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ACUTE DIGITALIS INTOXICATION — IS PACING STILL APPROPRIATE?

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ABSTRACT

Over a six year period, 92 patients intoxicated with either digitoxin or digoxin were admitted to our ICU. Fifty-one patients were treated with cardiac pacing and/or Fab fragments, and the mortality rate was 13% (14 were intoxications with digoxin, 36 with digitoxin, 1 was mixed). Forty-five cases were suicide attempts; six were accidental overdosages. Since cardiac pacing may trigger fatal arrhythmia or delay the administration of Fab fragments, we conducted a retrospective study to determine whether fatal outcomes could be related either to cardiac pacing or to unsatisfactory use of immunotherapy. In our study, prevention of life-threatening arrhythmia failed in 8% of cases with Fab and in 23% with pacing. Though Fab tended to be more effective, this difference was not significant. In our study, the main obstacles to the success of Fab were pacing-induced arrhythmias and delayed or insufficient administration of Fab. Iatrogenic accidents of cardiac pacing were frequent (14/39, 36%) and often fatal (5/39, 13%). In contrast, immunotherapy was not associated with any serious adverse effects (0/28, 0%) and was safer than cardiac pacing ($p < 0.05$). In conclusion, during digitalis intoxication, the pacemaker has limited preventive and curative effects, is difficult to handle, and exposes patients to

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severe iatrogenic accidents. Fab fragments act as a powerful antidote and are safer and much easier to use than pacing. These results encourage us to prescribe Fab fragments as first-line therapy during acute digitalis intoxication. *(Key Words: digoxin; digitoxin; intoxication; mortality; pacemaker, artificial; immunoglobulins, FAB; immunotherapy; cardiac pacing, artificial.)*

INTRODUCTION

Since the efficacy of digoxin-specific Fab fragments in life-threatening acute intoxication was demonstrated (1), numerous single case reports have confirmed their efficacy both in adults and children, both in digoxin and digitoxin intoxications (2-9). In addition to interim reports (10,11), four large series have established the efficacy and safety of Fab fragments in both acute intoxications and overdosage during maintenance therapy (12-15). However, some lethality has been reported in the largest series, ranging from 6% (12) to 29% (14). Several explanations have been proposed (10,15,16): delayed administration or insufficient Fab, incomplete response to Fab, underlying cardiac disease and other medical illnesses. The possible implications of cardiac pacing, often used to treat severe digitalis-induced bradycardia (17-21) before or instead of Fab, have not yet been assessed.

From 1967 to 1975, before Fab fragments were commercially available in France, the mortality rate of digitoxin intoxication in 124 subjects admitted to our ICU was 13.7% (18). Sixty-eight of these patients received conventional treatment including cardiac pacing. Since Fab fragments became available, 92 patients intoxicated with either digitoxin or digoxin were hospitalized in this same ICU, and the mortality rate remains at 13%. Thus, the introduction of Fab does not appear to improve prognosis. Therefore, it was important that cardiac pacing be assessed, since cardiac pacing may trigger fatal arrhythmia (18,20) or delay the administration of Fab fragments. We conducted a retrospective study of these 92 patients to determine whether persistent fatal outcomes could be related either to conventional treatment and more especially to cardiac pacing or unsatisfactory use of Fab.

MATERIALS AND METHODS

Patient Characteristics

Between September 1983 and December 1989, we admitted to our toxicological intensive care unit (ICU) 92 patients with toxic plasma glycoside concentration (measured by radioimmunoassay) as defined in our laboratory:

serum digoxin level > 2.5 nmol/L (1.95 ng/mL); serum digitoxin level > 30 nmol/L (23 ng/mL).

Treatments

All patients were treated conventionally with gastric lavage, repeated doses of activated charcoal, and atropine for bradycardia (19-22). Forty-one intoxicated patients survived without additional treatment. However, 51 severely intoxicated patients required treatment for cardiac arrhythmia, including cardiac pacing, Fab treatment or both.

Indications for pacing were: 1) severe bradycardia, unresponsive to atropine, mostly secondary to atrioventricular block (AVB) or to sinoatrial block; 2) hyperkalemia > 5 mmol/L (17-19). The pacemaker was adjusted to maintain a ventricular rate of 80-90 bpm (17). It must be stressed that the 39 pacemakers were not implanted in our hospital but in cardiology centers. In 31 cases, the pacemaker was fitted before arrival in our ICU (74%).

Indications for Fab fragments as monotherapy were: 1) life- threatening arrhythmia when it occurred after admission to our ICU: ventricular fibrillation (VF), ventricular asystole (VA) or severe bradycardia with second or third degree AVB (13,14). Each Fab treatment was prescribed and administered in our ICU. If life-threatening arrhythmia occurred while the patient was away from our ICU, administration of Fab was not possible. If Fab treatment succeeded in reversing bradycardia, a pacemaker was not subsequently implanted; 2) existence on admission of at least two poor prognostic factors according to Dally *et al.* (23): male, age over 55, underlying heart disease, presence of a first or second degree but well tolerated AVB, and hyperkalemia > 5 mmol/L (14,24).

Indications for both pacemaker and Fab fragments were: 1) life-threatening arrhythmia: either pacing-defect-related arrhythmias or occurrence of VF despite normal pacing; 2) existence of at least two life-threatening prognostic factors in patients admitted after pacemaker implantation, because of our experience that patients exhibiting poor prognostic factors had a high rate of mortality despite cardiac pacing alone (17,18).

Doses of Fab fragments. A full dose of Fab (equimolar neutralization) was administered when life-threatening arrhythmias occurred (curative dose). A full dose is the amount of Fab fragments required for the neutralization of the total body load of glycoside (16,25). Half equimolar neutralization was administered if the patient's condition was satisfactory but poor prognostic factors were present. This empirical or so-called prophylactic dosage (19) was intended to attenuate the severity of the digitalis intoxication before the occurrence of sudden arrhythmia.

Fab fragments were administered intravenously over one or two hours (in isotonic saline) or as rapidly as possible in life-threatening cases (8,16). Each vial of Digidot® (Böehringer Mannheim) contains 80 mg of Fab fragments and neutralizes 1 mg of either digitoxin or digoxin body load. The body load of glycoside was estimated from the plasma level, if known, or from the ingested amount (16).

Body load of glycoside (12,16,22):

= Ingested amount (mg) x digoxin bioavailability (60%) or digitoxin bioavailability (100%)

= Serum glycoside concentration (ng/mL) x volume of distribution (VD) x weight (kg), with VD = 5.6 L/kg for digoxin and 0.56 L/kg for digitoxin

When no data were available for the patient, ten vials were administered. As recommended by the manufacturer, ten extra vials were given if the first administration failed.

Trial Design

Among the 92 patients admitted between 1983 and 1990, 51 severely intoxicated patients were treated with a pacemaker and/or Fab fragments. To assess the efficacy of the different treatments, we retrospectively divided these 51 patients into three groups: patients treated with pacemaker alone, Group 1; patients treated with Fab alone, Group 2; patients treated with both pacemaker and Fab, Group 3. Then, we recorded in each group: age, sex, ingested amount of digitalis, digitalis serum level, serum potassium concentration, and the existence of conduction disturbances or underlying cardiac disease. Comparisons between the three groups were made using one way ANOVA followed by the Scheffe F-test for two by two comparisons for continuous variables and by the chi-square test for binomial variables. For all tests, the level of significance was set at 5%.

The safety of pacemaker or Fab fragments was assessed by recording their adverse effects. The previously described pacemaker adverse effects during digitalis intoxication are (17,18): thrombosis, traumatic or infectious complications and life-threatening arrhythmias secondary to defects of pacing (ventricular asystole), to pacemaker insertion (ventricular tachycardia or fibrillation) or to pacemaker adjustment (ventricular asystole or fibrillation). The previously described Fab adverse effects are (15): mild allergic complications; recrudescent digitalis toxicity secondary to the reappearance of circulating free digitalis some time after immunotherapy; occurrence of acute cardiac failure due to loss of inotropic support after withdrawal of digitalis.

The efficacy of these two treatments was assessed from their ability to prevent life-threatening arrhythmias, such as ventricular asystole or ventricular fibrillation. If such arrhythmia occurred in patients of Group 3, treated with both pacemaker and Fab fragments, it was considered a failure of pacing alone if Fab were administered after the occurrence of the arrhythmia, otherwise, it was considered that both treatments failed.

Death from digitalis intoxication usually results from ventricular fibrillation, ventricular asystole, pump failure (19-22) or from mesenteric infarct (9,26). As these causes can result from digitalis intoxication, adverse treatment effects, or independent events, we studied both the mechanisms of death and the contributory factors.

RESULTS

Among the 51 severely intoxicated patients, 23 were treated with cardiac pacing alone (Group 1), 12 were treated with Fab fragments alone (Group 2), and 16 were treated with both pacemaker and Fab (Group 3). Because pacemakers were mostly fitted before arrival in our ICU (74%), the mean time between intentional ingestion and admission was 12 $\pm$ 10 h. In Group 3, 10 out of the 16 patients (62%) received Fab despite satisfactory pacing, because they exhibited at least high degree AVB and either underlying heart disease or hyperkalemia > 5 mmol/L.

Fourteen intoxications were due to digoxin (27%), 36 to digitoxin (71%) and 1 to both (2%). The mean age was 61 $\pm$ 19 years (range 27-94). Thirty-three patients were females (65%). Six cases were accidental overdosage (12%). Remaining cases were suicidal attempts (88%). The ingested amount of glycosides ranged from 2 to 50 mg. Twelve of the 51 patients had a fatal outcome (23.5%).

The severity of intoxication and the mortality rate in each group are shown in Tables 1 and 2. Differences between the three groups were found for: sex, serum K^+ and conduction disturbances. For all these variables, comparison between pairs of groups showed no differences between Groups 1 and 2 and significant differences between each of these two groups and Group 3. As expected, the severity in Group 3, treated with both pacemaker and Fab, appears more severe than that of Groups 1 and 2.

1) *Pacemaker efficacy: Cardiac pacing failed 9 times out of 39 (23%) to prevent life-threatening arrhythmias (7 VF, 2 VA). Three VF occurred during normal pacing.* Four VF and 2 VA were subsequent to pacing-induced arrhythmias or pacing defects. Seven of these nine arrhythmias occurred before any administration of Fab.

TABLE 1

Characteristics of the 51 Intoxicated Patients

	Group 1 (n=23) PM	Group 2 (n=12) Fab	Group 3 (n=16) PM + Fab
Male	30%	8%	62%*
Mean age (yr)	62	67.4	56
Heart history	48%	41%	56%
Serum K (mEq/L1)	4.6±0.9	4.6±0.7	5.6±1.3*
Conduction disturbances	74%	58%	100%*
Ingested amount (mg)	9.4±3.7	9±5.3	15±13
Digitoxin (nmol/L)	184±85	221±73	260±123
Digoxin (nmol/L)	9.9±5.7	15±6.1	25.2±23.7
Fatalities	4 (17%)	3 (25%)	5 (31%)

No variables were significantly different between Groups 1 and 2. For several variables (*), comparison between pairs of groups showed significant differences between each of Group 1 or 2 and Group 3 ($p < 0.05$).

TABLE 2

Conduction Disturbances Encountered in Each Group

	SVT	SAB II	SAB III	AVB II	AVB III
Group 1	5	2	-	3	7
Group 2	4	-	-	1	2
Group 3	4	-	1	2	9

SVT: supraventricular tachycardia with slow ventricular response rate (below 50 bpm); SAB II or III: sinoatrial block of second or third-degree; AVB II or III: atrioventricular block of second or third-degree.

2) *Fab efficacy: Two patients in Group 3 received rapid administration of Fab after the occurrence of 1 VF and 1 VA.* These two patients were refractory to immunotherapy and died a few hours later, too soon for the ability of Fab to prevent recurrence of life-threatening arrhythmias to be assessed.

Thus, the efficacy of Fab fragments was assessed in 26 out of the 28 Fab-treated patients. In two cases out of 26 (8%), Fab fragments failed and fatal arrhythmia occurred (1 VA in Group 2, 1 VF in Group 3). The VA occurred 12 h after admission, while the patient was away from our hospital and could not receive a second dose of Fab. He died in the radiology department during fibrinolysis of an arterial clot of the leg. The VF occurred 100 h after admission to our ICU, so a second neutralization could be performed and was initially successful. Unfortunately, the patient died several days later from cardiac failure and anoxic brain damage. The difference in failure rates between immunotherapy (8%) and pacemaker (23%) was not significant ($p > 0.05$).

We also observed three recurrent AVB II or III, which are not life-threatening arrhythmias by our criteria, so they were not considered failures of Fab treatment. A second neutralization was performed in two patients and both were successful. The third patient presented a clinical picture of cardiac failure on day three and was transferred to a cardiology center in another hospital. He was paced soon after his arrival because of the recurrence of transient AVB III, but presented a VF and died (Group 3).

These five recurrent arrhythmias (20%) occurred 1 to 4 days (mean 61 h) after the first administration of Fab. Nausea or vomiting was present at the same time in three cases. These arrhythmias occurred after massive digitoxin intoxication with a mean plasma digitoxin level of 335 nmol/L (range 230-440 nmol/L). In each case, the first dose of Fab administered was less (67%; range 50-80%) than the neutralizing dose, estimated in retrospect from the serum level (15).

3) *Safety of cardiac pacing in the treatment of digitalis intoxication was assessed in 39 pacing-treated patients from Groups 1 and 3.* Fourteen adverse effects (36%) were recorded. These iatrogenic accidents were pacing-induced arrhythmias (6 cases), pacing defects (6 cases), and infectious complications (2 cases). The six pacing-induced arrhythmias occurred during or just after insertion (1 ventricular tachycardia, 3 VF) or subsequent to pacemaker adjustment (1 VA after a brief pause of pacing to study the underlying rhythm; 1 VF during reduction of ventricular rate from 80 bpm to 60 bpm). The six pacing defects occurred after ambulance transport (1 VA), external cardiac massage (1 patient), or accidental removal of the pacemaker by a confused patient, while no causes were found in three cases. The two infectious complications were staphylococcus epidermidis septicemias. One septicemia was complicated by fatal septic shock. Five out of these accidents (13%) had a fatal outcome (2 VF, 2 VA, 1 septic shock). Thus, the overall pacing-induced mortality was 42% (5 out of 12 fatalities).

4) *Safety of serotherapy during digitalis intoxication was assessed in 28 Fab-treated patients (Groups 2 and 3).* We recorded five cases of acute heart failure among these 28 patients (18%), and two other cases in Group 1. These seven patients were elderly (mean age 76, range 63-93), each with a history of chronic cardiac failure. Among the five Fab-treated patients, the signs of acute cardiac failure were present before immunotherapy began (three cases), or following cardiac massage and defibrillation (two cases). We did not observe any allergic complications. The rates of iatrogenic accidents with immunotherapy (0%) and pacemaker (36%) was significantly different ($p < 0.05$).

5) *Fatalities among pacing-treated patients: 9 out of the 39 pacing-treated patients died (23%).* The factors contributing to cardiac arrest were iatrogenic accidents of pacing (13%), cardiogenic shock (5%) or mesenteric infarct (5%).

6) *Fatalities among Fab-treated patients: 8 out of the 28 Fab-treated patients died (29%).* The administration of Fab was delayed in four cases, being given after the occurrence of a potentially fatal event (1 VA, 2 VF, 1 mesenteric infarct). In one case, they were given to a moribund patient (mixed digoxin-phenobarbital intoxication in a 93 year-old woman with brain anoxia). In the three remaining cases, the factors contributing to cardiac arrest were: infusion of insufficient Fab in all cases; pacemaker implantation and acute cardiac failure leading to VF in two cases, and fibrinolysis of an arterial clot of the leg that may have contributed to VA (through hyperkalemia for instance) in the last case (Table 3).

DISCUSSION

With 15 cases admitted each year between 1983-1989, acute digitalis poisoning represents 1.5% of overall admissions to the toxicologic intensive care unit. In contrast with the US, digitoxin is the cardiac glycoside used most frequently in suicide attempts in France (two thirds of glycoside intoxications).

Before commercial availability of Fab fragments, management of severe digitalis-induced arrhythmias relied on ventricular pacing and antiarrhythmic drugs (18,22). Cardiac pacing is a toxicodynamic treatment that prevents bradycardia, thus ensuring adequate cardiac output in patients with underlying heart disease. Pacing at 80 bpm is also suggested to protect against ventricular asystole and bradycardia-induced arrhythmias (18,27). Unfortunately, during digitalis poisoning, the fibrillatory threshold is lowered, and both accidental electrode displacement and manipulation of the pacemaker for adjustment

TABLE 3

Characteristics of the 12 Fatalities

	Age (yr)	Digitoxin (nmol/L)	Digoxin (nmol/L)	Serum K (mEq/L)	Mechanisms of death	Contributing factors
roup 1	78*	-	3.4	4.2	cardiogenic shock	cardiac failure
PM	94*	-	6.25	4.1	septic shock	staphyloccocus septicemia
1=23)	84*	32	-	6.6	ventricular asystole	pacing stopped
	69	240	-	4.4	ventricular fibrillation	PM implantation
roup 2	77*	-	11.8	3.6	ventricular asystole	fibrinolysis + insuf. dosage
Fab	93	-	22	5.3	brain anoxia	phenobarbital intoxication
1=12)	91	233	-	5.6	ventricular fibrillation	Fab delayed
roup 3	57	?	-	7.6	ventricular asystole	defect of pacing + Fab delaye
PM +	27	?	?	5.1	ventricular fibrillation	gastric lavage + Fab delayed
Fab	63	230	-	4.9	ventricular fibrillation	PM implantation + insuf. dosa
1=16)	82	151	-	5.9	multiple organ failure	mesenteric infarct + Fab delaye
	76	374	-	5.1	ventricular fibrillation	cardiac failure + insuf. dosa
ean						
- SD	74±19	210	10.8	5.2		

= accidental overdosage; ? = not assessed before Fab were administered; PM = pacemaker

of pacing, whether deliberate or accidental, may lead to overdrive inhibition of spontaneous rhythm. Furthermore, a long pacing period is often necessary with digitoxin intoxication (longer half-life than digoxin) and this can lead to severe infectious complications, as in the present and previous studies (18).

Immunotherapy with digoxin Fab fragments is the modern specific treatment for digitalis intoxication (8,12,15). This antidote has a dual action, toxicodynamic and toxicokinetic (25,28,29). The toxicodynamic action starts within minutes of administration. The active site of the antibody binds to a circulating digitalis molecule (digoxin or digitoxin) and generates a Fab-digitalis complex, unable to bind to receptors. Then, by mass action effect, the digitalis bound to receptors is displaced and the membrane ATPases are reactivated. Therefore, immunotherapy is able to prevent or reverse either directly or indirectly potentially life-threatening cardiac disturbances of digitalis poisoning: atrial or ventricular arrhythmias, conduction disturbances and myocardial depression (12-15,30). Complete reversal of toxicity is generally observed within 4 h of intravenous administration (14). Even digitoxin-induced hyperkalemia or ischemic colitis can be improved within hours (9,14). The Fab

fragments also possess a toxicokinetic action. With normal renal function, the Fab-digitalis complex excretion half-life is 10-20 h (25,13,31), shorter than both free digoxin (39 h with normal liver function) and free digitoxin half-life (161 h with normal kidney function) (22). This increase in the renal excretion of digitalis decreases the duration of the intoxication.

In this retrospective study we tried to assess the safety and efficacy of immunotherapy and pacing in 51 patients, mainly intoxicated with digitoxin.

The difference of efficacy between immunotherapy and pacemaker was not significant. Fab tended to be more effective, but some selection bias may have occurred as the assignment to each group was not random. Cases fitted with a pacemaker before referral to our ICU may have been more severe. The main risk of immunotherapy remains recrudescence of digitoxin toxicity (20%) between one to four days after Fab administration. This was partly responsible for 2 out of the 12 fatalities (7%), whereas pacemakers were partly responsible for 5 out of the 12 fatalities (42%). Most of these recurrent arrhythmias are preceded by nausea or vomiting and may be reversible after a second administration of Fab. In retrospect, recrudescent toxicity with Fab appears predictable, and mostly occurs in cases of massive digitoxin intoxication treated with sub-equimolar neutralization. In our study, the main obstacles to the success of Fab were pacing-induced arrhythmias and delayed or insufficient administration of Fab. We must stress that the clinical value of the sub-equimolar dose of Fab that we used in mild intoxications has not yet been assessed.

It is noteworthy that the 23% fatalities in our pacing-treated patients is similar to that reported by Bismuth *et al.* (18) in a population of 68 digitoxin intoxicated patients, all treated with cardiac pacing between 1967-1975 in this same hospital. In that study, the authors observed 16 fatal outcomes (23.5%). In eight cases (50%), iatrogenic mortality could be linked to pacing (5 VF, 2 VA, 1 septicemia).

Immunotherapy was safer than pacemaker ($p < 0.05$). Iatrogenic accidents of cardiac pacing were frequent (36%) and often fatal (13%). In contrast, serotherapy was not associated with any adverse effects. No allergic effects have been encountered, and there is no evidence that Fab fragments led to acute cardiac failure in our patients since signs of acute heart failure were always present before immunotherapy began or occurred after cardiac arrests.

In conclusion, during digitalis intoxication, the pacemaker has limited preventive and curative effects, is difficult to handle, and exposes patients to severe iatrogenic accidents. Fab fragments act as a powerful antidote (33,34) and are safer and much easier to use than pacing. These results encourage us to prescribe Fab fragments as first-line therapy during acute digitalis

intoxication. If immunotherapy fails to reverse severe bradycardia, cardiac pacing can be used. More effective use of immunotherapy will result from earlier administration and from finer tuned dosages of Fab fragments.

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