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Use of digoxin antibodies to treat digoxin poisoning: a subanalysis of the DIGITOX study

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BACKGROUND AND OBJECTIVE. Digoxin toxicity accounts for a small percentage of poisonings attended by emergency departments. This study aimed to evaluate whether treatment with digoxin-Fab (digoxin-specific antibody fragments) was used appropriately.

MATERIAL AND METHODS. Retrospective, observational, multicenter study in 15 hospital emergency departments in 8 Spanish autonomous communities over 7 years. We collected patient, clinical and treatment variables, and discharge destination. Patients were classified as having received digoxin-Fab treatment or not, and the decision to treat was evaluated as appropriate or not. We also assessed whether patients who were not treated with digoxin-Fab could have been.

RESULTS. Thirty-four of the 658 patients (5.2%) were treated with digoxin-Fab. The indication cited most often was the presence of bradycardia, particularly atrial fibrillation with a slow ventricular response. The next most common indication was a finding of a high digoxin concentration (> 6 ng/mL). For 33 of the 624 patients who did not receive digoxin-Fab treatment (5.3%), we later identified an indication that would have justified treatment, usually a high digoxin concentration (> 6 ng/mL) 6 hours after the last digoxin dose (in 31 patients). Three of the 33 patients (18.2%) who could have received digoxin-Fab treatment died; among the 34 patients who were treated, 4 died (11.8%) ($P < .001$).

CONCLUSIONS. Digoxin-Fab was administered to about 5% of patients with digoxin poisoning. At least an additional 5% of digoxin-poisoned patients could have benefited from treatment. Mortality was higher in untreated patients for whom treatment would have been indicated.

Keywords: Digoxin antibodies. Digoxin poisoning. DIGITOX study.

Uso de anticuerpos antidigoxina en pacientes con intoxicación por digoxina. Subanálisis del estudio DIGITOX

INTRODUCCIÓN. Las intoxicaciones por digoxina representan un pequeño porcentaje de las intoxicaciones atendidas en urgencias. El objetivo de este estudio fue evaluar si la administración de su antídoto específico, los anticuerpos antidigital (AcAD) se realizó conforme a los criterios de uso establecidos.

MATERIAL Y MÉTODOS. Estudio retrospectivo, observacional y multicéntrico en 15 servicios de urgencias hospitalarios de ocho comunidades autónomas durante 7 años. Se recogieron datos de filiación, clínica, tratamiento y destino al alta. Los pacientes se dividieron según recibían o no AcAD y se evaluó si la indicación se hizo siguiendo los criterios establecidos en 2012. Asimismo, se analizó entre los pacientes que no recibieron AcAD si existían casos en los que se hubieran podido administrar.

RESULTADOS. De los 658 casos incluidos en el estudio, se administraron AcAD en 34 ocasiones (5,2%). La indicación más frecuente fue la presencia de una bradiarritmia, en particular de una fibrilación auricular con respuesta ventricular lenta, seguida de la detec-

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Article Information: Received: 22-11-2023. Accepted: 23-12-2023. *Online:* 19-2-2024.
Editor in Charge: Elena Castejón-de la Encina.

ción de unas concentraciones elevadas de digoxina (> 6 ng/ml). Por otro lado, de los 624 casos en los que no se administraron AcAD, en 33 de ellos (5,3%) se identificó algún criterio para que se hubieran administrado, siendo el más frecuente la existencia de una digoxinemia muy elevada (> 6 ng/ml) a las 6 horas de la última ingesta, en 31 casos. Entre los 33 pacientes a los que se podría haber administrado AcAD y no se hizo, se produjeron 6 fallecimientos (18,2%) frente a los 4 fallecimientos de los 34 pacientes (11,8%) que sí recibieron tratamiento antidótico (p < 0,001).

CONCLUSIONES. Los AcAD se administran en un 5% de pacientes con intoxicación por digoxina. Al menos, otro 5% podría haberse beneficiado de su administración. La mortalidad de los pacientes que deberían haber sido tratados con AcAd y no lo fueron, es superior a los pacientes que sí recibieron tratamiento antidótico.

Palabras clave: Anticuerpos antidigoxina. Intoxicación por digoxina. Estudio DIGITOX.

Introduction

Acute poisonings are a frequent reason for consultation in emergency departments (EDs), accounting for up to 0.5–1% of all visits.[1,2] The most common toxicological consultations are related to alcohol, followed by illicit drugs of abuse and medications. Among the latter, poisonings caused by benzodiazepines are by far the most frequently treated in EDs. Other drugs, including digoxin, follow at a considerable distance. Digoxin poisoning has a higher incidence among elderly patients, in whom it can represent up to 25% of all drug-related poisonings.[3] Most cases are chronic poisonings, resulting from a progressive and accidental accumulation of the drug. However, acute poisonings also occur, generally related to suicidal intent. Both acute and chronic poisonings are potentially severe and may lead to fatal outcomes.[4,5]

Patients intoxicated with digoxin require immediate medical intervention, with special attention to hemodynamic status and possible electrocardiographic and electrolyte disturbances. Management is based on hemodynamic support measures, continuous electrocardiographic monitoring until serum digoxin concentrations have fallen at least to the therapeutic range, control of any arrhythmias that may occur, and correction of fluid and electrolyte abnormalities. In indicated cases, administration of anti-digoxin antibodies (Digoxin-Fab) should also be performed.[6]

Since the development and gradual implementation in Spain of the Antidote Network[7]—an initiative of the Antidotes Working Group of the Spanish Society of Hospital Pharmacy and the Catalan Society of Clinical Pharmacy—the availability of antidotes not routinely stocked in all emergency departments has improved, making the use of Digoxin-Fab increasingly accessible and positively influencing the prognosis of patients with digoxin poisoning.

This study presents a subanalysis of the DIGITOX study,[8] describing the use of Digoxin-Fab in digoxin poisonings across several Spanish emergency departments. It also assesses whether the indications for their administration adhered to established recommendations.[6] In addition, new considerations regarding the indication, dosage, and administration of Digoxin-Fab are discussed.

Material and methods

The DIGITOX study was an observational, retrospective, multicenter study in which 15 EDs participated across 8 Spanish autonomous communities. Data were collected over 7 years, from January 2015 to December 2021. The methodology for patient selection, classification of acute or chronic digoxin poisoning, data collection (including treatment administered), and outcome management have been described previously.[8] In this subanalysis, patients who received Digoxin-Fab treatment were evaluated to determine whether administration met established indications (Table 1).[6] Health records of patients who did not receive Digoxin-Fab were also reviewed to identify those who might have been candidates for this therapy. Plasma digoxin concentrations were determined according to standardized techniques in each participating center. In no case were free digoxin concentrations available. Functional dependence was assessed using the Barthel Index, and poisoning severity was determined using the Poisoning Severity Score (PSS).

Statistical analysis was performed using SPSS software (Statistical Package for the Social Sciences, SPSS Inc.), version 25.0 (IBM Corp). Normality of distribution was tested using the Kolmogorov–Smirnov test. The Mann–Whitney U testwas used to compare quantitative variables, and the chi-square test (with Fisher or Pearson correction as appropriate) was used to compare proportions. Results are expressed as number (percentage) or mean (standard deviation). A *P*-value < .05 was considered statistically significant. The DIGITOX study was conducted in accordance with the principles of the Declaration of Helsinki for research involving human subjects and was approved by the coordinating hospital's Ethics Committee (registry no. 2022_10303). The study was exempt from obtaining patient informed consent, as it was epidemiological in nature and used anonymized data.

Results

During the study period, 658 cases of digoxin poisoning were recorded across the 15 participating emergency departments. Overall DIGITOX results showed that patients had a mean age of 83.9 (7.9) years, with a predominance of women [509 (76.9%)]. A total of 315 patients (53.2%) had some degree of dependence (Barthel Index available for 33 patients who received Digoxin-Fab treatment and 600 who did not).

Most poisonings were chronic (95.9%), and the most frequent cause was accidental ingestion (653 patients, 99.2%). Poisoning severity was mild or moderate in 570 cases (86.6%), severe in 78 (11.8%), and fatal in 9 (1.4%).

Table 1. Life-threatening situations associated with digitalis toxicity indicating anti-digoxin antibody administration

– Bradyarrhythmia with ventricular rate < 40 beats/min that does not respond (maintains ventricular rate < 60 beats/min) after repeated doses of 0.5 mg IV atropine (up to a maximum of 2 mg).
– Ventricular extrasystoles with risk of ventricular tachycardia or fibrillation (frequent ventricular ectopy, couplets, triplets, multifocal beats, or R-on-T phenomenon).
– Ventricular tachycardia.
– Ventricular fibrillation.
– Asystole.
– Cardiogenic shock.
– Serum potassium > 5 mEq/L with other signs of digitalis toxicity in acute intoxication.
– Plasma digoxin concentration > 6 ng/mL (> 6 hours after ingestion).

Reproduced from Nogué S, *et al.* Emergencias. 2012;24:462–75.

Of the 658 cases included, Digoxin-Fab were administered in 34 cases (5.2%). Among these, 7 patients (20.6%) presented acute poisoning and 27 (79.4%) chronic poisoning. Thus, 25.9% of patients with acute poisoning and 4.3% of those with chronic toxicity received antidotal treatment ($P < .001$). Digoxin-Fab were more frequently administered to younger patients [78.7 (SD, 11.5) vs. 84.2 (SD, 7.6) years; $P = .003$], with higher digoxin concentrations at admission [5.8 (2.7) ng/mL vs. 3.6 (1.5) ng/mL; $P < .001$], and with greater severity according to the PSS score ($P < .001$). In 7 of the 34 patients (20.6%), a second Digoxin-Fab dose was required to control the manifestations of intoxication. The initial Digoxin-Fab dose was similar in cases of acute and chronic poisoning [249.17 (299.84) mg vs. 117.74 (91.0) mg, respectively; $P = .07$], and the total doses administered were 285.83 (276.70) mg vs. 135.30 (92.24) mg, respectively. Four patients (11.8%) treated with Digoxin-Fab died (two within the first seven days of hospitalization and two later), with no significant difference compared to patients who did not receive Digoxin-Fab, among whom 11.4% died. No serious adverse effects were detected (only one mild case of nausea and vomiting was reported) during or after Digoxin-Fab administration (Table 2).

Figure 1 illustrates the reasons for Digoxin-Fab administration. The most frequent indication was the presence of bradyarrhythmia, particularly atrial fibrillation with slow ventricular response, followed by high digoxin concentrations (> 6 ng/mL). A digoxinemia > 6 ng/mL was observed in 13 cases, 5 of which had unknown time since ingestion, although these also had another indication for Digoxin-Fab use. In 10 of the 34 cases in which antidotal treatment was administered, more than one criterion justified Digoxin-Fab administration. Conversely, among the 624 cases in which Digoxin-Fab were not administered, 33 (5.3%) met at least one criterion for having received the therapy (Figure 2), the most frequent being very high digoxin levels (> 6 ng/mL) measured 6 hours after the last dose in 31 cases. Among these 33 patients who could have received Digoxin-Fab but did not, there were 6 deaths (18.2%), compared with 4 deaths (11.8%) among the 34 patients who did receive antidotal treatment ($P < .001$).

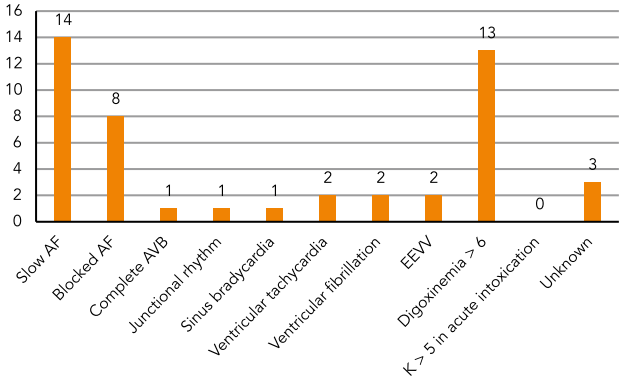

Figure 1. Reason for anti-digoxin antibody administration in the 34 treated patients.
EEVV: ventricular extrasystoles; AF: atrial fibrillation.

Table 2. Characteristics of patients according to whether they received anti-digoxin antibodies

	Yes n (%)	No n (%)	*P*
Total number	34 (5.4)	624 (94.8)	
Mean age, years (SD)	78.7 (11.5)	84.2 (7.6)	.003
Sex			
Men	5 (14.7)	144 (23.1)	ns
Women	29 (85.3)	480 (76.9)	
Type of poisoning			
Acute	7 (20.6)	20 (3.2)	< .001
Chronic	27 (79.4)	604 (96.8)	
Exposure intent			
Accidental	31 (91.2)	622 (99.6)	< .001
Suicidal	3 (8.8)	1 (0.2)	
Other	0	1 (0.2)	
Poisoning Severity Score[a]			
Minor	2 (5.9)	279 (44.7)	< .001
Moderate	15 (44.1)	274 (43.9)	
Severe	16 (47.1)	62 (9.9)	
Fatal	1 (2.9)	8 (1.3)	
Dependency according to Barthel Index			
Independent (> 90)	23 (67.6)	249 (41.5)	.012
Moderate (60–89)	4 (11.8)	197 (31.6)	
Dependent (< 60)	6 (17.6)	154 (32.8)	
Barthel Index	78.6 (30.2)	71.8 (28.6)	ns
Plasma digoxin level at admission (ng/mL)	5.8 (2.7)	3.6 (1.5)	< .001
Presence of symptoms	33 (97.1)	581 (93.1)	ns
Digestive symptoms	14 (41.2)	272 (43.6)	.013
Neurological symptoms	20 (58.8)	403 (64.6)	ns
Slow supraventricular arrhythmias	26 (76.5)	334 (53.5)	.032
Rapid supraventricular arrhythmias	1 (2.9)	15 (2.4)	ns
Ventricular arrhythmias	6 (17.6)	12 (1.9)	< .001
Asystole	3 (8.8)	2 (0.3)	< .001
Outcome			
Discharge < 12 hours	1 (2.9)	24 (3.8)	< .001
Discharge > 12 hours	3 (8.8)	91 (14.6)	
Admission to HW	18 (52.9)	486 (77.7)	
Admission to ICU	12 (52.9)	12 (1.9)	
Other	0	11 (1.8)	
Time in emergency department (hours)	28.2 (30.5)	18.7 (20.6)	ns
Length of stay (days)	14.9 (26.2)	7.7 (7.2)	.002
Deaths	4 (11.8)	71 (11.4)	ns

[a]In one case of IV digoxin administration, symptoms were not recorded.
[b]The Barthel Index was assessed in 33 patients who received anti-digoxin antibodies and in 600 patients who did not.
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HW: hospital ward; ICU: intensive care unit.

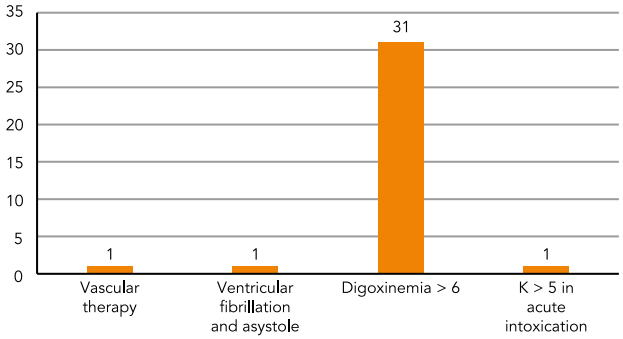

Figure 2. Cases in which anti-digoxin antibodies could have been administered but were not.

Discussion

Digoxin-Fab are ovine-derived immunoglobulin fragments with a low volume of distribution and primarily renal elimination. The therapeutic response after administration occurs approximately 30 minutes after infusion and should be complete within about 90 minutes. Most studies on the use of Digoxin-Fab refer to clinical case reports and small case series, as no controlled studies have been conducted,[9] although several series have demonstrated their effectiveness in the treatment of severe digoxin poisoning.[10-12]

In this subanalysis of the DIGITOX study, it was shown that the use of Digoxin-Fab in Spain remains limited, being employed in only 5% of all digoxin poisonings treated in emergency departments—lower than the 8% reported in a French study.[11] When Digoxin-Fab were used, they were administered preferentially in acute poisonings and in younger patients, with higher digoxin concentrations and greater severity according to the PSS, compared with patients who did not receive treatment.

In those cases in which Digoxin-Fab were administered, their use adhered to current recommendations.6 However, there was still a 5% subset of patients who met the criteria for Digoxin-Fab use but did not receive the antidote. Although the precise reasons for non-administration cannot be determined, one possible explanation is that Digoxin-Fab were not available in all emergency departments, a situation also described in the French study.[11] Among patients in the DIGITOX study who did not receive Digoxin-Fab, mortality was significantly higher than among those who did. It is expected that in the near future, the nationwide implementation of the Antidote Network will improve access to this treatment for patients who meet clear criteria for administration, thus improving prognosis and reducing mortality from digoxin poisoning.

The most common indications for Digoxin-Fab administration in the DIGITOX study were bradyarrhythmias, particularly atrial fibrillation with a slow ventricular response. In all these cases, administration was deemed appropriate; however, due to the retrospective nature of the study, it was not possible to confirm whether adequate doses of atropine had been given before Digoxin-Fab were indicated.

Despite the proven usefulness of Digoxin-Fab in patients with severe digoxin intoxication, their high cost has limited their use in some cases—especially among patients without immediate life-threatening risk—due to the absence of standardized administration criteria in such scenarios. Another controversial issue is Digoxin-Fab dosing, which has been questioned in several studies, either because of the need for concomitant therapies (e.g., correction of electrolyte abnormalities or other measures to increase heart rate) or because of the difficulty in assessing efficacy when empirical dosing is used.[13-15] According to the classical dosing approach, the required amount of antidote is calculated based on the total body load of digoxin (TBLD), often resulting in the administration of large Digoxin-Fab doses. Recently, for patients without immediate life-threatening conditions—and based on pharmacokinetic studies of digoxin and Digoxin-Fab—it has been proposed that treatment could be initiated with only one 40 mg vial in cases of chronic poisoning, or two vials (80 mg) in cases of acute poisoning, with the option to administer an additional dose if no clinical response is observed.[16] This low-dose approach has been clinically evaluated, showing good outcomes in patients with acute[17] and chronic[14] poisoning. However, in the latter, Digoxin-Fab administration did not appear to reduce mortality, suggesting that other factors—such as renal failure, potassium levels, and concomitant medications—may influence the final prognosis of intoxicated patients.[18] Of note, in the absence of free plasma digoxin concentration measurements, the response to Digoxin-Fab administration must be guided by clinical and electrocardiographic criteria.[19,20]

Another relevant aspect concerns the indications for Digoxin-Fab. In 2023, 2 new treatment algorithms were proposed for patients with digoxin poisoning,[21,22] differing in some aspects from the recommendations by Nogué *et al*.[6] Dijkam *et al*.[21] recommend treatment in cases of a single ingestion of 10 mg of digoxin in adults or 4 mg in children (in acute poisonings). They also propose treatment at digoxin concentrations differing from those of Nogué *et al*.[6] —specifically, Digoxin-Fab administration for levels exceeding 10 ng/mL at any time, or 7.8 ng/mL at 6 hours post-ingestion in acute adult poisonings, and 6 ng/mL in adults or 4 ng/mL in children in chronic intoxications. Conversely, Andrews *et al*.[22] proposed new management and treatment guidelines. Although their indications are similar, unlike Dijkam *et al*.[21] they do not distinguish between acute and chronic poisoning, and they adjust the potassium threshold to 6.5 mmol/L. Both publications include specific recommended Digoxin-Fab doses for each scenario. A major strength of these recent protocols is the emphasis on assessing patient severity at the time of decision-making and determining the need for immediate empirical treatment, based on a predefined number of vials. In the proposal by Andrews *et al*.,[22] in the absence of life-threatening situations, it is advised to await digoxin concentration results and calculate the TBLD before administering Digoxin-Fab—modifying previously established treatment approaches.[14,16,17] Because of the discrepancies among different reviews, guidelines, and recent studies—and considering that the recommendations by Nogué *et*

al.[6] were published over 12 years ago—we propose updated management and dosing guidelines, summarized in Table 3 and Figure 3.

This subanalysis of the DIGITOX study has the inherent limitations of retrospective designs. Moreover, as the study was not specifically designed to assess Digoxin-Fab treatment indications, the results should be interpreted with caution. Nonetheless, this represents the largest series conducted in Spain, with 658 cases, including 34 patients treated with Digoxin-Fab, reflecting routine clinical practice in Spanish emergency departments.

In Spain, Digoxin-Fab treatment is administered to approximately 5% of patients with digoxin poisoning, while another 5% could have benefited from its use. The updating of management and dosing protocols, along with the expansion of the Antidote Network, may improve treatment access for these patients. Currently, the Antidote Network includes most Spanish autonomous communities, with others in the process of joining.

We propose practical management and dosing guidelines that may assist in decision-making for patients with digoxin poisoning.

Table 3. Proposed treatment with anti-digoxin antibodies in patients with digoxin poisoning*

Adults**	Children**
Bradyarrhythmia with ventricular rate < 40 beats/min that does not respond (maintains ventricular rate < 60 beats/min) after repeated doses of 0.5 mg IV atropine (up to a maximum of 2 mg).	
Second- or third-degree atrioventricular block unresponsive to atropine.	
Ventricular extrasystoles with risk of ventricular tachycardia or fibrillation (frequent ventricular ectopy, couplets, triplets, multifocal beats, or R-on-T phenomenon).	
Asystole and severe ventricular arrhythmias: ventricular tachycardia and fibrillation.	
Cardiogenic shock.	
Serum potassium > 5 mEq/L with other signs of digitalis toxicity, only in acute poisoning.	
Digoxin concentration > 10 ng/mL after ingestion in acute poisoning, regardless of interval.	
Plasma digoxin concentration > 6 ng/mL (> 6 hours post-ingestion).	Plasma digoxin concentration > 4 ng/mL (> 6 hours post-ingestion).

* Always administer provided that, prior to the intoxication, the patient did not have a clearly documented limitation of therapeutic effort due to baseline condition.
** Some authors[21] also recommend treatment following a single ingestion ≥ 10 mg of digoxin in adults and ≥ 4 mg (or > 0.1 mg/kg) in children in cases of acute poisoning.

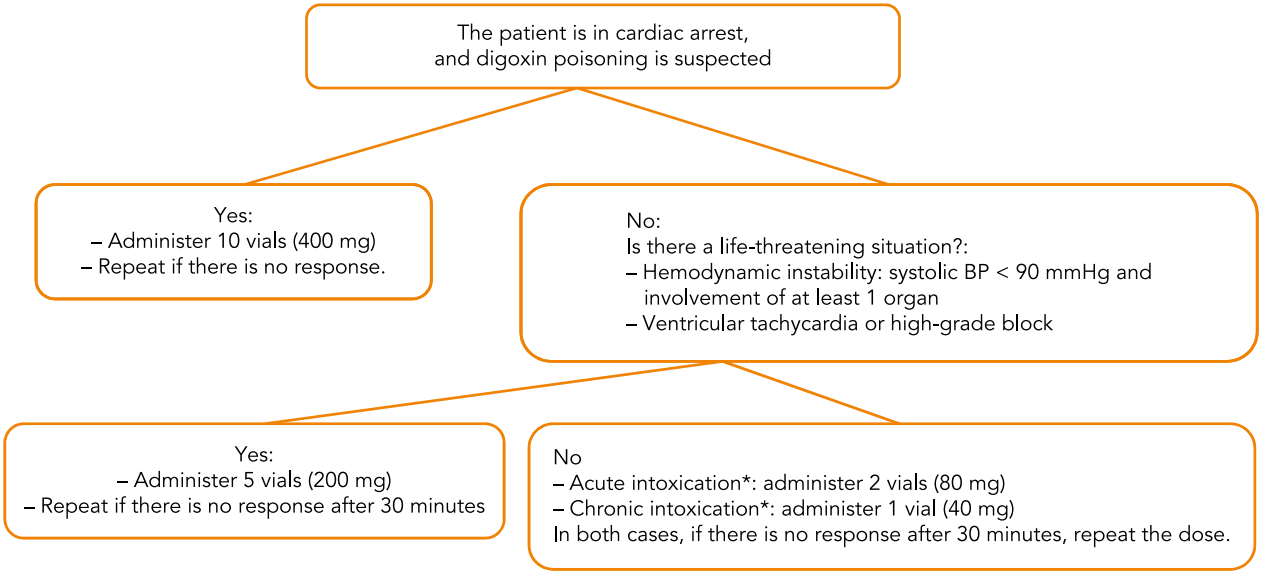

Figure 3. Proposed anti-digoxin antibody dosing protocol for patients with digoxin poisoning who meet criteria for antidote administration.
The response to Digoxin-Fab administration should be evaluated by measuring free digoxin concentration; if unavailable, clinical and electrocardiographic response should be assessed.
*Acute poisoning is defined as the deliberate ingestion of ≥ 2 mg of digoxin within < 12 hours, accompanied by symptoms or electrocardiographic findings consistent with digitalis intoxication.
**Chronic poisoning is defined as the presence of signs and symptoms suggestive of digitalis intoxication (neurological, gastrointestinal, or ECG findings) with digoxin levels > 2 ng/mL, measured at least 6 hours after the last dose in patients receiving chronic digoxin therapy.

ARTICLE INFORMATION

Conflict of Interest Disclosures: None reported.

Funding: This project was funded by BTG Specialty Pharmaceuticals. The sponsor had no involvement in study design, data collection, analysis, or manuscript preparation.

Ethical responsibilities: The authors have confirmed the maintenance of confidentiality and respect for the patient rights, agreement of publication, and transfer of rights to Revista Española de Urgencias y Emergencias.

Article not commissioned by the Editorial Board and with external peer review.

Note of the editors: This is a BOWMAN-generated English translation of the officially indexed Spanish-language article, which should be cited as Rev Esp Urg Emerg. 2024;3:90-95. In this translated version, the editors have supervised the process; however, it cannot be ruled out that some errors resulting from the artificial intelligence translation process may have gone unnoticed.

Acknowledgments: The authors thank Xavier Durán (AMIB–Assessoría Metodològica i Bioestadística, IMIM–Institut Hospital del Mar d'Investigacions Mèdiques) for statistical analysis, and Agustín Urdangarín, IT specialist.

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