Which medications used in paediatric practice have demonstrated natural health product-drug interactions?

Part A: Evidence-based answer and summary

Brad Johnston ND PhD Candidate, Sunita Vohra MD FRCPC MSc

A recent Canadian survey (1) of 1804 children and youth suggested that 49% had tried one or more complementary and alternative medicine therapies and 41% had used a natural health product (NHP) in the previous year. Similarly, a three-month survey (2) of 142 families in an American paediatric emergency department suggested that 45% of caregivers had given their children an herbal remedy in the previous year.

NHP use may be much higher within certain subgroups of the child and youth population (eg, children with serious and/or chronic conditions, such as cancer, cystic fibrosis, asthma, attention deficit hyperactivity disorder and eating disorders) (3-7). In particular, NHP use may be highest in paediatric populations with chronic disease who suffer relapses or other setbacks (3). Surveys have also shown that rates of NHP use are high (70%) among homeless youth, many of whom suffer from chronic mental and physical health conditions (8). Indeed, because children with serious, chronic or recurrent illnesses are the most likely to be on concurrent prescription medications, they may have the highest risk for clinically relevant NHP-drug interactions.

With expanding use, clinicians and researchers are focusing their attention on the potential for NHPs to interact with prescribed medications and alter their pharmacokinetics. Pharmacokinetics involves the study of the rate of movement of drugs within biological systems, as affected by absorption, distribution, metabolism and elimination from the body. Although the mechanisms of NHP-drug interactions are complex and not fully elucidated, interactions are primarily due to altered biotransformation; in particular, herbs may cause induction (or inhibition) of the hepatic cytochrome P450 (CYP) isozymes, rendering the index drug less (or more) active (Figure 1) (9). The CYP isozyme families most commonly involved in human liver metabolism are 1A, 2B, 2C, 2D, 2E and 3A. Many prescription drugs are metabolized through the CYP system, namely the CYP3A4 isoform (9). For example, St John's wort and garlic are metabolized through the 3A4 isoform and appear to induce other CYP isozymes (9). A recent overview (10) of pharmacokinetic clinical investigations of NHP-drug interactions found that no such clinical investigations have been conducted in children. The search included major electronic databases (CENTRAL, MEDLINE, EMBASE and AMED) from inception to August 2004. Studies investigating pharmacokinetic interactions between an NHP and the metabolism of a regulated medication were included. In an attempt to determine the relevance of

Figure 1 Sequential first-pass elimination of a theoretical drug through metabolism by the cytochrome P450 isoenzyme CYP3A4 and/or transport by P-glycoprotein (P-gp) in enterocytes of the small intestine and then hepatocytes of the liver. The percentage of the initial drug dose that is available before and after passage through the gut wall and liver is presented. Although the drug is 100% absorbed from the gastrointestinal tract, its bioavailability is only 15% after oral administration. Reprinted with permission from reference 31

potential NHP-drug interactions to the paediatric population, commonly used reference texts were used to identify drugs used in paediatric practice (eg, *Pediatric Dosage Handbook* [11] and *The Harriet Lane Handbook: A Manual for Pediatric House Officers, 16th Edition* [12]). Forty-four adult trials examining drug interactions with 11 different common herbal preparations and 11 traditional preparations were identified. Significant NHP-drug interactions were demonstrated in 18 studies among five common herbal remedies with 13 drugs prescribed in paediatric practice. In 18 studies, there was a decreased area under the curve (AUC) or concentration maximum (C_{max}), and, thus, decreased systemic bioavailability of the probe drug. Significant decreases in the AUC were demonstrated in trials with warfarin (when administered with American ginseng) (13), midazolam (with echinacea) (14), saquinavir (with garlic) (15) and alprazolam (with ginkgo biloba) (16). In addition, St John's wort significantly decreased the AUC or C_{max} when administered with alprazolam (AUC [17,18]), amitriptyline (AUC [19]), cyclosporin A (AUC [20]), digoxin (AUC [21,22]), fexofenadine (AUC and C_{max} [23]), indinavir (AUC [24]), midazolam (AUC and C_{max} [23]), omeprazole (AUC [25]), oral contraceptive (3-ketodesogestrel) (AUC [26]), simvastatin

Complementary and Alternative Research and Education (CARE) Program, Stollery Children's Hospital, and Department of Pediatrics, University of Alberta, Edmonton, Alberta

Correspondence: Dr Sunita Vohra, CARE Program, Stollery Children's Hospital, Department of Pediatrics, University of Alberta, Aberhart Centre #1, Room 8213, 11402 University Avenue Northwest, Edmonton, Alberta T6G 2J3. Telephone 780-407-3798, fax 780-407-2105, e-mail svohra@ualberta.ca

Accepted for publication April 5, 2005

TABLE 1
Summary of significant paediatric herb-drug interactions

Pharmacokinetic trial	Herb	Drug used in paediatric practice
Yuan et al, 2004 (13)	American ginseng	Warfarin
Gorski et al, 2004 (14)	Echinacea	Midazolam
Piscitelli et al, 2002 (15)	Garlic	Saquinavir
Markowitz et al, 2003 (16)	Ginkgo biloba	Alprazolam
Markowitz et al, 2000 (17)	St John's wort	Alprazolam
Markowitz et al, 2003 (18)	St John's wort	Alprazolam
Johne et al, 2002 (19)	St John's wort	Amitriptyline
Bauer et al, 2003 (20)	St John's wort	Cyclosporin A
Johne et al, 1999 (21)	St John's wort	Digoxin
Mueller et al, 2004 (22)	St John's wort	Digoxin
Dresser et al, 2003 (23)	St John's wort	Fexofenadine
Piscitelli et al, 2000 (24)	St John's wort	Indinavir
Wang et al, 2004 (25)	St John's wort	Omeprazole
Pfrunder et al, 2003 (26)	St John's wort	Oral contraceptive
Sugimoto et al, 2001 (27)	St John's wort	Simvastatin
Mai et al, 2003 (28)	St John's wort	Tacrolimus
Hebert et al, 2004 (29)	St John's wort	Tacrolimus
Jiang et al, 2004 (30)	St John's wort	Warfarin

REFERENCES

- Goldman RD, Vohra S. Complementary and alternative medicine use by children visiting a pediatric emergency department. Abstracts from the First Annual Complementary and Alternative Health Care and Paediatrics Forum, December 2 to 3, 2004. *Can J Clin Pharmacol* 2004;11:e254-56. (Abst 5)
- Lanski SL, Greenwald M, Perkins A, Simon HK. Herbal therapy use in a pediatric emergency department population: Expect the unexpected. *Pediatrics* 2003;111:981-5.
- Madsen H, Andersen S, Nielsen RG, Dolmer BS, Host A, Damkier A. Use of complementary/alternative medicine among paediatric patients. *Eur J Pediatr* 2003;162:334-41.
- Trigazis L, Tennankore D, Vohra S, Katzman DK. The use of herbal remedies by adolescents with eating disorders. *Int J Eat Disord* 2004;35:223-8.
- Simpson N, Roman K. Complementary medicine use in children: Extent and reasons. A population-based study. *Br J Gen Pract* 2001;51:914-6.
- Neuhouser ML, Patterson RE, Schwartz SM, Hedderson MM, Bowen DJ, Standish LJ. Use of alternative medicine by children with cancer in Washington state. *Prev Med* 2001;33:347-54.
- Chan E, Rappaport LA, Kemper KJ. Complementary and alternative therapies in childhood attention and hyperactivity problems. *J Dev Behav Pediatr* 2003;24:4-8.
- Breuner CC, Barry PJ, Kemper KJ. Alternative medicine use by homeless youth. *Arch Pediatr Adolesc Med* 1998;152:1071-5.
- Mills E, Wu P, Johnston BC, Gallicano K, Clarke M, Guyatt G. Natural health product-drug interactions: A systematic review of clinical trials. *Ther Drug Monit* 2005;27:549-57.
- Johnston BC, Wu P, Mills EJ. Herb-drug interaction implications for pediatric clinical practice: An overview of pharmacokinetic trials. *Arch Pediatr Adolesc Med* 2005;159:692.
- Taketomo CK, Hodding JH, Kraus DM, eds. *Pediatric Dosage Handbook*, 10th edn. Hudson: Lexi-Comp Inc, 2003.
- Gunn VL, Nechyba C. *The Harriet Lane Handbook: A Manual for Pediatric House Officers*, 16th edn. Philadelphia: Mosby Inc, 2002.
- Yuan CS, Wei G, Dey L, et al. Brief communication: American ginseng reduces warfarin's effect in healthy patients: A randomized, controlled trial. *Ann Intern Med* 2004;141:23-7.
- Gorski JC, Huang SM, Pinto A, et al. The effect of echinacea (*Echinacea purpurea* root) on cytochrome P450 activity in vivo. *Clin Pharmacol Ther* 2004;75:89-100.
- Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin Infect Dis* 2002;34:234-8.
- Markowitz JS, Donovan JL, Lindsay DeVane C, Sipkes L, Chavin KD. Multiple-dose administration of Ginkgo biloba did not affect cytochrome P-450 2D6 or 3A4 activity in normal volunteers. *J Clin Psychopharmacol* 2003;23:576-81.
- Markowitz JS, DeVane CL, Boulton DW, Carson SW, Nahas Z, Risch SC. Effect of St John's wort (*Hypericum perforatum*) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers. *Life Sci* 2000;66:PL133-9.
- Markowitz JS, Donovan JL, DeVane CL, et al. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *JAMA* 2003;290:1500-4.
- Johne A, Schmider J, Brockmoller J, et al. Decreased plasma levels of amitriptyline and its metabolites on comedication with an extract from St John's wort (*Hypericum perforatum*). *J Clin Psychopharmacol* 2002;22:46-54.
- Bauer S, Stormer E, Johne A, et al. Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. *Br J Clin Pharmacol* 2003;55:203-11.
- Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clin Pharmacol Ther* 1999;66:338-45.
- Mueller SC, Uehleke B, Woehling H, et al. Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin. *Clin Pharmacol Ther* 2004;75:546-57.
- Dresser GK, Schwarz UI, Wilkinson GR, Kim RB. Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. *Clin Pharmacol Ther* 2003;73:41-50.
- Piscitelli SC, Burstein AH, Chait D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. *Lancet* 2000;355:547-8.
- Wang LS, Zhou G, Zhu B, et al. St John's wort induces both cytochrome P450 3A4-catalyzed sulfoxidation and 2C19-dependent hydroxylation of omeprazole. *Clin Pharmacol Ther* 2004;75:191-7.
- Pfrunder A, Schiesser M, Gerber S, Haschke M, Bitzer J, Drewe J. Interaction of St John's wort with low-dose oral contraceptive therapy: A randomized controlled trial. *Br J Clin Pharmacol* 2003;56:683-90.
- Sugimoto K, Ohmori M, Tsuruoka S, et al. Different effects of St John's wort on the pharmacokinetics of simvastatin and pravastatin. *Clin Pharmacol Ther* 2001;70:518-24.
- Mai I, Stormer E, Bauer S, Kruger H, Budde K, Roots I. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. *Nephrol Dial Transplant* 2003;18:819-22.
- Hebert ME, Park JM, Chen YL, Akhtar S, Larson AM. Effects of St John's wort (*Hypericum perforatum*) on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2004;44:89-94.
- Jiang X, William KM, Liauw WS, et al. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol* 2004;57:592-9.
- Bailey DG, Dresser GK. Natural products and adverse drug interactions. *CMAJ* 2004;170:1531-2.

(AUC [27]), tacrolimus (AUC [28,29]) and warfarin (AUC [30]) (Table 1).

St John's wort has been studied most extensively, and the mechanism for NHP-drug interaction is best understood using this example. The strength and consistency of St John's wort's effect on reducing drug bioavailability suggests that it often has important effects in reducing systemic exposure of a variety of drugs. Whether patients take a conventional medication for a condition that is unrelated to the illness for which the patient is using a NHP (eg, fexofenadine for allergic rhinitis and St John's wort for depression) or they use two interacting compounds for the same illness (eg, amitriptyline and St John's wort), patients should be closely monitored for a lack of clinical response to standard dosing or an unexpected adverse event that could be due to undisclosed use or discontinuation of NHPs (9). St John's wort, along with garlic, American ginseng, ginkgo and echinacea should be avoided in children and youth taking medications that have demonstrated significant herb-drug interactions. The degree to which decreases in the AUC or C_{max} result in clinically relevant drug interactions will depend on the therapeutic index of the specific probe drugs and their minimum effective concentrations.

Which medications used in paediatric practice have demonstrated natural health product-drug interactions?

Part B: Clinical commentary

Daniel Roth MD MSc FRCPC, Brad Johnston ND PhD Candidate, Sunita Vohra MD FRCPC MSc

Herbal therapies and other forms of complementary and alternative medicine (CAM) are used by many Canadian children encountered in the ambulatory paediatric setting (1). Parents often administer natural health products (NHPs) and conventional medicines to their children simultaneously, but are usually unaware of potentially adverse pharmacological interactions (2). Physicians have a responsibility to be wary of these interactions, but does this mean that the conscientious paediatrician is at risk of being overwhelmed by yet another large arena of new health knowledge?

Current approaches to evidence-based medicine acknowledge that the ever-growing body of medical information is too vast for any individual physician to internalize (3). The physician's role as information manager is to know how to access current and relevant information that guides the response to clinical questions in a patient-centred manner. This is the principle that paediatricians should apply in their evidence-based approach to NHP-drug interactions.

The clinician's first step is to become comfortable seeking information about CAM use from patients and their parents. Most parents using CAM on their child want to talk about it with their paediatrician, but only a minority may do so (4). It is important that the paediatrician routinely screens for CAM use in a nonjudgmental manner that is most likely to render the desired information without compromising patient-physician rapport. Open-ended questions, such as "what do you do for your child when he or she has an earache or fever?", are suggested to initiate the discussion of CAM (5). If more specific questions are required, normalizing the use of CAM is suggested, for example, "some families pursue other therapies, such as natural health products (eg, echinacea and chamomile) or see other health care providers (eg, a chiropractor or naturopath) – does your child receive any of these products or therapies?"

The second step is to formulate an evidence-based response to the specific clinical question prompted by a patient's use of CAM or NHPs. For example, a postrenal transplantation adolescent is on tacrolimus for immunosuppression: are there any potentially adverse interactions if she starts to take St John's wort for depression? The systematic review discussed in Part A summarized the available evidence and illustrated that some of the most commonly

used NHPs (St John's wort, garlic, American ginseng, ginkgo biloba and echinacea) have known interactions with conventional drugs used in paediatric practice. Although there are currently no pharmacokinetic trials reporting NHP-drug interactions in children, pharmacokinetic and drug interaction data in children are often similarly lacking for conventional drugs (6). Whether considering use of an NHP or a conventional drug, paediatricians should always be cautious about applying adult pharmacokinetic data to children. Although the pharmacokinetics of some drugs, such as omeprazole, are similar in both adults and children (7), pharmacokinetic parameters are often developmentally dependent due to physiological differences that include children's relatively increased total body water composition, decreased adipose tissue and decreased skeletal muscle mass, and differences in glomerular filtration rates compared with those of adolescents and adults (8). Therefore, the absence of adverse effects in adults does not guarantee safety in children.

In regard to the case of the depressed adolescent mentioned above, the systematic review discussed in Part A cited a recent pharmacokinetic study (9) in which renal transplantation patients on tacrolimus who were coadministered St John's wort had significantly reduced peak and trough blood concentrations of tacrolimus, thereby increasing the risk of transplant rejection. The study did not include children or adolescents and was not a randomized, controlled trial. However, in the absence of more relevant or higher quality evidence, these findings suggest that the clinician should advise the patient to seek a different treatment for her mood disorder.

In addition to the pharmacokinetic interactions addressed in Part A, paediatricians should also consider possible pharmacodynamic interactions between conventional drugs and NHPs. Pharmacodynamics involves the biochemical and physiological processes underlying drug actions, such as cellular binding, uptake and intercellular metabolism. For example, in a young child taking phenobarbital for a seizure disorder, coadministration of valerian (a central nervous system depressant used as a sleep aid) could theoretically potentiate the sedating effects of a barbiturate or benzodiazepine.

Complementary and Alternative Research and Education (CARE) Program, Stollery Children's Hospital, and Department of Pediatrics, University of Alberta, Edmonton, Alberta

Correspondence: Dr Sunita Vohra, CARE Program, Stollery Children's Hospital, Department of Pediatrics, University of Alberta, Aberhart Centre #1, Room 8213, 11402 University Avenue Northwest, Edmonton, Alberta T6G 2J3. Telephone 780-407-3798, fax 780-407-2105, e-mail svohra@ualberta.ca

Where can the busy paediatrician find information on NHP-drug interactions to guide patient counselling and monitoring? As information managers, paediatricians need on-line resources that provide updated information about herbal pharmacology in an easy-to-access format. Recent reviews (10,11) of herbal medicines in the mainstream paediatric literature suggest several Internet resources. Evidence-based sources of NHP-related information that require a paid subscription are Natural Standard (<www.naturalstandard.com>) and Natural Medicines Comprehensive Database (<www.naturaldatabase.com>). Two recommended Web sites for information regarding NHP-drug interactions that can be accessed without a subscription are The Longwood Herbal Task Force (<www.longwoodherbal.org/valerian/valerian.htm>) and HerbMed (<www.herbmed.org>). The Longwood Herbal Task Force provides a 'monograph' for each herb, which identifies the author and his affiliation, indicates the date of the latest revision and cites all references. For example, the monograph for valerian states that although animal studies suggest that valerian may potentiate the effects of barbiturates, no such effects have been reported in humans (12).

It is important to recognize that in the absence of pharmacokinetic studies in human subjects, potential NHP-drug interactions are often inferred on theoretical grounds from laboratory studies, or based on individual case reports in which adverse events cannot always reliably be attributed to a specific NHP-drug interaction (13). Clinicians need to be aware of both conventional and complementary therapies used by their patients, and advise families when they have concerns. Monitoring for potential NHP-drug interactions requires clinical vigilance because routine laboratory tests to measure drug serum concentrations are unavailable for most agents used in paediatric practice. All suspected adverse events should be reported to Health Canada (<www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index_e.html>). In addition, the Canadian Paediatric Surveillance Program is planning a surveillance study to monitor adverse events related to CAM, including potential

NHP-drug interactions. Data from the study will help to guide future studies of NHP-drug interactions that are likely to be most relevant to Canadian paediatric practice.

FUNDING: Dr B Johnston holds a Sick Kids Foundation Duncan L Gordon Fellowship. Dr S Vohra is an Alberta Heritage Foundation for Medical Research Population Health Investigator and recipient of a Canadian Institute of Health Research New Investigator Award.

REFERENCES

1. Losier A, Taylor B, Fernandez CV. Use of alternative therapies by patients presenting to a pediatric emergency department. *J Emerg Med* 2005;28:267-71.
2. Lanski SL, Greenwald M, Perkins A, Simon HK. Herbal therapy use in a pediatric emergency department population: Expect the unexpected. *Pediatrics* 2003;111(5 Pt 1):981-5.
3. Slawson DC, Shaughnessy AF. Teaching evidence-based medicine: Should we be teaching information management instead? *Acad Med* 2005;80:685-9.
4. Sibinga EM, Ottolini MC, Duggan AK, Wilson MH. Parent-pediatrician communication about complementary and alternative medicine use for children. *Clin Pediatr (Phila)* 2004;43:367-73.
5. Buck ML, Michel RS. Talking with families about herbal therapies. *J Pediatr* 2000;136:673-8.
6. Groninger E, Proost JH, de Graaf SS. Pharmacokinetic studies in children with cancer. *Crit Rev Oncol Hematol* 2004;52:173-97.
7. Kearns GL, Andersson T, James LP, et al. Omeprazole disposition in children following single-dose administration. *J Clin Pharmacol* 2003;43:840-8.
8. Pediatric Subcommittee of the Medical Policy Coordinating Committee, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products. Food and Drug Administration, 1998. <www.fda.gov/cber/gdlns/pedphrm.htm> (Version current at November 13, 2006).
9. Mai I, Stormer E, Bauer S, Kruger H, Budde K, Roots I. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. *Nephrol Dial Transplant* 2003;18:819-22.
10. Woolf AD. Herbal remedies and children: Do they work? Are they harmful? *Pediatrics* 2003;112(1 Pt 2):240-6.
11. Gardiner P, Kemper KJ. Herbs in pediatric and adolescent medicine. *Pediatr Rev* 2000;21:44-57.
12. Kemper K. Valerian. 1999. The Longwood Herbal Task Force. <www.longwoodherbal.org/valerian/valerian.htm> (Version current at November 20, 2006).
13. Hu Z, Yang X, Ho PC, et al. Herb-drug interactions: A literature review. *Drugs* 2005;65:1239-82.

Internet addresses are current at time of publication