ARTICLE

Use of Dietary Supplements by Patients Taking Digoxin

Lillian S L Ting, Stephen J Shalansky, Erin Neall, and Mary H H Ensom

ABSTRACT

Background: The use of dietary supplements is common, and interactions with digoxin have been proposed. However, little is known about usage patterns of these supplements among patients taking digoxin.

Objectives: To determine the prevalence of use of dietary supplements and over-the-counter (OTC) medications among patients taking digoxin, and to correlate the occurrence of symptoms related to digoxin toxicity with supplement use.

Methods: One hundred and seventy-two adult patients who had been receiving digoxin therapy for at least 3 months were recruited. An open-label, cross-sectional, interviewer-administered survey was conducted to assess demographic characteristics, health status, details of digoxin therapy, and use of prescription and nonprescription medications. The use of supplements and interacting prescription medications was compared between participants reporting symptoms of digoxin toxicity and those who did not report such symptoms.

Results: Most of the patients (122 or 70.9%) were men; the mean age ± standard deviation was 65.2 ± 12.0 years, and patients had been taking digoxin for a mean of 5.9 years at 174.8 ± 77.9 µg/day. Thirty-seven (21.5%) of the patients were using herbal supplements, and 153 (89.0%) were taking OTC medications or nonherbal supplements. Four (2.3%) patients were taking herbal supplements that might interact with digoxin, and 50 (29.1%) took OTC drugs or nonherbal supplements with potential interactions. Between patients who reported symptoms of digoxin toxicity and those who did not reports such symptoms, there was no difference in the use of OTC medications or nonherbal supplements, herbal supplements, or prescription medications (except for diltiazem).

Conclusions: In this study, few of the patients were taking herbal supplements that could interact with digoxin, and no clinically significant herb–digoxin interactions were observed.

Key words: digoxin, dietary supplements, over-the-counter medications, herb–drug interactions, survey

RÉSUMÉ

Historique : L'emploi des suppléments diététiques est fréquent, et on croit qu'il pourrait y avoir interaction entre ceux-ci et la digoxine. On sait peu de choses des habitudes d'emploi de ces suppléments chez les patients qui prennent de la digoxine.

Objectifs : Déterminer la prévalence de l'utilisation de suppléments diététiques et de médicaments en vente libre (MVL) chez les patients qui prennent de la digoxine, et établir un lien entre l'emploi de suppléments diététiques et la survenue de symptômes liés à la toxicité digitalique.

Méthodes : On a recruté 172 patients adultes qui suivaient un traitement par la digoxine depuis au moins trois mois. Une enquête ouverte transversale a été menée au moyen d'une entrevue-sondage pour évaluer les caractéristiques démographiques, l'état de santé, les détails du traitement par la digoxine ainsi que l'emploi de médicaments en vente libre et de médicaments d'ordonnance. On a comparé l'emploi de suppléments diététiques et les interactions avec les médicaments d'ordonnance entre les patients qui avaient signalé des symptômes de toxicité digitalique et ceux qui n'en avaient pas signalé.

Résultats : La plupart des patients (122 ou 70,9 %) étaient des hommes; l'âge moyen ± l'écart-type des patients était de 65,2 ± 12,0 ans, et ils suivaient un traitement par la digoxine depuis en moyenne 5,9 ans, à raison de 174,8 ± 77,9 µg/jour. De ces patients, 37 (21,5 %) utilisaient des suppléments à base de plantes médicinales, et 153 (89,0 %) prenaient des MVL ou des suppléments autres qu'à base de plantes médicinales. Quatre (2,3 %) patients prenaient des suppléments à base de plantes médicinales qui avaient un potentiel d'interaction avec la digoxine, et 50 (29,1 %) prenaient des MVL ou des suppléments autres qu'à base de plantes médicinales qui avaient un potentiel d'interaction avec la digoxine. On n'a observé aucune différence pour ce qui est de l'emploi de MVL ou de suppléments autres qu'à base de plantes médicinales, de suppléments à base de plantes médicinales ou de médicaments d'ordonnance (à l'exception du diltiazem) entre les patients qui ont signalé des symptômes de toxicité digitalique et ceux qui n'ont pas signalé de tels symptômes.

Conclusions : Cette étude a révélé que seul un petit nombre de patients prenaient des suppléments à base de plantes médicinales qui avaient un potentiel d'interaction avec la digoxine, et aucune interaction plantes médicinales-digoxine cliniquement significative n'a été observée.

Mots clés : digoxine, suppléments diététiques, médicaments en vente libre, interactions plantes médicinales–médicaments, enquête

Can J Hosp Pharm 2008;61(1):30-40

INTRODUCTION

Digoxin is commonly used to treat heart failure and atrial fibrillation.[1-3] Its pharmacological effects include increasing the force of myocardial contractions, slowing the heart rate, and reducing the activity of the sympathetic nervous system.[1-3] Most of the adverse effects of digoxin are dose-dependent, the most common being cardiac side effects, gastrointestinal disturbances, and central nervous system disturbances.[1,4] Traditionally a therapeutic serum concentration range of 0.8 to 2 ng/mL (1.0 to 2.6 nmol/L) has been suggested, to prevent toxic effects that may occur at higher concentrations.[1,3-6] However, recent studies have suggested a lower digoxin concentration range, 0.5 to 0.8 or 0.9 ng/mL (0.6 to 1.0 or 1.2 nmol/L), for treatment efficacy, especially for women with heart failure[7,8]; in addition, to avoid potential toxic effects, it is now recommended that the serum digoxin level be less than 1.0 ng/mL (1.3 nmol/L) in patients with heart failure.[7-9] Because digoxin is subject to various drug–drug interactions and because it has a relatively narrow therapeutic index, the dosage should be adjusted according to body weight, age, renal function, concurrent medications, and clinical observations.[1]

Polypharmacy is increasingly common, especially among patients with cardiac diseases. Many patients take multiple prescription and over-the-counter (OTC) medications that could interact, particularly when regimens include agents with a narrow therapeutic index, like digoxin. For example, potassium-depleting diuretics, commonly used for patients with heart failure, can cause hypokalemia, which in turn increases the risk of digoxin toxicity. Macrolide antibiotics and tetracyclines may increase the bioavailability of digoxin, leading to elevated digoxin concentrations. Conversely, antacids and antidiarrheal agents may interfere with absorption of digoxin. In addition, other common medications used by patients with heart disease, such as ß-blockers, nonsteroidal anti-inflammatory drugs, spironolactone, and quinidine, may all lead to digoxin intoxication by elevating the serum concentration of digoxin.[1,3,5,10,11]

In North America, the use of dietary supplements, especially herbal products and vitamins, is increasing. A US survey revealed that the use of herbs by the general public increased from 12% in 1997 to 19% in 2002; however, consultation with a practitioner regarding the use of herbal medicines decreased from 15% to 5% over the same period.[12] In a recent survey by Health Canada, 71% of Canadians surveyed had used a natural health product (including vitamins, minerals, herbal remedies, and teas), and almost 40% of the users reported using natural health products on a daily basis.[13] Wood and others,[14] who surveyed a cohort of patients with cardiovascular disease in Nova Scotia, found that over 40% of the patients used oral nutritional supplements (herbal or nonherbal or both), and 65% of the supplement users cited their cardiovascular disease as the reason for doing so.

In light of the increased use of dietary supplements, the potential for herb–drug interactions in the context of cardiac disease should be evaluated. The available literature suggests a high potential for interactions between digoxin and dietary supplements, especially herbal products. Some herbal medicines are thought to interfere with digoxin monitoring[15] and others with the drug's pharmacodynamics (by inhibiting or potentiating its effects or by having additive digoxin-like effects). Licorice root (*Glycyrrhiza glabra*),[16-18] hawthorn (*Crataegus oxyacantha*),[18,19] St John's wort (*Hypericum perforatum*),[20,21] Siberian ginseng (*Eleutherococcus senticosus*),[22,23] and *Ginkgo biloba*[22,24] are examples of herbal medicines for which interactions with digoxin have been suggested. Although the literature on this subject outlines the potential danger of such interactions, there is a lack of studies evaluating the prevalence of dietary supplement use in conjunction with digoxin and the specific types of supplements used by this patient group. It is also unclear whether these interactions translate into clinically relevant adverse effects among patients taking digoxin.

The objectives of this study were to determine the prevalence of use of nonprescription medications, especially herbal supplements, in a group of patients receiving digoxin therapy and to assess the impact of literature-reported interactions between digoxin and dietary supplements or OTC medications on clinical symptoms commonly associated with digoxin toxicity in an outpatient setting.

METHODS

Study Design and Setting

This open-label, cross-sectional survey study was approved by the University of British Columbia/ Providence Healthcare Research Ethics Board. Patients receiving digoxin therapy were recruited at St Paul's Hospital, Vancouver, British Columbia, a 500-bed urban teaching hospital.

Definitions

For the purposes of this report, OTC medications are defined as medicinal products that are sold without a prescription. Examples include antacids, kaolin–pectin,

quinine, and acetylsalicylic acid. The term "herbal supplements" is used for oral botanical supplements such as herbs and herbal extracts that are sold without a prescription. Examples include aloe, ginseng, and licorice root. Nonherbal supplements are vitamins, minerals, potassium supplements, and other nonherbal dietary substances. The term "dietary supplements" includes both herbal and nonherbal supplements,[25] and the term "nonprescription medications" is used to refer collectively to both OTC medications and dietary supplements.

Study Population and Recruitment

Potential study participants were identified by reviewing charts from the cardiology, general medicine, renal, and vascular wards and the Healthy Heart Clinic (a cardiac rehabilitation clinic) of St Paul's Hospital. Patients were included if they were at least 19 years old, had obtained their prescription medications in British Columbia, had been taking digoxin as an outpatient for at least 3 months, were fluent in English, had provided informed consent, and were able to participate in an in-person or telephone interview. The study sample size, which was one of convenience, was determined by the number of patients that could be recruited between June 2001 and November 2003.

Three interviewers (including E.N.) contacted potential participants to explain the purpose of the study, without mentioning the emphasis on use of nonprescription medications. Patients were told that the interview would include questions about use of medications, both prescription and nonprescription, and diseases that might influence the effects of digoxin. Patients who were in hospital at the time they were identified as potential participants were contacted in person; outpatients initially received a letter from the primary caregiver, and the interviewer followed up by telephone.

Data Collection

The interviewer administered the survey (in person or by telephone), using a standardized questionnaire with questions about relevant exposures and symptoms during the month before the survey date. The questionnaire consisted mostly of checklists and fill-in-the-blank entries; the interview lasted about 10 to 15 minutes. Data collected included demographic characteristics, indication for digoxin therapy, duration of digoxin therapy, dose of digoxin, disease states (e.g., symptoms potentially related to heart failure or atrial fibrillation or both), number and date(s) of hospital admissions in the previous month, concurrent illnesses (impaired renal function, malignancy, thyroid disorder, acute diarrhea), symptoms potentially related to digoxin toxicity (anorexia, nausea, vomiting, diarrhea, changes in vision, headache, weakness or dizziness, mental disturbances),[26-28] dosage of nonprescription medications used in the past month, and whether usage patterns for nonprescription medications had changed over the past month. Participants were asked specifically about their use of 4 OTC products and 30 herbal supplements that have been reported as potentially interacting with digoxin (see Appendix 1)[16,21,23,29-33] and about their use of any other nonprescription medications not specifically listed. In addition, patient-specific records in the provincial prescription database (PharmaNet) were reviewed to obtain information on the use of prescription medications during the month before the survey date.

Statistical Analyses

Descriptive statistics were used to summarize demographic data, prevalence of diseases, concurrent illnesses, and the use of medications (prescription and nonprescription) with the potential of influencing digoxin therapy. Because herbal supplements were of special interest, nonherbal supplements were grouped with OTC medications in the detailed analysis of nonprescription medication use. To evaluate the associated risk of digoxin toxicity, case patients were identified as those reporting one or more symptoms potentially related to digoxin toxicity in the month before the interview. Univariate analysis was used to compare the prevalence of exposures between patients who did and those who did not report symptoms potentially related to digoxin toxicity. The χ^2 test and Fisher's exact test were employed, where appropriate, for categorical data; Student's t test was used for continuous variables. Statistical analyses were performed using SPSS software (version 12.0 for Windows, SPSS Inc, Chicago, Illinois). A p value less than 0.05 was deemed significant.

RESULTS

Patient Characteristics

Of the 447 potential participants identified in the chart review, 143 could not be contacted, and 132 were excluded for various reasons: declined to participate in the study, were excluded by their doctors, lacked sufficient proficiency in English, were no longer taking digoxin, had died, were in poor health, or were deaf. A total of 172 patients were enrolled for the study in person (n = 33, 19.2%) or by phone (n = 139, 80.8%) between June 2001 and November 2003. Participants' demographic characteristics, including digoxin use and concurrent illnesses, are

Table 1. Characteristics of 172 Adult Patients Taking Digoxin for Heart Conditions

Characteristic	No. (%) of Patients*	
Demographic		
Mean age ± SD (range) (years)	65.2±12.0	(22–90)
Sex		
Men	122	(70.9)
Women	50	(29.1)
Primary indication for digoxin		
Heart failure alone	60	(34.9)
Atrial fibrillation alone	55	(32.0)
Heart failure + atrial fibrillation	28	(16.3)
Not sure	18	(10.5)
Other†	11	(6.4)
Concurrent illness		
Acute diarrhea	32	(18.6)
Thyroid disorder	26	(15.1)
Hypothyroidism	21	(12.2)
Hyperthyroidism	3	(1.7)
Not sure	2	(1.2)
Impaired renal function	17	(9.9)
Malignancy	12	(7.0)
Digoxin therapy (mean ± SD, range)		
Duration‡ (years)	5.9±7.2	(0.25–52)
Dose (µg/day)	174.8±77.9	(62.5–500)
Average no. of tests of digoxin level per year	0.75±1.59	(0–12)
Patients with test of digoxin level in past year	47	(27.3)

SD = standard deviation.
*Except where indicated otherwise.
†Dilated idiopathic cardiomyopathy, pacemaker, leaky valve, coronary artery bypass graft(s), enlarged heart, coronary artery dissection, or myocardial infarction.
‡A total of 23 patients (13.4%) were unsure how long they had been taking digoxin.

summarized in Table 1. As expected, the most common indications for digoxin therapy were heart failure and/or atrial fibrillation (a total of 143 patients, 83.1%). Despite their digoxin therapy, most patients (151 or 87.8%) had experienced symptoms commonly associated with heart failure and/or atrial fibrillation in the month before the survey, including light-headedness, dizziness, loss of consciousness, heart palpitations, shortness of breath, fatigue, coughing, lung congestion, and swelling in the legs or ankles. Eighteen (10.5%) of the patients were unsure of the reason for digoxin therapy. Impaired renal function, thyroid disorder, and acute diarrhea were the relevant concurrent disorders most commonly reported. Twelve of the patients reported having cancer, but none had undergone chemotherapy in the month or year before the study. Only 47 (27.3%) of the patients had undergone testing for serum digoxin level in the past year.

Use of Nonprescription Medications

Table 2 summarizes the use of nonprescription medications (OTC drugs and/or dietary supplements) by the patients in the month before the study. Use of OTC drugs and/or nonherbal supplements was reported by 153 (89.0%) patients; nonherbal supplements (vitamins and minerals) were the most popular (used by 121 patients, 70.3% of the total sample). Common OTC medications included acetaminophen (19/172 patients, 11.0%) and acetylsalicylic acid (51/172 patients, 29.7%), neither of which is known to interact with digoxin.

Potentially interacting OTC medications and nonherbal supplements, namely antacids, potassium supplements, quinine, and kaolin–pectin, were used by 50 (29.1%) of the participants; antacids and potassium supplements were the most popular of these (Table 2). For 34 (68.0%) of these 50 patients, usage of OTC medications and nonherbal supplements in the month before the study was similar to usage over the previous year; only 9 (18.0%) of the 50 patients reported increased use.

Thirty-seven (21.5%) of all 172 patients reported having used herbal supplements in the previous month, but only 4/172 patients (2.3%) reported that they had used a herbal supplement that potentially interacts with digoxin. The most popular herbal

Table 2. Use of Nonprescription Medications,* in the Month Preceding the Study, by 172 Patients Receiving Digoxin Therapy

Substance	No. (%) of Patients	
Regular use of any nonprescription product	153	(89.0)
Use of nonherbal supplements	121	(70.3)
Potentially interacting over-the-counter products†‡		
Any	50	(29.1)
Antacid	37	(21.5)
Potassium supplement	15	(8.7)
Quinine	4	(2.3)
Kaolin–pectin	2	(1.2)
Any, but excluding potassium	41	(23.8)
Herbal supplements		
Any§	37	(21.5)
Potentially interacting‡¶	4	(2.3)
Ginseng (any type)	2	(1.2)
Cassia angustifolia	1	(0.6)
Cascara sagrada bark	1	(0.6)
Licorice root	1	(0.6)

*Over-the-counter products or dietary supplements or both.
†Includes antacids, potassium supplements, quinine, and kaolin–pectin.
‡Some patients used more than one potentially interacting substance.
§*Echinacea*, evening primrose oil, saw palmetto, strauss heartdrops, lecithin, cranberry capsules, garlic, *Ginkgo biloba*, fenugreek, apple cider, chamomile, flaxseed, chondroitin.
¶Includes ginseng, *Cassia angustifolia*, cascara sagrada bark, and licorice root.

supplements were *Echinacea*, evening primrose oil (*Oenothera biennis*), and saw palmetto (*Serenoa repens*). Of the 37 patients who used herbal supplements, 27 had used only 1 such supplement, 9 had used between 2 and 6 supplements, and 1 reported using 10 herbal supplements. The 135 participants who did not use herbal supplements gave the following reasons: not wanting to use additional medication (28 or 20.7%), not believing in the efficacy of herbal supplements (20 or 14.8%), being concerned about the safety of herbal supplements (17 or 12.6%), not knowing enough about herbal supplements (12 or 8.9%), being aware of herb–digoxin interactions (11 or 8.1%), counselling by physicians (8 or 5.9%), counselling by pharmacists (1 or 0.7%), and other reasons (7 or 5.2%). Thirty-one (23.0%) of the nonusers provided no reason.

Use of Prescription Medications

The mean number (± standard deviation) of prescription medications, including digoxin, taken during the month before the survey was 7.6 ± 2.8, and the number of concurrent prescription medications ranged from 1 to 17. Almost 90% of the patients (152 or 88.4%) had been exposed to one or more medications with the potential to influence digoxin therapy. The most common concurrent prescription medications of any type were furosemide, spironolactone, carvedilol, and amiodarone; the most common prescription medications with potential interactions with digoxin were also furosemide, spironolactone, carvedilol, and amiodarone (see also Table 3).

Twenty-seven of all participants (15.7%) reported starting a medication known to influence digoxin therapy in the month before the survey. The majority of patients (147 or 85.5%) reported no change in exposure to potentially interacting prescription medications in the past month relative to the past year; 11 (6.4%) reported less exposure and 14 (8.1%) reported more exposure.

Adverse Events Potentially Related to Digoxin or to Drug Interactions

A total of 109 patients (63.4%) reported adverse events potentially related to their digoxin therapy. The most common adverse effect (mentioned by 50 [45.9%] of those reporting adverse events) was changes in vision; other specific symptoms surveyed (e.g., diarrhea, anorexia, nausea) were experienced by about 30% of those with adverse effects. Overall, the majority of patients (155 or 90.1%) reported similar frequency of adverse events in the past month relative to the past year. Patients who had experienced these symptoms in the month before the interview had been receiving digoxin therapy for a

Table 3. Use of Potentially Interacting Medications (Prescription and Nonprescription) and Reporting of Symptoms Potentially Related to Digoxin Toxicity

Use of Potentially Interacting Substance	Overall Use (No. and % of Patients)	No. (%) of Patients with Symptoms Potentially Related to Digoxin Toxicity		
	(*n* = 172)	Yes (*n* = 109)	No (*n* = 63)	*p* value
Prescription medications other than digoxin				
Any	152 (88.4)	99 (90.8)	53 (84.1)	0.19
Furosemide	96 (55.8)	63 (57.8)	33 (52.4)	0.49
Spironolactone	72 (41.9)	48 (44.0)	24 (38.1)	0.45
Carvedilol	61 (35.5)	41 (37.6)	20 (31.7)	0.45
Amiodarone	30 (17.4)	18 (16.5)	12 (19.0)	0.67
Hydrochlorothiazide	13 (7.6)	7 (6.4)	6 (9.5)	0.46
Omeprazole	11 (6.4)	9 (8.3)	2 (3.2)	0.19
Diltiazem	9 (5.2)	2 (1.8)	7 (11.1)	0.008
Nonprescription medications				
Use of interacting OTC drug or nonherbal supplements*†	50 (29.1)	35 (32.1)	15 (23.8)	0.25
Use of interacting OTC drug (excluding potassium)*†	41 (23.8)	31 (28.4)	10 (15.9)	0.06
Use of potassium supplements	15 (8.7)	8 (7.3)	7 (11.1)	0.40
General use of herbal supplement(s) in past month	37 (21.5)	23 (21.1)	14 (22.2)	0.86
Use of potentially interacting herbal supplement(s) in past month	4 (2.3)	3 (2.8)	1 (1.6)	> 0.99
Cassia angustifolia	1 (0.6)	1 (0.9)	0 (0)	> 0.99
Cascara sagrada bark	1 (0.6)	1 (0.9)	0 (0)	> 0.99
Ginseng (any type)	2 (1.2)	2 (1.8)	0 (0)	> 0.99
Licorice root	1 (0.6)	0 (0)	1 (1.6)	> 0.99

OTC = over-the-counter
*Use of OTC product once per week or more.
†Potentially interacting OTC drugs include antacids, quinine, kaolin–pectin, and potassium supplements.

Table 4. Comparison of Patient Characteristics between Those Who Experienced Symptoms Potentially Related to Digoxin Toxicity and Those Who Did Not

Characteristic	Presence of Symptoms Potentially Related to Digoxin Toxicity*		
	Yes (*n* = 109)	No (*n* = 63)	*p* value†
Age (years)	64.3±11.8	66.7±12.3	0.22
Duration of digoxin therapy (years)	5.1±6.7	7.3±7.9	0.053
Dose of digoxin (µg/day)	170±84	183±66	0.32
Duration of current dosage (years)	3.4±4.5	6.0±7.7	0.005
Male sex	75 (68.8)	47 (74.6)	0.49
Impaired renal function	12 (11.0)	5 (7.9)	0.60
Thyroid disorder	19 (17.4)	7 (11.1)	0.38
Malignancy	10 (9.2)	2 (3.2)	0.21

*No. (%) of patients or mean ± standard deviation
†Student's *t* test for continuous data; χ^2 test for dichotomous data.

shorter period and had been receiving their current dosage for a shorter period than those who did not report these symptoms (Table 4). The 2 groups were similar in terms of all other variables (Table 4).

Table 3 summarizes the use of potentially interacting medications (both prescription and nonprescription) among patients who reported the symptoms specified in the survey and those who did not. Only the 7 most commonly used prescription medications are listed. There was no difference in the use of these prescription medications between those who reported symptoms and those who did not, except for diltiazem (p = 0.008). Furthermore, there were no differences in the use of OTC drugs, nonherbal supplements, and herbal supplements between the 2 groups; however, when potassium supplements were excluded, there was a trend toward

greater use of potentially interacting OTC medications among the patients who reported symptoms (p = 0.06).

DISCUSSION

Previous research on the frequency of use of alternative medications has focused on the general public or on cardiac patients in general.[34-38] In this study, we examined the use of nonprescription medications within a specific subpopulation, patients who were taking digoxin. Because both dietary supplements (herbal and nonherbal)[25] and OTC medications are commonly used, they were considered collectively as nonprescription medications in this study. To further distinguish the use of herbal supplements, nonherbal supplements (e.g., vitamins and minerals) were grouped with OTC medications in subsequent analysis. Since digoxin has a narrow therapeutic window and is subject to various drug–drug and herb–drug interactions that might increase the risk of toxic effects, the use of nonprescription medications in this patient population is of particular concern. In fact, several recent articles have reviewed interactions involving herbal products and cardiovascular drugs, highlighting the importance of this issue.[17-20,22,39-41]

Specifically, numerous herbal supplements have been proposed to interact with digoxin through various mechanisms. Herbs that contain cardiac glycosides, such as *Adonis*, foxglove (yellow and purple) (*Digitalis grandiflora* and *Digitalis purpurea*), hawthorn, milkweed (*Asclepias*), lily of the valley (*Convallaria majalis*), and Kyushin, may have an additive effect when used in conjunction with digoxin.[17-19,29,42] Herbal medications such as Siberian ginseng, Asian ginseng (*Panax*), and Dan Shen (*Salvia miltiorrhiza*) have been shown to cross-react with digoxin monitoring assays, producing falsely elevated digoxin levels.[15,19,23,43] Pharmacokinetic interactions have been suggested for St John's wort (via induction of P-glycoprotein) and guar gum (*Cyamopsis tetragonolobus*) (which reduces the absorption of digoxin).[19-21,39] Long-term use of stimulant laxatives such as *Cassia angustifolia*, cascara sagrada (*Rhamnus purshiana*), *Aloe vera*, licorice, and buckthorn (*Rhamnus*) may lead to hypokalemia, which could sensitize the heart tissue to digoxin and increase the risk of digoxin toxicity.[1,16,19,29,30] Several controlled pharmacokinetic studies in healthy subjects found that hawthorn, goldenseal (*Hydrastis canadensis*), kava kava (*Piper methysticum*), milk thistle (*Silybum marianum*), and black cohosh (*Cimicifuga racemosa*) had no significant effects on the pharmacokinetics of digoxin.[44-46] However, most of these conclusions were based on case reports and studies with small sample sizes, which provided limited clinical evidence showing that concurrent use of digoxin and herbal supplements compromises treatment outcomes.[39,47] The current study aimed to investigate the prevalence of nonprescription medication use by patients taking digoxin, with a focus on herbal supplements, and to determine whether use of herbal supplements was linked to digoxin-associated adverse events.

Overall, the prevalence of herbal supplement use in this study population (21.5%) was comparable to that for other surveys of patients with cardiovascular disease. For example, Pharand and others[48] reported that 17% of Canadian patients with cardiac disease used herbal products; Wood and others[14] reported that 32% of patients with cardiovascular disease used herbal supplements, and Yeh and others[49] reported that 18% did so. Saydah and Eberhardt[50] recently explored the 2002 National Health Interview Survey (US) and reported that 19.5% of patients with cardiovascular disease had used "biologically based" alternative medicines (i.e., herbs, special diets, vitamins) in the past 12 months. However, given the perceived risk of toxic effects and drug interactions associated with digoxin, it is noteworthy that the prevalence of herbal supplement use in their sample of patients taking digoxin was similar to that previously reported for cardiac patients in general. Although the use of herbal supplements was common among participants in the study reported here, only 4 patients (2.3% of the total sample) reported using herbal supplements that are purported to interact with digoxin, a rate much lower than reported previously (6% and 22%).[14,49] Initially, we speculated that the low frequency of use of potentially interacting herbal supplements might be due to patients being "herb-savvy" (i.e., well educated about potential interactions with digoxin). Interestingly, of the patients who did not use herbal supplements, 7.4% attributed the nonusage to physician and pharmacist counselling, and only 8.1% were aware of herb–digoxin interactions. These findings suggest that patient education and counselling about the use of herbal supplements are still wanting and improvement is warranted.

Among the patients surveyed, there was no difference in the prevalence of herbal supplement use between those reporting and those denying symptoms potentially related to digoxin toxicity. Although the lack of a difference may be attributable to the fact that only a few patients were using herbal supplements purported to interact with digoxin, the general use of herbal supplements did not appear to compromise the safety of digoxin therapy in the population studied. Since monitoring of digoxin level was rare (such that more than 70% of patients had undergone no digoxin monitoring in the past

year), the effects of herbal supplements that might interfere with digoxin assays were difficult to assess. Furthermore, using patient-reported symptoms as an outcome limits specificity. Symptoms potentially related to digoxin toxicity usually involve the cardiac and gastrointestinal systems[1] and can be difficult to attribute specifically to digoxin, as most patients are taking other medications as well. In addition, outcomes were documented qualitatively in this study; a quantitative (objective) measure of symptom severity and/or serum levels of digoxin might shed more light on the possible association between use of herbal supplements and digoxin toxicity. Also, even though patients were not told about the study's emphasis on herbal supplement use when they were interviewed, use of potentially interacting herbal supplements in this patient population might not have been detected because of nondisclosure. Previous authors have noted that patients were unlikely to report use of complementary and alternative medicines to physicians or pharmacists.[34-36] It is also important to consider that the quality, purity, and dosages of herbal supplements lack regulation and are highly variable. Nonetheless, despite numerous reports about the danger of herb–digoxin interactions, this clinical survey yielded no evidence of an elevated risk of digoxin toxicity.

In this study population, the use of OTC and nonherbal supplements, including those believed to interact with digoxin, was far more prevalent than the use of herbal supplements. Vitamins and minerals were the most popular nonherbal supplements. To date, there is no research evidence or mechanistic hypothesis to warn against the concurrent use of digoxin and vitamins. Although the use of antacids and kaolin–pectin is believed to decrease digoxin levels by interfering with digoxin absorption,[1] and the use of quinine (which was available over the counter in Canada during the study period) at doses greater than 600 mg/day may augment digoxin concentrations,[51-53] there was no difference in the occurrence of symptoms commonly associated with heart failure and atrial fibrillation (data not shown) or of digoxin toxic effects with use of these substances. Potassium supplements are frequently used by patients with cardiovascular disease to reduce hypokalemia induced by diuretics.[54] Whereas the concurrent use of potassium with digoxin is not necessarily a concern, there is a potential danger of digoxin toxicity if the use of potassium supplements is decreased or discontinued. When potassium supplements were excluded from the analysis, we found that patients who reported symptoms potentially related to digoxin toxicity tended to be more likely to use interacting OTC medications.

Although numerous prescription medications are known to elevate serum concentrations of digoxin, many of these are commonly used concurrently with digoxin in patients with cardiovascular disease.[5,55,56] In a recent study investigating the dispensing of 9 interacting medications in an outpatient setting, digoxin was dispensed along with one or more potentially interacting prescription medications for 25% of the patients.[11] In the study reported here, 88.4% of the patients were using one or more prescription medications reported to have some interaction with digoxin. As with nonprescription medications, no link was observed between symptoms potentially related to digoxin toxicity and use of specific prescription medications, except for diltiazem. However, since only a few patients were taking diltiazem (n = 9), this observation is probably due to chance. Since drug–drug interactions involving digoxin are well known, it is likely that many patients were counselled and their digoxin dosages adjusted accordingly to prevent toxic effects.

A major limitation of this study was the impossibility of determining whether symptoms of toxicity were due to interactions between a prescription drug and digoxin or between a herbal supplement and digoxin. The numerous medications and supplements used and the variety of dosages and regimens confound the assessment of clinical effects due to herb–digoxin interactions. Since it is difficult to assess the efficacy of digoxin by means of a survey, this study focused on the safety aspects of digoxin use and emphasized herb–digoxin interactions that might lead to toxic effects. Although having an interviewer administer the survey might have led to bias and disinclination of patients to fully disclose their use of supplements, this approach was deemed appropriate to ensure the accuracy and completeness of data collection. For similar reasons, only English-speaking patients were included in the survey, to minimize the risk of miscommunication and the need for translation. Since patients' ethnicity was not recorded and data were not analyzed by age, patterns of supplement use specific to certain ethnic or age groups might have been overlooked. The survey used the common names of herbal supplements, but some herbal supplements have a variety of names, and it was not feasible to identify all of these names; as such, it is possible that the use of supplements with multiple names was underestimated. The authors recognize that the Latin binomial naming system for plants provides an unambiguous way of identifying herbal products, but patients may not recognize these names. The names of various herbal supplements have therefore been reported in Appendix

1 and elsewhere in this article as they appeared in the survey; scientific names, which are provided parenthetically throughout the article, were not used in the original survey. Although the study sample was a convenience sample, retrospective analysis showed that the sample size of 172 patients yielded margins of error of less than 5% around the 89.0% prevalence of use of any nonprescription product and approximately 6% around the 21.5% prevalence of use of any herbal supplement, assuming a 95% confidence interval and a large relevant population.[57]

Although the use of herbal supplements has increased in recent years, the pattern of use among patients taking concurrent prescription medications, such as digoxin, is not well understood. Major concerns have been raised about the use of herbal supplements in conjunction with cardiovascular mediations such as digoxin and warfarin, given that numerous potential interactions have been reported and given that these medications have narrow therapeutic indexes.[40,58-61] Previous investigations conducted by our group have indicated a higher prevalence of use of herbal supplements among patients receiving warfarin than among those taking digoxin, with 36% to 39% of patients taking warfarin also taking potentially interacting herbal supplements.[62,63] Research groups in other countries have reported a high prevalence of use of herbal supplements in conjunction with warfarin (19% to 27%),[61,64,65] which emphasizes the need to be mindful of herbal supplement use by patients with cardiovascular disease. Although the data reported here suggest that general use of herbal supplements may not be a concern for patients taking digoxin in a "real-world setting", health care providers should always ask about the use of these supplements when collecting medical histories from patients. Potential herb–drug interactions should be considered when modifying therapy or when an adverse reaction is apparent. In addition, health care providers should be nonjudgmental and knowledgeable about herbal supplements, in order to promote open communication with and provide better education for patients. Further study is required to determine whether the supplement usage pattern reported here is unique to this cohort of patients or whether patients taking digoxin generally have a lower prevalence of supplement use. Future research should strive to characterize both the efficacy and the adverse effects of digoxin and should employ a quantitative approach (e.g., by determining digoxin levels). In addition, inclusion of non-English-speaking patients would afford a more complete view of supplement use in a diverse population such as Canada's.

CONCLUSIONS

The use of herbal supplements in conjunction with digoxin was common among the patients surveyed in this study; however, only a small percentage of patients used herbal supplements that were purported to interact with digoxin. In spite of the perceived dangers of herb–digoxin interactions, no direct link was observed between use of a herbal supplement and symptoms potentially related to digoxin toxicity. On the contrary, the prevalence of use of OTC medications and nonherbal supplements was much higher than the use of herbal supplements in this patient group and appeared to have a greater likelihood of influencing the safety of digoxin therapy. Nonetheless, health care providers should be aware of the potential implications of herbal supplement use and should better educate patients regarding the potential for herb–drug interactions.

References

1. Lanoxin® (digoxin) tablets [product insert]. Research Triangle (NC): GlaxoSmithKline; 2001 Aug.
2. Gheorghiade M, Adams KF Jr, Colucci WS. Digoxin in the management of cardiovascular disorders. *Circulation* 2004;109 (24):2959-2964.
3. Eichhorn EJ, Gheorghiade M. Digoxin. *Prog Cardiovasc Dis* 2002;44(4):251-266.
4. Bauman JL, Didomenico RJ, Galanter WL. Mechanisms, manifestations, and management of digoxin toxicity in the modern era. *Am J Cardiovasc Drugs* 2006;6(2):77-86.
5. Schentag JJ, Bang AJ, Kozinski-Tober JL. Digoxin. In: Burton ME, editor. *Applied pharmacokinetics and pharmacodynamics: principles of therapeutic drug monitoring.* 4th ed. Baltimore (MD): Lippincott Williams & Wilkins; 2003. p. 410.
6. Ahmed A, Rich MW, Love TE, Lloyd-Jones DM, Aban IB, Colucci WS, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J* 2006;27(2):178-186.
7. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003;289(7):871-878.
8. Adams KF Jr, Patterson JH, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. *J Am Coll Cardiol* 2005;46(3):497-504.
9. Heart Failure Society of America. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. *J Card Fail* 2006;12(1):10-38.
10. Eichhorn EJ, Gheorghiade M. Digoxin—new perspective on an old drug. *N Engl J Med* 2002;347(18):1394-1395.
11. Lafata JE, Schultz L, Simpkins J, Chan KA, Horn JR, Kaatz S, et al. Potential drug–drug interactions in the outpatient setting. *Med Care* 2006;44(6):534-541.
12. Tindle HA, Davis RB, Phillips RS, Eisenberg DM. Trends in use of complementary and alternative medicine by US adults: 1997–2002. *Altern Ther Health Med* 2005;11(1):42-49.
13. *Baseline natural health products survey among consumers.* Ottawa (ON): Health Canada, Ipsos-Reid Research Company; 2005 Mar.
14. Wood MJ, Stewart RL, Merry H, Johnstone DE, Cox JL. Use of complementary and alternative medical therapies in patients with cardiovascular disease. *Am Heart J* 2003;145(5):806-812.

15. Dasgupta A, Wu S, Actor J, Olsen M, Wells A, Datta P. Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays. Significant variation in digoxin-like immunoreactivity among commercial ginsengs. *Am J Clin Pathol* 2003;119(2):298-303.
16. Corsi FM, Galgani S, Gasparini C, Giacanelli M, Piazza G. Acute hypokalemic myopathy due to chronic licorice ingestion: report of a case. *Ital J Neurol Sci* 1983;4(4):493-497.
17. Izzo AA, Di Carlo G, Borrelli F, Ernst E. Cardiovascular pharmacotherapy and herbal medicines: the risk of drug interaction. *Int J Cardiol* 2005;98(1):1-14.
18. Chung MK. Vitamins, supplements, herbal medicines, and arrhythmias. *Cardiol Rev* 2004;12(2):73-84.
19. Awang DV, Fugh-Berman A. Herbal interactions with cardiovascular drugs. *J Cardiovasc Nurs* 2002;16(4):64-70.
20. Izzo AA. Drug interactions with St. John's wort (*Hypericum perforatum*): a review of the clinical evidence. *Int J Clin Pharmacol Ther* 2004;42(3):139-148.
21. 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(4):338-345.
22. Hu Z, Yang X, Ho PC, Chan SY, Heng PW, Chan E, et al. Herb–drug interactions: a literature review. *Drugs* 2005;65(9): 1239-1282.
23. McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. *CMAJ* 1996;155(3):293-295.
24. Mauro VF, Mauro LS, Kleshinski JF, Khuder SA, Wang Y, Erhardt PW. Impact of ginkgo biloba on the pharmacokinetics of digoxin. *Am J Ther* 2003;10(4):247-251.
25. Dietary Supplement Health and Education Act of 1994. Rockville (MD): US Food and Drug Administration Center for Food Safety and Applied Nutrition; 1995 [cited 2007 Mar 10]. Available from: http://www.cfsan.fda.gov/~dms/dietsupp.html
26. Miura T, Kojima R, Sugiura Y, Mizutani M, Takatsu F, Suzuki Y. Effect of aging on the incidence of digoxin toxicity. *Ann Pharmacother* 2000;34(4):427-432.
27. Smith TW. Digitalis. Mechanisms of action and clinical use. *N Engl J Med* 1988;318(6):358-365.
28. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336(8):525-533.
29. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug–herb interactions. *Arch Intern Med* 1998;158(20):2200-2211.
30. Shalansky S. The use of alternative medicines in patients with cardiovascular disease: an evidence-based review and practical considerations. *Can J Hosp Pharm* 2001;54(3 Suppl 2):2-15.
31. Blumenthal M. Industry alert: plantain adulterated with digitalis. *Herbal Gram* 1997;40:28-29.
32. Hobbs C, Foster S. Hawthorn: a literature review. *HerbalGram*1990;22:19-33.
33. Fushimi R, Tachi J, Amino N, Miyai K. Chinese medicine interfering with digoxin immunoassay. *Lancet* 1989;1(8633):339.
34. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 1998;280(18):1569-1575.
35. Leung JM, Dzankic S, Manku K, Yuan S. The prevalence and predictors of the use of alternative medicine in presurgical patients in five California hospitals. *Anesth Analg* 2001;93(4):1062-1068.
36. Liu EH, Turner LM, Lin SX, Klaus L, Choi LY, Whitworth J, et al. Use of alternative medicine by patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2000;120(2):335-341.
37. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA* 2002;287(3):337-344.
38. Kennedy J. Herb and supplement use in the US adult population. *Clin Ther* 2005;27(11):1847-1858.
39. Izzo AA. Herb–drug interactions: an overview of the clinical evidence. *Fundam Clin Pharmacol* 2005;19(1):1-16.
40. Greenblatt DJ, von Moltke LL. Interaction of warfarin with drugs, natural substances, and foods. *J Clin Pharmacol* 2005;45(2): 127-132.
41. Madabushi R, Frank B, Drewelow B, Derendorf H, Butterweck V. Hyperforin in St. John's wort drug interactions. *Eur J Clin Pharmacol* 2006;62(3):225-233.
42. Cheng TO. Herb digoxin interactions. *Int J Cardiol* 2006;110(1):93.
43. Chow L, Johnson M, Wells A, Dasgupta A. Effect of the traditional Chinese medicines Chan Su, Lu-Shen-Wan, Dan Shen, and Asian ginseng on serum digoxin measurement by Tina-quant (Roche) and Synchron LX system (Beckman) digoxin immunoassays. *J Clin Lab Anal* 2003;17(1):22-27.
44. Tankanow R, Tamer HR, Streetman DS, Smith SG, Welton JL, Annesley T, et al. Interaction study between digoxin and a preparation of hawthorn (*Crataegus oxyacantha*). *J Clin Pharmacol* 2003;43(6):637-642.
45. Gurley BJ, Barone GW, Williams DK, Carrier J, Breen P, Yates CR, et al. Effect of milk thistle (*Silybum marianum*) and black cohosh (*Cimicifuga racemosa*) supplementation on digoxin pharmacokinetics in humans. *Drug Metab Dispos* 2006;34(1):69-74.
46. Gurley BJ, Swain A, Barone GW, Williams DK, Breen P, Yates CR, et al. Effect of goldenseal (*Hydrastis canadensis*) and kava kava (*Piper methysticum*) supplementation on digoxin pharmacokinetics in humans. *Drug Metab Dispos* 2007; 35(2):240-245.
47. Fugh-Berman A. Herb–drug interactions. *Lancet* 2000;355 (9198):134-138.
48. Pharand C, Ackman ML, Jackevicius CA, Paradiso-Hardy FL, Pearson GJ, Canadian Cardiovascular Pharmacists Network. Use of OTC and herbal products in patients with cardiovascular disease. *Ann Pharmacother* 2003;37(6):899-904.
49. Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. *Am J Cardiol* 2006; 98(5):673-680.
50. Saydah SH, Eberhardt MS. Use of complementary and alternative medicine among adults with chronic diseases: United States 2002. *J Altern Complement Med* 2006;12(8):805-812.
51. Wandell M, Powell JR, Hager WD, Fenster PE, Graves PE, Conrad KA, et al. Effect of quinine on digoxin kinetics. *Clin Pharmacol Ther* 1980;28(4):425-430.
52. Bigger JT Jr. The quinidine–digoxin interaction. *Mod Concepts Cardiovasc Dis* 1982;51(1):73-78.
53. Pedersen KE, Christiansen BD, Klitgaard NA, Nielsen-Kudsk F. Effect of quinidine on digoxin bioavailability. *Eur J Clin Pharmacol* 1983;24(1):41-47.
54. Ackman ML, Campbell JB, Buzak KA, Tsuyuki RT, Montague TJ, Teo KK. Use of nonprescription medications by patients with congestive heart failure. *Ann Pharmacother* 1999;33(6):674-679.
55. Marcus FI. Pharmacokinetic interactions between digoxin and other drugs. *J Am Coll Cardiol* 1985;5(5 Suppl A):82A-90A.
56. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet* 1988;15(4):227-244.
57. Sample size calculator [Internet]. Dulles (VA): Raosoft Inc; 2004 [cited 2007 Jun 20]. Available from: http://www.raosoft.com/samplesize.html
58. Jiang X, Blair EY, McLachlan AJ. Investigation of the effects of herbal medicines on warfarin response in healthy subjects: a population pharmacokinetic–pharmacodynamic modeling approach. *J Clin Pharmacol* 2006;46(11):1370-1378.
59. Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol* 2005;59(4):425-432.
60. Cheng TO. Warfarin interaction with herbal drugs and food. *Int J Cardiol* 2007;119(1):107-108.

61. Ramsay NA, Kenny MW, Davies G, Patel JP. Complementary and alternative medicine use among patients starting warfarin. *Br J Haematol* 2005;130(5):777-780.
62. Shalansky SJ, Lynd L, Ignaszewski A, Kerr C, Vickars L, Abd-Elmessih E. The effect of complementary and alternative medicine usage patterns on warfarin-related adverse events [abstract]. *Can J Cardiol* 2003;19(Suppl A):164A.
63. Shalansky SJ, Lynd L, Ignaszewski A, Kerr C, Vickars L. The risk of adverse events associated with complementary and alternative medicine amongst a cohort of patients taking warfarin [abstract]. *Can J Cardiol* 2003;19(Suppl A):163A.
64. Smith L, Ernst E, Ewings P, Myers P, Smith C. Co-ingestion of herbal medicines and warfarin. *Br J Gen Pract* 2004;54(503):439-441.
65. Wong RS, Cheng G, Chan TY. Use of herbal medicines by patients receiving warfarin. *Drug Saf* 2003;26(8):585-588.

Lillian S L Ting, MSc(Pharm Sci), is a PhD Candidate, Divisions of Clinical Pharmacy and of Pharmaceutics and Biopharmaceutics, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia.

Stephen J Shalansky, PharmD, FCSHP, was, at the time this study was conducted, with the Department of Pharmacy, St Paul's Hospital, Providence HealthCare, Vancouver, British Columbia. He is now Director, Pharmacy Operations, Coastal Health Services, Vancouver Coastal Health, British Columbia.

Erin Neall, BSc(Pharm Sci), was, at the time this study was conducted, a student in the Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia. She is now Pharmacy Manager, Pharmasave 246, Delta, British Columbia.

Mary H H Ensom, PharmD, FASHP, FCCP, FCSHP, FCAHS, is a Clinical Pharmacy Specialist, Children's and Women's Health Centre of British Columbia, Vancouver, British Columbia; and Professor and Director, Doctor of Pharmacy Program, Faculty of Pharmaceutical Sciences, and Distinguished University Scholar, The University of British Columbia, Vancouver, British Columbia. She is also the Editor of *CJHP*.

Address correspondence to:
Lillian S L Ting
Faculty of Pharmaceutical Sciences
University of British Columbia
2146 East Mall
Vancouver BC
V6T 1Z3

e-mail: lting@shaw.ca

Appendix 1. List of Herbal Supplements about which Patients Were Specifically Queried in a Survey about Use of Nonprescription Products in Conjunction with Digoxin

Name as Presented to Survey Participants	Scientific Name*
Adonis (pheasant's eye)	
Aloe	*Aloe vera*
Broom	*Cytisus scoparius*
Buckthorn	*Rhamnus*
Cascara sagrada bark	*Rhamnus purshiana*
Cassia senna	Same
Cassia angustifolia	Same
Dogbane	*Apocynum*
False hellebore	*Veratrum viride*
Figwort	*Scrophulariaceae*
Foxglove, yellow	*Digitalis grandiflora*
Foxglove, purple	*Digitalis purpurea*
Ginseng, Siberian	*Eleutherococcus senticosus*
Ginseng, Asian or Oriental	*Panax*
Hawthorn berry	*Crataegus oxyacantha*
Indian snakeroot	*Rauwolfia serpentine*
Kyushin	
Licorice root	*Glycyrrhiza glabra*
Lily of the valley	*Convallaria majalis*
Ma huang	*Ephedra sinica*
Motherwort	*Leonurus cardiaca*
Psyllium (black and blonde seed)	*Plantago*
Pleurisy root	*Asclepias tuberose*
Rhubarb, Chinese	*Rheum palmatum, Rheum officinale*
St John's wort	*Hypericum perforatum*
Senna fruit	*Cassia senna*
Strophanthus	Same
Uzara root	*Xysmalobium undulatum*
White squill	*Urginea maritime*
Wild ipecac	*Euphorbia ipecacuanhae*

*If applicable.