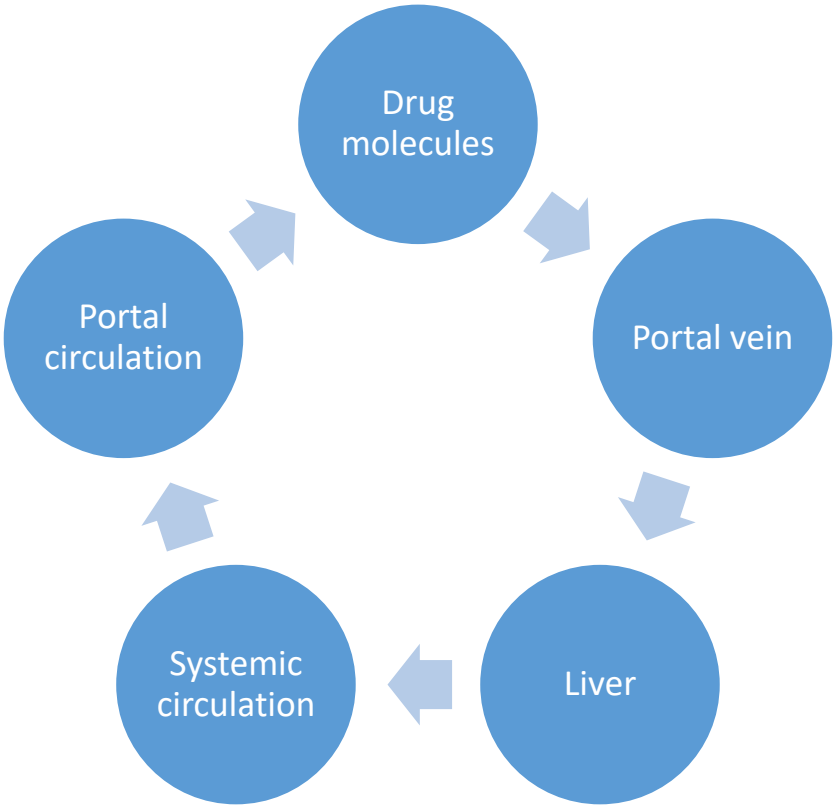

Figure 1- circulation process after oral drug absorption.

Hepatic First Pass Effect

Drugs given by the oral route are absorbed from the stomach and the small intestine into the hepatic portal vein. This blood vessel goes directly to the liver. The process of biotransformation begins and the drug will begin to be metabolised in preparation for

excretion from the body. The drug molecules in the plasma move through the system as shown in figure 1

The drug molecules are now metabolised by the liver enzymes in the normal fashion and this 'first pass effect' reduces the fraction of the dose administered that then goes on to reach the systemic circulation and become available for therapeutic effect. This process occurs in the hepatic microsomal enzymes and includes the cytochrome P450 enzymes. For drugs given orally the amount of first pass metabolism known to occur has been factored into oral dosing by the pharmaceutical companies. This means that the bioavailability, which is a known factor, has been considered when dose and dose ranges are advised in the BNF. It is important therefore for the prescriber to be aware of any hepatic dysfunction when prescribing oral drugs. If there is compromised liver function or disease such as cirrhosis then first pass metabolism will be compromised. This could lead to more active drug entering the systemic circulation due to the reduced liver enzyme functionality and may cause side effects, adverse effects or toxicity. Drug dosing may need to be reduced in patients in this situation. Some drugs are completely destroyed by liver enzyme systems at this first pass stage and will not enter the general systemic circulation. An example of such a drug is glyceryl trinitrate (GTN) which is metabolized completely by the liver and inactivated. Therefore you will find GTN being given via routes other than orally with sublingual being a very good alternative route.

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out the bioavailability for a drug from your area of practice when given orally and compare this to the figure of 100% bioavailability for drugs given IV.

Use this information to reflect on the degree of first pass metabolism that occurs to produce a bioavailability of this level for the drug you have chosen.

Not all oral drugs are completely destroyed by the liver at first pass, but many clinically significant drugs do undergo an extensive first pass effect. Therefore, the doses of some drugs are considerably higher when given by the oral route compared to their dosing if given IV.

For example, morphine undergoes significant first pass metabolism when given orally with about a 30% bioavailability (Stevens & Ghazi, 2000). This means that the doses we give orally tend to be much higher than if we give the drug by a route when first pass is avoided, such as IM, IV or rectally. We must be aware of the differences in dosing when switching routes of administration as the first pass effect can be prominent for some drugs. This is essential to avoid overdosing when switching from oral to IV or under-dosing if we are switching administration from IV to oral routes.

There are many drugs for which the first pass effect is negligible or clinically irrelevant, and paracetamol is a good example. We can give the same dose orally, rectally and even IV with very little effect on the drugs bioavailability, its therapeutic effect or side effects/ adverse outcomes. One advantage of the IV route is that time to onset of effect is reduced and the patients feel the analgesic effect sooner.

Sometimes first pass effect can make the prediction of therapeutic effect difficult and some drugs require careful monitoring when initially prescribed and slowly increased until the affect is achieved. For example, propranolol has a bioavailability of around 10% when given orally as up to 90% of the active drug is lost due to the first pass effect (Summary of Product

Characteristics retrieved from Electronic Medicines Compendium). This figure however is unpredictable and is dependent on interindividual variability which means monitoring of the onset of effect is required as is careful titration up to effect to avoid side effects or adverse effects.

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out the differences, if any, in doses by oral and non-oral routes for a drug from your area of practice. Relate this to the first pass effect and reflect on how you will use this knowledge and information in your area of practice.

Gastrointestinal First Pass Effect

Some drugs if given by the oral route can undergo a first pass effect in the lumen of the gut. This means that the drug molecules can be rendered inactive before they have even been absorbed into the blood stream. Drugs that undergo this process cannot be given by the oral route.

The gastrointestinal tract can affect drug absorption in 3 ways

- Acidic environment: the stomach ph. can mean that some drugs would not survive the acid environment if given in oral form
- Bacterial enzymes: enzymes present in the stomach to start to break down food into constituent nutrients can also break down drug molecules and render them useless
- Intestinal membrane enzymes: the enzymes here may destroy the drug

There are many drugs that cannot be given orally for the above reasons, they include insulin which can be destroyed by acid and broken down by enzymes, and penicillin G which is destroyed by gastric acid.

CAN WE ADD A PHOTO OR SOMETHING HERE? PERHAPS AN INSULIN VIAL?

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out if any of the drugs from your area of practice cannot be given orally and related this to the first pass effect. Find out if this is by gastric first pass effect or by hepatic first pass effect.

This has been a brief introduction to the concept of first pass metabolism. In future articles in this series we will explore aspects of pharmacodynamic actions in more detail, looking in more detail at agonists and antagonists.

References & Further Reading

Barber and Robertson (2015) Essentials of Pharmacology for Nurses 3rd Edition McGraw Hill London

BNF Online https://www.bnf.org/products/bnf-online/

Electronic Medicines Compendium https://www.medicines.org.uk/emc/

Stevens, R.A. & Ghazi, S.M. (2000). Routes of Opioid Analgesic Therapy in the Management of Cancer Pain, Journal of Moffatt Cancer Centre, Retrieved from http://www.medscape.com/viewarticle/408974_2