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Assessment of digoxin antibody use in patients with elevated serum digoxin following chronic or acute exposure

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Abstract *Objective:* To evaluate the use of antidotal therapy in patients with an elevated digitalis concentration following chronic or acute exposure. *Design and setting:* Retrospective review of patient records over 2 years in 20 city hospitals in France. *Patients:* Overall 838 patients with an elevated serum digitalis concentration (digoxin > 1.95 ng/ml or digitoxin > 23 ng/ml) were included in the study. Of these, 67 (8%) had received antidotal therapy with Fab fragments. *Measurements and results:* The relationships between previously reported prognostic criteria and use of antidotal therapy were investigated. We identified five independent factors that were associated with the use of antidotal therapy: acute overdose (OR 15.74), Fab fragment availability in the hospital (11.06), serum potassium (1.81), and heart rate (0.96). Mortality was significantly lower in Fab-treated (6%, 4/67) than untreated patients (15%, 117/770). *Conclusions:* Antidotal therapy is underused in patients with an elevated digitalis concentration especially in patients with chronic digitalis exposure. These patients in our series presented a higher mortality rate than patients with acute poisoning. Although they were older and tended to have a history of cardiac disease, they did not differ from patients with acute poisoning with regard to the main severity criteria and prognostic factors. The use of identical criteria for antidotal treatment after acute and chronic poisoning should help optimize outcomes. Fab fragment availability is insufficient in France but ranks only second after type of poisoning (acute or chronic) in the multivariate association with Fab treatment.

Keywords Digitalis · Poisoning · Antidote · Digitalis antibodies · Immuno-toxicotherapy

Introduction

Ever since Sir William Withering suggested in 1785 that digitalis may have beneficial effects, drugs containing digitalis glycosides have been regularly prescribed to patients with heart complaints [1, 2]. However, digitalis therapy can arouse concern particularly because of the high incidence of chronic, unintentional digitalis intoxications resulting from a narrow therapeutic index, and changes in pharmacokinetics due to age, illness, or drug interactions. Acute digitalis poisoning, on the other hand, is rare [3–5]. Mortality from digitalis poisoning is still high despite the advent of transvenous and, more recently, transcutaneous cardiac pacing and despite the introduction in the 1970s and early 1980s of antidotal treatment with digoxin-specific Fab fragments [6, 8]. The reported mortality rate in several case series is 20–30% [5, 7–12]. Indications for antidotal treatment are based on severity of intoxication and

adverse prognostic factors. These are derived largely from studies in acutely intoxicated patients, including patients having intentionally taken an overdose [4, 13–16], but it is also often used in patients with chronic poisoning [17] although this practice has never been evaluated. The primary aim of this study was to identify factors associated with the use of antidotal therapy in patients with an acute or a chronic digitalis overdose. The secondary aim was to compare patients with acute and chronic poisoning.

Materials and methods

We systematically reviewed patients with a laboratory-confirmed elevated digitalis concentration following chronic or acute exposure. This was defined as a serum digoxin concentration greater than 1.95 ng/ml or serum digitoxin concentration greater than 23 ng/ml [8]. We included digitoxin although it has fallen out of favor in recent years because digitoxin-poisoned patients have been used to establish many of the adverse prognostic criteria [13–16]. We obtained the data on digitalis concentrations directly from hospital laboratories in order not to exclude patients with a discharge diagnosis other than digitalis poisoning.

We included patients from 20 hospitals in France. The inclusion period spanned 2 years (1999–2000) in 19 hospitals but was extended to 11 years (1990–2000) in a center with a toxicological intensive care unit (Fernand Widal, Paris) in order to enroll a larger number of patients with acute poisoning. Standard treatments, including criteria for Fab fragment administration, were coded in this center during these 11 years [7, 8]. We identified 1,137 patients with laboratory-defined elevated digitalis concentration.

We obtained relevant information on each hospitalization unit. Whenever possible we obtained the patient's medical record and recorded the patient's age and gender, any underlying presence or history of cardiac disease (hypertension, arrhythmia, angina pectoris, acute myocardial infarction, heart failure or other), and the circumstances of the overdose (acute or chronic, intentional or accidental). We documented the following previously reported prognostic criteria: Glasgow coma scale, systolic arterial blood pressure, heart rate, serum potassium, and creatinine concentrations, digitalis concentration, and ECG data (third-degree sinoatrial block, second- or third-degree atrioventricular block, ventricular tachycardia or fibrillation). We recorded the highest digitalis concentration and the clinical and biological parameter values available for the timepoint closest to this digitalis concentration measurement. We also recorded any treatment given, including atropine, treatment with Fab fragments, and cardiac pacing, and the final outcome with date of discharge or death.

Results are expressed as medians and IQR. To identify the factors associated with the use of antidotal therapy we compared patients who did or did not receive Fab fragments. We compared categorical data by Fisher's exact and χ^2 tests, and continuous data by the Mann–Whitney test. We identified independent factors by entering the significant variables in the univariate analyses into a backward stepwise logistic regression model (Statview 5.0, SAS Institute, Cary, N.C., USA). Differences with a p level less than 0.05 were considered statistically significant.

Table 1 Characteristics of French hospitals enrolling patients with digitalis exposure (*NA*, not available; *ICU*, intensive care unit; *CICU*, cardiology ICU; *ED*, emergency department)

	Beds	ICU	CICU	Fab fragment availability	Visits to ED/year	Inclusions	Missing data (%)	Fab treatment
Arpajon	410	Yes	No	Yes	24,000	8	0	2
Bondy	316	Yes	No	No	62,500	8	3	0
Orsay	430	Yes	No	No	18,000	18	23	2
Morlaix	1,193	Yes	Yes	No	21,500	21	13	0
Nantes	1,738	Yes	Yes	Yes	85,100	182	25	1
Digne les bains	230	Yes	Yes	No	14,000	17	0	0
Châlon-sur-Saone	360	Yes	No	No	26,500	60	0	0
Lannion	366	Yes	Yes	No	21,400	8	5	0
Meaux	542	Yes	Yes	No	33,500	3	1	0
Versailles	836	Yes	Yes	No	50,000	46	20	0
Aulnay-sous-bois	749	Yes	Yes	No	55,700	30	27	1
Brest	2,107	Yes	Yes	No	50,000	99	61	1
Bobigny	550	Yes	No	Yes	29,000	32	4	2
Fort-de-France	630	Yes	Yes	Yes	33,800	49	NA	0
Toulon	528	Yes	Yes	Yes	35,000	52	21	2
Montfermeil	400	Yes	Yes	Yes	30,000	17	31	0
Gonesse	700	Yes	Yes	No	45,000	51	50	0
Corbeil	900	Yes	Yes	Yes	26,000	23	NA	0
Widal, Paris	350	Yes	No	Yes	0	79	0	42
Lariboisière, Paris	704	Yes	Yes	Yes	76,700	35	4	14
Total	–	–	–	–	–	838		67

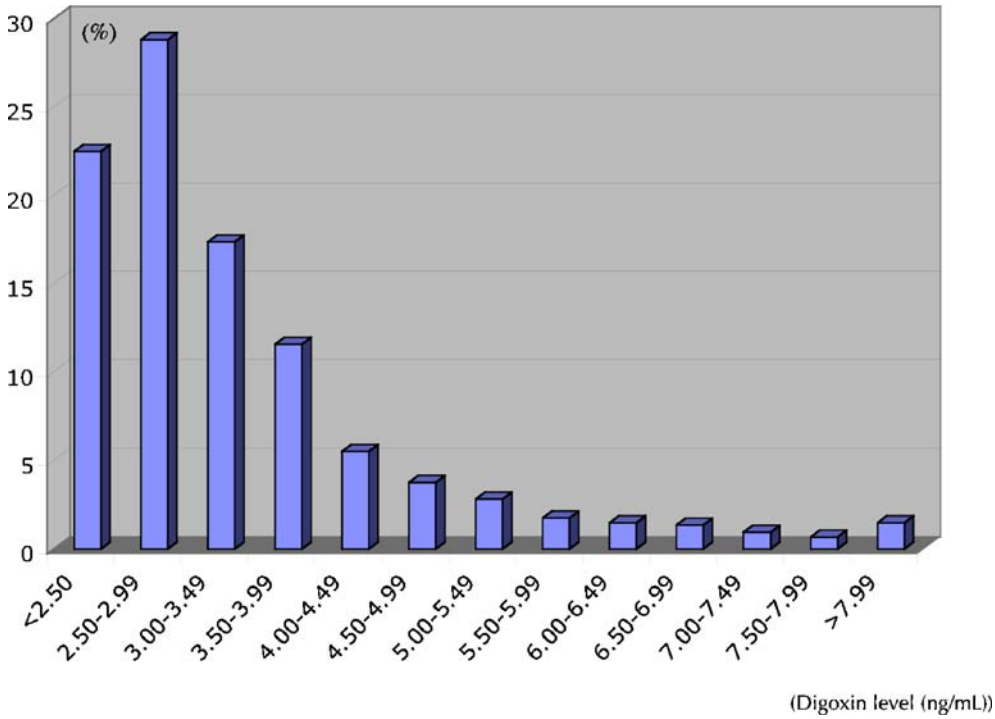

Fig. 1 Distribution of digoxin levels in the included patients ($n = 743$)

Table 2 Patient characteristics; results are expressed as medians (interquartile range) unless specificied otherwise

	n	Antidotal treatment ($n = 67$)	No antidotal treatment ($n = 781$)	*p*
Age, median (years; IQR)	831	74 (49–84)	82 (74–88)	0.0003
Age < 55 years		21 (31%)	397 (52%)	0.001
Serum digoxin concentration	758	6.7 (4.7–11.4)	3.0 (2.5–3.7)	< 0.0001
Serum digitoxin concentration	73	130 (93–189)	35 (27–52)	< 0.0001
Glasgow coma scale	795	15 (15–15)	15 (15–15)	< 0.0001
Heart rate (beats/min)	817	52 (45–70)	75 (62–88)	0.02
< 60 beats/min		42 (63%)	136 (18%)	< 0.0001
< 40 beats/min		13 (19%)	38 (5%)	0.16
Systolic blood pressure (mmHg)	786	135 (112–150)	130 (114–150)	0.2
< 100 mmHg		8 (12%)	56 (7%)	0.15
Potassium concentration (mmol/l)	801	4.6 (4.3–5.3)	4.5 (4.0–4.9)	0.01
> 4.5 mmol/l		35 (56%)	390 (52%)	0.6
> 5.0 mmol/l		20 (32%)	177 (24%)	0.2
Serum creatinine (μmol/l)	815	101 (68–147)	118 (87–167)	0.0002
Female gender	847	51 (76%)	509 (65%)	0.06
History of cardiac disease	844	45 (67%)	734 (94%)	< 0.0001
Fab fragment availability	726	63 (97%)	312 (47%)	< 0.0001
Acute poisoning	837	48 (73%)	68 (9%)	< 0.0001
Conduction disturbances	848	13 (19%)	86 (11%)	0.047
Ventricular arrhythmia	848	4 (6%)	12 (2%)	0.03

Results

Clinical data were not available for 299 (26%), including 11 in whom the circumstances of intoxication were unknown. The distribution of the 838 included patients (74%) across centers is given in Table 1 with information on the type of center. The median number of patients per center was 31 (interquartile range, IQR, 17–51). The overdose occurred during chronic therapy in 722 patients (86%).

Table 3 Independent factors associated with antidotal treatment in a multivariate analysis ($n = 743$) (*OR*, odds ratio; *CI*, confidence interval)

	OR	95% CI	*p*
Acute poisoning	15.74	6.60–37.39	< 0.0001
Fab fragment availability	11.06	2.88–42.54	0.0005
Potassium concentration	1.81	1.22–2.69	0.003
Heart rate	0.96	0.94–0.98	< 0.0001

Table 4 Prognostic factors, treatment, and mortality according to type of digitalis exposure (*SBP*, systolic blood pressure)

	Chronic exposure ($n = 722$)		Acute exposure ($n = 116$)		p
	n	%	n	%	
Previously reported prognostic factors and life threatening situations					
Male sex	247	34	34	29	NS
Age > 55 years	697	96	59	51	< 0.0001
Cardiac history	712	99	63	54	< 0.0001
Heart rate < 60 beat/min	126	17	48	41	< 0.0001
Heart rate < 40 beat/min	23	3	3	3	NS
Second- or third-degree atrioventricular block	81	11	17	15	NS
Ventricular fibrillation or tachycardia	11	1	5	4	< 0.05
Cardiogenic shock (SBP < 100 mmHg)	52	7	10	9	NS
Serum potassium > 5.0 mmol/l	168	23	25	22	NS
Serum potassium > 4.5 mmol/l	369	51	49	42	NS
Treatment					
Atropine	35	4.8	37	31.9	< 0.0001
Fab fragments	19	2.6	48	41.4	< 0.0001
Electrosystolic cardiac pacing	9	1.2	3	2.6	NS
Mortality[a]	114	16	6	5	< 0.005

[a] Data unavailable for eight patients (1%) with chronic intoxication and two (2%) with acute intoxication

Acute poisoning ($n = 116$) was due to suicide attempts in 101 patients (12%) and was accidental in 15 (2%). The distribution of patients according to digitalis concentration is illustrated in Fig. 1. Of the 838 patients 67 (8%) received antidotal therapy with Fab fragments. Table 2 compares the demographic, clinical, biological, and electrocardiographic characteristics of the two groups.

Table 2 presents the distribution of patients according to previously reported prognostic factors. All recorded variables except systolic blood pressure were significant in these univariate analyses and were entered into a multivariate analysis. Five of these factors proved to be independent: acute overdose, Fab fragment availability in the hospital, digitalis dose, serum potassium, and heart rate (Table 3). Mortality rate was significantly lower in Fab-treated than untreated patients: 6% (4/67) vs. 15% (117/770, $p = 0.045$).

As antidotal therapy and acute poisoning were strongly correlated, we compared previously reported prognostic factors and therapy in patients with an elevated digitalis concentration following acute and chronic exposure (Table 4). Highly significant differences were found only for age (above 55 years), cardiac history, heart rate (< 60 beats/min), and treatment by atropine or Fab fragments. Two of the 114 deaths after chronic exposure and two of the six deaths after acute poisoning occurred in patients who received Fab treatment, i. e., a total of 4/120 (3%; Table 4).

Discussion

In this retrospective study of a large cohort of patients in French hospitals only 8% of patients with an elevated digitalis concentration were treated by Fab fragments. Fab fragments were administered to 41% of patients with acute poisoning but to only 2% of patients with chronic exposure. Antidote therapy, rather than being governed by established prognostic criteria, was governed firstly by the circumstances of intoxication (acute rather than chronic) and secondly by low Fab fragment availability. A higher mortality rate was recorded in patients with chronic rather than acute exposure (16% vs. 5%).

Established prognostic factors such as age, hyperkalemia (> 5 mmol/l), severe bradycardia (< 40 beats/min), and conduction and rhythms disturbances are currently considered to warrant immediate life-saving antidotal treatment or prophylaxis [4, 8, 13–17]. However, in our study several of these factors were only poorly or not significantly associated with the use of antidotal therapy and did not differ between patients with acute and chronic exposure.

Age was not an independent prognostic factor for antidote therapy in our multivariate analysis. Elderly patients are particularly at risk of digitalis toxicity probably on account of physiological changes, underlying illness, or interactions from multiple drug use [4]. There is a known relationship between age and death from acute digitalis poisoning [13] which may prove to be even stronger in a fragile, older population suffering from chronic intoxication. The median age of our patients with chronic digitalis exposure was 83 years (25% of patients above 88 years of age) and considerably older than the age of patients of the Digitalis Investigation Group [2] (mean age: 63 years, 26% over 70 years old).

Serum potassium concentration was a poor indicator for antidote therapy in our multivariate analysis. Serum potassium is correlated with the degree of inhibition of the Na^+K^+ATPase pump by digitalis, and the relationship between hyperkalemia and digitalis poisoning severity is well

established [15, 17]. In patients with chronic poisoning, renal failure, which is common, enhances serum potassium. Antidotal treatment quickly brings down the potassium level and reduces mortality [4, 7, 12, 17]. It reduced the mortality rate from 90% to 12.5% in a study of 150 patients with acute or chronic intoxication with a serum potassium above 6.4 mmol/l. Hyperkalemia is thought to be less frequent in chronic than acute intoxication [4, 18], but this was not the case in our study.

Bradycardia and conduction disturbances were poorly related to antidotal treatment although these factors are reported to lead to an increased risk of ventricular rhythm disturbances and increased mortality in patients with either acute or chronic digitalis poisoning [8]. According to one report, atrioventricular block was present on admission in 39% of patients who subsequently survived compared to 77% of patients who died [14]. Of the 126 patients with chronic digitalis exposure who presented with bradycardia (< 60 beats/min) in our study only 35 received atropine. Cardiac pacing was used in only 9 of 126 patients as Fab treatment has become the gold standard [4, 8, 12, 17]. Underlying cardiac disease is associated with increased mortality in acute digitalis poisoning [13, 14]. The reported mortality rate is 40% in patients with heart failure compared to 10% in patients without [13]. A history of cardiac disease was more frequent in our patients with chronic rather than acute intoxication because they were older.

Although serum potassium, pulse rate, and conduction disturbances did not differ significantly in our study between acute and chronic digitalis exposure, these two categories of patients were nevertheless not managed in the same way. Paradoxically, fewer patients with chronic exposure (2%) received Fab fragments than patients with acute poisoning (41%). This could partly account for their higher mortality rate (16% vs. 5%). We therefore strongly recommend that to reduce mortality and until such time as prospective data become available, early prophylaxis be based on identical criteria for antidotal treatment in acute and chronic poisoning, as follows:

- Life threatening toxicity: Indication for a curative (i. e., equimolar) neutralization
  - Arrhythmia: ventricular fibrillation or tachycardia
  - Bradycardia with heart rate < 40/min after atropine injection (1 mg)
  - Hyperkalemia > 5 mmol/l
  - Cardiogenic shock

- Poor prognostic factors: Indication for a prophylactic (i. e., half-equimolar) neutralization
  - Male sex
  - Age over 55 years
  - Underlying heart disease
  - Severe bradycardia with second- or third-degree atrioventricular block
  - Bradycardia (heart rate < 60/min) after atropine injection (1 mg)
  - Hyperkalemia > 4.5 mmol/l

Atropine and especially with Fab fragment treatment were no doubt insufficient in our population of patients with chronic exposure. Insufficient use of Fab treatment in our study could have several reasons: (a) French clinical practice guidelines do not mention the use of Fab fragments in emergency care [19], (b) the incidence and potential severity of digitalis poisoning are underestimated and knowledge of how such poisoning should be managed is lacking, (c) there is concern on the effects of digitalis withdrawal, (d) Fab fragments were available in only 24% of French city hospitals [20], (e) the cost of Fab fragments, (f) and age and comorbidities in patients with chronic exposure [18].

Although one might intuitively expect antidote availability to be the key factor in undertreatment, our multivariate analysis revealed a much stronger relationship between antidotal treatment and circumstances of intoxication (acute or chronic) than between treatment and antidote availability. We have recently shown that early prophylactic treatment with Fab fragments can help reduce mortality in both chronic and acute poisoning [21]. Patients with poor prognostic criteria (age, moderate hyperkaliemia, moderate bradycardia, history of cardiac disease) require Fab treatment to avoid the onset of complications such as ventricular arrhythmias and/or asystole associated with a high mortality rate [14, 16, 17].

The potential limitations of our study are: (a) Data were missing for 23% of patients with an elevated digitalis concentration which may have introduced a systematic bias; bias was limited to some extent by the size of the study population. (b) Most patients with acute poisoning were admitted by a single center; however, this bias was limited as treatment, including Fab fragment therapy, was coded, and did not change during the study period [7, 21]. (c) The cause and circumstances of death were not recorded; this would be a challenge even for a prospective study as such elderly populations present many comorbidities, thus rendering the establishment of cause-effect relationships problematical.

Conclusion

Antidotal therapy was underused in patients with an elevated digitalis concentration especially in those with chronic digitalis exposure. These patients presented a higher mortality rate than patients with acute poisoning. Although they were older and tended to have a history of cardiac disease, they did not differ from patients with acute poisoning with regard to the main severity criteria and prognostic factors. The use of identical criteria for antidotal treatment after acute and chronic poisoning should

help optimize outcomes. Fab fragment availability is insufficient in France but ranks only second after type of poisoning (acute or chronic) in the multivariate association with Fab treatment.

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