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Food, drugs, and bioavailability

The term "bioavailability" refers to that proportion of a drug which reaches the systemic circulation unchanged after a particular route of administration. When drugs are taken by mouth their bioavailability is determined by factors in the drug—which include the nature of the molecule, its stability, and the formulation administered[1]—and in the patient—such as a reduced intestinal surface area as a result of coeliac disease or intestinal resection[2] and whether or not the drug is taken with a meal. In addition, drugs may undergo "presystemic" metabolism in either the intestine,[3] the liver,[4] or, less commonly, the lungs.

This "first pass" metabolism in the liver is important in limiting the bioavailability of many cardiovascular drugs, including several lipid soluble β adrenoceptor antagonists such as alprenolol, labetalol, metoprolol, and propranolol (possibly oxprenolol also) as well as the antiarrhythmic agents lignocaine and verapamil.[5] Some tricyclic antidepressants and various opiate analgesics also undergo presystemic metabolism, but apparently some (perhaps half) of this process occurs in the intestinal wall.[3] The same is true for the vasodilator hydralazine and other drugs which undergo N-acetylation.

The extent of presystemic drug metabolism is frequently dose dependent,[4] but other important influences include age, smoking habits, and concurrent drug treatment (which can modify microsomal enzyme activity).[6] In addition, liver disease—especially cirrhosis—may lead to increased drug bioavailability as a result of diminished hepatic metabolism and shunting of blood through portosystemic anastomoses.[7]

Finally, food and other substances present in the diet can influence drug bioavailability.[8] The first effect of food is to modify gastric emptying and so the rate of drug absorption. Because food may delay their absorption the oral hypoglycaemic agents glipizide and glibenclamide need to be given before breakfast.[9] Secondly, cations in foodstuffs (principally calcium) will chelate with most tetracyclines to reduce their intestinal absorption. Thirdly, food may reduce absorption from the gastrointestinal tract of drugs which are partly ionised, hexamethonium and amiloride, for example. Other drugs whose absorption is impaired by food include the antihypertensives atenolol and captopril and the antituberculous compounds rifampicin and isoniazid.[10] The long term ingestion of foods such as charcoal broiled hamburgers (which contain polycyclic hydrocarbons) may increase the extent of presystemic metabolism of drugs and hence reduce their bioavailability,[11] but whether this action is due to enzyme induction in the intestinal wall or (more likely) within the liver is disputed. The effect is similar to that of smoking and of drugs, which share the ability to induce microsomal enzyme oxidation.

Sometimes, however, the absorption of drugs is increased if they are taken with a meal—examples are nitrofurantoin and hydrochlorothiazide.[10] Furthermore, recent reports have shown that the apparent bioavailability of many more drugs—including propranolol, labetalol, metoprolol, and hydralazine—is increased by their coadministration with food.[10] Most of these studies have simply shown an increase in the plasma concentration or in the area under the concentration time curve (or both) of the drug when it is given with food. These results are not conclusive evidence of an alteration in bioavailability. One alternative explanation is a higher than normal protein binding in the plasma, a phenomenon seen in both Crohn's disease and rheumatoid arthritis.[12] In the case of labetalol the effects of food on its pharmacokinetics have been studied after both intravenous and oral administration showing fairly convincingly that its hepatic metabolism is diminished in the presence of food.[13] Possible explanations include an increased rate of drug absorption and altered blood flow through the liver[14]—factors which would be important if a preferred metabolic pathway had already been saturated. A third possibility is that blood (and the drug) might be shunted either within the liver or around it. None of these possibilities is easy to investigate. But one approach would be to give the drug under study by mouth and another such as lignocaine (which also undergoes extensive first pass metabolism in the liver) by the intravenous route.[15] Detailed pharmacokinetic analysis might then shed light on the mechanisms.

For the practising clinician the practical implications of all this research are straightforward. Most drugs may be given at mealtimes. Food remains an obvious—and convenient—daily ritual with which to associate the administration of drugs. Not only is compliance likely to be improved by giving drugs with meals but also for some drugs (for example, theophylline) unwanted effects may be reduced. The two important exceptions warrant repetition: hypoglycaemic agents should be taken half an hour or so before breakfast, and milk or milk products should not be taken

within an hour or two of tetracyclines (except doxycycline and minocycline).

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Treatment for aging brains

Anyone who has tried to compete with children in the seemingly simple task of picking up pairs of cards from an upturned pack realises that the speed of response deteriorates with age. Few psychological tests are standardised for use with the aged.[1] Many depend on speed of response, and old people are less likely to guess.[2] Is speed to be the only gauge? Cohen and Faulkner concluded that older adults are impaired when greater processing is required.[3] That, however, depends on the test. My mother completes the daily crossword in five to 10 minutes, while I usually fail to finish it. Is my comparative failure a measure of lack of practice or impaired processing of the test?

Doctors do themselves and their patients an injustice if they believe that a failing memory is a sign of old age: in examining the elderly may we not find what we expect to find? Because we see old age as a problem, do we report only negative findings? If a patient has loss of memory the first question should be "is anything that I am prescribing causing it?" The doctor should suspect all drugs. Digoxin, barbiturates, short and long acting benzodiazepines, tricyclic antidepressants, antihistamines, diuretics, indomethacin, and recently naproxen and ibuprofen,[4] Septrin, cimetidine, the anti-Parkinsonian drugs levodopa, bromocriptine, and benzhexol,[5] and tranquillisers may all cause confusion. The list is endless: indeed, it is surprising that the medicated aged pass any mental tests at all. If one or another doctor is not causing the problem, then alcohol excess should be considered. A recent onset of heavy drinking suggests depression.

Some 5-10% of patients presenting with impaired cognition may have depressive pseudodementia.[6] Patients with confusion and depression respond to questioning with "don't knows" or emotional distress, while demented patients respond uncritically. All doctors should beware of falling into the trap of "failing" a patient on direct questioning about the time and place if he or she has had no opportunity to learn the facts. Then by a thorough history, clinical examination, and appropriate investigations the doctor should search for the potentially treatable: subnutrition with vitamin deficiency, hypothyroidism, hypoglycaemia, hyponatraemia, hypercalcaemia, vitamin B_{12} deficiency, and hydrocephalus. A fluctuating clinical course with focal neurological signs and islands of preserved mental function suggests multi-infarct dementia.[7] Hypertension may indicate Binswanger's disease, encephalopathy affecting the white matter.[8]

In the absence of a specific diagnosis, what treatment is possible? A recent study in Southampton found that the decrement in the consolidation of new learning was prevented by an oral form of procaine bound to haematoporphyrin (Geriatricum-Schwarzhaupt KH_3) in 335 healthy elderly volunteers.[9] The study compared the effect over two years of 50 mg KH_3 once daily with placebo in a double blind trial. On three measures—two neuromuscular (incontinence ($p<0{\cdot}05$) and grip strength ($p<0{\cdot}01$)) and one cognitive (delayed free recall ($p<0{\cdot}05$))—an effect was found in favour of KH_3. No other mental test results were improved. The authors wondered if they could justify attributing three beneficial changes to treatment when so many other measures showed no difference from placebo and expressed surprise that the study substantiated the claims made by Aslan in 1974 that intramuscular procaine increased psychometric activity and muscle strength in the elderly.[10]

These findings by Professor Hall and his coworkers will encourage others to search for "the elixir of youth" with no side effects.[9] That is not, however, KH_3 in its present form. Fifteen people withdrew from the study and only two were taking placebo ($p<0{\cdot}005$): a characteristic migrainous headache occurred in four patients and a systemic lupus erythematosus syndrome in another.

Scepticism about the benefits of drugs for failing memories is justified and healthy, and well documented research on the lines of that being carried out in Southampton is needed.[11] Until better evidence is available I think I shall tell my mother to go on doing the crossword: like other organs may not brains deteriorate with disuse?

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