Digoxin Immunoassays on the ARCHITECT i2000SR and ARCHITECT c8000 Analyzers Are Free From Interferences of Asian, Siberian, and American Ginseng

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Asian, Siberian, and American ginseng are known to interfere with serum digoxin measurements using fluorescence polarization technology, Digoxin II and Digoxin III assays (Abbott Laboratories, Green Oaks, IL) as well as other digoxin assays. Abbott Laboratories more recently launched two new digoxin assays: iDigoxin, a chemiluminescent microparticle immunoassay for application on the ARCHITECT i1000SR and i2000SR immunoassay analyzers, and cDigoxin, a particle-enhanced turbidimetric inhibition immunoassay for application on the ARCHITECT c4000, c8000, and c1600 clinical chemistry analyzers; and we studied potential interferences of ginsengs with these two assays in vitro. When aliquots of drug-free serum pool treated with activated

charcoal were supplemented with extracts of various ginsengs, no significant apparent digoxin values were observed. In addition, when aliquots of the digoxin pool prepared from patients taking digoxin were further supplemented with these ginseng extracts and the digoxin values were re-measured, we observed no statistically significant difference in observed digoxin values compared to the original digoxin value of the pool. These results further establish that relatively new digoxin assays for application on the ARCHITECT analyzers that employ specific monoclonal antibodies against digoxin are free from interferences from Asian, Siberian, and American ginseng. *J. Clin. Lab. Anal.* 29:1–4, 2015. © 2014 Wiley Periodicals, Inc.

Key words: ginseng; digoxin; ARCHITECT; iDigoxin; cDigoxin

INTRODUCTION

Herbal medicines are readily available worldwide from stores without prescriptions and the use of herbal medicines among the general population is on the rise. Ginseng is a widely used herbal product in China, many other Asian countries, and the United States. For thousands of years, ginseng has been used as a heart tonic and also for treating anorexia, hypodynamia, shortness of breath, palpitation, insomnia, impotence, hemorrhage, and diabetes. Modern research has indicated that components of ginsengs (ginsenosides, polysaccharides, peptides, polyacetylenic alcohol, etc.) may have pharmacological actions, although reliable data to unambiguously establish efficacy of ginseng are still lacking due to poor qualities of many clinical trials (1). However, Mucalo recently commented that currently available data support the hypothesis that American ginseng is effective in im-

proving glycemic control in patients with type 2 diabetes (2).

The most commonly used type of ginseng is Asian ginseng, often sold as *Panax* ginseng. The other commonly used type of ginseng is Siberian ginseng, which is derived from the roots of *Eleutherococcus senticosus*. Siberian ginseng is different from Asian ginseng in that *Panax*-type ginsenosides are not found in Siberian ginseng. North American ginseng is the extract of *Panax quinquefolius*, which is a slightly different species than *Panax* ginseng.

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In the United States, ginseng is the most common herbal remedy taken by the general population (20%) followed by *Echinacea* (19%), *Ginkgo biloba* (15%), and St. John's Wort (14%) (3).

Asian ginseng and American ginseng contain ginsenosides but ginsenoside Rf is only present in Asian ginseng. In contrast, Siberian ginseng contains a different class of steroid glycosides known as eleutherosides. Although a complex mixture of various ginsenosides are present in Asian and American ginseng as well as a complex mixture of many eleutherosides is present in Siberian ginseng, in general these compounds have structural similarity with digoxin. Due to structural similarity between ginsenosides and digoxin, Asian ginseng interferes with serum digoxin measurement by the fluorescence polarization (FPIA) immunoassay (4). McRae reported a case where Siberian ginseng interfered with serum digoxin measurement. In one patient, a serum digoxin level of 5.2 ng/ml was reported but the patient had no symptoms of digoxin toxicity. The patient was taking Siberian ginseng. On discontinuation of Siberian ginseng, his digoxin level returned to therapeutic range (5). Interference of Asian and Siberian ginseng with FPIA for digoxin is significant (6). However, Abbott Laboratories no longer market this assay. Nevertheless other digoxin immunoassays are also affected by Asian, Siberian, and American ginseng (7,8). More recently, Abbott Laboratories has marketed two new digoxin assays: iDigoxin (iDig), a chemiluminescent microparticle immunoassay for application on the ARCHITECT i1000SR and i2000SR analyzers, and Multigent Digoxin, a particle-enhanced turbidimetric inhibition immunoassay for application on the ARCHITECT c4000, c8000, and c1600 analyzers (cDigoxin (cDig)), but the potential interference of Asian, Siberian, and American ginseng on these digoxin assays has not been reported before. Here, we report our findings on lack of interference of various ginsengs on these two relatively new digoxin assays.

MATERIALS AND METHODS

All ginseng products were liquid extracts and were purchased from a Chinese herbal store in Houston, Texas. Siberian ginseng was the Z-T brand manufactured in China and distributed by Z-T Universal Inc. (Glen Head, NY). Asian ginseng was the Song Shiu Pan brand *Panax* Ginseng manufactured in China. The North American ginseng was produced by Herba Natural Products Inc. (Brooklyn, NY). Digoxin assays were run on both ARCHITECT i2000 SR analyzer (iDig) and ARCHITECT c8000 analyzer (cDig) according to the protocols recommended by the manufacturer (Abbott Laboratories, Green oaks, IL). Both digoxin immunoassays utilize a specific monoclonal antibody against digoxin.

Drug-free serum pool was treated with activated charcoal (50 mg/ml of serum) for 20 min in order to remove any potentially present digoxin-like immunoreactive substances. Then, activated charcoal was removed by centrifugation and digoxin value was measured using LOCI (luminescent oxygen channeling immunoassay) digoxin immunoassay on the Vista 1500 analyzer (Siemens Diagnostic, Deerfield, IL). The value of apparent digoxin was not detected. Then aliquots of the charcoal treated drug-free serum pool were further supplemented with 5, 10, or 20 μ l of Asian, Siberian, or American ginseng per milliliter of the serum. We also prepared a digoxin serum pool using specimens from patients taking digoxin. These specimens are submitted to our clinical laboratory for therapeutic drug monitoring of digoxin and after performing such tests and reporting results to ordering physicians, these specimens are stored for a week and then discarded. We prepared digoxin pool by combining several digoxin specimens after de-identification according to the protocol approved by the IRB. These specimens would have been otherwise discarded. The digoxin concentration of the digoxin pool was 1.08 ng/ml using LOCI digoxin assay and the Vista 1500 analyzer. Aliquots of this pool were further supplemented with 5, 10, or 20 μ l of Asian, Siberian, or American ginseng per milliliter of the digoxin pool. Then all specimens were sent to the Abbott Laboratories in Chicago, and digoxin measurements were performed by scientists of Abbott Laboratories using i2000 SR and c8000 analyzer. Statistical analyses were performed using Student's *t*-test, two-tailed. A difference was considered statistically different only at 95% confidence interval ($P < 0.05$).

RESULTS

The limit of detection for the iDig assay is 0.3 ng/ml and detection limit of the cDig assay is 0.15 ng/ml. When aliquots of drug-free serum were supplemented with Asian, Siberian, and American ginseng and apparent digoxin values were measured using iDig assay, we observed 0.0 ng/ml values indicating that these ginsengs do not cross-react with iDig assay. When values were measured using cDig assay, we observed very low numbers (Table 1) but not zero values. However, all these numbers were below the detection limit (0.15 ng/ml) of the assay indicating that cDig assay also has no cross-reactivity with these ginsengs.

When aliquots of the digoxin pool were supplemented with various ginsengs and digoxin concentration were re-measured by iDig and cDig assays, observed digoxin values did not statistically differ from digoxin values of the original pool. For example, using iDig assay, concentration of digoxin in the digoxin pool 1 was 0.92 ng/ml. In the presence of 20 μ l of Asian ginseng per milliliter of the

TABLE 1. Apparent Digoxin Concentrations When Aliquots of Drug-Free Serum Were Supplemented With Various Ginsengs and Digoxin Concentrations Were Measured by ARCHITECT Digoxin Assays

Specimen	Apparent digoxin concentration (ng/ml), Mean (SD), <i>n</i> = 3	
	ARCHITECT i2000 ^a	ARCHITECT c8000
+5 µl/ml Asian ginseng	0.0	0.06 (0.03)
+10 µl/ml Asian ginseng	0.0	0.06 (0.01)
+20 µl/ml Asian ginseng	0.0	0.03 (0.01)
+5 µl/ml Siberian ginseng	0.0	0.03 (0.01)
+10 µl/ml Siberian ginseng	0.0	0.04 (0.01)
+20 µl/ml Siberian ginseng	0.0	0.03 (0.00)
+5 µl/ml American ginseng	0.0	0.03 (0.00)
+10 µl/ml North American ginseng	0.0	0.03 (0.01)
+20 µl/ml North American ginseng	0.0	0.03 (0.01)

^aStandard deviation was not calculated as all values were 0.0.

TABLE 2. Apparent Digoxin Concentrations When Aliquots of Drug Pool Were Supplemented With Various Ginsengs and Digoxin Concentrations Were Measured by ARCHITECT Digoxin Assays

Specimen	Apparent digoxin concentration (ng/ml), Mean (SD), <i>n</i> = 3	
	ARCHITECT i2000	ARCHITECT c8000
Digoxin pool 1	0.92 (0.02)	1.06 (0.01)
+10 µl/ml Asian ginseng	0.91 (0.02)	1.07 (0.01)
+20 µl/ml Asian ginseng	0.93 (0.03)	1.03 (0.01)
+5 µl/ml Siberian ginseng	0.92 (0.02)	1.04 (0.02)
+10 µl/ml Siberian ginseng	0.90 (0.02)	1.04 (0.02)
+20 µl/ml Siberian ginseng	0.93 (0.03)	1.04 (0.01)
+5 µl/ml American ginseng	0.88 (0.01)	1.00 (0.03)
+10 µl/ml North American ginseng	0.92 (0.02)	1.05 (0.01)
+20 µl/ml North American ginseng	0.92 (0.02)	1.05 (0.01)

digoxin pool, the digoxin concentration was 0.93 ng/ml, which was not statistically different from the digoxin value of the original digoxin pool 1. Similar observations were made when aliquots of digoxin pool 1 were supplemented with Siberian and Asian ginseng, and digoxin values were measured using iDig assay. Similar results were also observed when digoxin values were measured using cDig assay (Table 2).

DISCUSSION

In our investigation, we selected concentrations of various ginsengs that should mimic in vivo concentration after taking recommended amount of digoxin or severe

overdose as explained earlier (4). Our investigations indicate that in contrast to previous reports where various ginsengs can affect microparticle digoxin immunoassay or Digoxin III assay, relatively new iDig and cDig assays are completely free from interferences of Asian, Siberian, and American ginseng. This may be due to the use of specific monoclonal antibody against digoxin used in these new digoxin immunoassays. Interference of spironolactone, potassium canrenoate, and their common metabolite canrenone in digoxin immunoassays has been reported. However, we reported earlier than both iDig and cDig assays are completely free from interferences of spironolactone, potassium canrenoate, and their common metabolite canrenone (9).

Because ginsengs are one of the best-selling herbs in the United States (2) and ginsengs are indicated in traditional Chinese medicine as a tonic for heart, it is possible that a patient taking digoxin may also take ginseng. Digitalis glycosides have been in use in medicine for more than 200 years and despite development of new cardioactive drugs, digoxin is still used today for treating various cardiac disorders including congestive heart failure. The main pharmacological action of digoxin includes a dose-dependent increase in myocardial contractility and a negative chronotropic action. Digitalis also increases the refractory period and decreases impulse velocity in certain myocardial tissue (such as the AV node). The electrophysiological properties of digitalis are reflected in the ECG by shortening of QT interval. Both digoxin and digitoxin have narrow therapeutic indices and therapeutic drug monitoring is essential for achieving optimal efficacy as well as to avoid toxicity. Therapeutic range of digoxin usually is considered as 0.8–2.0 ng/ml, but there is a substantial overlap between therapeutic and toxic concentrations. Moreover, mild-to-moderate renal failure may also significantly increase risk of digoxin therapy (10). Digoxin toxicity may occur with lower digoxin dosage if hypokalemia, hypomagnesemia, or hypothyroidism coexist. Likewise, the concomitant use of drugs such as quinidine, verapamil, spironolactone, flecainide, and amiodarone can increase serum digoxin concentrations and increase the risk of digoxin toxicity. Adams et al. reported that a beneficial effect of digoxin in women was observed at serum concentrations from 0.5 to 0.9 ng/ml, whereas serum concentrations at or over 1.2 ng/ml appeared harmful (11). Therefore, interferences in serum digoxin measurement using immunoassays are clinically problematic because a clinician may adjust digoxin dose based on a falsely elevated or decreased digoxin concentration due to interference. This is particularly problematic due to very narrow therapeutic range of digoxin.

We conclude that relatively new iDig and cDig assays are completely free from interference from Asian, Siberian, and American ginseng. Therefore, these assays

can be used in clinical settings for therapeutic drug monitoring of digoxin even in patients self-medicating themselves with ginseng.

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