

## Brief Report

CONTAMINATION OF BOTANICAL  
DIETARY SUPPLEMENTS BY  
*DIGITALIS LANATA*

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FOR many years, the Food and Drug Administration (FDA) regulated botanical dietary-supplement ingredients, in most circumstances, under the provisions for food additives of the Federal Food, Drug, and Cosmetic Act to ensure that they were safe and wholesome. Currently, dietary supplements (such as botanical products, vitamins and minerals, amino acids, and tissue extracts) are regulated under the Dietary Supplement Health and Education Act of 1994, which includes several provisions that apply only to dietary supplements and dietary ingredients of dietary supplements. Included in these provisions was the removal of the ingredients of dietary supplements from regulation as food additives and the requirement that the FDA bear the burden of proof that a marketed dietary supplement presents a serious or unreasonable risk under the conditions of use on the label or as commonly consumed. This requirement is in contrast to what is required for drugs, which must be shown to be safe and effective for a particular indication before they are approved for marketing.

The case of a previously healthy patient who presented with a toxic serum digoxin level after the ingestion of botanical dietary supplements was reported to the FDA in 1997. We sought to determine the source of the patient's exposure to cardiac glycosides and to investigate the extent and duration of distribution of the suspect raw material and the products containing it. We also investigated a sec-

ond case, which was reported to the FDA about a month after the first.

## CASE REPORTS

## Patient 1

In May 1997, the Center for Food Safety and Applied Nutrition of the FDA received a report of a previously well 23-year-old woman who presented to a hospital emergency room because of persistent nausea, vomiting, lethargy, and the sensation of irregular heartbeats. An electrocardiogram revealed a high-degree atrioventricular block (complete heart block). The patient was admitted to the telemetry unit of the hospital for electrocardiographic monitoring. Because the cardiac findings were suggestive of digitalis toxicity, a serum digoxin assay was performed the next day. By polyclonal digoxin immunoassay (DGN A assay, Dade Behring, Glasgow, Del.), the patient's serum digoxin level was found to be 3.66 ng per milliliter (4.69 nmol per liter; therapeutic reference range, 0.9 to 2.0 ng per milliliter [1.15 to 2.56 nmol per liter]). The patient's blood urea nitrogen, creatinine, calcium, magnesium, sodium, potassium, chloride, and total carbon dioxide levels were normal. Over the next 72 hours, the patient continued to have electrocardiographic abnormalities and elevated serum digoxin levels (3.09 ng per milliliter [3.96 nmol per liter] on day 3). She was treated empirically with 380 mg (10 vials) of ovine digoxin immune Fab (Digibind, Glaxo Wellcome, Research Triangle Park, N.C.) but there was no clinical response. On day 5, when the serum digoxin level was 2.29 ng per milliliter (2.93 nmol per liter), she was treated with cholestyramine. There was clinical improvement over the next 24 hours, and the patient was discharged on the sixth hospital day, with a serum digoxin level of 1.91 ng per milliliter (2.45 nmol per liter).

The patient's medical history was notable for her use of an oral regimen of dietary supplements for the purpose of "internal cleansing" beginning one week before admission. These supplements were marketed as a "program" and, according to the label and accompanying materials, consisted of the following products: tablets to "gently assist in the systemic cleansing of the body, and in the removal of impurities from the intestinal tract" (a combination of 14 herbs); tablets to be used as an herbal "nutritional supplement" (a combination of 11 herbs, plus amylase and cellulase); a liquid clay (hydrated bentonite); a fibrous bulking powder (psyllium-husk powder), to be mixed with the hydrated bentonite to form a shake-like drink; and capsules to "normalize bowel pH and help maintain a healthy bowel environment" (a combination of *Bifidobacterium infantis*, *B. bifidum*, *B. longum*, *Lactobacillus acidophilus*, *L. casei*, *L. plantarum*, colostrum, and fructo-oligosaccharides). After 24 hours, the patient began to experience lethargy, nausea, and severe vomiting. The patient continued the regimen for an additional two days (for a total of three days), at which time she discontinued using the products because of vomiting. She restarted the regimen, at a reduced dosage, two days before admission. However, because of persistent nausea, irregular heartbeats, and hot flashes, the patient was evaluated in the emergency room, as described above.

## Patient 2

Approximately one month later, the FDA received a report of a 46-year-old woman, without a history of heart disease, who had been hospitalized for the evaluation of visual disturbances (described as "yellow scintillations"), nausea, vomiting, shortness of breath, palpitations, and what was described as chest pressure. Approximately five days before admission, she had begun the internal-cleansing program described above, using the same products except for the psyllium-husk powder, for which she substituted a different botanical preparation. After the third day of the program (two days before admission), she discontinued the products because of persistent vomiting.

The patient was evaluated at a hospital emergency room, at which time an electrocardiogram showed a normal sinus rhythm

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with nonspecific ST-segment and T-wave changes. A serum digoxin assay was performed with polyclonal antibodies (AxSYM Digoxin II assay, Abbott Laboratories, Abbott Park, Ill.), and the patient's digoxin level was found to be 0.9 ng per milliliter (1.15 nmol per liter; therapeutic reference range, 0.8 to 2.0 ng per milliliter [1.02 to 2.56 nmol per liter]). The patient's blood urea nitrogen, creatinine, calcium, magnesium, sodium, potassium, chloride, and total carbon dioxide levels were normal. The patient had an elevated total creatine kinase level of 347 U per liter (reference range, 24 to 195), with a normal MB fraction. Repeated determinations of creatine kinase levels at 6 and 12 hours were 284 and 260 U per liter, respectively, with normal MB fractions. The patient underwent electrocardiographic monitoring over the next 36 hours, during which time she had brief episodes of first- and second-degree atrioventricular heart block. The patient was discharged for outpatient follow-up.

## METHODS

### Analyses of Botanical Materials for Cardiac Glycosides

The five products used by Patient 1 were each screened for the presence of cardiac glycosides with the use of the Kedde reaction, a colorimetric assay that detects the aglycone moiety of cardiac glycosides, and thin-layer chromatography.<sup>1-4</sup> Only one of the products tested positive (see the Results section). Samples of the raw material of each of the individual ingredients making up the suspect botanical product were then obtained from the manufacturer. Extracts of each ingredient were prepared and analyzed by the Kedde reaction and by thin-layer chromatography.<sup>1-4</sup> Identification of the cardiac glycosides in the raw material that had tested positive was confirmed by liquid chromatography and mass spectrometry. The plant species was verified by microscopical examination.<sup>5</sup> Additional samples of suspect bulk raw material were provided by the sources identified in our subsequent investigation (see below) of the material and were analyzed as described above. Quantitative analyses of the cardiac glycosides detected in the samples were not performed. Lanatosides A and B (Natural Products Repository, National Cancer Institute, Bethesda, Md.) and lanatoside C, digoxin, and digitoxin (Sigma Chemical, St. Louis) were used as standards in the assays.

### Investigation of the Source of Contamination

We traced the raw material that tested positive for the presence of cardiac glycosides and that had been used in the manufacture of the botanical product consumed by Patients 1 and 2 back to its supplier by contacting the retail distributor of the finished product (i.e., the firm that distributed the product under its own label but did not actually manufacture or label the product). Shipping records and invoices were obtained in order to document from whom the distributor had purchased the bulk raw material and to which companies the distributor had sent the raw material for manufacture of the finished product. When available, samples of the suspect bulk raw material were obtained from each supplier, distributor, or manufacturer for analysis. Subsequent reports of adverse events were matched with the lot numbers of the finished products that had tested positive for cardiac glycosides.

## RESULTS

### Identification of *Digitalis lanata* Ehrhart

Of the five dietary supplements consumed by Patient 1, only one — the product used to assist in the “cleansing” of the body, made up of 14 herbal ingredients — tested positive for cardiac glycosides, as determined by the Kedde reaction and thin-layer chromatography. Analyses (by the Kedde reaction and thin-layer chromatography) of each of the bulk raw-material ingredients listed on the label of the

botanical product that tested positive indicated that the material listed as plantain contained cardiac glycosides. Analyses by liquid chromatography and mass spectrometry confirmed the presence of lanatosides A, B, and C. On the basis of the detection of lanatosides (the so-called native or primary glycosides found in *Digitalis lanata*)<sup>2-8</sup> and the presence of microscopic anatomical elements characteristic of *D. lanata* (e.g., specific structural features of the glandular trichomes [epidermal hairs]),<sup>5</sup> we concluded that *D. lanata* Ehrhart was present in the material labeled as plantain. Quantitation of the amount of *D. lanata* present in the material labeled as plantain was not performed.

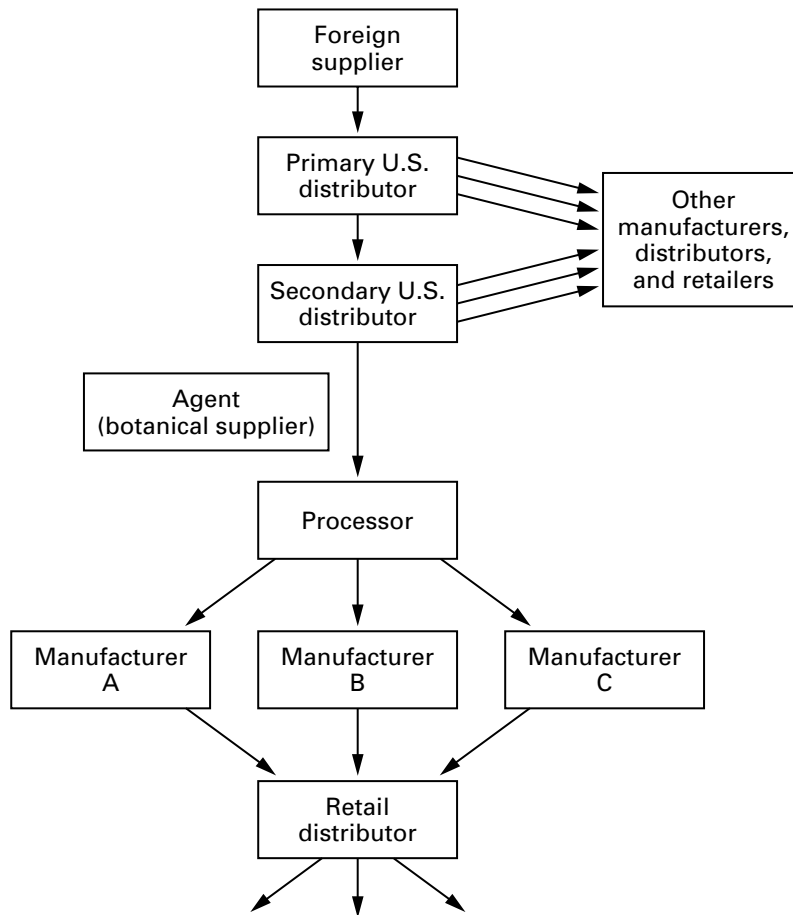
### Investigation of the Source of Contamination

Investigations tracing the source of the contaminated product indicated that approximately 2700 kg (6000 lb) of plantain had been imported into the United States from Germany and had been shipped to numerous manufacturers, distributors, and retailers over a period of about two years (Fig. 1). Samples of bulk plantain had been retained by the foreign source. After notification by the primary U.S. distributor, the foreign source tested this material, and the material was reported to be positive for cardiac glycosides.

Analyses performed by the FDA on samples of bulk raw material labeled as plantain and obtained from major suppliers, distributors, and manufacturers indicated that more than 150 manufacturers, distributors, and retailers received potentially contaminated plantain. Thirteen voluntary recalls of contaminated plantain or products containing plantain were initiated by manufacturers and distributors. Eight firms that were directly involved in the handling and distribution of contaminated plantain received warning letters from the FDA. Press releases were issued twice and posted on the FDA's Web site to warn consumers against the consumption of certain botanical dietary supplements labeled as containing the ingredient plantain.

## DISCUSSION

Our investigations indicated that the imported raw material labeled as plantain contained *D. lanata* and that this contaminated plantain had been supplied and distributed for use as a dietary supplement in the United States for a period of approximately two years. Patients 1 and 2 had consumed the same brand-name product with the same lot number. It was not determined how the imported raw material had become contaminated. Plantain is an herb of the genus *plantago* (not to be confused with the tropical banana plant [of the genus *musca*], whose fruit is also called plantain and is available in grocery stores). Depending on the species of plantain (*plantago*), the leaves may be prepared as a tea, processed into a



**Figure 1.** Flowchart Showing the Sources and Distribution of Contaminated Plantain Imported into the United States.

The retail firm that distributed the contaminated botanical dietary-supplement products ingested by Patients 1 and 2 under its own label contracted with three manufacturers over a period of approximately one year to manufacture dietary supplements containing plantain. All three manufacturers (denoted A, B, and C) received contaminated plantain from the same processor. This plantain had come from a foreign supplier through a primary U.S. distributor. An agent (botanical supplier) served as an intermediary between the retail distributor, the secondary U.S. distributor, and the processor. The agent purchased a quantity of plantain from the secondary U.S. distributor and, at the request of the retail distributor, had it shipped to the processor for custom milling. The powdered plant material was then sold to the retail distributor, after which the material was shipped from the processor to the three manufacturers for further processing into finished dietary supplements. After milling the plantain, the agent (botanical supplier) provided to the retail distributor a "certificate of analysis," indicating that the plant material was plantain powder, with a description of certain of its physical characteristics, such as color and flavor. The contaminated botanical dietary supplements ingested by Patients 1 and 2 had been produced by Manufacturer C and had the same lot numbers. In total, at least 150 manufacturers, distributors, and retailers were identified as having received potentially contaminated plantain.

powder for use in tablets and capsules, or used externally as a poultice.<sup>9</sup>

After the investigation of the source of the contaminated product, several major U.S. suppliers of herbs and botanical products were contacted by the FDA in order to obtain samples of bulk plantain (either reserved portions of previously distributed plantain or plantain that was currently being distributed). Of the samples provided (by seven firms), all

tested negative for the presence of lanatosides (data not shown).

It is probable that the cardiac findings, symptoms, and elevated serum digoxin level of Patient 1 were due to the ingestion of contaminated plantain. In the case of Patient 2, the symptoms and signs and electrocardiographic changes were nonspecific and could have been related to other factors. However, the presence of digoxin in the serum, albeit at a low

level (the blood specimen was obtained about 48 hours after the patient stopped using the product), suggests that this finding may have been related to her ingestion of contaminated plantain.

*D. lanata* has been reported to contain at least 60 cardiac glycosides, all sharing strong similarities in physical structure.<sup>3,4</sup> These similarities include an aglycone moiety (consisting of a steroid nucleus plus a lactone ring at the C-17 position) and a sugar moiety (usually consisting of one to four monosaccharides) linked to C-3 of the steroid nucleus.<sup>3-8,10</sup> The aglycone portion of the molecule is essential for pharmacologic activity; however, the pharmacokinetic properties are influenced by the number and type of sugar molecules as well as by substituents on the steroid nucleus, which modify the lipophilic properties of the molecule.<sup>7,8,10-12</sup>

Lanatosides are cardiac glycosides that are characteristic of *D. lanata*. They are referred to as native or primary glycosides.<sup>4,5,7</sup> Lanatosides have an acetylated molecule of digitoxose next to the terminal glucose that distinguishes them from the primary glycosides found in *D. purpurea* (known as purpurea glycosides), which do not have an acetyl group on the third digitoxose.<sup>3-8</sup> The leaves of *D. lanata* contain lanatosides A, B, C, D, and E; the type of lanatoside depends on the structure of the aglycone. However, the chief constituents are glycosides from the A and C series.<sup>3,4,13</sup> Thus, the finding of lanatosides A and C by liquid chromatography and mass spectrometry in the product consumed by the patients, particularly lanatoside C, for which there is not a corresponding primary glycoside occurring in *D. purpurea*, confirms the identification of *D. lanata*. On enzymatic hydrolysis (resulting in the loss of glucose) and mild alkaline hydrolysis (resulting in the loss of the acetyl group), lanatoside A yields digitoxin and lanatoside C yields digoxin.<sup>6-8</sup> These facts may be of clinical importance, suggesting the possibility that the patients who ingested the contaminated material may have been exposed to cardiac glycosides exhibiting pharmacologic properties of both digitoxin and digoxin.

Although the chemical structures of digitoxin and digoxin differ only in that digoxin has an extra hydroxyl at the C-12 position of the aglycone portion of the molecule, the substances have very different properties in terms of lipid solubility (high for digitoxin and medium for digoxin), gastrointestinal absorption (95 to 100 percent for digitoxin and 70 to 85 percent for digoxin), average half-life (168 hours for digitoxin and 40 hours for digoxin), plasma protein binding (>90 percent for digitoxin and 20 to 40 percent for digoxin), the volume of distribution (0.6 liter per kilogram of body weight for digitoxin and 6.3 liters per kilogram for digoxin), and the primary route of metabolism and elimination (extensive hepatic metabolism with excretion into the

gut through the bile for digitoxin [the resultant metabolites, some of which are cardioactive, as well as unchanged digitoxin, may undergo reabsorption] and excretion, primarily of the unchanged form, by the kidneys for digoxin).<sup>8,10,12</sup> These differences may account for the relatively prolonged symptoms exhibited by the two patients, even after they stopped ingesting the botanical product.

Similarly, the lack of a therapeutic response to ovine digoxin immune Fab in Patient 1 may have been due to the presence of digitoxin (or a precursor molecule), for which ovine digoxin immune Fab has lower binding affinity than for digoxin.<sup>14-16</sup> In addition, other unidentified cardiac glycosides may have contributed to the lack of effectiveness of ovine digoxin immune Fab. Because of these factors, it may be necessary to use a greater initial dose of digoxin immune Fab than would be anticipated on the basis of the patient's serum digoxin level to achieve a therapeutic effect.<sup>17</sup>

It is also important to keep in mind that after the ingestion of a cardiac glycoside-containing plant, in contrast to purified extracts of single cardiac glycosides, numerous cardiac glycosides are likely to be present. Some of these glycosides may have a certain degree of cross-reactivity, depending on the specificity of the antibodies used in the immunoassay. Thus, a serum digoxin assay with polyclonal antibodies, as was used for the patients discussed in this report, would be expected to detect many of the cardiac glycosides present in *D. lanata* because of the structural similarities between the cardiac glycosides. However, even with this type of serum digoxin assay, the measured digoxin level might not be commensurate with the patient's clinical picture, because it is possible that some potent cardiac glycosides would not be adequately measured by the assay.<sup>18-20</sup>

Intoxication resulting from the ingestion of plants containing cardiac glycosides has been reported in isolated incidents, usually as a result of accidental ingestion, frequently in young children, or as suicide attempts.<sup>21</sup> Some of these plants include foxglove (species not stated),<sup>22</sup> *D. purpurea* (purple foxglove),<sup>23,24</sup> squill,<sup>25</sup> *Nerium oleander* (common oleander or rose laurel),<sup>26-31</sup> and yellow oleander.<sup>31-33</sup> However, to our knowledge, these are the first cases involving the widespread distribution and marketing in the United States of a raw material intended for use as a dietary supplement that contained *D. lanata*.

Several factors may offer an explanation of how this contaminated plantain was able to be so widely distributed for such a long time. First, there are currently no federal regulations that establish specific criteria for purity, identification, and manufacturing procedures of dietary supplements (of which botanical products are one type). Second, there are no requirements for mandatory reporting to the FDA of adverse events by the manufacturer or distributor of

these products. Third, the use of dietary supplements is frequently not ascertained as part of a patient's medical history.<sup>34</sup> Fourth, some of the symptoms of cardiac glycoside poisoning are similar to the expected side effects of the botanical product (e.g., nausea, vomiting, and abdominal pain), so patients may not attribute their symptoms to contamination of the product or seek medical care. Moreover, there is a common perception that because a product is natural it must be safe.<sup>34,35</sup> Fifth, the medical community, as well as consumers, may be unaware that adverse events associated with dietary supplements can be reported to the FDA, including the FDA's MedWatch program. And finally, consumers may be reluctant to report adverse events that may have resulted from the use of dietary supplements or to report the extent of their use to mainstream health care professionals.<sup>34</sup>

For many of these reasons, it is likely that there was underreporting to the FDA of adverse events occurring as a result of the use of contaminated plantain. It is also possible that factors inherent in the internal-cleansing program (e.g., the use of hydrated bentonite and the occurrence of diarrhea) may have mitigated some of the potential toxic effects of *D. lanata* by decreasing its absorption. Similarly, in the case of teas, depending on their solubility and method of preparation, it is possible that some cardioactive glycosides in the leaves of *D. lanata* may not have been fully extracted with water.

An interest in self-care, whether for the treatment or prevention of specific disorders or for health promotion, appears to be engaging an ever-growing proportion of the U.S. population.<sup>36,37</sup> Concurrent with this interest has been the increased use of dietary supplements.<sup>36,38</sup> We report this investigation to heighten awareness among health care providers — both conventional and alternative-medicine practitioners — of factors that may influence the reporting of adverse events related to dietary supplements and to underscore the need to report such adverse events to the FDA.

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