Bio-avaiIability of Drugs

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The bioavailabiity of ingested drugs is influenced both by absorption and by the extent of metabolism occurring in the fir st pass through the liver. As most thugs are swallowed the emphasis in this article will be on absorption from the gastrointestinal tract with a brief reference to the problems associated with intramuscular injection.

Drug absorption is governed mainly by the physiocochemical properties of the drug[1] in particular its lipid solubility, the degree of ionisation, and its molecular size. Lipid soluble drugs are well absorbed across the mucosal cells by passive diffusion. The absorption of drugs that are weak acids or weak bases is in addition, determined by their dissociation constant and the pH of the environment.[2,3] Acidip drugs will be mostly unionised in an acid medium and, since cell membranes are freely permeable only to the unionised form of a acidic drugs, such as aspirin, phenobarbitone, and warfarin, should be better absorbed from the gastric contents than from the more neutral upper small intestine.[4,5,6] The converse would apply for basic drugs for instance, propranolol or impramine. In practice, many weakly acidic drugs are better absorbed from the upper intestine than from the stomach, owing to the greater absorptive surface of the small intestine and also partly because drugs such as aspirin are more soluble in neutral or alkaline solutions than in acidic solutions. Drugs that are strong acids or bases - for instance, quarternary ammonium compounds such as neostigmine are completely ionised in aqueous solution and therefore poorly absorbed from all regions of the gut.[7]

Some drugs are designed for - minimal absorption in order to exert their pharmacological effect in the large intestine for instance, the pro drug sulphasalzine which is metabolized by the intestinal bacterial in the colon to liberate sulphapyridine and 5 aminosalicylate.[8] Although most drugs are absorbed by passive diffusion, vitamins and drugs related to the steroids, amino-acids or pyriinidines, for example, levodopamay be absorbed by active processes normally involved in the absorption of endogenous substances[9].

Factors Influencing Bioavailability

Formulation

For solid dosage formulation two factors must be taken into consideration: drug disintegration and drug dissolution. Only drugs that in solution will be absorbed, and the dissolution rate may vary greatly depencLing on the formulation or the drug salt used[10]. After the problems with altered response and toxicity due to different formulations of phenytoin and digoxin much has been said of the need to use a particular brand of various drugs.[1,11] Pharmadokinetic studies have shown differences in bioavailability among various brands of a wide range of drugs. In practice, the changes noted are of little or no clinical significance for most drugs. Formulation requires more serious consideration when using drugs with a narrow therapeutic index, such as phenytoin, digoxin, lithium, and warfarin where a small change in bioavailabillty may alter the drug concentration to a level outside its therapeutically useful range. When using these drugs the same formulation should be adhered to throughout treatment[2].

Some drugs, notably penicillin G and erythromycin are unstable in an acid environment and therefore their bioavailability is low after oral administration. Penicillins with a modified side chain attached to 6-aminopenicillanic acid, such as ampicillin are better absorbed from the gastrointestinal tract but in addition have a differen.t antibacterial spectrum.[13] Enteric-coated formulations of erythromycin are available, which protect the drug from the acidic stomach secretions. In other cases enteric coating may be used to protect the irritant effect of the drug, with aspirin or iron preparations. Sustained release

formulations are also available, but these are useful only for drugs with a large therapeutic index, a biological half-life of three to eight hours, and for those drugs that are not absorbed by active processes. Drugs such as propranolol and theophylline have proved to be suitable candidates for sustained release formulation.

Gastric Motility

A decrease in gastric motility will tend to slow the rate but not alter the extent of drug absorption (Prescott, 1969).[14] Differences in absorption rate are important when an immediate effect is required as with analgesics or hypnotics, but are unimportant for drugs administered chronically, as steadystate drug concentration is not changed.[15] Anticholinergics and antihistamines delay gastric emptying due to their atropine like effects and may decrease the rate of absorption of a concomitantly administered drug. Examples of drugs causing an increase in the rate of gastric emptying are few for example, metoclopramide.

Food and Fluid Volume

Many of the effects of food on drug availability may be explained in terms of effects on gastric emptying. The presence of food in the stomach delays gastric emptying, and this may slow down drug absorption. The total absorption of several antibiotics e.g. penicillins, erythro. mycin[16] and tetracyclines is decreased when given with food, and these drugs should be administered at least one hour before or three hours after meals. In the case of acid - labile penicillins and erythromycin the decreased absorption is partly due to prolonged time in the stomach, which results in increased degradation of the drug. Tetracyclines may undergo chelation with metal ions present in the diet, and this will impair absorption.[17,18]

Fluid volume appears to have a considerable effect on drug absorption, most drugs being better absorbed when taken with an increased volume of water. This may be due to more rapid stomach emptying of large volumes of fluid, or for drugs in solid dosage forms to increased dissolution of drugs that are not freely water soluble.

Disease

The effect of gastrointestinal and systemic disease on drug absorption has not been extensively studied.[19] As mentioned, diseases altering gastric motility will not affect the extent of drug absorption. The gastrointestinal tract has a very large surface area, and for most drugs, problems with absorption would be expected only in severe malabsorption disorders, as in some cases of coelic disease or extensive small bowel resection. Absorption may be more seriously altered for drugs that are absorbed primarily from a localised area of the small intestine - e.g., iron from the duodenum and upper jejunum (reduced in entropathy) and B_{21}[20] from the terminal ileum (reduced in Crohn's disease). It has been suggested that oral contraceptives might fail if an episode of diarrhoea decreases the enterohepatic circulation of the oestrogen component. Liver disease with biliary obstruction may reduce the absorption of some fat soluble drugs, but for most drugs the effects on first-pass metabolism and drug clearance are more important than changes in absorption.

Congestive cardiac failure delays absorption of some drugs e.g. thiazide diuretics, quinidine, and digoxin-possibly owing to oedema of the intestinal mucosa or to decreased blood flow. In practice, it is not usually necessary to alter drug dosage because of theoretical considerations of impaired drug absorption in disease states.

Age

Until recent years[21] there has been little interest in the elderly. Studies suggest that for drugs that are absorbed by passive diffusion there is no appreciable change with age. Drugs absorbed by an active process such as methyldopa and levodopa, might be expected to have decreased blood concentrations in the elderly. Increased bioavailability of levodopa, however, has been noted in elderly patients with Parkiiison's dis. ease[9]. This is possibly due to reduced metabolism in the gut wall, and the effect may

not occur when preparations containing a dopa decar boxylase, levodopa inhibitor are prescribed e.g., levodopa + carbidopa.

Drug - Drug Interactions

Drug interactions affecting absorption may be due to a direct reaction between the drugs within the bowel lumen or to the effect of one of the drugs on bowel function, e.g., altered motility. The former type may be reduced by administering the drugs at different times.

Many interactions have been reported, but the problem is to assess their clinical importance. In many examples at least one of the interacting drugs is either not commonly used or could be replaced by a niore rational choice of treatment. Cholestyramine binds to several drugs and has been shown to reduce the absorption of warfarin and digoxin,[22] Since both these drugs have a narrow therapeutic index, this is of clinical importance, but the scope for this interaction to occur is limited as cholestyramine is not commonly used. Another frequently quoted example is the chelation interaction between tetracyclines and iron or antacids.[18,23] If these drugs are necessary in the same patient there should be at least two hours interval between their administration. Other studies[23] have suggested that the time taken to attain peak plasma concentration of lithium carbonate is shortened by metoclopraniide and lengthened by propantheline, an atropine like compound. This may make the plasma concentration monitoring of lithium more difficult to interpret. Although propantheline is little used now, a wide variety of drugs with atropine like actions such as tricyclic antidepressants, phenothiazines, and disopyramide may produce similar effects through delayed gastric emptying.[24,25] Antibiotics such as ampicillin may interfere with the enterohepatic circulation of oestrogen by altering the gut bacterial flora, and the decrease of plasma oestrogen concentration could result in contraceptive failure. Care should always be taken when drugs are administered concurrently but clinically important interactions are more likely to result from mechanisms other than change in absorption.

Parentral Administration

It is a general impression that intramuscular injection will lead to a more rapid onset of drug action. Although this is usually the case, it does not apply to all drugs. Phenytoin is slowly and irregularly absorbed after intramuscular injection, which leads to difficulty in achieving satisfactory control of seizures.[26] Also the delayed absorption may lead to toxicity after change to the oral route. If it is impossible to give the drug by mouth then slow intravenous administration is more reliable. Diazepam is also better absorbed when taken orally. Similarly, if a deep intramuscular injection is given, a good therapeutic plasma level can be achieved. If there is decreased peripheral circulation the intramuscular and subcutaneous routes are not satisfactory sites for drug administration. However, in shock, the intramuscular route of drug administration should be adopted.

In conclusion, many interacting factors will contribute to inter individual differences in drug absorption. Mostly these affect the rate but not the extent of absorption and are therefore important only when an immediate therapeutic effect is required. When pronounced inter individual differences in therapeutic response have been noted, these have been mainly attributed to differences in metabolism or excretion, rather than absorption.

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