COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COMMITTEE ON SAFETY OF MEDICINES

STATEMENT ON A JOINT COT/CSM ONE DAY MEETING ON DIET - DRUG INTERACTIONS

Introduction

1. Interaction between different drugs is a well-understood phenomenon. There are also a small number of well-characterised examples of interactions between food and drugs, but the extent and significance of diet and drug interaction is unclear.

2. The COT and the Committee on the Safety of Medicines[a] (CSM) held a joint meeting on the 2nd February 2005 to consider the issue of interactions between drugs and the diet. A range of topics covering many aspects of the subjects was considered. Information from the talks and subsequent discussions is summarised in the following statement.

Background

3. Interactions between different drugs may occur as a result of previous exposure or concomitant use. Interactions can be divided into two types, pharmacokinetic[b] and pharmacodynamic[c]. Pharmacokinetic interactions involve alterations to the absorption, metabolism and excretion of a drug in the body, while pharmacodynamic interactions involve more direct alterations in the effect of the drug (e.g. via common receptors), and are less common. Elderly patients in long term care may be taking an average of 7 medications[1] so that the potential for interactions in some individuals is great.

4. Some foods or food components may also have effects on drugs (referred to in this statement as food-drug interaction). It has been suggested[2] that there are over 200 drugs whose action or toxicity is affected by food. Many of these interactions occur via a limited number of pathways such as stimulating or

[a] The Committee on the Safety of Medicines is now known as the Commission on Human Medicines

[b] Pharmacokinetics describes the fate of a drug in the body including a mathematical account of their absorption, distribution, metabolism and excretion.

[c] Pharmacodynamics is the interaction of drugs with target sites such as receptors, leading to therapeutic or adverse effects.

inhibiting a particular enzyme system, thus effects occurring in one system may be applicable to multiple drugs. The effect that the presence or absence of food may have on a particular drug and the activities of metabolic enzymes are routinely considered in the investigations of new drugs (see paragraph 24).

5. The risk of food-drug interactions is likely to be highest in individuals taking multiple medications, or drugs with a narrow therapeutic index such as warfarin, lithium, theophylline, phenytoin and levodopa, or, where individuals may be taking high doses of vitamin, mineral or herbal supplements or functional foods[d]. Foods which have a high potential for interactions include grapefruit juice, milk and dairy products, fatty foods and potassium rich foods. Not only can some food components affect drug action or toxicity, drugs may affect the way an individual handles food and thus their nutritional status (referred to here as drug-food interactions). As with drug-drug interactions, food-drug interactions can be divided into pharmacokinetic and pharmacodynamic interactions. Fewer drug-food interactions have been identified and so they are normally considered individually.

Types of food-drug interaction

Pharmacokinetic interactions

6. Some food components may lead to reduced, increased or delayed absorption of drugs depending on the intestinal contents. Drugs may form inactive complexes with food components, while the fat content of food will affect the absorption of lipid-soluble and non lipid-soluble drugs in opposing ways. Splachnic blood flow (blood flow in the internal organs) can be increased by high protein meals but is unaffected by carbohydrate[3]; increased splachnic blood flow will increase drug absorption. Ketoconazole absorption is increased by the acidity of the intestinal environment which is food dependent. The first peak in the plasma levels of a drug occurs after initial gastric emptying, a second peak in plasma levels may occur when drugs are taken with food if the presence of the food delays further gastric emptying. Non specific food-drug effects may also occur due to changes in the normal motility of the intestinal tract.

7. Examples of more specific effects of foods on the absorption, distribution, metabolism and excretion of drugs are summarised in Table 1. It should be noted that while some foods can result in a clinically significant effect on drug pharmacokinetics, many of the interactions demonstrated experimentally may not affect the overall clinical effect of a drug in most people. For example, consumption of 250 g of cabbage and Brussels sprouts was necessary to cause a decrease in plasma area under the curve (AUC) and increased clearance of oxazepam, but this did not result in a change to the mean plasma half life of the drug[4].

8. The effect of food components on the metabolism of particular drugs may be different depending on whether short term inhibition or chronic induction of an

[d] Functional foods are foods which are claimed to have health promoting or disease preventing properties, such as margarines containing plant sterols.

enzyme system has occurred. Reported effects on drug metabolising enzymes have mostly involved the cytochrome P450 and conjugating enzyme systems, but other enzymes may also be involved. For example, vitamin B6 (pyridoxine) stimulates peripheral dopa-decarboxylase activity which increases the metabolism and decreases the efficacy of the drug[5]. Consequently, decarboxylase inhibitors are used with L-dopa to compensate for this effect. Vitamin B6 has also been reported to reduce plasma phenytoin and phenobarbital levels because of their metabolism by pyridoxine-dependent hydroxylase[6]. The clinical significance of this latter interaction is uncertain.

Table 1. Summary of individual food-drug interactions.

Food	**Drug**	**Interaction**	**Significance ?**	**Reference**
Absorption				
Milk and dairy products	Antibiotics (tetracycline and 4-quinolones)	Formation of non-absorbed chelates with calcium and magnesium ions.	Clinically significant, patients advised to leave 2 hr gap between drug and dairy consumption.	7
Milk and dairy products	Bismuth chelate	Ulcer –healing properties decreased	Clinically significant if milk volume is large.	7
High fat or carbohydrate diets	Theophylline	Bioavailability decreased by carbohydrate, increased by fat.	Could be clinically significant due to narrow therapeutic index	2
Distribution				
High fat diets	Various (includes warfarin)	Displacement of drug from albumin binding sites by free fatty acids	Significance unclear, may depend on drug concerned	8
Metabolism				
High protein, low-carbohydrate diets	Theophylline	Cytochrome P 450 (CYP) metabolism stimulated. Precise mechanism uncertain.	Could be clinically significant due to narrow therapeutic index	9
Grapefruit juice, St John's wort	Various (includes cyclosporine, terfenadine, statins, protease inhibitors)	Inhibition of CYP 3A4 enzyme-mediated metabolism	Yes, dosage adjustment may be required.	10
Grapefruit juice, St John's wort	Various	Inhibition of plasma glycoprotein drug efflux transporter MDR1	Unclear	10
Cruciferous vegetables	Antipyrine, phenacetin	Indoles induce CYP1A2	Unlikely to be of significance. Modest effect on CYP1A2 induction.	5 10
Cooked	Phenacetin	CYP1A induced by	Modest effects only	10

meats		heterocyclic amines decreases bioavailability.		
Broccoli	Chlorzax azone	CYP2E1 inhibited by sulphorane	Unclear	10
Brussels sprouts, cabbage	Paracetamol Oxazepam	Glucuronidation and clearance increased Clearance also increase but not by increased glucuronidation	Unclear –likely to be modest at normal dietary intakes. Unlikely to be significant.	4 4
Brussels sprouts, cabbage.	Paracetamol metabolites (and other compounds detoxified by glutathione conjugation.	Glutathione S transferase induced by sulphoranes, increases metabolism.	Unlikely to result in significant effects	10
Vitamin B6	L-dopa	Stimulation of peripheral dopa-decarboxylase	Yes, supplementation with pyridoxine not recommended	5
Excretion				
Fruit, vegetables	Phenobarbital	Increasing urinary alkalinity increases excretion	Unclear	8
Meat, eggs	Amphetamine	Increasing urinary acidity increases excretion	Unclear	8

Pharmacodynamic interactions

9. Pharmacodynamic interactions, which include pharmacological and receptor interactions are less common. Interactions of food constituents with drug targets are known to occur *in vitro* but often the concentrations occurring *in vivo* may be too low to be significant clinically. For example, curcumin a component of turmeric is known to be an inhibitor of COX-2 (cyclo-oxygenase 2)[e,11]. However curcumin is poorly absorbed *in vivo* [12]and so is unlikely to have any effect at realistic dietary intakes.

10. One of the most well documented pharmacodynamic interactions involves monoamine oxidase inhibitors (MAOIs) and the amino acid tyramine which is found in a variety of aged, overripe and pickled foods and to a lesser extent in chocolate and yeast-containing foods[2]. Tyramine is indirectly sympathomimetic, that is, it mimics the actions of hormones of the sympathetic nervous system such as noradrenaline. By suppressing its metabolism, MAOIs elevate noradrenaline levels in the circulation. However, tyramine metabolism is also suppressed, thus

[e] An enzyme which mediates prostaglandin synthesis during inflammation.

intact tyramine can then enter the circulation and release noradrenaline from local stores in the nerve endings. This prolongs the action of noradrenaline on the adrenergic receptors, potentially resulting in a marked increase in blood pressure, cardiac arrhythmia, hyperthermia and cerebral haemorrhage. Similarly Ma huang, an ephedra containing herbal medicine, can react with MAOIs resulting in a hypertensive crisis[2].

11. The medicinal herb St John's wort which is used to treat depression, has mild inhibitory effects on monoamine oxidase and serotonin reuptake, which may result in pharmacodynamic interactions with SSRI (selective serotonin reuptake inhibitor) drugs such as fluoxetine and paroxetine[13].

Notable diet-drug interactions

Grapefruit juice

12. Among the best known food–drug interactions are those of grapefruit juice and drugs metabolised by CYP3A4. Grapefruit juice inhibits CYP3A4 which is the major form of cytochrome P450 in the human liver and gut. Inhibition of CYP3A in the gut by the furanocoumarins present in grapefruit juice may result in increased drug bioavailability, this in turn may result in enhanced or reduced drug activity and/or increased side effects. Up to half of clinically used drugs are metabolised by CYP3A4, resulting in a number of potentially significant adverse effects. For example, the effects of calcium channel blockers are enhanced resulting in a risk of hypertension and myocardial ischaemia[14]. Similarly, the central nervous system (CNS) depressant effects of benzodiazepines are increased as a result of increased absorption. Other drugs affected by grapefruit juice include hydroxymethylglutaryl Co-enxyme A (HMG-Co-A) reductase anti-cholesterol drugs, immunosuppressants such as cyclosporin, protease inhibitors, and anti-histamines.

13. The multidrug resistance 1 (MDR1) glycoprotein is a drug transporter that is inhibited by grapefruit juice. MDR1 transports drug molecules from the cells of the gut wall back into the intestinal lumen, thus inhibition of MDR1 can also result in increased bioavailability of the drug[15]. Thus the effect of grapefruit juice on the bioavailability of certain drugs can be further enhanced by its effects on the MDR1 glycoprotein since many substrates for CYP3A4 are also substrates for MDR 1.

14. The plasma concentration of the anti-histamine fexofenadine is decreased by grapefruit juice as result of inhibition of intestinal organic anion transporting polypeptide A[16].

15. Alteration to drug metabolism may occur with consumption of both processed and freshly squeezed grapefruit juice and grapefruit segments. The maximum interaction occurs between 0 and 4 hours of consuming grapefruit but some interaction may persist for up to 24 hours[17].

Alcohol

16. Ethanol has both pharmacokinetic and pharmacodynamic effects, and can interact both with drugs and with food[18]. Pharmacokinetic interactions generally occur in the liver and involve many classes of drugs including antibiotics and antihistamines. For example, ethanol induces CYP2E1, which may lead to either increased or decreased efficacy or toxicity, depending on the drug. The ethanol induced increase in CYP2E1 enhances the breakdown of paracetamol increasing the formation of the toxic quinonimide products and the depletion of glutathione, which in turn may result in an increased risk of paracetamol hepatotoxicity[5]. Ethanol may potentiate the sedative effect of opiates and benzodiazepines by pharmacodynamic interactions with the GABA (gamma amino butyric acid) complex of receptors.

17. Ethanol can also contribute towards vitamin deficiency, hinder the absorption of drugs and result in abnormal vitamin D metabolism, via interference with steroid metabolism. Inhibition of alcohol dehydrogenase by cephalosporins and ketoconazole reduces ethanol breakdown.

Warfarin

18. The indoles present in green vegetables are able to induce CYPIA2 increasing warfarin metabolism and thus may reduce its effectiveness and increase the risk of clotting[10]. Warfarin efficacy is also reduced by competition with high levels of dietary vitamin K which favour synthesis of clotting factors. Cranberry juice has been reported to reduce warfarin metabolism, possibly via inhibition of CYP2C9 by the flavanoids present in the juice[19]. Other foods reported to reduce warfarin efficacy include large quantities of ice cream, soya beans and avocados[7]. The clinical significance and prevalence of these latter reports is unclear.

Lithium

19. Dietary sodium restriction may increase tubular reabsorption of therapeutic agents in the kidney as normal homeostatic mechanisms operate to maintain sodium levels. For example, serum lithium is reabsorbed along with sodium and thus can be increased to potentially toxic levels[20, 21]. Increased sodium intake may have the converse effect. Once stabilised on lithium, patients should not alter their sodium intake.

Herbals

20. Herbal products may have the legal status of either medicines or of food. A recent literature review[22] of theoretically possible interactions involving complementary and alternative medicine reported that in the last 15 years, there were 56 articles reporting interactions between drugs and herbs, 44 of which concerned St John's Wort (see paragraph 22 below) compared to 44 articles reporting interactions between food and drugs, 24 of which were related to grapefruit juice.

21. There are several aspects of herbal products which increase their potential for interaction with food or drugs. Synthetic drugs tend to have one active ingredient, while herbal medications usually have several active components, thereby increasing the potential for interactions with other drugs or components of the diet. The composition of synthetic drugs is constant, the composition of herbal medicines can vary. In addition, the therapeutic window of herbal drugs is usually wide, while that of synthetic drugs tends to be narrow. Identification of interactions may be difficult because many patients do not inform their doctors that they are taking herbal or other complementary products.

22. The medicinal herb St John's wort can interact with a variety of drugs. It can induce CYP3A4 activity resulting in a reduction in plasma levels of drugs such as cyclosporin or the anti-HIV drug indinavir. It is thought that the effect on CYP3A4 may occur via interaction with the pregnane X receptor (PXR) which induces CYP3A4 activity[23]. St John's wort can also induce the MDR1 transporter, reducing, for example, plasma concentrations of digoxin[24].

Drug-food interactions.

23. As noted above, there are a few examples of drugs which affect an individual's handling of food and consequently their nutritional status. This may be due to the mode of action of the drug, for example, diuretics may promote urinary mineral loss and anti-cholesterol drugs may deplete fat soluble vitamins. It is therefore important to seek a balance between optimising a patient's nutritional needs and the drug levels necessary for efficacy. More specifically, anti-convulsant drugs such as phenytoin may act as folate antagonists and precipitate folate deficiency[25]. Drug-food effects may be less direct; for example antibiotics may alter enteric micro-organisms resulting in reduced absorption of fat-soluble vitamins[26]. Drug-induced enzyme activity may increase the metabolism of vitamins.

Prediction of potential interactions

24. Pharmaceutical companies are required to consider potential drug-drug interactions as part of the pre-clinical data supporting applications for marketing authorisations for new chemical entities. An interaction is considered to be clinically relevant when the therapeutic activity or toxicity of the drug is affected to such an extent that adjustment of the medication or medical intervention is required, or when concomitant use of drugs could occur when both are used as therapeutically recommended.

25. Guidelines are available[27] which cover pharmacokinetic and pharmacodynamic issues, though these do not take into account factors such as age, gender, ethnic origin, physical activity and time of administration (which may affect drug disposition). Relevant factors that should be studied include: the effect of food on the drug; the physicochemical properties of the drug and formulation; pharmacokinetics, pharmacodynamic properties such as effects on the gut (motility, pH, bile secretion, blood flow); the potential for toxic damage to the

gastrointestinal tract. Potential inhibition of MDR1 should be considered, as should factors affecting drug distribution which may influence interactions. For example, the displacement of drugs from plasma proteins would be assessed by protein binding, tissue distribution and other studies.

26. Metabolic interaction studies are mainly required where metabolic pathways account for 30% or more of drug elimination or where active or toxic metabolites are formed by minor pathways. The primary CYP isozymes responsible for drug metabolism are determined, and it also is established whether the drug is an inducer or inhibitor of these systems. Phase II metabolism (conjugation of the initial metabolites produced by Phase I metabolism) should also be assessed. A variety of these enzyme systems could be affected by food or food components, but this is not specifically assessed.

27. Pharmacodynamic effects may be predictable from the pharmacokinetic profile of the drug, if it is likely to be co-administered with drugs which have a mechanism or end organ response that could result in additivity, synergy, or opposing effects. Examples include MAOIs and other antidepressants. Information is necessary on whether the mechanism is primary or secondary. The product would undergo *in vitro* receptor profiling with a range of ligand binding studies (on receptors, ion channels and transporters); positive binding results might require *in vitro* or *in vivo* functional tests to look at agonist or antagonist effects. It should then be considered whether any effects would occur at the therapeutic dose.

28. In the EU, specific interactions between drugs and food do not have to be considered and clinical trials are not conducted using a standard diet.

Vulnerable groups

29. It is possible that certain population sub-groups may be more vulnerable to the effects of food-drug and drug-food interactions, although information on this area is limited.

30. The elderly may have differences in body composition which affect drug distribution[28], while reduced absorption occurs in the frail elderly who are also prone to malabsorption syndrome, eat inappropriate food and who may suffer from inflammatory bowel disease or other chronic diseases. While the activity of some metabolic enzymes is unchanged in older people, liver blood flow and size are reduced so that overall metabolic clearance of xenobiotics is reduced[29]. Renal excretion is also reduced in older people. Many older people may be taking multiple medicines increasing the potential for interactions[26].

31. Children may be vulnerable to potential interactions as they have high inter-individual variability and different, frequently higher, nutrient requirements. Whilst dosages for children can be estimated by allowing for bodyweight or body surface area this does not account for other age-related pharmacokinetic differences such as organ development[28].

Obesity

32. Diet may have an indirect effect on drug action mediated by body weight. Obesity is characterised by a number of changes in body composition[30]. These include increased adipose and lean tissue mass, increased organ mass with fatty infiltration, increased cardiac outflow and blood volume and changes in plasma protein binding.

33. The absorption of drugs in the clinically obese may occur in an unpredictable fashion[31]. The volume of distribution for a drug might be difficult to predict, for example, whether lipophilic drugs will be absorbed into fat tissues and, if so, what the consequences of such absorption might be. Obese patients may have an increased volume of distribution into adipose tissue for barbiturates and diazepam, whereas digoxin and cyclosporin may have a lower volume of distribution than expected.

34. Characteristic alterations in lipoproteins may inhibit protein binding of drugs, for example, α-1-acid glycoprotein may increase the degree of protein binding of triazolam and propranolol[31]. However, albumin binding is generally unaffected[32].

35. Obese patients are at an increased risk of venous thrombotic embolism (VTE). An even greater risk of VTE is associated with being overweight (BMI >25) and using combined oral contraception, where the risk of VTE is 10-fold higher than in women of lower body weight[33].

36. In females, obesity is linked with an increased conversion of oestradiol to oestrone and an increased production of testosterone. There is also an association between increased body weight (>70 kg) and an increased risk of contraceptive failure[34].

37. Obesity may also alter hepatic oxidative metabolism of some drugs, for example, CYP 2E1 levels are increased resulting in a predisposition to drug toxicity mediated by this enzyme[35]. Changes have also been reported for the phase II conjugation pathways in the liver, such as glucuronidation and sulphation. Drugs such as lorazepam and oxazepam are more rapidly cleared from the blood in obese patients due to increased excretion as a glucuronide conjugate[31]. However, the pharmacokinetics of other pharmaceuticals, such as salicylates and procainamide, are not significantly altered.

38. Increased adipose tissue results in increased clearance of prednisolone, prednisone and carbamazepine[31] changes in oestradiol metabolism, and increased resistance to insulin[30]. Some of the reported changes are reversed on weight loss. Renal function can also be affected in obesity. Glomerular filtration rates and tubular secretion are increased and as a result, drugs such as ciprofloxacin, cimetidin, procainamide and lithium are more rapidly cleared[31].

39. Treatment for obesity may also influence drug action. For example, obese patients may undergo gastric surgical procedures to limit the ability to digest consumed food, or be prescribed pancreatic lipase inhibitors such as orlistat,

which blocks the hydrolysis of dietary fat and thereby inhibits its absorption. This may have an impact upon, for example, the absorption of fat-soluble vitamins.

Future issues

40. The range of foods available is developing rapidly, resulting in a potential for more interactions in the future. Some of these possibilities are considered below.

41. Some functional foods are designed to promote well being by altering the microbiological content of the intestine. The enterohepatic circulation of many drugs depends on microfloral ß-glucuronidase which itself depends on the microfloral population. Thus functional foods of this type might result in food-drug interactions.

42. The phytoestrogen genistein is an isoflavanoid found in soya. Genestein has multiple effects on receptors, enzymes and a variety of their activities *in vivo* and *in vitro*[36]. These include induction via the steroid and xenobiotic pregnane X receptor, inhibition of thyroid peroxidase, topoisomerase II, protein kinases, *in vivo*, cell proliferation. Genestein is also a potent sulphotransferase inhibitor, and inhibits the enzymes glucuronidase and aromatase, 17ß-hydroxysteroid oxidoreductases. It can modulate sex hormone binding protein and has a high affinity for the estrogen receptor. These multiple activities could have the potential for both pharmacokinetic and pharmacodynamic interactions affecting hormone control and therapy.

43. Current health advice is to reduce the sodium content of the diet. However, it should not be assumed that replacement of sodium by potassium salts, either domestically or by food manufacturers, would necessarily have health benefits. Increased potassium levels can lead to hyperkalaemia and in turn to cardiac abnormalities. Drugs such as potassium-sparing diuretics, ACE inhibitors and COX-2 anti-inflammatory agents are known to result in elevated potassium as a result of impaired potassium clearance; in combination with a potassium rich diet, serious interactions could occur[37]. Elevated potassium is of particular concern in subjects with impaired renal function who are unable to regulate potassium levels.

Conclusions

44. Food and food constituents have the potential to affect all aspects of the absorption, distribution, metabolism and excretion of drugs. The effects may vary depending on whether there is single, concomitant or prolonged exposure. Certain food constituents alter metabolic parameters such as enzymes which can have opposing or unpredictable effects on different drugs. Often the most appropriate practical advice is that patients stabilised on a particular drug should not change their diet.

45. Food itself is a complex mixture of both macro and micronutrients, making interactions and potential interactions difficult to assess. The use of food

supplements such as micronutrients and herbal products also increase the scope for interactions.

46. Interactions have most frequently been demonstrated under experimental conditions. To assess the clinical significance of individual reactions, it is necessary to consider the likely consumption of the food and drug and the severity of the potential outcome. For example the well-documented interactions between grapefruit juice and a range of drugs is widely known and clinically important since it could result in severe outcomes in a few individuals. In contrast, milk and dairy products can reduce the uptake of certain antibiotics, and both milk and dairy products and antibiotics are widely consumed. In practice, however, interactions between them are likely to be overlooked as they are unlikely to be life threatening.

47. There are few data on vulnerable groups but it seems that the most likely population subgroups vulnerable to food-drug interactions are the elderly, particularly the frail elderly, and children.

48. In some cases practitioners have built up knowledge about interactions in specific groups of patients taking particular drugs such as the interaction between St John's wort and anti-HIV drugs such as indinavir. It is important that this type of information is appropriately disseminated.

49. On the basis of current evidence the issue of food-drug interaction is a real one but not one of great clinical significance for the majority of the population. However, data are limited and further interactions may be identified in the future. Rather than widespread public information, it is most appropriate that practitioners and prescribers should be aware of the potential for food-drug interactions and should consider them both when prescribing drugs and where lack of efficacy or unexpected adverse reactions have occurred.

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