

The effects of food on drug bioavailability

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Introduction

The oral administration of drugs is convenient, and linking drug doses to daily routines such as meal times can improve compliance (Haynes *et al.*, 1979). However, interindividual variation in drug response, particularly following oral administration, has long been a problem. Since this variation can result in therapeutic failure or drug toxicity, the 'art of bespoke prescribing' (Routledge, 1988) remains a major goal of clinical pharmacology. In the past variation in the composition, strength or formulation of the drug has often been responsible for such problems. Nowadays, at least in the 'developed world' (Melrose, 1982), such formulation problems are rare, but even so dose-response relationships still vary from patient to patient. While such variation may result from pharmacodynamic factors, as is often the case with warfarin for example (Routledge *et al.*, 1979), pharmacokinetic factors are also important.

To produce a clinical response, a drug must achieve an effective concentration at its site of action, which must be maintained for an adequate length of time. For orally administered systemic agents, this involves the transfer of the drug from the gut to the systemic circulation. In order to achieve this the drug must first enter solution, and then pass into the portal blood—i.e. it must undergo absorption. This process occurs mainly by passive diffusion, though there are exceptions (for example L-dopa; Ther & Winne, 1971), and is located mainly in the small bowel. Following or during absorption, drugs are subject to the action of enzymes prior to their distribution to the body. This may result in the partial or total biotransformation of the drug to pharmacologically active or inactive derivatives. The main sites of 'presystemic' biotransformation are the gut wall, the liver and in the case of some drugs the lungs (George & Shand, 1982). Clearly some drugs act topically upon the gastrointestinal mucosa, and do not require absorption to be effective. The therapeutic effect of such drugs e.g. chelated bismuth preparations—can be perturbed by food, but this is not through changes in bioavailability, and is therefore not considered in this article.

The term 'bioavailability' is used to describe

the fraction of drug dose which reaches the systemic circulation unchanged, and this therefore takes account of all the processes described above. Many of the factors which influence bioavailability can be changed by food, both 'acutely', if a drug is taken with a meal, and 'chronically', where regularly consumed food items influence drug disposition. The nature of these interactions is complicated, and is influenced by the quantity and composition of food. It should also be noted that as well as changing the pharmacokinetics of some drugs, food can alter their pharmacodynamic effects. This subject is not, strictly speaking, within the remit of the present article, but needs to be dealt with briefly. Perhaps the most clinically relevant example concerns the sulphonylureas glibenclamide and glipizide. The bioavailability of neither is perturbed by food (although the rate of absorption of glipizide is reduced in the nonfasted state), but their therapeutic effect is significantly increased by taking the drugs prior to meals (Wahlin-Boll *et al.*, 1980; Sartor *et al.*, 1982). The exact reason for this is not clear, but may concern food effects on pancreatic and hepatic function.

Before reviewing specific examples of effects of food upon drug bioavailability, the theoretical basis for these interactions will be considered. This is not out of academic interest, but so that the physician can attempt to predict food/drug interactions from a few basic principles. In fact, the nature of such interactions is often so complex that prediction from theory is difficult, and consequently the development of new drugs should include assessment of food effects. Nonetheless, knowledge of the background theory can prove clinically useful especially when trying to interpret drug failure or adverse reactions in an individual patient.

The effects of food

Changes in gastric emptying

Few drugs are absorbed to an important degree by the stomach, both acidic and basic drugs are

mainly absorbed in the small bowel. However, gastric function can have major effects on both the rate and extent of drug absorption.

In the fasting state, gastric motility is not uniform, but passes through cycles termed migrating motor complexes (MMC). These MMC last about 2 h in total, but are divided into four phases, of which phase 3 results in the strongest contractions but lasts only about 15 min (so called housekeeper waves; Golub *et al.*, 1986). Non nutrient liquids are moved quickly from the stomach throughout the MMC, but solids of particle size 2 mm—e.g. partly dissolved drug—are only moved into the intestine during the brief phase 3. Consequently, readily soluble drugs are cleared rapidly from the fasting stomach to their site of absorption, but poorly soluble drugs may take longer. Of course, the majority of drugs form suspensions or solutions rapidly in the gastric content (British Pharmacopoeia, 1985), and are thus moved quickly from the fasting stomach. There are however some poorly water soluble drugs (for example griseofulvin) whose passage into the small bowel can be delayed because of slow dissolution and consequent large particle size.

The presence of food in the stomach changes gastric motility to a typical postprandial pattern, during which gastric secretion and residence time are increased. The duration of the postprandial phase varies with the volume, physical structure and composition of the chyme. Gastric residence time increases with increasing volumes, but this increase is less marked for purely liquid meals than for those containing solids, and is increased particularly by chyme of low pH and high osmolality (Walter-Sack, 1987a). Consequently it is usual for the RATE of absorption of drugs to be slower when taken with meals compared with the fasted state, and this can be important for drugs which need to act promptly such as analgesics or sedatives. The EXTENT of absorption however is usually unchanged, and of course it is the extent rather than the rate of absorption which is a determinant of bioavailability.

For some drugs, the extent of absorption can be increased by meals. This may be because residence time and fluid volume are greater producing better dissolution (Greenblatt *et al.*, 1978). In particular, poorly water soluble drugs (e.g. griseofulvin, mebendazole and halofantrine), when taken as a solid formulation may not enter solution readily in the stomach. Administration of such drugs with very fatty foods can increase bioavailability, possibly by such mechanisms as the formation of solutions in the dietary oil. Conversely, the extent of

absorption of other compounds can be decreased by meals. In the case of acid labile drugs, such as penicillin and erythromycin, prolonged exposure to gastric acid may be the cause (Welling, 1984). In the case of levodopa, absorption occurs readily in both stomach and small bowel, and food-induced delay in gastric emptying enhances gastric absorption of the drug. However, DOPA-decarboxylase, the enzyme responsible for levodopa degradation, is present in gastric mucosa at high concentration, and the net effect of delayed gastric emptying is to increase the presystemic metabolism of the drug (Bianchine & Shaw, 1976).

The influence of drug formulation on interactions with food can be predicted, to an extent, from knowledge of gastric function as described above. On the whole, solutions and suspensions are less prone to food interactions than solid formulations. On the other hand, enteric coated drugs often prove more susceptible, since retention of the capsule in the stomach delays drug release.

Drug chelation

It is well known that certain drugs can interact with food constituents, resulting in reduction in drug bioavailability. Good examples of this include the interactions between first generation tetracyclines and dietary calcium (this is not so much of a problem with doxycycline) (Siegel, 1978), between penicillamine and heavy metal ions (Schuna *et al.*, 1983) and between iron formulations and tannic acid (found in tea) (Disler *et al.*, 1975).

Changes in the activity of drug metabolising enzymes

Food can contain, or become contaminated with, xenobiotics which affect hepatic or gut wall drug-metabolising enzymes. Brassica species vegetables (sprouts, cabbage, broccoli, spinach and cauliflower) have been extensively studied (Pantuck *et al.*, 1979, 1984), and it is likely that many other examples await discovery worldwide. The brassica species contain enzyme inducing indoles which, if taken in sufficient quantity for long enough, can reduce the bioavailability of some drugs by increasing their rate of metabolic clearance. Phenacetin is the drug most extensively studied in this context.

While some foods 'naturally' contain xenobiotics, others can become contaminated with them. The most widely studied example of contamination during food preparation is charcoal broiling of beef (Conney *et al.*, 1976; Pantuck

et al., 1976), and some techniques of food smoking have also been studied (Santodonato *et al.*, 1981). These processes cause contamination with certain polycyclic hydrocarbons capable of potent induction of drug metabolising enzymes. It must be said that the quantities of both Brassica vegetables and charcoal-cooked beef which the subject must consume, before perturbing drug disposition, is large. The majority of patients would be unlikely to eat enough of them for long enough to see an effect.

It is likely that these fairly extensively studied contaminants represent only a fraction of those which exist worldwide. Apart from contamination during cooking, foods can also acquire xenobiotics during storage. One group of examples are the aflatoxins which are of fungal origin, and when consumed in sufficient quantity have a range of effects including carcinogenicity and hepatotoxicity. In animal models certain of the aflatoxins have been shown to have acute effects on drug metabolising enzymes; for example aflatoxin B1 lowers the activity of UDP glucuronyl transferase and glutathione S transferase (Rajpurohit & Krishnaswamy, 1988). Aflatoxins have been shown to contaminate massively the diets of many 'Third World' populations (Coulter *et al.*, 1984; Hendrickse, 1985) and their effect, if any, on the bioavailability of drugs in man requires investigation. Furthermore, some authors have suggested that aflatoxins are causative in kwashiorkor (Hendrickse, 1985), a syndrome which is known to perturb drug disposition (Krishnaswamy, 1983).

Mention must be made of ethanol which, in British practice, is a more commonly recognised food 'contaminant' with effects on drug metabolism. While acute ethanol ingestion can inhibit drug metabolism (most commonly relevant in the setting of paracetamol overdose), chronic ingestion is a commonly encountered cause of major induction of drug metabolism. Chronic alcohol abuse may result in changes of drug disposition not only after oral medication, but also following the parenteral administration of high clearance drugs.

This section has so far considered only the effect of food contaminants on drug metabolising enzymes. Contaminants apart, the composition of the diet has effects on the activity of drug metabolising enzymes (Walter-Sack, 1987b). A high protein diet can increase the activity of mixed function oxidases, and this can affect the bioavailability of some drugs (e.g. propranolol and theophyllines; Fagan *et al.*, 1987). Unfortunately much of the world's population lacks the chance of eating even contaminated food, and many are chronically or acutely starving.

Starvation too affects drug bioavailability (Krishnaswamy, 1983), but of course this is usually the least of the patient's problems.

Changes in splanchnic blood flow and plasma protein binding

The effect of food on presystemic drug clearance, through changes in splanchnic blood flow and plasma protein binding, has been extensively reviewed by Melander *et al.* (1988), Melander & McLean (1983) and Melander (1978). These mechanisms are pertinent to food-induced changes in the bioavailability of labetalol, propranolol, metoprolol and hydralazine (see below).

Clinically important examples

Since food may change the bioavailability of many drugs, and hence influence their dose-response relationships, awareness of the more clinically-relevant examples is of benefit to the practising physician. The main purpose of the present article is to provide an up-date of those examples considered to be of most clinical relevance (Table 1).

Food reduces bioavailability

Antimicrobial agents Food reduces the bioavailability of the non-esterified penicillins (Cronk *et al.*, 1960), ampicillin (Jordan *et al.*, 1981) and amoxycillin (Welling, 1977). Similarly the absorption of many of the cephalosporins is either delayed or reduced by food (McCracken *et al.*, 1978). The effect of food on the bioavailability of various derivatives of erythromycin has been reviewed by Welling (1977). Briefly, the bioavailability of free erythromycin base and that of its stearate is reduced in the non-fasted state, while that of the less water soluble and less acid-labile estolate is increased. The bioavailability of isoniazid and rifampicin, used extensively for the treatment of tuberculosis and multibacillary leprosy (rifampicin only) is reduced to a significant degree by concomitant food (Melander *et al.*, 1976; Polasa & Krishnaswamy, 1983). Rifampicin in particular is an expensive drug for the majority of the countries in which it is employed, and its optimal use is therefore important. Another relatively expensive drug employed widely both in the developed and 'third' world is the antifungal agent ketoconazole. Mannisto *et al.* (1982) have shown that the AUC for ketoconazole is significantly reduced by a high carbohydrate, low fat meal

Table 1 Drugs whose bioavailability can be altered to a clinically important degree by food

Drug	Reference
<i>Bioavailability decreased</i>	
Penicillin	Cronk <i>et al.</i> (1960)
Ampicillin	Jordan <i>et al.</i> (1981)
Amoxicillin	Welling <i>et al.</i> (1977)
Cephalosporins	McCracken <i>et al.</i> (1978)
Erythromycin	Welling (1977)
Tetracycline	Neuvonen (1976)
Rifampicin	Polasa & Krishnaswamy (1983)
Isoniazid	Melander <i>et al.</i> (1976)
Ketoconazole	Mannisto <i>et al.</i> (1982)
Atenolol	Melander <i>et al.</i> (1979a)
Captopril	Singhvi <i>et al.</i> (1982)
<i>Bioavailability increased</i>	
Propranolol	Melander <i>et al.</i> (1977a)
Metoprolol	Melander <i>et al.</i> (1977a)
Labetalol	Daneshmend & Roberts (1982)
Propafenone	Axelson <i>et al.</i> (1987)
Hydralazine	Melander <i>et al.</i> (1977b)
Griseofulvin	Palma <i>et al.</i> (1986)
Nitrofurantoin	Rosenberg & Bates (1976)
Mebendazole	Munst <i>et al.</i> (1980)
Flubendazole	Michiels <i>et al.</i> (1982)
Halofantrine	Milton <i>et al.</i> (1989)
Phenytoin	Melander <i>et al.</i> (1979b)
Dicoumarol	Melander & Wahlin (1978)
<i>Drugs with significant pharmacodynamic interaction with food</i>	
Glibenclamide	Wahlin-Boll <i>et al.</i> (1980)
Glipizide	Sartor <i>et al.</i> (1982)

(14.38 ± 2.21 compared with $8.75 \pm 1.33 \mu\text{g ml}^{-1} \text{h}$; $P < 0.05$). The mechanism by which this occurs is not clear.

Antihypertensive drugs In contrast to the lipophilic β -adrenoceptor antagonists propranolol and metoprolol described below, the bioavailability of the hydrophilic drug atenolol is reduced by food. Melander *et al.* (1979a) showed that while food initially increases the rate of absorption of atenolol, its oral AUC is reduced by about 20%. Similarly, the bioavailability of the angiotensin converting enzyme inhibitor captopril appears to be reduced when taken with food. In this example the reduction is of the order of 35–40% (Singhvi *et al.*, 1982). Such reductions in bioavailability would probably be of clinical significance over the long-term, for patients who habitually take their medication

with meals, but in practice their short-term clinical significance is probably small.

Analgesics While the remit of the present article concerns food effects on bioavailability, food more usually delays drug absorption without reducing the extent of absorption. This can be of major importance to the patient however, since the onset of drug action can be delayed or even abolished if therapeutic concentrations fail to be achieved in the plasma. Consequently such interactions do warrant a mention. Delay of the onset of therapeutic effect is particularly important regarding analgesics. Non steroidal anti-inflammatory drugs including aspirin (Bogentoft *et al.*, 1978), diclofenac (Willis *et al.*, 1981) and piroxicam (Ishizaki *et al.*, 1979) are absorbed more slowly with food than in the fasted state. Though their bioavailability may not be reduced, this is unlikely to reassure the patient whose main concern is to be rid of the pain quickly.

Food increases bioavailability

Antihypertensive and antiarrhythmic drugs The intestinal absorption of propranolol, metoprolol, labetalol and hydralazine is virtually complete, but administration of the drugs to non-fasted subjects significantly increases their bioavailability (Melander *et al.*, 1977a,b; Daneshmend & Roberts, 1982). This effect is likely to be due to transient food-induced changes in drug absorption rate, splanchnic blood flow, plasma protein binding and activity of drug metabolising enzymes, causing temporary reduction of first pass metabolism. These mechanisms have been reviewed recently by Melander *et al.* (1988). This effect has been demonstrated particularly convincingly in the case of labetalol, where Daneshmend & Roberts (1982) gave the drug to fasting and non-fasting subjects both orally and intravenously. In this study oral bioavailability increased from 0.26 ± 0.03 (fasted) to 0.36 ± 0.05 (non fasted; $P < 0.05$), while AUC following i.v. dosing fell significantly as predicted. In the case of these antihypertensive drugs, the effect of food can be of clinical importance, and patients should be aware of the need to take their medication at set times in relation to meals.

Propafenone is a class 1C antiarrhythmic drug subject to extensive first-pass oxidative metabolism, which displays significant polymorphism –populations being phenotyped as rapid or slow metabolisers (Siddoway *et al.*, 1983). With the exception of slow metabolisers who are in the minority, food has been shown to increase

the bioavailability of propafenone in healthy volunteers (Axelson *et al.*, 1987). The maximal extent of this effect was 638%, but its clinical importance is not clear. Propafenone is metabolised to 5-hydroxy propafenone which is pharmacologically active (von Philipsborn *et al.*, 1984), and which was not measured in the study of Axelson *et al.* (1987). Even so, until further clarification is available it seems wise to advise patients to take this drug in a constant relationship to meals.

Recommendations concerning thiazide diuretics and food are probably of less pressing importance given their wide therapeutic index and flat dose-response curve. Long term drug failure however would clearly be important for a hypertensive patient. Unfortunately data on food effects with hydrochlorothiazide are conflicting. While Beerman & Groschinsky-Grind (1978) found that food enhanced the bioavailability of hydrochlorothiazide, more recently Barbhaiya *et al.* (1982) have found the opposite effect. This apparent conflict may result from the difference between fasting schedules employed by the two studies. In clinical practice, it seems unlikely that food-induced changes in the kinetics of this thiazide would lead to important problems.

It is appropriate to mention one example of a drug whose bioavailability is apparently uninfluenced by food. Verapamil is a calcium channel blocking agent widely used in the treatment of hypertension and angina (Hamman *et al.*, 1984). It is a high clearance drug with a large first pass effect, and on theoretical grounds one might predict that food would increase its bioavailability in much the same way as observed with metoprolol. In fact this seems not to be the case; a high-protein meal has been reported to have no effect on verapamil bioavailability (Woodcock *et al.*, 1986).

Antimicrobial drugs It has long been known that the bioavailability of the antifungal agent griseofulvin, and the urinary antiseptic agent nitrofurantoin is increased by high fat content meals. In the case of griseofulvin, the maximum plasma concentration increases by about 80%, while AUC increases by about 30%. This has been said to be due to either fat-induced, or bile salt-induced increase in the rate of absorption from the small bowel (Crouse, 1961; Bates *et al.*, 1966). However more recently, Palma *et al.* (1986) have shown that the effect is due to enhancement of solubilisation of griseofulvin by fat, and that fat and bile salts have no direct effect on the rate of its absorption. Since the drug has a relatively wide therapeutic index, the

interaction is usually not of great clinical significance, though it should be remembered that griseofulvin produces concentration dependent induction of some liver enzymes. Nitrofurantoin is also poorly soluble in water, and incompletely absorbed following oral administration.

Coadministration with food increases the bioavailability of nitrofurantoin by up to 400% (Rosenberg & Bates, 1976). This effect is maximal for those formulations of the drug with the poorest dissolution characteristics, suggesting that the effect is at least in part due to better dissolution resulting from delayed gastric emptying (Rosenberg & Bates, 1976). In contrast to these observations concerning nitrofurantoin, the bioavailability of the newer quinolone antibiotics (e.g. ciprofloxacin) is not greatly perturbed by food (Neuman, 1988). Finally on the subject of antibacterial drugs, as mentioned above, the bioavailability of erythromycin estolate formulations, but not of the stearate, is increased by food.

Most of the drugs referred to so far are in standard use in the United Kingdom, but mention must be made of some drugs rarely used in British practice. The clinical pharmacokinetics of antihelminthic drugs have recently been reviewed by Edwards & Breckenridge (1988). One of these, mebendazole, when given to fasting healthy subjects, achieved plasma concentrations below 18 nmol l^{-1} ; when the same dose was given to the same subjects with fatty food, the peak plasma concentrations were 91, 112 and 142 nmol l^{-1} and AUC was similarly increased (Munst *et al.*, 1980). Flubendazole is a *p*-fluoro derivative of mebendazole. When given with fatty food, like mebendazole it achieves higher plasma concentrations (Michiels *et al.*, 1982). The principal clinical importance of these observations is that higher systemic concentrations of these poorly absorbed drugs can be obtained by coadministration with fatty food, and this is advantageous when treating systemic helminth infections (e.g. hydatid). Another drug used mainly in the tropics, and whose bioavailability seems to be increased by food, is the phenanthrenemethanol antimalarial drug halofantrine. This compound is clinically effective against multi drug resistant *Plasmodium falciparum* in many parts of the world. Unfortunately the absorption of halofantrine is incomplete after oral administration, and can be erratic with some of the formulations under assessment (Horton, 1988). Following a fatty meal, Milton *et al.* (1989) have shown that AUC for both the parent drug and its equipotent desbutyl metabolite increase from 3.9 ± 2.6 and $8.8 \pm 3.5 \text{ mg l}^{-1} \text{ h}$ respectively, to 11.3 ± 3.5

and $10.7 \pm 3.2 \text{ mg l}^{-1} \text{ h}$ respectively. The clinical relevance of this observation is not yet clear, but if the drug is to be used for 'presumptive' self treatment by otherwise fit travellers taking a standard European diet, the effect may be important.

Antiepileptic drugs Phenytoin has unpleasant, and sometimes dangerous, concentration dependent adverse effects. The situation is complicated by the drug's saturatable hepatic metabolism, making phenytoin a potentially difficult drug to use to optimum effect. Inter individual variation in response to phenytoin can arise from its time of administration with relation to meals, since food increases both the rate of appearance of the drug in the plasma and its oral bioavailability. The effect seems to be due to an increase in the rate and extent of absorption, and not to perturbation of first pass metabolism (Melander *et al.*, 1979b).

Anticoagulants Melander & Wahlin (1978) have shown that the extent of absorption of dicoumarol is significantly increased by food. However, this drug is not used frequently in the U.K. Food seems not to perturb the bioavailability of the more frequently used drugs warfarin and phenindione, although there is one report suggesting reduced effectiveness of these agents in the presence of food (Welling, 1984).

References

- Axelsson, J. E., Chan, G., Kirsten, E. B., Mason, W. D., Lanman, R. C. & Kerr, C. R. (1987). Food increases the bioavailability of propafenone. *Br. J. clin. Pharmacol.*, **23**, 735-743.
- Barbhaiya, R., Craig, W., Corrick-West, H. & Welling P. (1982). Pharmacokinetics of hydrochlorothiazide in fasted and non-fasted subjects: a comparison of plasma level and urinary excretion methods. *J. pharm. Sci.*, **71**, 245-248.
- Bates, T. R., Gibaldi, M. & Kanig, J. L. (1966). Solubilising properties of bile salt solutions, I: effect of temperature and bile salt concentrations on solubilisation of glutethemide, griseofulvin and hexestrol. *J. pharm. Sci.*, **55**, 191-199.
- Beerman, B. & Groschinsky-Grind, M. (1978). Anti-hypertensive effect of various doses of hydrochlorothiazide and its relation to the plasma level of the drug. *Eur. J. clin. Pharmacol.*, **13**, 195-201.
- Bianchine, J. & Shaw, G. (1976). Clinical pharmacokinetics of levodopa in Parkinson's disease. *Clin. Pharmacokin.*, **1**, 313-338.
- Bogentoft, C., Carlsson, I., Ekenved, G. & Magnusson, A. (1978). Influence of food on the absorption of acetylsalicylic acid from enteric coated dosage forms. *Eur. J. clin. Pharmacol.*, **14**, 351-355.
- Brandt, J. L., Castleman, L., Ruskin, H. D., Greenwald, J. & Kelly, J. J. (1955). The effect of oral protein and glucose feeding on splanchnic blood flow and oxygen utilization in normal and cirrhotic subjects. *J. clin. Invest.*, **34**, 1017-1025.
- British Pharmacopoeia (1985). London: HMSO.
- Caldwell, J. & Marsh, M. V. (1982). Metabolism of drugs by the gastrointestinal tract. In *Presystemic drug eliminations*, eds George, C. F. & Shand, D. G. London: Butterworth Scientific.
- Conney, A. H., Pantuck, E. J., Hsiao, K., Garland, W. A., Anderson, K. E., Alvares, A. P. & Kappas, A. (1976). Enhanced phenacetin metabolism in

Conclusions

- (i) In both short and long-term drug treatment compliance is often difficult and in the elderly can be impossible. Consequently, linking drug doses to regular events such as meals makes sense, and has been shown to improve compliance (Haynes *et al.*, 1976). Drugs will often be taken before the meal, on an empty stomach, and if even a short time elapses before the food is taken, much of the drug will usually have been cleared from the stomach and no interaction with the food will occur. Drugs taken at the same time as food are more prone to interaction by the mechanisms described above, but even here there are few clinically important examples.
- (ii) If coadministration of a drug with food does cause therapeutic failure, then the drug concerned needs to be taken on an empty stomach. Fortunately such examples are few and include; glibenclamide, glipizide, atenolol, captopril and several antibiotics, including isoniazid and rifampicin.
- (iii) Because of the risk of concentration-dependent adverse effects, some drugs should be taken at set times with relation to meals. These include: phenytoin, propafenone, labetalol, propranolol, and metoprolol.
- (iv) Some drugs which are poorly absorbed after oral administration but lack a parenteral formulation, can be made more systemically available by administration with food. These include: mebendazole, flubendazole, nitrofurantoin, griseofulvin and halofantrine.

- human subjects fed charcoal broiled beef. *Clin. Pharmac. Ther.*, **20**, 633-642.
- Coulter, J. B. S., Lamplugh, S. M. & Omer, M. I. A. (1984). Aflatoxins in human breast milk. *Annals Trop. Paediatr.*, **4**, 61-66.
- Cronk, G. A., Wheatly, W. B., Fellers, G. F. & Albright, H. (1960). The relationship of food intake to the absorption of potassium alpha-phenoxethyl penicillin and potassium phenoxymethyl penicillin from the gastrointestinal tract. *Am. J. med. Sci.*, **240**, 219-225.
- Crouse, R. G. (1961). Human pharmacology of griseofulvin: the effect of fat intake on gastrointestinal absorption. *J. invest. Dermatol.*, **37**, 520-528.
- Daneshmend, T. K. & Roberts, C. J. C. (1982). The influence of food on the oral and intravenous pharmacokinetics of a high clearance drug: a study with labetalol. *Br. J. clin. Pharmacol.*, **14**, 73-78.
- Disler, P. B., Lynch, S. R., Charlton, R. W., Torrance, J. D., Bothwell, T. H., Walker, R. B. & Mayet, F. (1975). The effect of tea on iron absorption. *Gut*, **16**, 193-200.
- Drasar, B. S., Shiner, M. & McLeod, G. M. (1969). Studies on the intestinal flora, I: the bacterial flora of the gastrointestinal tract in healthy and achlorhydric persons. *Gastroenterology*, **56**, 71-79.
- Edwards, G. & Breckenridge, A. M. (1988). The clinical pharmacokinetics of antihelminthic drugs. *Clin. Pharmacokin.*, **15**, 67-93.
- Fagan, T. C., Walle, T., Oexmann, M. J., Walle, U. K., Bai, S. A. & Gaffney, T. E. (1987). Increased clearance of propranolol and theophylline by high-protein compared with high-carbohydrate diet. *Clin. Pharmac. Ther.*, **41**, 402-406.
- George, C. F. (1984). Food, drugs and bioavailability. *Br. med. J.*, **289**, 1093-1094.
- George, C. F. & Shand, D. G. (1982). Presystemic drug elimination. In *Clinical pharmacology and therapeutics*, 1. London, Boston, Sydney, Wellington, Durban, Toronto: Butterworth Scientific.
- Golub, A. L., Frost, R. W., Betlach, C. J. & Gonzalez, M. A. (1986). Physiologic considerations in drug absorption from the gastrointestinal tract. *J. Allergy clin. Immunol.*, **78**, 689-694.
- Greenblatt, D. J., Allen, M. D., MacLaughlin, D. S., Harmatz, J. S. & Shader, R. I. (1978). Diazepam absorption: effects of food and antacids. *Clin. Pharmac. Ther.*, **24**, 600-609.
- Hamman, S. R., Blouin, R. A. & McAllister, R. G. (1984). Clinical pharmacokinetics of verapamil. *Clin. Pharmacokin.*, **9**, 26-41.
- Haynes, R., Sackett, D. & Gibson, E. (1976). Improvements of medication compliance in uncontrolled hypertension. *Lancet*, **i**, 1256-1268.
- Hendrickse, R. G. (1985). Aflatoxins and child health in the tropics—the Stanley Davidson Lecture. *Chronicle*, **15**, 138-156.
- Horton, R. J. (1988). Introduction of halofantrine for malaria treatment. *Parasitol. Today*, **4**, 238-239.
- Ishizaki, T., Nomura, T. & Abe, T. (1979). Pharmacokinetics of piroxicam a new non steroidal anti inflammatory under fasting and postprandial states in man. *J. Pharmacokin. Biopharm.*, **7**, 369-381.
- Jordan, M. C., de Main, J. B. & Kirby, W. M. M. (1981). Clinical pharmacology of pivampicillin as compared with ampicillin. *Antimicrob. Agents Chemother.*, **10**, 438-441.
- Krishnaswamy, K. (1983). Drug metabolism and pharmacokinetics in malnutrition. In *Handbook of clinical pharmacokinetics*, ed Gibaldi, M. & Prescott, L. New York, Tokyo, Mexico, Sydney, Auckland, Hong Kong: Adis Health Science Press.
- Mannisto, P. T., Mantyla, R., Nykanen, S., Lamminsivu, U. & Ottoila, P. (1982). Impairing effect of food on ketoconazole absorption. *Antimicrob. Agents Chemother.*, **21**, 730-733.
- McCracken, G. H., Ginsburg, C. M., Clahsen, J. C. & Thomas, M. L. (1978). Pharmacologic evaluation of orally administered antibiotics in infants and children: effect of feeding on bioavailability. *Pediatrics*, **62**, 738-743.
- Melander, A. (1978). Influence of food on the bioavailability of drugs. *Clin. Pharmacokin.*, **3**, 337-351.
- Melander, A., Brante, G., Johansson, O. & Wahlin-Boll, E. (1979b). Influence of food on the absorption of phenytoin in man. *Eur. J. clin. Pharmacol.*, **15**, 269-274.
- Melander, A., Danielson, K. & Hanson, A. (1976). Reduction of isoniazid bioavailability in normal men by concomitant intake of food. *Acta med. Scand.*, **200**, 93-97.
- Melander, A., Danielson, K., Hanson, A., Ruddell, B., Schersten, B., Thulin, T. & Wahlin, E. (1977b). Enhancement of hydralazine bioavailability by food. *Clin. Pharmac. Ther.*, **22**, 104-107.
- Melander, A., Danielson, K., Schersten, B. & Wahlin, E. (1977a). Enhancement of the bioavailability of propranolol and metoprolol by food. *Clin. Pharmac. Ther.*, **22**, 108-112.
- Melander, A., Lalka, D. & McLean, A. (1988). Influence of food on the presystemic clearance of drugs. *Pharmac. Ther.*, **38**, 253-267.
- Melander, A. & McLean, A. (1983). Influence of food intake on presystemic clearance of drugs. *Clin. Pharmacokin.*, **8**, 286-296.
- Melander, A., Stenberg, P., Liedholm, H., Schersten, B. & Wahlin-Boll, E. (1979a). Food-induced reduction in bioavailability of atenolol. *Eur. J. clin. Pharmacol.*, **16**, 327-330.
- Melander, A. & Wahlin, E. (1978). Enhancement of dicoumarol bioavailability by concomitant food intake. *Eur. J. clin. Pharmacol.*, **14**, 441-444.
- Melrose, D. (1982). *Bitter pills: medicines and the third world poor*. Oxford U.K.: Oxfam.
- Michiels, M., Hendricks, R., Keykants, M. & van den Bossche, H. (1982). The pharmacokinetics of mebendazole and flubendazole in animals and man. *Arch. int. Pharmacodyn. Ther.*, **256**, 180-191.
- Milton, K. A., Edwards, G., Ward, S. A., Orme, M. L'E. & Breckenridge, A. M. (1989). Pharmacokinetics of halofantrine in man: effects of food and dose size. *Br. J. clin. Pharmacol.*, **28**, 71-77.
- Munst, G., Karlaganis, G. & Bircher, J. (1980). Plasma concentrations of mebendazole during

- treatment of echinococcosis: Preliminary results. *Eur. J. clin. Pharmacol.*, **17**, 375-378.
- Neuman, M. (1988). Clinical pharmacokinetics of the newer antibacterial 4-quinolones. *Clin. Pharmacokin.*, **14**, 96-121.
- Neuvonen, P. J. (1976). Interactions with the absorption of tetracyclines. *Drugs*, **11**, 45-54.
- Palma, R., Vidon, N., Houin, G., Pfeiffer, A., Rongier, M., Barre, J. & Bernier, J. (1986). Influence of bile salts and lipids on intestinal absorption of griseofulvin in man. *Eur. J. clin. Pharmacol.*, **31**, 319-325.
- Pantuck, E. J., Hsiao, K. C., Conney, A. H., Garland, W. A., Kappas, A., Anderson, K. E. & Alvarez, A. P. (1976). Effect of charcoal broiled beef on phenacetin metabolism in man. *Science*, **194**, 1055-1057.
- Pantuck, E. J., Pantuck, C. B., Garland, W. A., Mins, B. H., Wattenberg, L. W., Anderson, K. E., Kappas, A. & Conney, A. H. (1979). Stimulatory effect of brussel sprouts and cabbage on human drug metabolism. *Clin. Pharmac. Ther.*, **25**, 88-95.
- Pantuck, E. J., Pantuck, C. B., Anderson, K. E., Wattenberg, L. W., Conney, A. H. & Kappas, A. (1984). Effect of brussel sprouts and cabbage on drug conjugation. *Clin. Pharmac. Ther.*, **35**, 161-169.
- Polasa, K. & Krishnaswamy, K. (1983). Effect of food on bioavailability of rifampicin. *J. clin. Pharmacol.*, **23**, 433-437.
- Rajpurohit, R. & Krishnaswamy, K. (1988). Differences in response of glucuronide and glutathione conjugating enzymes to aflatoxin beta₁ and N-acetylaminofluorene in underfed rats. *J. Toxicol. Environ. Health*, **24**, 103-109.
- Rosenberg, H. A. & Bates, T. R. (1976). The influence of food on nitrofurantoin bioavailability. *Clin. Pharmac. Ther.*, **20**, 227-232.
- Routledge, P. A. (1988). Clinical pharmacology and the art of bespoke prescribing. *Br. J. clin. Pharmacol.*, **26**, 339-347.
- Routledge, P. A., Chapman, D. H., Davies, D. M. & Rawlins, M. D. (1979). Factors affecting warfarin requirements—A prospective population study. *Eur. J. clin. Pharmacol.*, **15**, 319-322.
- Santodonato, J., Howard, P. & Dasu, D. (1981). Health and ecological assessment of polynuclear aromatic hydrocarbons. *J. Environ. Path. Tox.*, **5**, 364.
- Sartor, G., Lundquist, I., Melander, A., Schersten, B. & Wahlin-Boll, E. (1982). Improved effect of glibenclamide on administration before breakfast. *Eur. J. clin. Pharmacol.*, **21**, 403-408.
- Schuna, A., Osman, M. A., Patel, R. B., Welling, P. G. & Sundstrom, W. P. (1983). Influence of food on the bioavailability of penicillamine. *J. Rheumatol.*, **10**, 95-97.
- Siddoway, L. A., McAllister, C. B., Wang, T., Bergstrand, R. H., Roden, D., Wilkinson, G. R. & Woosley, R. L. (1983). Polymorphic oxidative metabolism of propafenone in man. *Circulation*, **68** (Suppl. III), 64.
- Siegel, D. (1978). Tetracyclines: new look at old antibiotic. *N.Y. State J. Med.*, **78**, 950-1115.
- Singhvi, S. M., McInstry, D., Shaw, J. M., Willard, D. A. & Migdalof, B. (1982). The effect of food on the bioavailability of captopril in healthy subjects. *J. clin. Pharmacol.*, **22**, 135-40.
- Ther, L. & Winne, D. (1971). Drug absorption. *Ann. Rev. Pharmacol.*, **11**, 57-70.
- von Phillipsborn, G., Gries, J., Hoffman, H. P., Kreiskott, H., Kretzschmar, R., Muller, C. D., Raschack, M. & Teschendorf, H. J. (1984). Pharmacological studies on propafenone and its main metabolite 5-hydroxy-propafenone. *Arzneim.-Forsch./Drug Res.*, **34**, 1489-1497.
- Wahlin-Boll, E., Melander, A., Sartor, G. & Schersten, B. (1980). Influence of food intake on the absorption and effect of glipizide in diabetics and in healthy subjects. *Eur. J. clin. Pharmacol.*, **18**, 279-283.
- Walter-Sack, I. (1987a). The influence of food on the systemic availability of drugs. Part 1 drug absorption. *Klin. Wochenschr.*, **65**, 927-935.
- Walter-Sack, I. (1987b). The influence of food on the systemic availability of drugs. Part 2 drug metabolism and renal excretion. *Klin. Wochenschr.*, **65**, 1062-1072.
- Welling, P. G. (1977). Influence of food and diet on gastrointestinal drug absorption, a review. *J. Pharmacokin. Biopharm.*, **5**, 291-334.
- Welling, P. G. (1984). Interactions affecting drug absorption. *Clin. Pharmacokin.*, **9**, 404-434.
- Welling, P. G., Huang, H., Koch, P. A., Craig, W. A. & Madsen, P. O. (1977). Bioavailability of ampicillin and amoxycillin in fasted and non-fasted subjects. *J. pharm. Sci.*, **66**, 549-552.
- Willis, J. V., Jack, D. B., Kendall, M. J. & John, V. A. (1981). The influence of food on the absorption of diclofenac as determined by the urinary excretion of unchanged drug and its major metabolites during chronic administration. *Eur. J. clin. Pharmacol.*, **19**, 39-44.
- Woodcock, B. G., Kraemer, N. & Rietbrock, N. (1986). Effect of a high protein meal on the bioavailability of verapamil. *Br. J. clin. Pharmacol.*, **21**, 337-338.

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