ORIGINAL RESEARCH ARTICLE

Adverse Events Associated with Use of Digoxin Immune Fab Reported to the US Food and Drug Administration Adverse Event Reporting System, 1986–2019

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Abstract

Background Digoxin immune fab products, DigiBind and DigiFab, are antidotes for the treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose. Although approved by the US Food and Drug Administration (FDA) in 1986 (DigiBind) and 2001 (DigiFab), there remains a paucity of literature describing the safety of these products in the postmarketing setting.

Objective We sought to assess US adverse event (AE) reports submitted to the FDA Adverse Event Reporting System (FAERS) for DigiBind and DigiFab in the postmarketing period.

Patients and Methods We searched reports for DigiBind and DigiFab submitted from the time of each product approval through December 31, 2019. Descriptive statistics were used to assess AE reports for DigiBind and DigiFab. Empirical Bayes geometric means (EBGMs) and their 90% confidence intervals were computed to identify disproportionate (i.e., at least twice the expected) reporting of DigiBind and DigiFab. Reports describing selected AEs and death outcomes were individually reviewed.

Results A total of 78 DigiBind and 43 DigiFab reports were identified, of which 68 DigiBind (87.2%) and 27 DigiFab (62.8%) reports were serious. Among the most frequently reported AEs for both products [DigiBind, DigiFab, respectively] were cardiac (bradycardia [3.8%, 3.9%], cardiac arrest [3.3%, 3.9%], and hypotension [2.4%, 2.6%]) and non-cardiac (nausea [1.9%, 2.6%] and hyperkalemia [1.4%, 1.9%]) events. These AEs were labeled events or confounded by indication for use (digoxin toxicity). Nineteen (24.4%) DigiBind and 13 (30.2%) DigiFab reports described an outcome of death, of which seven (53.8%) DigiFab reports were attributed to poisoning with non-digoxin cardiac glycosides. No deaths could be attributed to DigiBind or DigiFab administration.

Conclusions Our analysis did not identify new safety concerns for DigiBind or DigiFab. Most AEs reported were labeled events or confounded by indication for use.

1 Introduction

Digoxin immune fab, a sterile, purified, and lyophilized preparation of digoxin-immune ovine fab (monovalent) immunoglobulin fragments, is indicated for the treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose [1]. Digoxin-specific antibody prepared from sheep antiserum was first introduced in 1967

as an immunoassay for digoxin in human serum [2], and in 1976 it was used to treat a patient with life-threatening digoxin toxicity [3]. The first digoxin immune fab product, DigiBind, was licensed by the US Food and Drug Administration (FDA) in April 1986. In August 2001, the FDA approved a second product, DigiFab. There have been no other digoxin immune fab products approved in the USA. DigiBind (immunized with digoxin) and DigiFab (immunized with a digoxin derivative, digoxin dicarboxymethylamine) possess similar pharmacokinetic properties and are clinically interchangeable [4, 5]. Digoxin immune fab has a greater affinity for digoxin than digoxin has for its sodium pump receptor. After administration, digoxin immune fab binds to molecules of digoxin, thereby reducing free digoxin levels and its cardio-toxic effects [5].

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Key Points

Postmarketing DigiBind and DigiFab reports submitted to the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) revealed that adverse events (AEs) were generally consistent with the safety experience observed in pre-licensure clinical trials and the products' package inserts.

Cardiac (bradycardia, cardiac arrest, and hypotension) and non-cardiac (nausea and hyperkalemia) AEs were among the most commonly reported for both products.

A substantial number of death reports were attributed to glycoside poisoning with agents other than digoxin (off-label use), but no deaths were attributed to DigiBind and DigiFab.

Between 2007 and 2009, nearly 3500 US hospitalizations among patients 65 years of age or older were associated with digoxin-related adverse events (AEs), and digoxin was the most commonly implicated agent in emergency department visits for adverse drug events that resulted in hospitalization [6]. These and other clinical scenarios present opportunities for patient exposure to digoxin immune fab. Notably, most of the safety information available for DigiBind and DigiFab has been derived from small clinical trials and observational studies [7]; thus, the safety profile of these agents, particularly for rare and serious events occurring in the postmarketing setting, is unknown. To address this information gap, we reviewed DigiBind and DigiFab AE reports submitted to the FDA Adverse Event Reporting System (FAERS) following approval of each product in the USA.

2 Methods

2.1 FAERS Database

FAERS is a spontaneous, passive surveillance system that collects information on AEs, medication errors, and product quality issues associated with drugs and biologic products [8]. The database collects information on patient demographics, medical history, concomitant medications, description and outcome of the AE, and source of the report. Reported events are coded according to the Medical Dictionary for Regulatory Activities (MedDRA), which includes broad (System Organ Class [SOC]) and specific event categories (e.g., Preferred Term [PT]) [9]. Our analysis was based on MedDRA version 22.1. A single FAERS report is assigned one or more PTs, and each PT is included within a corresponding primary (and secondary, if applicable) SOC. Based on the extent of clinically relevant information included in ten key data fields, each report is assigned a completeness score; a penalty is assigned for missing information, thereby lowering the completeness score [10]. FAERS reports can be submitted as "expedited reports" (serious and unexpected AEs required to be reported by pharmaceutical companies to the US FDA within 15 days of receipt), "direct reports" (submitted directly to the US FDA by health care professionals or consumers outside of pharmaceutical companies), or "non-expedited reports" (serious expected events and nonserious events submitted by pharmaceutical companies to the US FDA on a regular basis). A report is considered serious when an AE(s) results in death, life-threatening illness, hospitalization or prolongation of existing hospitalization, permanent disability, or birth defect [11]. The outcome of the AE(s) is specified by the individual submitting the report, and one or more outcomes may be specified per report. All the information in a FAERS report, including the case narrative, is available to FDA reviewers performing postmarketing surveillance activities.

We searched the FAERS database for all US reports submitted for DigiBind or DigiFab from the product approval date (DigiBind April 29, 1986; DigiFab August 31, 2001) through December 31, 2019. We allowed follow-up information to be submitted on these reports through March 31, 2020, the study data lock point (DLP). In September 2011, DigiBind was discontinued in the USA (unrelated to a safety concern); however, reports may be submitted to FAERS at any time, even after a product has been discontinued. We excluded foreign reports because DigiBind and DigiFab approval and marketing dates varied from those in the USA and clinical practice and drug usage patterns potentially differ between countries.

2.2 Data Analysis

2.2.1 Descriptive Analysis

We separately assessed all AEs reported for DigiBind and DigiFab using descriptive statistics (Stata/IC 13.1; StataCorp LLC, College Station, Texas), without regard for potential duplicate reports. Age and sex statistics included information gleaned from manual review of reports when the information was not available in the relevant age and sex data fields but was specified in the report text.

2.2.2 Data Mining Analysis

We conducted empirical Bayes data mining using the Multi-Item Gamma Poisson Shrinker algorithm in the Oracle Empirica™ Signal system to assess for disproportional reporting of AEs reported for DigiBind and DigiFab. The

Empirica Signal system utilizes a case-matching algorithm applied to all FAERS reports that systematically identifies likely duplicate reports [12]. Analyses were limited to US reports, undertaken separately for DigiBind and DigiFab, and adjusted for year of report received at the FDA, sex, and age. The main statistical score computed was the empirical Bayes geometric mean (EBGM) and the 90% confidence interval, with the lower and upper 95% confidence bounds represented as EB05 and EB95, respectively [12]. The EBGM reflects the relative reporting rate after Bayesian smoothing for a drug/biologic–event pair relative to all other drug/biologic–event pairs in the FAERS database [13]. An EB05 ≥ 2 is the threshold commonly used by the FDA as a criterion for considering an AE a potential signal to be further investigated. This threshold is associated with a high probability of a drug/biologic–event pair being reported at least twice as often as expected under the assumption that drug/biologic–events are randomly paired [14]. Data mining findings are used for signal detection but do not imply a causal association between the drug/biologic–event pair identified.

2.2.3 Case Reviews

We reviewed all death reports to determine the stated cause of death and events surrounding the death. We also reviewed reports describing AEs of special interest, including unlabeled events (AEs not included on the US Package Insert [USPI]), medication errors, and off-label use. Duplicate reports were excluded from individual case review.

2.3 Ethics

This safety review was exempt from institutional review board approval or informed patient consent because it met the criteria for exemption from the Office for Protection from Research Risks, as specified in the Department of Health and Human Services regulations [15].

3 Results

We identified a total of 78 DigiBind and 43 DigiFab reports submitted to the FAERS during each study period, of which 87.2% DigiBind and 62.8% DigiFab reports were serious (Table 1). Among reports with specified age, the median (range) patient age was 73 (0–93) and 66 (16–101) years for DigiBind and DigiFab, respectively. A greater percentage of reports were submitted for females, individuals ≥ 65 years of age, and as expedited reports. More than half of reports had a completeness score below 60%. Death was reported

as an outcome for 24.4% of reports for DigiBind and 30.2% of reports for DigiFab.

3.1 Most Frequently Reported PTs for DigiBind and DigiFab

In total, there were 212 PTs describing 78 DigiBind reports and 155 PTs describing 43 DigiFab reports (Table 2). Among the most frequent PTs reported for both products were cardiac (bradycardia, cardiac arrest, and hypotension) or non-cardiac (nausea and hyperkalemia) events. The majority of PTs represented labeled events, of which many were confounded by indication for product use. PTs describing unlabeled AEs included medication error, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, dermatitis, and pancreatitis.

3.2 Data Mining (Disproportionality Analyses)

Bradycardia, cardiac arrest, toxicity to various agents, and cardioactive drug level increased were disproportionately reported for both DigiBind and DigiFab (Table 3). In addition, ventricular tachycardia was reported more than twice as frequently as expected for DigiBind, and medication error, off-label use, and completed suicide were disproportionately reported for DigiFab.

3.3 Case Review

3.3.1 Death Reports

A total of 19 DigiBind and 13 DigiFab reports with an outcome of death were identified (Table 4). Among DigiBind reports with specified age (63.2%), 67% of deaths occurred among individuals 65 years of age or older (median age 70.5 years), and most reports (78.9%) did not specify the cause of death. In contrast, among DigiFab death reports with specified age (84.6%), the median age was 39 (range 19–90) years, with more than half (53.8%) of the total deaths attributed to intentional poisoning by agents other than digoxin (e.g., English yew, *Piedra China*, *Almendra quema grasa*, *Cerbera odollam*, and oleander leaves).

3.3.2 Unlabeled AEs

The unlabeled AEs reported for DigiBind included dermatitis (*n* = 3), AST/ALT elevation (*n* = 3), and pancreatitis (*n* = 3). Only one dermatitis report provided clinical details and described an associated allergic reaction (no other details). After excluding two duplicate reports (one AST/ALT elevation report and one pancreatitis report), the remaining

Table 1 Description of US adverse event reports submitted to FAERS for DigiBind and DigiFab through December 31, 2019

Report	DigiBind[a] No. (%)	DigiFab[b] No. (%)
Total reports	78 (100)	43 (100)
Serious	68 (87.2)	27 (62.8)
Sex		
Females	44 (56.4)	18 (41.9)
Males	22 (28.2)	16 (37.2)
Not specified	12 (15.4)	9 (20.9)
Age (years)		
< 65	15 (19.2)	14 (32.6)
≥ 65	40 (51.3)	17 (39.5)
Not specified	23 (29.5)	12 (27.9)
Year received at FDA		
1986–1990	27 (34.6)	N/A
1991–1995	30 (38.5)	N/A
2001–2010	18 (23.1)	5 (11.6)
2011–2019	3 (3.8)[c]	38 (88.4)
Type of report		
Expedited (15-day)	40 (51.3)	26 (60.5)
Not expedited	28 (35.9)	11 (25.6)
Direct	10 (12.8)	6 (14.0)
Completeness score[d]		
< 20%	11 (14.1)	7 (16.3)
20–39%	30 (38.5)	15 (34.9)
40–59%	9 (11.5)	17 (39.5)
60–79%	20 (25.6)	2 (4.7)
≥ 80%	8 (10.3)	2 (4.7)
Reported outcome		
Death	19 (24.4)	13 (30.2)
Non-death		
Hospitalized, disabled, life-threatening, or required intervention	27 (34.6)	4 (9.3)
Other	22 (28.2)	10 (23.3)
Not reported	10 (12.8)	16 (37.2)

FAERS FDA Adverse Event Reporting System, *FDA* Food and Drug Administration, *N/A* not applicable, *No.* number of reports

[a]In the USA, DigiBind was approved on 4/22/1986 and discontinued on 9/14/2011. Table includes DigiBind reports submitted to FAERS through 12/31/2019

[b]In the USA, DigiFab was approved on 8/31/2001. Table includes DigiFab reports submitted to FAERS through 12/31/2019

[c]The last report for DigiBind was submitted to FAERS in 2015

[d]The completeness score is derived from the amount of clinically relevant information available on reports and whether they are recorded in a usable way. The formula to calculate the completeness score is $CS = (1 − P1) * (1 − P2)…(1 − P10)$, where P denotes a predetermined penalty for each of the ten elements. When information is present or meaningful, the penalty is zero

reports of AST/ALT elevation and pancreatitis described either a patient with multiple comorbidities or lacked clinical details, thereby limiting causality assessments.

3.3.3 Medication Error

There were five DigiBind medication error reports. Three reports described accidental overdose (higher dose than indicated on the USPI) of DigiBind, of which two reports did not describe any AE and one described transient atrial fibrillation. There were two product-related reports; one was related to a label issue and the other to an administration issue (with no description of an AE). There were six DigiFab medication error reports; five referred to mislabeling of dose information on the vial and one report described a falsely increased digoxin level.

3.3.4 Off-Label Use (Non-digoxin Cardiac Glycoside Poisoning)

There were 12 DigiFab reports describing off-label use. Except for one report related to digoxin toxicity, all other reports described use of DigiFab for treatment of intentional poisoning by a cardiac glycoside-related product other than digoxin. A case listing of reports involving non-digoxin cardiac glycoside poisoning (11 reports with a PT of off-label use and one report with a PT of cardiac arrest) is presented in Table 5. Of 12 reports describing non-digoxin poisoning, the median (range) age of patients was 33 (16–86) years. Most reports were submitted for males (58.3%) and individuals < 65 years of age (83.3%). The ingested poisoning agents included *Almendra quema grasa*, *Piedra China*, *Taxus baccata* (English or European yew), oleander leaves, toad head, *Cerbera odollam* seeds, Jamaican stones, *Convallaria majalis*, and *Crataegus mexicana* root. The median (range) amount of DigiFab administered to these 12 cases was 9.5 (2–33) vials (40 mg per vial); seven reports were associated with a death outcome.

4 Discussion

To our knowledge, this study of DigiBind and DigiFab is the first to describe AEs reported in the postmarketing period in the population at large. We found that the majority of AEs represented labeled events described in the USPI or were confounded by indication for product use.

Table 2 Most Common PTs included in US adverse event reports submitted to FAERS for DigiBind and DigiFab through December 31, 2019

PT	DigiBind (78 total reports) No. (%)	DigiFab (43 total reports) No. (%)	Labeled event[b]
Total PTs	212	155	N/A
Toxicity to various agents	17 (8.0)	7 (4.5)	Yes
Off-label use	N/A	12 (7.7)	N/A
Drug ineffective	14 (6.6)	10 (6.5)	Effectiveness
Bradycardia	8 (3.8)	6 (3.9)	Yes
Blood creatinine increased	7 (3.3)	[a]	Yes
Cardiac arrest	7 (3.3)	6 (3.9)	Yes
Medication error	5 (2.4)	6 (3.9)	No
Completed suicide	N/A	5 (3.2)	Yes
Atrioventricular block complete	5 (2.4)	[a]	Yes
Cardioactive drug level increased	5 (2.4)	4 (2.6)	Yes
Hypotension	5 (2.4)	4 (2.6)	Yes
Renal failure	5 (2.4)	3 (1.9)	Yes
Ventricular tachycardia	5 (2.4)	[a]	Yes
Arrhythmia	4 (1.9)	[a]	Yes
Nausea	4 (1.9)	4 (2.6)	Yes
Overdose	4 (1.9)	N/A	Yes
Abdominal pain	3 (1.4)	[a]	Yes
Alanine aminotransferase increased	3 (1.4)	N/A	No
Aspartate aminotransferase increased	3 (1.4)	N/A	No
Blood urea increased	3 (1.4)	[a]	Yes
Cardiac failure congestive	3 (1.4)	N/A	Yes
Dermatitis	3 (1.4)	N/A	No
Hyperkalemia	3 (1.4)	3 (1.9)	Yes
Pancreatitis	3 (1.4)	N/A	No
Sudden death (or death)	3 (1.4)	3 (1.9)	Yes
Vomiting	3 (1.4)	[a]	Yes
Acute kidney injury	N/A	3 (1.9)	Yes
Drug ineffective for unapproved indication	N/A	3 (1.9)	Effectiveness

FAERS FDA Adverse Event Reporting System, *FDA* Food and Drug Administration, *N/A* not applicable, *No.* number of reports, *PT* Preferred Term

[a]Number of reports < 3

[b] PTs describing adverse events (safety) that are included in the US Package Insert are considered labeled events. PTs that reflect product effectiveness rather than safety are noted accordingly. A PT included in a FAERS report does not imply causality

Although digoxin use declined in the USA between 2005 and 2014 [16], between 2007 and 2009, digoxin toxicity accounted for more than 80% of emergency department visits resulting in hospitalization related to adverse drug events among patients 65 years of age or older [6]. Based on the Premier Perspective Comparative Hospital Database, which included data collected from more than 450 US hospitals, Hauptman et al. identified 22,629 patients diagnosed with digoxin toxicity, including 3086 patients treated with digoxin immune fab, between 2007 and 2011, and estimated that 41,754 hospital visits were associated with

digoxin immune fab treatment nationwide [17]. While we do not have information on the number of patients exposed to DigiBind and DigiFab over the time periods of our study, the relatively limited number of FAERS reports may reflect the favorable safety profile of these agents. Previous clinical trials and observational studies reported that the most common adverse reactions related to digoxin immune fab included allergic reactions, hypokalemia, exacerbation of heart failure, increased ventricular response in atrial fibrillation, and recrudescence of digoxin toxicity [7, 18–21]. In our analysis of FAERS reports, the majority of reported AEs for

Table 3. PTs for DigiBind and DigiFab reported disproportionately to FAERS through December 31, 2019 according to SOC

| SOC | DigiBind | | DigiFab | |
PT	No.	EBGM (90% CI)	No.	EBGM (90% CI)
Cardiac disorders				
Bradycardia	8	5.5 (2.9–10.1)	6	57.7 (25.9–113.5)
Cardiac arrest	7	4.3 (2.2–7.6)	6	26.1 (5.1–65.8)
Ventricular tachycardia	5	5.1 (2.1–16.5)	a	a
Injury, poisoning, and procedural complications				
Medication error	a	a	6	6.3 (2.7–20.0)
Off-label use[b]	a	a	12	5.2 (3.2– 8.3)
Toxicity to various agents	16	43.1 (27.9–64.2)	7	5.2 (2.7– 9.8)
Investigations				
Cardioactive drug level increased	5	150.6 (65.7–306.2)	4	206.5 (80.0–459.0)
Psychiatric disorders				
Completed suicide	a	a	5	7.6 (2.5–35.7)

Each analysis was limited to the relevant time period (DigiBind: 4/29/1986–12/31/2019; DigiFab: 8/31/2001–12/31/2019) and adjusted for year report received at the FDA, sex, and age. An elevated EBGM does not imply a causal association

CI confidence interval, *EB05* lower 95% confidence bound, *EBGM* Empirical Bayes geometric mean, *FAERS* FDA Adverse Event Reporting System, *FDA* Food and Drug Administration, *PT* Preferred Term, *SOC* System Organ Class

[a]EB05 < 2.0

[b]DigiFab administered following ingestion of *Almendra quema grasa* (*n* = 1), *Cerbera odollam* seeds (*n* = 3), *Convallaria majalis* (*n* = 1), *Crataegus mexcicana* (*n* = 1), *Taxus baccata* (English yew or European yew) (*n* = 2), Jamaican stone (*n* = 1), oleander leaves (*n* = 1), *Piedra China* (*n* = 1), or toad head (*n* = 1)

DigiBind and DigiFab were clinical manifestations associated with digoxin toxicity (e.g., bradycardia, cardiac arrest, atrioventricular block, nausea, vomiting, and hyperkalemia) and were therefore confounded by indication for product use. In the data mining analyses, these AEs were also disproportionately reported, highlighting that signal identification does not imply causality and may reflect concomitant drug use, confounding by indication, or other factors. Because patients prescribed digoxin are frequently elderly, have multiple underlying comorbidities (e.g., congestive heart failure, renal impairment), and multiple co-administered medications (polypharmacy), these factors can obscure the recognition of digoxin immune fab-related AEs. We did not observe all of the AEs identified by previous clinical and observational studies, possibly due to the rarity of AEs associated with these products, underreporting of AEs to FAERS, or limited product utilization.

We identified unlabeled AEs in our review of FAERS reports, e.g., dermatitis, ALT/AST increased, and pancreatitis. However, we were unable to undertake a meaningful causality assessment due to the paucity of information included on the reports, concomitant medications reported, and multiple underlying patient comorbidities. Medication error reports were related to administration of a higher dose than recommended on the USPI (without a reported AE) or product issues not related to a safety concern.

As cardiac glycoside-related products have become increasingly available on the internet for nonmedicinal purposes, non-digoxin cardiac glycoside poisonings have been increasingly reported in the USA [22, 23]. Consistent with this observation, we found that FAERS reports describing off-label use were limited to DigiFab and submitted in more recent calendar years (2011–2019). Most of these reports referenced intentional poisoning with herbs and supplements structurally related to cardiac glycosides, with few patients having an elevated serum digoxin level. The reports described clinical manifestations similar to those observed with digoxin toxicity, including bradycardia, atrioventricular block, nausea, vomiting, abdominal pain, and hyperkalemia. Literature reports have described successful use of digoxin immune fab in managing non-digoxin cardiac glycoside poisonings with oleander leaves [24], toad venom [25], and some Chinese herbal supplements [26, 27]; others have reported unfavorable outcomes, including in cases of severe yew poisoning [28, 29].

Table 4 Characterization of deaths for US adverse event reports submitted to FAERS for DigiBind and DigiFab through December 31, 2019

Characteristic	DigiBind No. (%)	DigiFab No. (%)
Total death reports	19 (100)	13 (100)
Sex		
Females	10 (52.6)	5 (38.5)
Males	5 (26.3)	6 (46.2)
Not specified	4 (21.1)	2 (15.4)
Age (years)		
< 65	4 (21.1)	6[a] (46.2)
≥ 65	8 (42.1)	5[b] (38.5)
Not specified	7 (36.8)	2 (15.4)
Time from hospital admission to death (h)		
< 24	3 (15.8)	7 (53.8)
≥ 24	3 (15.8)	4 (30.8)
Not specified	13 (68.4)	2 (15.4)
Causes of death		
Digoxin toxicity	1 (5.3)	2 (15.4)
Suicide	1 (5.3)	7 (53.8)
Underlying comorbidities	2 (10.5)	2 (15.4)
Not specified	15 (78.9)	2 (15.4)

Each analysis was limited to the relevant time period (DigiBind: 4/29/1986–12/31/2019, DigiFab: 8/31/2001–12/31/2019)

FAERS FDA Adverse Event Reporting System, *FDA* Food and Drug Administration, *No.* number of reports

[a]Ages: 19, 22, 30, 33, 33, 39 years; all were exposed to agents other than digoxin

[b]Ages: 73, 74, 74, 80, 90 years; all were exposed to digoxin, except one

An important strength of our study is the national representation of AEs reported for DigiBind and DigiFab in the real-world setting, during a postmarketing study period of more than 30 years. Limitations include absence of denominator data and reliance on passive surveillance, which is associated with underreporting, duplicate reporting, varying report quality, and reporting bias (e.g., tendency to report more severe AEs, such as death, and those occurring closer to the time of product administration) [30]. In addition, we did not have information on product distribution and utilization, thereby limiting an assessment of frequency of AEs and reporting rates.

5 Conclusions

In summary, our analysis of FAERS reports did not raise new safety concerns for DigiBind or DigiFab. Most AEs reported were labeled events included in the USPI or confounded by indication for product use.

Table 5 Reports of DigiFab and non-digoxin cardiac glycoside poisoning submitted to FAERS through December 31, 2019

Case #	Sex	Age	Agents	Clinical manifestations	Interval from poisoning to admission	Serum potassium (mmol/L)	Serum digoxin (ng/mL)	DigiFab (vials)	Outcome
1	Female	33	*Almendra quema grasa*[a]	Lethargic, bradycardia, prolonged QRS	Unknown	8.9	N/A	9	Death
2	Male	74	Oleander leaves	Nausea, vomiting, bradycardia, cardiorespiratory arrest	"Couple of hours"	N/A	3.23	N/A	Death
3	Female	33	*Cerbera odollam*[b]	Vomiting, diaphoresis, altered mental status, bradycardia, AV block, VT	Unknown	8.9	3.1	10	Death
4	Male	30	*C. odollam*	Vomiting, bradycardia, AV block, cardiac arrest	12 h	10.1	1.6	13	Death
5	Male	22	*C. odollam*	Vomiting, diarrhea, bradycardia, AV block	7 h	5.2	1.3	20	Death
6	Male	19	*Taxus baccata* (English yew)[c]	Vomiting, tachycardia, cardiac arrest	Unknown	N/A	N/A	N/A	Death
7	Female	44	*T. baccata*	unconscious, bradycardia, long QT interval	Unknown	N/A	< 0.1	2	Recovered
8	Female	86	*Convallaria majalis*[d]	Nausea, vomiting, abdominal pain, bradycardia, LBBB	1 week	7.2	4.9	10	Unknown
9	Female	16	*Crataegus mexicana*[e]	Nausea, vomiting, diarrhea, drowsiness, bradycardia, AV block	8 h	N/A	0.7	2	Recovered
10	Male	29	Toad head[f]	Vomiting, bradycardia	Unknown	6.9	0.98	10	Recovered
11	Male	49	Jamaican stones[g]	Nausea, vomiting, abdominal pain, bradycardia	2 h	6.1	N/A	3	Recovered
12	Male	39	*Piedra China*	Vomiting, diaphoresis, bradycardia, AV block, cardiac arrest	Unknown	4.6	1.14	33	Death

AV atrioventricular; *FAERS* FDA Adverse Event Reporting System, *FDA* Food and Drug Administration, *LBBB* left bundle branch block, *N/A* information not available, *VT* ventricular tachycardia

[a]*Almendra quema grasa*, also known as "fat-burning almond," is a weight-loss supplement. It is a nut derived from *Thevetia peruviana* (*Cascabela thevetia*) that contains cardiac glycosides. The plant is native throughout Mexico and in Central America. It is a relative of *Nerium oleander*, from which it derives its common name, yellow oleander

[b]*C. odollam*, commonly referred to as suicide tree, pong-pong, mintolla, or othalam, is a plant species in the family *Apocynaceae*. Its kernel contains cerberin, a digoxin-type cardenolide and cardiac glycoside toxin. This species is native to India and other parts of Southeast Asia

[c]*T. baccata* is an ornamental tree known as yew (common yew, English yew, European yew) that is native to Western, Central, and Southern Europe; Northwest Africa; Northern Iran, and Southwest Asia. Most parts of the plant are poisonous because they contain taxine alkaloids, of which the highest concentration is in the seeds

[d]*C. majalis*, commonly called lily of the valley, is a woodland flowering plant. It is native throughout the Northern Hemisphere in Asia and Europe. The plant has been used in herbal medicines for mild congestive heart failure and arrhythmias. All parts of the plant are potentially poisonous, causing nausea, vomiting, and irregular cardiac rhythm if ingested

[e]*C. mexicana* is a species of hawthorn plant known by the common name of *tejocote* and is native to the mountains of Mexico and parts of Guatemala. It has been marketed as a weight-loss supplement through the internet, and several hawthorn species have been found to have positive inotropic effects

[f]Several toad species contain bufadienolides in their skin, venom glands, and eggs. Bufadienolides are cardioactive steroids with properties similar to digoxin

[g]Jamaican stones or *Piedra China* is a topical aphrodisiac. It is derived from toad venom and is also referred to as Rock Hard, Love Stone, *Piedra China*, or *Chan su*

Declarations

Funding Not applicable.

Conflicts of interest The authors do not have any conflicts of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions SW had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: SW. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: SW and GMD (data mining). Supervision: GMD. Note: The opinions and information in this article are those of the authors and do not represent the views or policies of the US Food and Drug Administration.

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