The Whitehall-Robins Report
WHITEHALL® ROBINS TREATING YOU WITH CARE®
FEBRUARY 2000 VOL. 9, NO. 1

Drug-Nutrient Interactions

José A. Morais, MD, FRCPC, Assistant Professor of Medicine, McGill University
Division of Geriatric Medicine, McGill University Health Centre

Introduction

Drugs are potent chemical agents developed to treat many medical conditions and to improve patients' quality of life. Historically, these active ingredients were extracted from plants and from naturally occurring foods[1]; some of them are still being sold by the growing market of health-food stores. Not surprisingly, drugs share the same route of absorption and metabolism as nutrients with the potential for mutual interactions responsible for adverse drug reactions, known as drug-nutrient interactions. The interactions between drugs and nutrients occur in both directions, i.e., drugs may alter the nutritional status and dietary habits, or nutritional deficiencies may alter drug action or toxicity (Table 1). The knowledge of these interactions may help health professionals obtain the maximum effect of a drug and avoid unnecessary side effects that would diminish the compliance of patients.

Drugs and General Nutritional Status

Drugs may alter nutritional status because they can increase or decrease food intake. Drugs, such as neuroleptics, benzodiazepines, tricyclic antidepressants (TAD), can directly stimulate the appetite centre in the central nervous system leading to weight gain, whereas amphetamine-like drugs and selective serotonin-reuptake inhibitors (SSRIs) do the opposite[2]. Weight gain has been observed with sulfonylurea drugs used to treat diabetes mellitus (e.g., glyburide). This weight gain is a result of increased insulin secretion by the pancreas. Appetite alterations can also be caused by indirect mechanisms through changes in taste perception, as in the case of lithium, metronidazole and metformin. Any drug that is responsible for the appearance of gastrointestinal symptoms will contribute to decreased appetite and induce protein-energy malnutrition. Examples of this are dyspepsia, caused by nonsteroidal antiinflammatory drugs (NSAIDs), constipation induced by narcotics and nausea from theophylline or digitalis glycoside preparations.

Drugs and Mineral and Vitamin Deficiencies

Drugs may also induce vitamin and mineral deficiencies by affecting their absorption, by altering their metabolism or by increasing nutrient loss. For example, medications that increase stomach pH will decrease iron absorption by decreasing the rate of conversion of ferric iron to its absorbable ferrous form. Mineral oil, if taken in the postprandial period will reduce absorption of fat-soluble vitamins, including carotenes and vitamin D. The metabolism of vitamin D in the liver is altered by the anticonvulsant phenytoin, leading to decreased calcium absorption and osteomalacia[3]. Warfarin, an oral anticoagulant that is a vitamin K antagonist, contributes to osteoporosis due to the lack of vitamin K stimulation on new bone formation[4]. Acetylsalicylic acid (ASA) overuse is associated with folic acid deficiency, as is methrotrexate by inhibition of the dihydrofolate reductase enzyme. Examples of increased nutrient losses are potassium, magnesium and zinc depletion by diuretics, increased renal calcium excretion induced by glucocorticoids and iron losses in the gastrointestinal tract by NSAIDs.

Effects of Diet on Drug Bioavailability

Drug bioavailability depends on the absorption of the active compound by the gastrointestinal tract. Absorption can be delayed by the effect of the meal in slowing gastric emptying but it rarely affects bioavailability. While food usually reduces or delays drug absorption, some drugs' absorption is promoted with food. This is the case with diazepam, erythromycin, hydralazine, hydrochlorothiazide and metoprolol. The meal content also has an effect on absorption, as with the once-a-day preparation of theophylline that is increased by a high-fat meal[5]. The opposite effect of a high-fat meal is seen for zidovudine, an antiretroviral agent. A high-protein meal will also diminish the absorption of levo-dopa due to competition by amino acids for absorption[6]. Bioavailability can be affected by the fiber content of the meal that binds to the drug and decreases its absorption, as seen with lithium, levothyroxine preparations and lovastatin. Another mechanism that decreases the absorption of drugs is chelation, which consists of the binding of minerals to drugs to form an insoluble non-absorbable product. This is the case for ciprofloxacin and the new antiresorptive agents, biphosphonates (ethididronate and alendronate). Their effectiveness is compromised when concurrently ingested with calcium supplements or dairy products[7].

Nutritional Status Affecting Drug Metabolism

The nutritional status of a patient may alter drug distribution and metabolism. Drug distribution is affected because protein-energy malnutrition is associated with low body fat depots and loss of lean body mass[8]. This implies that the volume of distribution for water-soluble drugs (digitalis, cimetidine) is reduced in malnutrition with increased risks of side effects. Serum binding proteins are also reduced[9], contributing to a higher free plasma drug concentration of drugs that are highly bound to plasma proteins (>90%): lithium, digoxin, valproate, phenytoin, warfarin, NSAIDS and ASA . This physiological change allows more of the drug to diffuse out of the vascular compartment and to reach the drug receptor site. Due to an increased free plasma concentration, the plasma clearance is also accelerated with decreased therapeutic effect for phenytoin after a single dose administration. Most importantly, many biotransformation reactions in the liver are reduced with malnutrition, especially those involving phase II reactions by cytochrome P450 isoenzymes[10]. Medications that are eliminated by hepatic metabolism will have their half-lives increased with higher risks of toxicity. This is the case with many drugs, including TAD, neuroleptics, antiarrythmics, etc. The opposite effect of a high protein content meal in stimulating the cytochrome P450 isoenzymes, as is the effect of vegetables of the Brassica family (cabbage, brussels sprouts) will result in a decreased therapeutic effect of many medications. Recently, the inhibition of the isoenzyme CYP3A4 by grapefruit juice has attracted attention because of the increased therapeutic effect seen with most calcium channel antagonists (felodipine, nifedipine, nimodipine and verapamil). The plasma concentration of other drugs metabolized by the same isoenzyme is also elevated: cholesterol-lowering agents of the statins family, cisapride, midazolam, triazolam and cyclosporin[11].

Incompatibility of Drugs and Nutrients

There is a third type of drug-nutrient interaction with clear detrimental effects due to incompatibility of certain drugs and nutrients[12]. This is the case for the irreversible monoamine oxidase (MAO) inhibitors (phenelzine and tranylcypromine) with food containing tyramine (old cheese and red wine). Tyramine is metabolized by the MAO enzyme and accumulates in the body when inhibitors are given to treat depressive mood disorders. It reaches toxic levels that are responsible for headaches, nausea, vomiting, palpitations, hypertensive crisis and eventually, cerebrovascular accidents. Similar reactions are observed with isoniazid-treated patients who eat food containing large amounts of histamine such as sardinella, skipjack or tuna[13]. The disulfiram-like reaction is another example of this category of interactions observed when metronidazole, nitrofurantoin, griseofulvin or chlorpropamide are taken in association with

alcohol. The disulfiram reaction manifests itself by headaches, nausea, vomiting, chest and abdominal pains. Avoidance of these associations will minimize or avoid such side-effects.

Drug-Nutrient Interactions of Clinical Relevance

Most nutrient deficiencies are caused by prolonged use of medications for the treatment of chronic conditions and in patients with a borderline nutritional status, e.g. frail elderly persons and patients with inflammatory bowel disease. Polypharmacy is also recognized as being a risk factor for nutrient depletion and is often seen in the elderly[14]. Table 2 illustrates clinically relevant drug-nutrient interactions. The choice of the drugs was elicited by the frequency and the seriousness of the drug-nutrient interactions seen in clinical practice, especially among elderly persons.

Protein-energy malnutrition may arise from digitalis glycoside (digoxin) with borderline high therapeutic concentrations because of severe anorexia with or without nausea and vomiting. This condition is called "digitalis cachexia". The centrally mediated effect of SSRIs on appetite suppression is also a common cause of weight loss. General malabsorption can be a consequence of the chronic use of colchicine to treat gout because this drug can create a structural defect in the intestinal mucosa. As already stated, specific and severe mineral depletion is seen with diuretics for potassium, sodium, magnesium, zinc and calcium (with the exception of thiazides). The chronic use of NSAIDs or ASA to treat arthritis is responsible for iron deficiency anemia, induced by blood loss in the gastrointestinal tract. Specific folate deficiency may be caused by the chronic use of methotrexate for rheumatoid arthritis (mechanism discussed above) and of cholestyramine and colestipol to treat hypercholesterolemia through binding of bile acids. Both phenytoin and phenobarbital employed to control seizure disorders can alter vitamin D metabolism through several mechanisms, including inhibition of hepatic vitamin D 25-hydroxylase, resulting in osteomalacia. The effect of anticonvulsants on bone density can be affected by calcium and vitamin D supplements. Glucocorticoids are drugs with systemic manifestations that are employed in many serious medical conditions. Unfortunately, they also contribute to an array of side effects, including osteoporosis, electrolyte abnormalities (hypernatremia and hypokalemia), hyperglycemia and negative nitrogen balance, responsible for loss of lean body mass. These side effects can be prevented in part with diet counseling and use of biphosphonates.

Conclusions

An awareness that drug-nutrient interactions could increase or decrease drug action and/or contribute to dietary deficiencies is of particular importance in the management of patients receiving medications. The chronic use of drugs requires close monitoring of nutritional status. Some modification in the diet will maximize benefits of the medication and ensure maintenance of good nutritional status.

Table 1: Mechanisms of Drug-Nutrient Interactions

I. Drugs may alter nutritional status
- May ↑ or ↓ food intake
- May induce vitamin or mineral deficiencies
  - by affecting absorption of nutrients
  - by altering nutrient metabolism
  - by increasing nutrient loss

II. Dietary habits or nutritional deficiencies may alter drug action or toxicity
- Food may alter drug bioavailability
- Diet may alter drug metabolism
- Nutritional status may alter drug distribution & metabolism

III. Drug-nutrient incompatibilities
- Tyramine reactions
- Disulfiram reactions

Table 2: Examples of Clinical Relevant Drug-Nutrient Interactions

Drug	Mechanism	Nutrient Affected
Digoxin	Anorexia, nausea, vomiting	Protein-energy malnutrition
SSRIs	Anorexia and nausea	Protein-energy malnutrition
Colchicine	Structural defect in intestinal mucosa	Protein-energy malnutrition
Diuretic	Alterations in renal tubular function	Loss of Na, K, Zn, Mg, Ca (not thiazides)
NSAIDs, ASA	Gastrointestinal blood loss	Iron deficiency
Methotrexate	Inhibition of dihydrofolate reductase	Folate
Cholestyramine, colestipol	Binding of bile acids	Folate
Glucocorticoids	Increased Ca excretion, altered glucose metabolism, electrolyte imbalances	Ca (osteoporosis), hyperglycemia, ↑ Na, ↓ K
Phenytoin, phenobarbital	Inhibition of liver vitamin D 25-hydroxylase	Vitamin D (osteomalacia)

SSRIs: Selective serotonin reuptake inhibitors, e.g., fluoxetine, sertraline, fluoxamine
NSAIDs: Nonsteroidal antiinflammatory drugs, e.g., ibuprofen, indomethacin, naproxen
ASA: Acetylsalicylic acid

The Whitehall-Robins Report is a Whitehall-Robins publication that focuses on current issues on the role of vitamins and minerals in health promotion and disease prevention. Complimentary copies are distributed to Canadian health care professionals active or with a special interest in nutrition. Each issue is written and/or reviewed by independent health care professionals with expertise in the chosen topic.
Editor: Whitehall-Robins Inc.
If you have any comments about the Whitehall-Robins Report or would like to be added to the mailing list, please write to:
The Editor: The Whitehall-Robins Report,
5975 Whittle Road, Mississauga, ON L4Z 3M6

REFERENCES **1.** Camp J. Magic, Myth and Medicine. New York, Taplinger Publishing Co., 1974. **2.** Stock MJ. Sibutramine: a review of the pharmacology of a novel anti-obesity agent. Int J Obes Relat Metab Disord 1997;21(suppl):S25-29. **3.** Ray JG, Adachi JR. Anticonvulsants and bone disease: a systematic overview of their association and possible preventive strategies. Can J Clin Pharmacol 1998;4:217-223. **4.** Heaney RP. Nutritional factors in osteoporosis. Annu Rev Nutr 1993;13:287-316. **5.** Karim A, Burns T, Janky D, Hurwitz A. Food induced changes in theophylline absorption from controlled release formulations. II. Importance of meal composition and dosing time relative to meal intake in assessing changes in absorption. Clin Pharmcol Ther 1985;38:642-647. **6.** Goldin BR, Goldman P. The metabolism of L-dopa: the role of the intestinal microflora. Fed Proc 1973;32:798. **7.** The Medical Letter. Ethididronate for postmenopausal osteoporosis. Vol. 14, No. 19 (M.L. 833), January 11,1991. **8.** Shizgal HM. Nutritional assessment with body composition measurements. JPEN 1987;11(suppl):S42-47. **9.** Ashton M, Bolme P, Zerihum G, Holmberg K, Paalzow LK. Disposition of salicylic acid in malnourished Ethiopian children after single oral dose. Clin Pharmacokinet 1993;25(suppl):S483-494. **10.** Mandl J, Banhegyi G, Kalapos MP, Garzo T. Increased oxidation and decreased conjugation of drugs in the liver caused by starvation. Altered metabolism of certain aromatic compounds and acetone. Chemico-Biological Interactions 1995;96:87-101. **11.** Bailey DG, Malcom J, Arnold O, Spence JD. Grapefruit juice-drug interactions. Brit J Clin Pharmacol 1998;46:101-110. **12.** Roe DA. Interactions between drugs and nutrients. Med Clin N Amer 1979;63:985-1007. **13.** Uragoda CG. Histamine poisoning in tuberculous patients after ingestion of tuna fish. Ann Rev Resp Dis 1980;121:157-160. **14.** Steward RB, Cooper JW. Polypharmacy in the aged. Drugs & Aging 1994;9:73-80.