Important drug nutrient interactions

Pamela Mason
Why is a drug nutrient interaction?
Types and mechanisms of interaction
Influence of drugs on nutrition
Interactions between supplements and drugs
Interactions involving St John’s wort and grapefruit juice
Risk and implications of interactions
Patient care
What is a drug nutrient interaction?

That which results from a physical, chemical, physiological or pathophysiological relationship between a drug and a nutrient. The interaction is considered significant from a clinical perspective if therapeutic response is altered (reduced or enhanced)
Context

- Potential for interactions appear infinite, *but*
- What proportion of these have been identified?
- What number of the identified subset are clinically relevant?
Diagnosis

- Any outcome should be consistent
- A reasonable temporal relationship between the intake of the drug, the nutrient and the observed effect
- The association should be plausible
Clinical effects

- Failure of drug therapy
- Nutritional deficiencies
- Adverse drug events
- Discontinuation of the drug
Types of interactions

- Pharmacokinetic (e.g., tetracyclines and calcium, iron; levothyroxine and calcium)
- Pharmacodynamic (e.g., vitamin B6 and levodopa, St John’s wort and anticoagulants, antiepileptics, cytotoxics)
- Drug and nutrient/supplement have similar action (e.g., fish oils and anticoagulants; St John’s wort and antidepressants)
- Supplement counteracts drug (e.g., echinacea and immunosuppressants)
- Beneficial interactions
  - probiotics and antibiotics
Drugs influence:

- Ingestion
  - Appetite
  - Taste
- Secretion
  - Oral secretion
  - Gastric acid secretion
- Absorption
  - Gastrointestinal drug metabolising enzymes
  - Gastrointestinal transporters
- Gastrointestinal motility
- Gastrointestinal flora (immunity)
- Nutrient metabolism
- Nutrient excretion
Drugs and appetite

Reduce appetite
- Amantadine
- Digoxin
- Fluoxetine
- Levodopa
- Lithium
- Metformin
- Penicillamine

Increase appetite
- Cyproheptadine
- MAOIs
- Tricyclics
- Valproate
Drugs and taste

- ACE inhibitors
- Allopurinol
- Amiodarone
- Baclofen
- Griseofulvin
- Lithium
- Metformin
- Metronidazole
- Penicillamine
- Terbinafine
Drugs and oral secretion

- Suppression of saliva production – dry mouth (xerostomia)
- Anticholinergics (eg, antihistamines, tricyclics, orphenadrine, oxybutinin, procyclidine, propantheline, trihexyphenidyl hydrochloride)
- Selegeline
Gastric acid secretion

- Influence on intrinsic factor- vitamin B12 absorption
- Proton pump inhibitors 1-3
- H2 receptor antagonists 1-3

Drugs and intrinsic factor

- Allopurinol
- Colestyramine
- Colchicine
- Metformin
- Methyldopa
- Neomycin
Drugs and absorption

- Modulation of mucosal enzymes
- Modulation of intestinal transporters
- Formation of insoluble complexes (eg, tetracyclines, quinolones, doxycycline, lymecycline, minocycline, penicillamine)
- Binding of bile acids (eg, colestyramine, colestipol)
Gastrointestinal drug metabolising enzymes and transporters

- Cytochrome P450 (CYP)3A4 – regulates oral bioavailability of drugs and nutrients
  - Grapefruit juice
  - St John’s wort

- P-glycoprotein
  - Inhibition (eg, water soluble vitamin E)
    - Increased bioavailability of ciclosporin1 and digoxin2
  - Induction (eg, St John’s wort3)
    - Reduced bioavailability of ciclosporin, digoxin and indinavir

JPEN 2001;25:132-41

Gastrointestinal motility

- Benzhexol
- Benztropine
- Dicyclomine
- Oxybutinin
- Procyclidine
- Propantheline
- Tricyclic antidepressants
Gastrointestinal flora

- Antibiotics
  - Destruction of gut flora
  - Antibiotic associated diarrhoea
  - Reduction in production of B vitamins and vitamin K
Probiotics

- Lactobacillus GG and Saccharomyces boulardii – trials indicate benefit of both in prevention of antibiotic-associated diarrhoea
- S boulardii – trials indicate benefit in Clostridium difficile disease (less convincing evidence for Lactobacillus GG)
## Probiotics in antibiotic-associated diarrhoea – meta-analyses

<table>
<thead>
<tr>
<th>Number of trials</th>
<th>Relative risk (RR)</th>
<th>95% CI</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>9</td>
<td>0.37</td>
<td>0.26-0.53; P&lt;0.001</td>
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<tr>
<td>BMJ 2002;324:1361</td>
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<tr>
<td>22</td>
<td>0.39</td>
<td>0.27-0.57</td>
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<tr>
<td>Aliment Pharmacol Ther 2002;16:1461-7</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>0.43</td>
<td>0.23-0.78</td>
<td>NNT =10 (S boulardii)</td>
</tr>
<tr>
<td>Aliment Pharmacol Ther 2005;22:365-72</td>
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<tr>
<td>25</td>
<td>0.43</td>
<td>0.31-0.58, p&lt;0.001</td>
<td>(S Boulardii, Lactobacillus GG, probiotic mixture)</td>
</tr>
<tr>
<td>Am J Gastroenterol 2006;101:812-22</td>
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<td></td>
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</table>
## Drugs and nutrient metabolism

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frusemide</td>
<td>Thiamine</td>
</tr>
<tr>
<td>Isoniazid, hydralazine, penicillamine, OCs, theophylline</td>
<td>Pyridoxine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Folic acid</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Vitamin K</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td></td>
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<tr>
<td>Trimethoprim</td>
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Grapefruit juice interactions
(BNF 57, Appendix 1)

- Buspirone
- Calcium channel blockers (felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nislodipine, verapamil)
- Carbamazepine
- Ciclosporin
- Ethinyloestradiol
- Saquinavir
- Sildenafil
- Sirolimus and tacrolimus
- Simvastatin
Grapefruit juice inhibits 2 of the 6 major P450 enzymes: 3A4 and 1A2
3A4 is located in the liver (30%) and gut wall (70%)
Grapefruit juice selectively inhibits gut wall 3A4 with little effect on hepatic 3A4

- Effects on oral drugs (eg oral midazolam vs IV midazolam)

Grapefruit juice components responsible:
- Flavonoids: naringenin, naringin
- Furanocoumarins: bergamottin, 6’,7’-dihydroxybergamottin

Whole grapefruit
Confectionery made from grapefruit peel?

Inhibition is fully developed after 1 glass of juice and lasts up to 24 hours
St John’s wort interactions
BNF 57, Appendix 1

- Anticoagulants
- Antidepressants
- Antiepileptics – carbamazepine, phenytoin, primidone
- Antimalarials
- Antipsychotics
- Antivirals
- 5-HT antagonists
- Oral contraceptives
- Ciclosporin
- Digoxin
- Phenobarbitone
- Tacrolimus
- Theophylline
Mechanisms of SJW interactions

- Induction of intestinal transporter (e.g. P-gp) activity
- Increased activity of CYP3A4 (liver and intestine) and CYP2B6
- Additive serotonergic effects with SSRIs (e.g., paroxetine, sertraline, trazodone, nefazodone)
Pharmacokinetic interactions with SJW

**CYP3A4 substrates**
- Antiarrhythmics (digoxin, quinidine, amiodarone)
- Calcium channel blockers (diltiazem, verapamil, nifedipine)
- Immunosuppressants (ciclosporin, tacrolimus)
- Protease inhibitors (amprenavir, indinavir, saquinavir, indinavir, nelfinavir, saquinavir)
- Antiepileptics (carbamazepine)
## Interactions with vitamin and mineral supplements

<table>
<thead>
<tr>
<th>Supplement (precipitant)</th>
<th>Drug (object)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid</td>
<td>Phenytoin</td>
<td>↓ drug effect</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Levodopa</td>
<td>↓ drug effect</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Ciclosporin</td>
<td>↑ drug effect</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Anticoagulants</td>
<td>↓ drug effect</td>
</tr>
<tr>
<td>Calcium</td>
<td>Thyroid hormone</td>
<td>May reduce drug absorption</td>
</tr>
<tr>
<td>Iron</td>
<td>ACE inhibitors</td>
<td>May interfere with drug absorption</td>
</tr>
<tr>
<td></td>
<td>Levodopa/carbidopa</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>ACE inhibitors</td>
<td>↑ risk of hyperkalaemia</td>
</tr>
<tr>
<td>Divalent minerals</td>
<td>Pencillamine</td>
<td>↓ drug availability</td>
</tr>
<tr>
<td></td>
<td>4-quinolones</td>
<td>↓ drug availability</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
<td>↓ drug availability</td>
</tr>
</tbody>
</table>
### Some proposed interactions between non-nutrient supplements and drugs

<table>
<thead>
<tr>
<th>Supplement (precipitant)</th>
<th>Drug (object)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-adenosyl-methionine</td>
<td>SSRIs</td>
<td>Risk for serotonin syndrome</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Warfarin</td>
<td>May potentiate drug effect</td>
</tr>
<tr>
<td>Co-enzyme Q</td>
<td>Warfarin</td>
<td>May antagonise drug effect</td>
</tr>
<tr>
<td>Dong quai</td>
<td>Warfarin</td>
<td>May potentiate drug effect</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Immunosuppressants</td>
<td>Potential for altered drug effectiveness</td>
</tr>
<tr>
<td>Feverfew</td>
<td>NSAIDs</td>
<td>Additive inhibition of prostaglandin production</td>
</tr>
<tr>
<td>Fish oils</td>
<td>Anticoagulants</td>
<td>May have additive effects (by different mechanisms)</td>
</tr>
<tr>
<td>Garlic</td>
<td>Saquinavir</td>
<td>May reduce blood levels of the drug</td>
</tr>
<tr>
<td>Genistein</td>
<td>Paclitaxel</td>
<td>May improve availability of drug</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Oral hypoglycaemics</td>
<td>Additive hypoglycaemic effects</td>
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<tr>
<td>Ginkgo biloba</td>
<td>Anticoagulants</td>
<td>Possibly increased bleeding</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>Warfarin</td>
<td>May potentiate drug effect</td>
</tr>
<tr>
<td>Valerian</td>
<td>Sedative drugs</td>
<td>May potentiate sedative effects</td>
</tr>
</tbody>
</table>
Prevalence of supplement and medicine use

- US study in 1539 adults - 44% on prescribed medicines; 20% of these using herbal or high dose vitamins
- UK study on 164 herbal medicine users - 59% had taken conventional medicines
- Canada study in 195 older patients - 97% on prescription medicines and 17% using natural health products
- Studies in cancer and HIV patients 50-65% using supplements/CAM
- US study in 979 pre-operative patients undergoing anaesthesia – 17.4% reported current use of herbal or dietary supplements
Risk of interaction

- Survey of 458 US patients taking prescription medicines
- 197 (43%) taking supplements
- Vitamins, minerals, ginkgo biloba, garlic, saw palmetto, ginseng
- 89 (45%) had potential for interaction
- 6% were potentially serious

Arch Intern Med 2004;164:630-6
Study in cancer patients

- Supplements used by 61% of cancer patients (121 patients)
- 65 patients (54%) reported taking >1 supplement
- Risk for interaction identified in 12% of patients
- Documentation on medical record in only 28% of patients taking supplements

Am J Clin Oncol 2006;29:178-82
Mayo Clinic Study

- 1795 patients in 6 specialty clinics
- 39.6% reported use of supplements
- 107 potentially clinically significant interactions
- Supplements: 68% of interactions accounted for with garlic, valerian, gingko, St John’s wort
- Drugs: 94% accounted for with antithrombotic medicines, sedatives, antidepressants and antidiabetic agents
- No patient seriously harmed

Patients at risk

- Multiple or long-term drug regimens
- Diseases that prejudice nutritional status
- Enteral or parenteral nutrition
- Poor diet
- Medication taken at mealtimes
- Drugs with narrow therapeutic margins
- Drugs that alter taste, appetite or cause GI disturbances
Patient care

- Use only essential drugs for as short a time as possible
- Take diet-supplement- herbal-drug histories
- Consider timing of medication in relation to food
- Clinical monitoring
- Changing drug therapy where necessary
Conclusion

- Interactions a concern in the context of increased use of medication and supplements
- Much more data and evidence to generate
- Clinical significance of some interactions not well understood
- Patients should be routinely screened for supplement and herbal use
Finally...

Thank you for listening!

pamelamason@apotek.org.uk