Interactions of OTCs with prescription and non-prescription medicines

Clinically significant interactions between popular OTC, herbal and complementary medicines and 'regular' prescription and non-prescription drugs are discussed.

JOE TALMUD
Dip Pharm

Drug Information Pharmacist
Medicines Information Centre
Division of Pharmacology
Faculty of Health Sciences
University of Cape Town

Joe Talmud qualified as a pharmacist at Cape Technical College in 1973. He did various locums in retail and hospital pharmacy and ran his own pharmacy from 1975 to 1997. He joined the Medicines Information Centre in 1984 part-time and trained in drug information. He was appointed full-time in 1996, and is responsible for answering drug-related queries and continuing education.

CASE STUDY

A 78-year-old woman presented at a clinic complaining of several weeks of headache which was persistent and sited over the vertex. On examination she was found to have blood pressure readings of 170 - 180/100 - 115 mmHg and was placed on hydrochlorothiazide 25 mg in the morning.After a week she had severe pain in her left big toe which was hot and throbbing, and she bought diclofenac tablets at the pharmacy. A week later she was brought into the clinic in a wheelchair by her daughter, who told the doctor that her mother was very short of breath and unable to walk more than a few steps. Congestive cardiac failure and aggravated hypertension was diagnosed. The diuretic dose was doubled to 50 mg daily and nifedipine was added to control her blood pressure. A week later she presented again, this time with bilateral pedal oedema.The doctor added 40 mg of furosemide to treat her swollen ankles. No sooner had she begun the furosemide than she again had severe throbbing pain in her left toe and phoned the pharmacy to send round some more diclofenac.

Can we explain what has happened?

The elderly are particularly sensitive to high doses of diuretics and 25 mg of hydrochlorothiazide was sufficient to raise her blood uric acid and precipitate an acute attack of gout.The addition of diclofenac (and this would apply to any non-steroidal anti-inflammatory drug) caused acute sodium and water retention, tipping her into congestive cardiac failure (CCF).When the diuretic dose was doubled this caused another attack of gout.The diclofenac also raised her blood pressure (by vasoconstriction of the afferent renal artery) as elderly folk usually have impaired renal function. Ankle oedema is a common side-effect of the dihydropyridine calcium channel blockers (nifedipine, amlodipine, felodipine etc.) and adding a diuretic won't solve the problem. Nifedipine is not the ideal drug to treat CCF as it elevates sympathetic tone which is already elevated by the CCF.

In a recent survey in Denmark of 492 people aged 75+ years, 87% were receiving prescribed medicines while 72% of these were also taking over-the-counter (OTC) drugs. On average these elderly folk were taking 4.2 different prescribed drugs and 2.5 OTC drugs.[1] Drug policies in Western countries generally support responsible self-medication with OTC drugs. In many European countries such medicines are sold only in pharmacies.[2] In the USA, however, non-prescription drugs are available at health food stores, service stations, supermarkets and pharmacies, there being no restriction on their sale through these outlets. Because of the possibility of adverse events such as the recent concerns relating to the potential

for hepatotoxicity of kava kava, a popular herbal anxiolytic, and the possibility of potentially serious drug interactions,[3] it is mandatory to take a comprehensive drug history including OTCs, herbal medicines and complementary substances, e.g. DHEA, ginseng, St John's wort etc. in **every** case. Research suggests that drug interactions are responsible for considerable patient morbidity and mortality.

WHAT IS A CLINICALLY SIGNIFICANT DRUG INTERACTION?

It should be one

- with rapid onset of action, say within hours
- of life-threatening severity, or able to cause deterioration in the patient's status or be sufficiently uncomfortable or inconvenient
- with documented support based on reports in the biomedical literature
- with a high likelihood of occurring in clinical practice.

Age-related changes such as loss of total body water, muscle content and mass, serum albumin, reduced cardiac and renal function are all capable of increasing the risk of drug interactions. These changes contribute to altered drug absorption, distribution, metabolism and excretion.[4,5]

SMOKING

Cigarette smoking remains prevalent in most countries. It can affect drug therapy by both pharmacokinetic and pharmacodynamic mechanisms (Table I). The mechanism most often involved in drug-cigarette interactions is the induction of liver metabolism. Drugs whose metabolism is induced by cigarette smoking include theophylline, caffeine, haloperidol, heparin and propranolol. The implication here is that the drugs are cleared much faster, and plasma concentrations fall. Cigarette smoking is also associated with pharmacodynamic interactions, e.g. a lower magnitude of blood pressure lowering by beta-blockers, less sedation with benzodiazepines and less analgesia from some opioids, most likely reflecting the stimulant effects of nicotine.[6]

Table I. Some interactions between smoking and drugs

Drug	Effects of smoking
Alcohol	Delayed gastric emptying
Caffeine	Increased clearance by 56%
Clozapine	Decreased plasma concentration by 28%
Fluvoxamine	Decreased plasma concentration by 47%
Insulin	Possible higher requirements in smokers
Olanzapine	Increased clearance
Theophylline	Increased clearance
Warfarin	Decreased plasma concentration

ALCOHOL

Alcohol in all its forms and guises, from trifle to cough mixture and from Dutch medicines to 'light beer' is a central nervous system depressant and impairs the ability to drive safely and operate machinery. The consumption of even small quantities, added to OTC drugs such as antihistamines in cough and cold preparations, multi-ingredient painkillers, asthma mixtures with theophylline, and cimetidine, is a recipe for potential disaster.

HERBAL AND COMPLEMENTARY DRUGS

Herbal and complementary drugs are now widely used by all sectors of the population and are frequently not disclosed by the patient as they are considered 'natural' and therefore 'safe'. Nothing could be further from the truth! St John's wort (hypericin, hypericum) used as an antidepressant has powerful liver enzyme-inducing properties which increase the metabolism of drugs, thereby decreasing the efficacy of many drugs including oral contraceptives, cyclosporin (thus increasing the risk of organ graft rejection), warfarin and theophylline. Because of its serotonin-like action, adding serotonin-enhancing drugs such as sertraline, pethidine, tramadol, clomipramine or fluoxetine, for example, increases the risk of inducing the potentially lethal serotonin syndrome.[7]

Decongestants should also not be used in patients with thyroid disease, epilepsy, any form of heart disease, diabetes or prostatism.

Ginkgo biloba is used in Alzheimer's disease, and to treat memory impairment in the elderly and circulatory disorders. Its constituents have antiplatelet activity and there are cases on record of spontaneous bleeding in patients on warfarin or aspirin. There is also one case on record of hypertension when ginkgo was taken with a thiazide diuretic, although this is not readily explainable.[7]

Garlic is being promoted to lower cholesterol and blood pressure. It also has antiplatelet activity. Increased international normalised ratio (INR) has been reported when given with warfarin, and hypoglycaemia has occurred in a diabetic woman taking chlorpropamide.[7] Kava kava is used as an anxiolytic and may have additive effects with benzodiazepines, particularly alprazolam[8] and dopamine blockers such as prochlorperazine and metoclopramide. Ginseng, sold as a tonic, may interact with warfarin and monoamine-oxidase inhibitors. Echinacea should not be given together with immunosuppressants.

Saw palmetto does not appear to interact with other drugs.[7] Fluvoxamine significantly increases melatonin levels, leading to increased drowsiness, while melatonin use with nifedipine leads to increased blood pressure.[8] Side-effects of caffeine (restlessness, jitteriness and insomnia) are exacerbated by quinolone (e.g. ciprofloxacin), antibiotics and SSRIs e.g. paroxetine.[9] Grapefruit, a part of many a breakfast, is a liver enzyme inhibitor and will increase the plasma levels of many drugs that are metabolised by the cytochrome p450 enzyme system. Examples include the calcium channel blockers, carbamazepine, clozapine, cisapride, some antiretroviral agents, statins, sildenafil, antihistamines (particularly the new generation non-sedating types) and warfarin.These combinations are to be avoided.[10]

ANTACIDS AND H_2 RECEPTOR BLOCKERS

These drugs are frequently bought OTC and present drug interaction problems with theophylline, warfarin and phenytoin. Ranitidine, famotidine or nizatidine should be used instead of cimetidine which may raise theophylline levels by 33 - 50% with consequent toxicity. Cimetidine should not be used with warfarin as bleeding may occur. Ranitidine or famotidine may be tried, but the INR should be closely monitored. Antacids chelate fluoroquinolones, rifampicin, azithromycin and tetracyclines. Their combination must either be avoided or their doses spaced 3 - 4 hours apart.The rate and extent of absorption of some hypoglycaemic agents may be influenced by antacids, as is ketoconazole, but evidently not fluconazole. Similar chelating effects occur with sucralfate. Separating digoxin, phenytoin, beta blocker and benzodiazepine dosing well away from antacids is advisable.[4] The addition of cimetidine to beta-blockers may decrease their clearance. Similarly cimetidine interacts with antiarrhythmic drugs such as quinidine, flecainide and procainamide.These agents have narrow therapeutic indices and extra caution is warranted when these are given with cimetidine.

Herbal and comple - mentary drugs are now widely used by all sectors of the population and are frequently not dis - closed by the patient as they are considered 'natural' and therefore 'safe'.

ANTIHISTAMINES AND ANTI-NAUSEANTS

Neither 'old-generation agents' such as chlorpheniramine, cinnarizine, promethazine or cyclizine nor the new-generation antihistamines such as loratidine should be combined with alcohol in any form. Remember too that many medicines in liquid form may contain substantial amounts of alcohol. Examples include 'Dutch medicines' such as boegoe-essens and versterkdruppels. Combination with anxiolytics such as benzodiazepines, valerian and kava should be avoided due to excessive drowsiness, sedation and motor inco-ordination.The anticholinergic effects of the antihistamines will also aggravate urinary retention, blurred vision, constipation and glaucoma.[4]

DECONGESTANTS

Cold, flu and sinus preparations (decongestants) invariably contain pseudoephedrine, phenylephrine and/or phenylpropanolamine together with antihistamines and analgesics. Being sympathomimetics, they are able to reverse the effects of beta-blockers and other antihypertensive and anti-anginal agents. These would include drugs such as ACE-inhibitors (e.g. enalapril), calcium channel blockers (e.g. nifedipine, verapamil), methyldopa, etc. Decongestants should also not be used in patients

with thyroid disease, epilepsy, any form of heart disease, diabetes or prostatism. Combination of decongestants with monoamine oxidase inhibitors such as tranylcypromine or moclobemide may cause a hypertensive crisis. If a patient is taking a phenothiazine such as chlorpromazine or thioridazine, the addition of any of the decongestants could cause tachycardia or other potentially dangerous arrythmias.[9] Alkalinisation of the urine with sodium bicarbonate or other urinary alkalinisers causes retention of pseudoephedrine and ephedrine which may lead to tachycardia, tremors, anxiety and insomnia.[9]

ANALGESICS

Aspirin and paracetamol are freely available in supermarkets, cafés, shops and at petrol stations under no professional control. Both these agents can interact with anticoagulants such as warfarin, leading to an increased risk of bleeding. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac etc. can increase the anticoagulant effect of warfarin and increase the risk of gastrointestinal bleeding as both drugs are gastrotoxic. NSAIDs inhibit the action of many classes of anti-hypertensives because of salt and water retention. Ibuprofen and other NSAIDs reduce the excretion of cardiac glycosides such as digoxin. This can be particularly dangerous in the very young and the elderly. The combination of NSAIDs and lithium may be potentially serious as lithium salts are retained in the blood and toxicity can ensue. Similarly methotrexate toxicity, sometimes life-threatening, has been seen in patients given NSAIDs especially when renal function is impaired.[9] The dose of paracetamol may have to be increased if a TB patient is taking rifampicin concurrently, due to liver enzyme induction. The absorption of aspirin is impaired by antacids and doses should be spaced 2 hours apart.[5] Codeine, noscapine and pholcodeine appear in many OTC preparations including cough mixtures, anti-diarrhoea medicines and flu preparations and duplication should be avoided. Aspirin displaces phenytoin from plasma proteins and may lead to phenytoin toxicity.[10]

LAXATIVES

Be on the lookout for laxatives containing magnesium, potassium or phosphates in patients with renal impairment, as there is increased absorption of these agents and decreased elimination. Bisacodyl reduces digoxin levels, while antacids will impair absorption of digoxin. Bulk laxatives may impair absorption of a number of drugs and doses should be spaced at least 2 hours apart.[5,9]

BRONCHODILATORS

Fenoterol, salbutamol, terbutaline, formoterol and theophylline are all capable of causing tremor, tachycardia, headache, anxiety and lowering of serum potassium. They may interact with drugs such as tricyclic antidepressants, caffeine-containing preparations including coffee and cola drinks, and phenothiazines, increasing the risks of cardiac arrythmias and lengthening of the QT interval. Theophylline should not be given together with macrolide antibiotics such as erythromycin and roxithromycin or with quinolones such as ciprofloxacin or SSRIs such as fluvoxamine, as serum levels are raised and theophylline toxicity is a potentially serious consequence.[4]

TOPICAL PREPARATIONS

Frequently reported is the interaction between oral topical or vaginally administered miconazole for fungal infections in patients on warfarin. The anticoagulant effect is markedly increased and bleeding can occur. Similarly, alcohol-containing after-shave lotions or shampoos containing beer have been reported to cause severe nausea, flushing and tachycardia when used in patients taking disulfiram (Antabuse).[9,10]

CONCLUSION

In summary, it is critically important to take a comprehensive medication history, not forgetting any substances/drugs that the patient might otherwise not mention. This may happen when either the patient or the doctor does not consider certain substances to be medicines, or the patient may be too embarrassed to tell the doctor that they have been adding to the prescription, or because the patients thinks that the doctor's medicines are ineffective.

References available on request.

IN A NUTSHELL

72% of people taking prescription medication also take OTC preparations.

Doctors should be aware of clinically significant drug interactions when prescribing.

Habits and OTC preparations which may cause interactions:

- smoking
- alcohol
- herbal and complementary drugs
- antacids and H_2-receptor blockers
- antihistamines and anti-nauseants
- decongestants
- analgesics
- laxatives
- bronchodilators
- topical preparations.

It is critically important to take a comprehensive medication history.