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Effect of Food on Pharmacokinetics of Clindamycin: A Review

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ABSTRACT:
The term "bioavailability" refers to that proportion of a drug which reaches the systemic circulation unchanged after a particular route of administration. 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. Among all the routes of drug administration the oral route administration of drugs is convenient, and linking drug doses to daily routines such as meal times can improve compliance.

Keywords: Food effect on bioavailability, Bioequivalence

I. INTRODUCTION:

Inter-individual 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' remains a major goal of clinical pharmacology.[1-3] 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'[4], such formulation problems are rare, but even so dose-response relationships still vary from patient to patient. 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 and in the patient-such as a reduced intestinal surface area as a result of coeliac disease or intestinal resection and whether or not the drug is taken with a meal. [5-6]

For oral route of administration the absorption process can be affected by a number of factors including:

1) Physicochemical properties of the drug and the dosage form;
2) Gastric acidity;
3) Gastric and intestinal motility;
4) Gastro-intestinal (GI) related diseases; and
5) Concurrent food administration.

Amongst these, concurrent food administration is the most common and yet most easily controllable factor. The two pharmacokinetic parameters that may be affected are the extent of absorption i.e. oral bioavailability, and the rate of absorption. 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. [7-8]

With increasing generic substitution, food– drug interaction studies have gained considerable importance. Food–drug interaction studies focus on the effect of food on the release and absorption of a drug. In view of dramatic and clinically relevant food effects observed with certain Theophylline sustained release formulations, bioequivalence between a Test and a Reference formulation under only one nutritional condition, e.g. fasting, is by no means sufficient to allow generic substitution.[9-12] The reported food effects, with AUC increases of 100 % and decreases of 50 % for certain formulations, are far beyond the usually accepted 25 % increase and 20 % decrease in bioequivalence studies between formulations.[13] The CPMP (2001) guidance on bioequivalence also addresses this issue with particular emphasis on controlled release formulations. The FDA (2002) guidance recommends a study comparing the bioavailability under fasting and fed conditions for all orally administered modified release drug products. Modified release formulations include two

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essentially different types of release modifications, so-called 'prolonged release' formulations and 'delayed release' formulations.

Understanding the possible clinical implications of taking medicines with or without a meal is important for achieving quality use of medicines. Although the effect of food is not clinically important for many drugs, there are food–drug interactions which may have adverse consequences. Often these interactions can be avoided by advising the patient to take their medicines at the same time with respect to meals.

CLASSIFICATION OF FOOD EFFECTS

Early characterization of food effect response is important in drug development to provide dosing conditions that will minimize variability in drug absorption during pivotal clinical trials. Food effect studies are also important in testing in vivo performance of a dosage form under widely different physiological conditions.

The various ways in which food can affect gastrointestinal (GI) physiology, and thereby drug absorption, are summarized in Figure: 1 [14]

Of great importance for the drug absorption process are changes in gastric emptying time, GI motility, splanchnic blood flow, and GI secretion.

EFFECT OF FOOD ON BIOAVAILABILITY OF DRUGS:

Broadly food can affect both the rate and extent of absorption.

Rate of Absorption

Meals slow down gastric emptying and this can delay drug absorption. The composition of the meal influences the rate of gastric emptying – high fat meals lead to delayed gastric emptying. A delay in the drug reaching the small intestine can delay its subsequent absorption into the systemic circulation. Based on these observations, oral administration of a medicine under fasting conditions is often recommended when rapid absorption (and hence rapid onset of therapeutic effect) is needed. For most medicines, especially those used for chronic conditions, a delay in the onset of absorption is of no clinical consequence as long as the amount of drug absorbed is unaffected.

Extent of Absorption

Food has the potential to either increase or decrease the extent of drug absorption. Understanding food–drug interaction mechanisms enables the clinician to provide appropriate advice to patients about taking medicines with respect to the timing and composition of meals. The effect of food depends on the physicochemical and pharmacokinetic characteristics of the drugs. [15] The clinical significance of the effect will in turn depend on the pharmacodynamic characteristics of the drug. For example, the poorly water soluble antiretroviral drug saquinavir should be taken with food to allow bile enhancement of its dissolution which then facilitates absorption. The extent of absorption is more than doubled by taking saquinavir after a full cooked breakfast. Taking saquinavir on an empty stomach reduces its bioavailability and could lead to therapeutic failure. Delayed gastric emptying after a meal and the associated gastric acid secretions can reduce the bioavailability of some medicines that are acid labile. The constituents of a meal may also specifically interact with drugs. Calcium and other cations in food can form insoluble chelates with some medicines preventing their optimal absorption. Bisphosphonates are therefore recommended to be taken with plain water to prevent the formation of chelates which significantly reduce bioavailability.

MECHANISM OF FOOD EFFECT:

Interaction Mechanisms

Four main mechanisms involved in this type of interaction are:

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). [16] 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, and are thus moved quickly from the fasting stomach. [17] There are however some poorly water soluble drugs (for example

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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. [18] 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. [19] 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. [20] 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. [21] 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), between penicillamine and heavy metal ions and between iron formulations and tannic acid (found in tea). [22-24]

Changes in the activity of drug metabolizing 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, and it is likely that many other examples await discovery worldwide. [25, 26] 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, and some techniques of food smoking have also been studied. [27-29] These processes cause contamination with certain polycyclic hydrocarbons capable of potent induction of drug metabolizing 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 is 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 Bi lowers the activity of UDP glucuronyl transferase and glutathione S transferase. [30]Aflatoxins have been shown to contaminate massively the diets of many 'Third World' populations and their effect, if any, on the

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bioavailability of drugs in man requires investigation. Furthermore, some authors have suggested that aflatoxins are causative in kwashiorkor, a syndrome which is known to perturb drug disposition. [31-33]

Mention must be made of ethanol which, in British practice, is a more commonly recognized 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 charges 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 metabolizing enzymes. Contaminants apart, the composition of the diet has effects on the activity of drug metabolising enzymes. [34] 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). [35] 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, but of course this is usually the least of the patient's problems. [36]

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 & McLean (1983) and Melander (1978).[37-39] These mechanisms are pertinent to food-induced changes in the bioavailability of labetalol, propranolol, metoprolol and hydralazine (see below).

Potential Therapeutic Strategy

Administration of oral medication at fixed time in relation to meals is expected to improve patient's compliance by acting as a reminder to the patients. In fact, this has been used as a strategy by some to guide the patients when to take their medication. Concurrent administration of a drug with food may also be used therapeutically to reduce the adverse effect of some drug on GI tract. Examples are NSAIDs and some antibiotics. Use of NSAIDs is associated with a high incidence rate of GI upset. Consequently, concurrent administration of NSAIDs with food (or antacid) is usually recommended in order to reduce drug-induced GI discomfort. In this case, although the rate of absorption of NSAIDs is reduced, this is of minor clinical significance in comparison with the potential drug-induced adverse effects.

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 practicing physician.

Food Reduces Bioavailability

Antimicrobial agents Food reduce the bioavailability of the non-esterified penicillins, ampicillin and amoxycillin. Similarly the absorption of many of the cephalosporins is either delayed or reduced by food. 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 nonfasted 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. 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 (14.38 ± 2.21 compared with 8.75 ± 1.33, ug ml-' h; $P < 0.05$). The mechanism by which this occurs is not clear. [40-46]

Antihypertensive drugs In contrast to the lipophilic ,-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%. 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. [47-48]

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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, diclofenac and piroxicam 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. [49-51]

Food Increases Bioavailability

Antihypertensive and antiarrhythmicdrugs 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. 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 metabolizing 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. [52-54] The influence of food on the oral and intravenous pharmacokinetics of a high clearance drug: a study with labetalol. 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 IC antiarrhythmic drug subject to extensive first-pass oxidative metabolism, which displays significant polymorphism -populations being phenotyped as rapid or slow metabolisers. With the exception of slow metabolisers who are in the minority, food has been shown to increase the bioavailability of propafenone in healthy volunteers. The maximal extent of this effect was 638%, but its clinical importance is not clear. Propafenone is metabolized to 5-hydroxy propafenone which is pharmacologically active, 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. [55-57]

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. [58, 59]

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. 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. [60, 61]

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. 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

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water, and incompletely absorbed following oral administration. [62- 64]

Coadministration with food increases the bioavailability of nitrofurantoin by up to 400%. 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. In contrast to these observations concerning nitrofurantoin, the bioavailability of the newer quinolone antibiotics (e.g. ciprofloxacin) is not greatly perturbed by food. 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. [65, 66]

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 has recently been reviewed by Edwards & Breckenridge (1988). One of these, mebendazole, when given to fasting healthy subjects, achieved plasma concentrations below 18 nmol - 1; when the same dose was given to the same subjects with fatty food, the peak plasma concentrations were 91, 112 and 142 nmol 1- 1 and AUC was similarly increased. Flubendazole is a p-fluoro derivative of mebendazole. When given with fatty food, like mebendazole it achieves higher plasma concentrations. 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. 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 ± 3.5 mg 1-1 h respectively, to 11.3 ± 3.5 and 10.7 ± 3.2 mg l-1 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 travelers taking a standard European diet, the effect may be important. [67- 71]

Antiepileptic drugs Phenytoin have 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.[72]

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.[73, 74]

II. CONCLUSION:

The product information approved by the Therapeutic Goods Administration is the main source of information about the possible effects of food on drug absorption. This information is generally derived from a 'food effect study' that is conducted during drug development.

Prescribing a drug regimen that fits in with the patient's daily routine (which is usually centered on mealtimes) can enhance the patient's adherence to treatment. This leads to the general recommendation that patients should take their medicines at prescribed and consistent times relative to their meals.

Once the drugs are prescribed by the doctor or in case of over the counter medications, herbal products, dietary supplements etc., usually the first question asked by the patient to the health care provider is whether to take the drug with food, fluid, juices or with milk. At times it was not easy to answer all these questions because of the non availability of the data regarding food-drug interactions. Food-drug interaction is a wide domain and the food that a patient takes can affect the rate and extent of drug bioavailability to the body. It is now being acknowledged by an increasing number of pharmacists, physicians and other research workers in medical sciences. The potential for food-drug interactions is sufficiently great that the US Food and Drug Administration now requires studies as to the effects of food on

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drug absorption as part of biopharmaceutical characterization of almost every new drug intended for oral administration and this requirement is also being applied for new dosage forms of established drugs. Previously it was said that food intake generally impairs the absorption of drugs and drugs should be taken on an empty stomach whenever possible and that the variations in bioavailability could be usefully decreased if drugs were administered with food only when their irritative effects on the gastric mucosa make this necessary. One reason for these assumptions seems to be that the rate and partly also the extent of drug absorption depends mainly on the rate of gastric emptying and that food intake affects drug absorption negatively because of its slowing of gastric emptying rate. [75-80]

REFERENCES:

[1]. Prentis RA., Lis Y, and Walker SR.: pharmaceutical innovation by seven uk-owned pharmaceutical companies (1964–1985). Br. J. Clin. Pharmacol. **25:** 387–396, 1988.
[2]. Haynes, R., Sackett, D. & Gibson, E. (1976). Improvements of medication compliance in uncontrolled hypertension. Lancet, i, 1256-1268.
[3]. Routledge, P. A. (1988). Clinical pharmacology and the art of bespoke prescribing. Br. J. clin. Pharmac., 26, 339-347.
[4]. Melrose, D. (1982). Bitter pills: medicines and the third world poor. Oxford U.K.: Oxfam.
[5]. Florence AT, Salole EG. The clinical relevance of the formulation of medicines. In: Lawson DH, Richards RHE, eds. Clinical pharmacy and hospital drug management. London: Chapman and Hall, 1982:1-37.
[6]. Parsons RL, David JA., Gastrointestinal disease and drug absorption. In: Prescott LF, Nimmo WS, eds. Drug absorption. New York: Adis Press, 1981:262-77.
[7]. Wahlin-Boll, E.. Mclander. A.. Sartor. 6. & Scherten, B. (1980). Influence of food intake on the absorption and effect of glipizide in diabetics and in healthy subjects. Eur. J. clin. Pharmac., 18, 279-283.
[8]. Sartor, G., Lundquist, I., Melander, A., Schersten, B. & Wahlin-Boll. E. (1982). lmprovcd cffect of glibenclaimide on administration before breakfast. Eur. J. clin. Pharmac., 21. 403-408.
[9]. Cummins CL, Wu CY and Benet LZ. Sex-related differences in the clearance of cytochrome P450 3A4 substrates may be caused by Pglycoprotein. Clinical Pharmacology and Therapeutics. 2002;72:474–89.
[10]. Dietrich R, Brausse R, Bautz A and Diletti E. Validation of the in-vitro dissolution method used for the new sustained-release theophylline pellet formulation. Arzneimittelforschung/ Drug Research. 1988;38:1220–8.
[11]. Diletti E, Hauschke D and Steinijans VW. Sample size determination for bioequivalence assessment by means of confidence intervals. International Journal of Clinical Pharmacology, Therapy and Toxicology. 1991;29:1–8.
[12]. Duursema L, Müller FO, Hundt HKL, Heyns A, du P, Meyer BH and Luus HG. (Model to detect warfarin–drug interactions in man. Drug Investigation. 1992;4: 395–402.
[13]. Fitton A. and Wiseman L. Pantoprazole – a review of its pharmacological properties and therapeutic use in acid-related disorders. Drugs 1996; 51: 460–82.
[14]. Karim A. Importance of food effect studies early in drug development. In: Midha, K.K. and Nagai, T. (eds)Bioavailability, bioequivalence and pharmacokinetic studies. International conference of F.I.P. "Bio-International '96", Tokyo, Japan, 221– 9, Business Center of Academic Societies Japan, Tokyo, 1996.
[15]. Schmidt LE, Dalhoff K. Food-drug interactions. Drugs 2002;62:1481-1502.
[16]. 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.
[17]. British Pharmacopoeia (1985). London: HMSO.
[18]. Walter-Sack, I. (1987a). The influence of food on the systemic availability of drugs. Part 1 drug absorption. Klin. Wochenschr., 65, 927-935.
[19]. 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.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 554-563 www.ijprajournal.com ISSN: 2249-7781

[20]. Welling, P. G. (1984). Interactions affecting drug absorption. Clin. Pharmacokin.. 9. 404-434.
[21]. Bianchine, J. & Shaw, G. (1976). Clinical pharmacokinetics of levodopa in Parkinson's disease. Clin. Pharmacokin., 1, 313-338.
[22]. Siegel, D. (1978). Tetracyclines: new look at old antibiotic. N. Y. State J. Med., 78, 950-1115.
[23]. 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.
[24]. 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.
[25]. 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.
[26]. 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 conju^,ation. Clin. Pharmac. Ther., 35, 161-169.
[27]. Conney, A. H., Pantuck, E. J., Hsiao, K., Garland, W. A., Anderson, K. E., Alvares, A. P. & Kappas, A. (1976). Enhanced phenacetin metabolism in human subjects fed charcoal broiled beef. Clin. Pharmac. Ther., 20, 633-642.
[28]. Pantuck, E. J., Hsiao, K. C., Conney, A. H., Garlano, 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.
[29]. Santodonato, J., Howard, P. & Dasu, D. (1981). Health and ecological assessment of polynuclear aromatic hydrocarbons. J. Environ. Path. Tox., 5. 364.
[30]. Rajpurohit, R. & Krishnaswamy, K. (1988). Differences in response of glucuronide and glutathione conjugating enzymes to aflatoxin beta, and Nacetylaminofluorene in underfed rats. J. Toxicol. Environ. Health, 24, 103-109.
[31]. Coulter, J. B. S., Lamplugh, S. M. & Omer, M. I. A. (1984). Aflatoxins in human breast milk. Annals Trop. Paediat., 4, 61-66.
[32]. Hendrickse, R. G. (1985). Aflatoxins and child health in the tropics-the Stanley Davidson Lecture. Chronicle, 15, 138-156.
[33]. Krishnaswamy, K. (1983). Drug metabolism and pharmacokinetics in malnutrition. In Handbook of clinical pharmacokinetics. cd Gibaldi, M. & Prescott, L. New York, Tokyo, Mexico, Sydney. Auckland, Hong Kong: Adis Health Science Press.
[34]. Walter-Sack, 1. (1987b). The influence of food on the systemic availability of drugs. Part 2 drug metabolism and rcnal cxcretion. Klin. Wochecnsch,r.. 65. 1062-1072.
[35]. 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, 402406.
[36]. Krishnaswamy, K. (1983). Drug metabolism and pharmacokinetics in malnutrition. In Handbook of clinical pharmacokinetics. cd Gibaldi, M. & Prescott, L. New York, Tokyo, Mexico, Sydney. Auckland, Hong Kong: Adis Health Science Press.
[37]. Melander, A., Lalka, D. & McLean, A. (1988). Influence of food on the presystemic clearance of drugs. Pharmac. Ther., 38, 253-267.
[38]. Melander, A. & McLean, A. (1983). Influence of food intake on presystemic clearance of drugs. Clin. Pharmacokin., 8, 286-296.
[39]. Melander, A. (1978). Influence of food on the bioavailability of drugs. Clin. Pharmacokin., 3, 337- 351.
[40]. Cronk, G. A., Wheatly, W. B., Fellers, G. F. & Albright, H. (1960). The relationship of food intake to the absorption of potassium alpha-phenoxyethyl penicillin and potassium phenoxymethyl penicillin from the gastrointestinal tract. Am. J. med. Sci., 240, 219-225.
[41]. Jordan, M. C., de Main, J. B. & Kirby, W. M. M. (1981). Clinical pharmacology of pivampicillin as compared with amicillin. Antimicrob. Agents Chemother., 10, 438-441.
[42]. 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.

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[43]. Welling, P. G. (1977). Influence of food and diet on gastrointestinal drug absorption, a review. J. Pharmacokin. Biopharm., 5, 291-334.
[44]. 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.
[45]. Polasa, K. & Krishnaswamy, K. (1983). Effect of food on bioavailability of rifampicin. J. clin. Pharmac., 23, 433-437.
[46]. 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.
[47]. Melander, A., Stenberg, P., Liedholm, H., Schersten, B. & Wahlin-Boll, E. (1979a). Food-induced reduction in bioavailability of atenolol. Eur. J. clin. Pharmac., 16, 327-330.
[48]. Singhvi, S. M., Mclnstry, D., Shaw, J. M., Willard, D. A. & Migdalof, B. (1982). The effect of food on the bioavailability of captopril in healthy subjects. J. clin. Pharmac., 22, 135-40.
[49]. Bogentoft, C., Carlsson, I., Ekenved, G. & Magnusson, . (1978). Influence of food on the absorption of acetylsalicylic acid from enteric coated dosage forms. Eur. J. clin. Pharmac., 14, 351-355.
[50]. 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. Pliarmac., 19, 39-44.
[51]. 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.
[52]. 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.
[53]. 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.
[54]. Daneshmend, T. K. & Roberts, C. J. C. (1982).
[55]. 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.
[56]. Axelson, 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. Pharmac., 23, 735-743.
[57]. Von Phillipsborn. G.. Grics. J.. Hoffman. H. P.. Kreiskott. H.. Kretzschmar. R.. Muller. C. D..Raschack, M. & Tcschendorf. H. J. (1984). Pharmacological studies on propafenone and its main metabolite 5-hydiroxy-pr-opafenonc. Arznwitn1. - Forsch./Drug Res.. 34. 1489-1497.
[58]. Beerman, B. & Groschinsky-Grind, M. (1978). Antihypertensive effect of various doses of hydrochlorothiazide and its relation to the plasma level of the drug. Eur. J. clin. Pharmac., 13, 195-201.
[59]. 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.
[60]. Hamman, S. R., Blouin, R. A. & McAllister, R. G. (1984). Clinical pharmacokinetics of verapamil. Clin. Pharmacokin., 9, 26-41.
[61]. Woodcock, B. G., Kraemer. N. & Rietbrock, N. (1986). Effect of a high protein meal on the bioavailability of verapamil. Br. J. clin. Pl/armac.. 21. 337-338.
[62]. Crounse, R. G. (1961). Human pharmacology of griseofulvin: the effect of fat intake on gastrointestinal absorption. J. invest. Dermatol., 37, 520-528.
[63]. 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.
[64]. 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. Pharmac., 31, 319-325.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 554-563 www.ijprajournal.com ISSN: 2249-7781

[65]. Rosenberg, H. A. & Bates, T. R. (1976). The influence of food on nitrofurantoin bioavailability. Clin. Pharmac. Tlher.. 20. 227-232.
[66]. Neuman, M. (1988). Clinical pharmacokinetics of the newer antibacterial 4-quinolones. Clin. Pharmacokin., 14, 96-121.
[67]. Edwards, G. & Breckenridge, A. M. (1988). The clinical pharmacokinetics of antihelminthic drugs. Clin. Pharmacokin., 15, 67-93.
[68]. Munst, G., Karlaganis, G. & Bircher, J. (1980). Plasma concentrations of mebendazole during 628 P. A. Winstanley & M. L'E. Orme treatment of echinococcosis: Preliminary results. Eur. J. Cdin1. Phartnac.. 17. 375-378.
[69]. 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.
[70]. Horton, R. J. (1988). Introduction of halofantrine for malaria treatment. Parasitol. Today, 4, 238-239.
[71]. 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. Pharmac., 28, 71-77.
[72]. Melander, A., Brante, G., Johansson, 0. & Wahlin- Boll, E. (1979b). Influence of food on the absorption of phenytoin in man. Eur. J. clin. Pharmac., 15, 269-274.
[73]. Melander, A. & Wahlin, E. (1978). Enhancement of dicoumarol bioavailability by concomitant food intake. Eur. J. clin. Pharmac., 14, 441 444.
[74]. Welling, P. G. (1984). Interactions affecting drug absorption. Clin. Pharmacokin.. 9. 404-434.
[75]. Nakajima M, Uematsu T, Nakajima S, Nagata O, Yamaguchi T. Phase 1 study of HSR-803. Jpn Pharmacol Ther 1993; 21(11): 4157-73.
[76]. Mushiroda T, Douya R, Takahara E, Nagata O. The involvement of flavin containing monooxygenase but not CYP3A4 in metabolism of itopride hydrochloride, a gastrokinetic agent: comparison with cisapride and mosapride citrate. Drug Metab Dispos 2000; 28: 1231-37.
[77]. Banka NH. Role of prokinetics in dyspepsia. Gastroenterol Today 2003; 7: 1-4.
[78]. Iwanga Y, Kemura T, Miyashita N et al. Characterisation of acetylcholinesterase inhibition by itopride. Jpn J Pharmacol 1994; 66: 317-22.
[79]. Iwanga Y, Miyashita N, Morikawa K, Mizumoto A, Kondo Y, Itoh Z. A novel water soluble dopamine-2 antagonist with anticholinesterase activity in gastrointestinal motor activity. Gastroenterol 1990; 99: 57-64.
[80]. Pasricha PJ. Prokinetic agents, antiemetics agents used in irritable bowel syndrome. In: Hardman JG et al (eds.), Goodman and Gilman'ss The Pharmacological Basis of Therapeutics, 10th edition, New York, McGraw Hill Book Inc. 2001; pp 1021.

Fig 1:Classification of the food effect responses of prototype drugs on the basis of: (i) stability, chelation and/or complexation; (ii) effect on metabolism, and (iii) effect on permeability and/or solubility