Drug interactions with grapefruit

I was glad to see James Maskalyk's review of grapefruit and drug interactions,[1] as I have been concerned for some time about the need to increase awareness of this issue.[2,3] However, I would like to comment on drugs that were listed as if the effects were equal. Some patients enjoy grapefruit, and it is unkind to impose an unnecessary prohibition.

The magnitude of the grapefruit effect is related to the bioavailability of the drug. Felodipine, with a bioavailability of only 15%, had on average a tripling of blood levels with grapefruit, whereas nifedipine, with a bioavailability of 60%, had only a 30% increase in area under the curve (AUC). Amlodipine, which is approximately 80% bioavailable, is hardly affected by grapefruit.[4] Similarly, whereas simvastatin and lovastatin, which are only 5% bioavailable, have a 15-fold increase in AUC with grapefruit,[5,6] levels of atorvastatin increase only by 2.5-fold.[7]

I therefore tend to tell patients on amlodipine and atorvastatin that grapefruit is likely to have only a minor effect.

J. David Spence
Stroke Prevention and Atherosclerosis Research Centre
Robarts Research Institute
London, Ont.

References

1. Maskalyk J. Grapefruit juice: potential drug interactions. *CMAJ* 2002;167(3):279-80.
2. Spence JD. Drug interactions with grapefruit juice: Whose responsibility is it to warn the public? *Clin Pharmacol Ther* 1997;61:395-400.
3. Bailey DG, Spence JD, Munoz C, Arnold JM. Interaction of citrus juices with felodipine and nifedipine. *Lancet* 1991;337:268-9.
4. Vincent J, Harris SI, Foulds G, Dogolo LC, Willavize S, Friedman HL. Lack of effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of amlodipine. *Br J Clin Pharmacol* 2000;50(5):455-63.
5. Kantola T, Kivisto KT, Neuvonen PJ. Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1998;63(4):397-402.
6. Lilja JJ, Kivisto KT, Neuvonen PJ. Grapefruit juice–simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. *Clin Pharmacol Ther* 1998;64(5):477-83.
7. Lilja JJ, Kivisto KT, Neuvonen PJ. Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. *Clin Pharmacol Ther* 1999;66(2):118-27.

Folic acid fortification: time for a concentrated effort

Vidia Persad and colleagues[1] nicely show that folic acid fortification of cereal grains is rapidly followed by a remarkable reduction in the incidence of spina bifida and anencephaly. Their data indicate that countries that do not fortify grain are allowing thousands of babies to be born each year with these preventable defects.[2,3]

As wonderful as this prevention is, data suggest that increased concentration of folic acid in flour would further reduce these birth defects. Although the rate of spina bifida that is not preventable with folic acid is unknown, data from a community trial in China showed that taking 400 mg/d of folic acid reduced the prevalence to about 6 per 10 000 in high- and low-risk areas.[4] The Chinese data suggest that increasing the concentration of folic acid in grains in Canada would reduce the incidence of spina bifida and anencephaly in Canada by least an additional 50%.

Before fortification, it was estimated that fortification at 140 mg/100 g of flour (the concentration required in the US and Canada) would increase the average women's daily consumption of folic acid by 100 mg. Some subsequent estimates suggest that the average woman consumes 200 mg/d of folic acid. The US Public Health Service and Institute of Medicine recommend that all women of reproductive age consume 400 mg/d of synthetic folic acid.

The US Centers for Disease Control and Prevention and the March of Dimes suggest that fortification concentration should be at least 350 mg/100 g of grain. In 2000 the UK Committee on Medical Aspects of Food and Nutrition Policy (COMA) recommended a concentration of 240 mg/100 g of grain.[5] Chile has implemented a concentration of 220 mg/100 g; however, women in Chile consume about twice as much flour as women in Canada and the United States.

Canadian nutrition regulators discouraged the US Food and Drug Administration from requiring fortification, saying that Canadians did not need folic acid fortification. Persad and colleagues have shown this not to be the case. Fortunately for Canadian children and their families, commercial interests forced Canadian regulators to adopt the US standard. Perhaps Canadian regulators will now show leadership in North America by increasing folic acid fortification concentration to at least 240 mg/100 g, as recommended by COMA.

Godfrey P. Oakley, Jr.
Visiting Professor of Epidemiology
Rollins School of Public Health
Emory University
Atlanta, Ga.

References

1. Persad VL, Van den Hof MC, Dube JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *CMAJ* 2002;167(3):241-5.
2. Oakley GP. Delaying folic acid fortification of flour. *BMJ* 2002;324:1348-9.
3. Oakley GP. Inertia on folic acid fortification: public health malpractice. *Teratology* 2002;66:44-54.
4. Berry RJ, Li Z, Erickson JD, Li S, Moore CA, Wang H, et al. Prevention of neural-tube defects with folic acid in China. China–U.S. Collaborative Project for Neural Tube Defect Prevention [published erratum appears in *N Engl J Med* 1999;341(24):1864]. *N Engl J Med* 1999;341(20):1485-90.
5. Folic acid and the prevention of disease. Report of the Committee on Medical Aspects of Food and Nutrition Policy. *Rep Health Soc Subj* (Lond) 2000;50:i-xv, 1-101.

[Two of the authors respond:]

We thank Godfrey Oakley for his comments on our article[1] and agree that current folic acid fortification levels may be inadequate. Unfortunately, it is difficult to determine the lowest level needed to minimize the occurrence of open neural tube defects; some suggest that there is no need for fortification, although others recommend as much as 350 mg/100 g of grain. A consensus will be difficult to achieve. Meanwhile, it is important that further population-based studies on the effects of fortification be undertaken not only to help determine such a level but also to rule out theoretical adverse effects. It is also impor-

tant to continue advocating periconceptual folic acid supplementation and sound nutrition.

Michiel C. Van den Hof
Vidia L. Persad
Department of Obstetrics and Gynaecology
Dalhousie University
Halifax, NS

Reference
1. Persad VL, Van den Hof MC, Dube JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *CMAJ* 2002;167(3):241-5.

Puzzling vitamin D results

I am puzzled by the seasonal mean values for 1,25-dihydroxy vitamin D [1,25-$(OH)_2$D] published in Table 2 of the article by Diana Rucker and colleagues.[1] They are about twice as high as those from a similar study done in Denmark,[2] which showed a mean of 29 pg/ml (75.4 pmol/L).

Two of the seasonal mean values (168.1, 148.9) are above the normal range quoted for the assay (45–145). This assay range seems to be correct, but the study data seem to be high.

I am particularly concerned that this study did not place much greater emphasis on the values of the active hormone 1,25-$(OH)_2$D than on the intermediate metabolite 25-hydroxy vitamin D [25(OH)D]. This is especially important in elderly populations, as extrarenal hydroxylase activity in inflammatory macrophages has been shown to generate a normal 1,25-$(OH)_2$D value from depressed levels of circulating 25(OH)D.

Trevor G. Marshall
Research Director
Yarc Inc.
Thousand Oaks, Calif.

References
1. Rucker D, Allan JA, Fick GH, Hanley DA. Vitamin D insufficiency in a population of healthy western Canadians. *CMAJ* 2002;166(12):1517-24.
2. Brot C, Jorgensen NR, Sorensen OH. The influence of smoking on vitamin D status and calcium metabolism. *Eur J Clin Nutr* 1999;53(12): 920-6.

[One of the authors responds:]

I thank Trevor Marshall for paying such close attention to our article,[1] and I wish I had done the same in my proofreading. The normal range for the 1,25-$(OH)_2$D, or calcitriol, assay published in our paper was incorrect and was that for the earlier INCSTAR (later to become Diasorin) assay kit for calcitriol. This assay was in use at the Foothills Medical Centre when I submitted my grant proposal for this project. However, the current Diasorin calcitriol assay kit is currently used, in both my laboratory and the Calgary Health Region clinical laboratory, and the normal range (2 standard deviations above and below the mean for a group of healthy hospital workers) is 55–190 pmol/L. This is the range we should have included in Table 2, and our reported 1,25-$(OH)_2$D levels were within it.

Our 1,25-$(OH)_2$D assay still provided results consistent with known vitamin D physiology. The 2 seasons with the highest mean levels of 1,25-$(OH)_2$D were associated with the highest mean levels of parathyroid hormone and the lowest mean levels of serum inorganic phosphate, both known stimuli to conversion of 25(OH)D to 1,25-$(OH)_2$D by renal 1α-hydroxylase.

Although 1,25-$(OH)_2$D is the most biologically active form of vitamin D, it is generally accepted that, when assessing patients' vitamin D stores, measurement of 25(OH)D in blood is much more clinically useful than that of 1,25-$(OH)_2$D.[2,3] Serum 25(OH)D levels are consistently low in malabsorption syndromes and clinical osteomalacia, although 1,25-$(OH)_2$D levels may be normal or high.[4] In osteomalacia due to vitamin D deficiency, the serum 25(OH)D level, not the 1,25-$(OH)_2$D level, correlates with the mineralization status of bone.[5] Recent identification of 1α-hydroxylase activity in nonrenal tissue provides a plausible explanation of how 25(OH)D may mediate vitamin D action at a cellular level,[6,7] and evidence also exists of direct effects of 25(OH)D on calcium absorption.[8]

David A. Hanley
Professor and Head
Division of Endocrinology and Metabolism
Department of Medicine
University of Calgary
Calgary, Alta.

References
1. Rucker D, Allan JA, Fick GH, Hanley DA. Vitamin D insufficiency in a population of healthy western Canadians. *CMAJ* 2002;166(12):1517-24.
2. Holick MF. The use and interpretation of assays for vitamin D and its metabolites. *J Nutr* 1990; 120(Suppl 11):1464-9.
3. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* 1999;69(5):842-56.