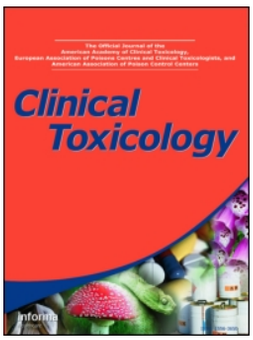

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CLINICAL RESEARCH

Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-1)

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ABSTRACT

Context: We hypothesized that in chronic digoxin toxicity, anti-digoxin antibodies (Fab) would be efficacious in binding digoxin, but this may not translate into improved clinical outcomes. **Objective:** This study aims to investigate changes in free digoxin concentrations and clinical effects on heart rate and potassium concentrations in chronic digoxin poisoning when anti-digoxin Fab are given. **Materials and methods:** This is a prospective observational study. Patients were recruited if they have been treated with anti-digoxin Fab for chronic digoxin poisoning. Data was entered into a standardised prospective form, supplemented with medical records. Their serum or plasma was collected, analysed for free and bound digoxin and free anti-digoxin Fab concentrations. **Results:** From September 2013 to February 2015, 36 patients (median age, 78 years; 22 females) were recruited from 18 hospitals. Median heart rate (HR) was 49 beats/min. Initial median digoxin and potassium concentrations were 4.7 nmol/L (3.6 μg/L) (range: 2.3–11.2 nmol/L) and 5.3 mmol/L (range: 2.9–9.2 mmol/L) respectively. Beta-blockers ($n = 18$), calcium antagonists ($n = 6$), spironolactone and/or angiotensin blocking agents ($n = 24$) were also used concomitantly. Renal impairment and gastrointestinal symptoms were present in 31 (86%) and 22 (63%) patients respectively. Five patients died from conditions unrelated to digoxin toxicity. Median change in HR was 8 beats/min post-Fab with no effect on blood pressure; they were 4, 10 and 17 beats/min for the 1, 2 and ≥3 vials of anti-digoxin Fab groups respectively. Concomitant treatments with potassium lowering agents (12/36) and inotropic drugs (7/36) were used. Gastrointestinal effects resolved in all 22 patients. The median decrease for potassium was 0.3 mmol/L. Digoxin concentration reduced from 3.8 to 0 nmol/L post-Fab. There was a rebound observed in the free digoxin concentration in 25 patients but none had associated clinical deterioration. **Conclusions:** One to two vials of anti-digoxin Fab initially bound all free digoxin confirming Fab efficacy. However, this was associated with only a moderate improvement in HR and potassium, suggesting bradyarrhythmia and hyperkalaemia may be from other co-morbidities.

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Introduction

It was estimated in 2010 that there were more than 33.5 million people who had atrial fibrillation worldwide.[1] Digoxin is frequently used to control atrial fibrillation, one third of patients with atrial fibrillation are put on digoxin.[2] Digoxin inhibits the Na^+–K^+–ATPase on cardiac and other tissues and elevates intracellular Ca^{2+} concentration via the Na^+–Ca^{2+} exchanger resulting in positive inotropy and bradycardia, increased automaticity and ventricular ectopics.[3] Digoxin has been shown to be safe if the digoxin concentration is kept below 1 μg/L (1.3 nmol/L).[4]

Although digoxin specific antibodies (anti-digoxin Fab) are recommended to be used in patients who developed digoxin toxicity with cardiac symptoms, there is ongoing controversy about the effectiveness and dose of anti-digoxin Fab. The typically recommended doses aim to bind half or all of the estimated digoxin body load.[5,6] However, anti-digoxin Fab is expensive (US$750 per 40 mg vial), has a limited shelf life, and therefore it is difficult to keep adequate supplies if large doses are recommended. There are also adverse reactions from large anti-digoxin Fab doses such as allergic reactions, hypokalaemia, rapid atrial fibrillation and the loss of inotropic effect from digoxin.[7,8]

Anti-digoxin Fab derived from sheep has been available since the late 1970s. One vial (38–40 mg) of anti-digoxin Fab can neutralise about 0.5 mg digoxin. In patients on regular digoxin or who have chronic toxicity, only a small proportion of digoxin is in the circulation and immediately available to be bound by anti-digoxin Fab.[9] This is because digoxin has a large volume of distribution, albeit somewhat reduced with age and abnormal renal function.[10,11] Hence the anti-digoxin Fab dose required to treat symptomatic patients with cardiac toxicity may be much less than that based on the estimated total digoxin body load. It is also unclear if all clinical effects seen in patients with digoxin toxicity are reversible or even due to digoxin itself and thus potentially modified with anti-digoxin Fab.

Patients with chronic digoxin toxicity are a heterogeneous group of patients with multiple co-morbidities, most

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commonly renal failure, dehydration and cardiac failure.[12–14] This means that patients who present unwell with a high digoxin concentration are rarely solely digoxin toxic, and in many cases the elevated digoxin concentration is a reflection of another problem, such as renal impairment. Treatment of these patients will also generally involve multiple interventions. Although anti-digoxin Fab is commonly given in this setting, it is difficult and often impossible to determine if it is responsible for any improvement in an individual patient.

We hypothesised that anti-digoxin Fab would be efficacious in binding to digoxin, but this may not translate into improved clinical outcomes. The objectives of this study were to investigate the clinical syndrome of chronic digoxin poisoning and measure free and total digoxin concentrations, free anti-digoxin Fab and determine the average clinical response to anti-digoxin Fab regarding improvement in heart rate (HR) and potassium concentrations.

Methods

This digoxin overdose and response to antibody (DORA) study (an arm of the Australian Toxicology Monitoring [ATOM] project) is a prospective observational study of patients with digoxin toxicity who are administered anti-digoxin Fab (Phebra Pharmaceutical Company, Lane Cove West, Australia). Patients were recruited from hospitals in the State of New South Wales, Australia, through the New South Wales Poisons Information Centre from September 2013 to February 2015. The study was approved by the South Eastern Sydney Local Health District Human Research and Ethics Committee to cover all involved institutions including The Children's Hospital at Westmead where the Poison Centre is located.

Patients

Patients were recruited through the Poison Centre to the DORA study if they meet the following inclusion criteria, an elevated digoxin concentration (>2.6 nmol/L or 2 μg/L) and symptoms or signs attributable to digoxin toxicity such as cardiac arrhythmia, hyperkalaemia, or renal failure and were administered anti-digoxin Fab. One patient with a total digoxin concentration of 2.3nmol/L with bradycardia was also included in the study. Patients were excluded from the analysis if they had acute or acute-on-chronic digoxin poisoning. The decision to administer anti-digoxin Fab was determined by the clinical toxicologist on call and the treating team in the hospital. Anti-digoxin Fab was administered intravenously over 20–30 min. Consent was obtained from the patient or the next of kin to perform assays for digoxin and anti-digoxin Fab, as well as view the medical record. A standardised data form was used to enter patient information which included patient demographics (age, sex, and weight), a brief past medical history, symptoms of digoxin toxicity (cardiac arrhythmias, gastrointestinal, and neurological symptoms), current medications, clinical effects (HR, blood pressure [BP]), laboratory investigations (digoxin concentration, potassium, creatinine in serum or plasma), treatments (dose and timing of anti-digoxin Fab) and outcomes (change in potassium concentration, HR and BP post anti-digoxin Fab treatment). The data form was faxed back to the study coordinating centre where the data was entered into a microsoft excel spread sheet. Medical records were retrieved from the hospitals to obtain additional clinical information that was not on the data form and to obtain a copy of the electrocardiogram (ECG). Where possible, multiple serum or plasma samples were collected pre and post anti-digoxin Fab administration from the patient, centrifuged and stored at −80 °C. The samples were then transported to the study centre for analysis of total and free digoxin concentrations, as well as free digoxin antibody concentrations.

Free and bound digoxin concentration and anti-digoxin Fab measurement in serum or plasma

Free and bound digoxin was separated by Millipore Amicon Centrifree devices, 4104 (Merck Millipore Ltd, Billerica, MA). Ultrafiltration was performed by adding a 0.3 mL sample to the filtration device and then centrifuging for 20 min at 3000 rpm. Protein concentration in the ultrafiltrates was measured using the Bradford method with Bradford Dye Reagent #500-0205 (Bio-Rad Laboratories Inc., Hercules, CA), as a check for membrane leakage. Free digoxin in the ultrafiltrate was measured along with total digoxin in the original sample on an Abbott Architect analyser (Abbott Laboratories, Abbott Park, IL) using the Multigent kit 1E06-21 (DIAGON Kft., Budapest, Hungary). The lowest reportable limit is 0.2 nmol/L and is recorded as 0 if the result is <0.2 nmol/L.

Free anti-digoxin Fab was measured by enzyme immunoassay using a modification of a previously developed assay for detection of horse derived antivenoms.[15] In brief, microplates were coated with 100 μl of a solution of digoxin conjugated to bovine serum albumin (BSA: 3.6 μg/mL in 0.05 M carbonate buffer pH 9.5) for 1 h at room temperature then at 4 °C overnight. After washing once, 300 μl/well of a blocking solution of 0.5% phosphate buffered solution (PBS) in BSA was applied for 1 h, then the plate was washed again. Patients' samples were added at dilutions of 1:20 or 1:200 in 100 μl PBS. A standard solution of anti-digoxin Fab (500 ng/mL in PBS) was then added as sequential dilutions. After 1 h, samples and standards were removed, and the plate washed three times. To each well, 100 μl of a 3.8 μg/mL solution of donkey anti-sheep antibodies conjugated to horseradish peroxidase (Sigma Aldrich, St. Louis, MO) was then added. After 1 h, the plate was washed three times, and a solution of tetramethylbenzidine was added (100 μl/well) followed by 50 μl of 1M H_2SO_4. The plate was read at 450 nm in a BioTek Synergy HT plate reader (BioTek, Winooski, VT).

Digoxin concentrations of ultra-filtrated samples (36 samples from 26 patients, pre-administration of anti-digoxin Fab) were 83 ± 6% of those found in the whole sample, reflecting the binding to albumin.[16]

Analysis

Medians, interquartile ranges (IQR) and ranges are used to summarise continuous data. All graphical analysis was done

Table 1. Patient demographics and baseline characteristics.

Total number of patients	36
Median age	78 years (IQR: 70–85; range: 58–92)
Female (%)	22 (61%)
Body weight (kg)	68 kg (range: 39–95)
Median daily digoxin dose (μg)	125 μg (range: 62.5–750)
Median creatinine concentration	228 μmol/L (range: 90–770)
Median initial potassium concentration	5.3 mmol/L (range: 2.9–9.2)
Median heart rate (min^{-1})	49 (IQR: 35–65; range: 20–120)
HR ≤45 (min^{-1})	17 (47%)
Median initial systolic blood pressure (mm Hg)	109 (range: 75–180)
Median initial total digoxin concentration	4.7 nmol/L (IQR: 3.3–6.4; range: 2.3–11.2)
Median no. vials anti-digoxin Fab used	2 (range: 0.5–10)
No. patients taking beta-blockers (%)	18 (50%)
No. patients taking calcium antagonists (%)	6 (16.7%)
No. patients taking angiotensin converting enzyme inhibitors, angiotensin receptor blockers and/or spironolactone (%)	24 (67%)

IQR: interquartile range.

Table 2. Details of the five patients who died.

Sex/age	Free digoxin concentration before & after anti-dig Fab (nmol/L)	Anti-dig Fab (mg)	HR per minute before & after anti-dig Fab	K (mmol/L) before & after anti-dig Fab	Cr (μmol/L) before anti-dig Fab	Details
F69	4→0	40	120→120	6.1→5.9	196	Respiratory & cardiac failure.
F72	4.7→0	80	73→73	6.6→6.4	167	Severe congestive cardiac failure.
F87	2→0	80	65→71	7.5→6.2	237	Respiratory & cardiac failure.
F90	3.9→0	80	64→62	7.2→5.2	429	Urosepsis, shock, chronic renal failure.
F83	2.9→0.8	40	52→60	4.7→4.9	100	Respiratory failure, shock.

F: female; M: male; HR: heart rate; Anti-dig Fab: anti-digoxin Fab; Cr: Creatinine.

in Prism 6.05 for Windows (GraphPad Software, San Diego, CA, www.graphpad.com).

Results

There were 36 patients with chronic digoxin poisoning treated with anti-digoxin Fab recruited to the DORA study during the 18-month study period. Demographics of the 36 patients are summarised in Table 1. The median patient age was 78 years (range: 58–92 years) with a female predominance (22; 61%). The median daily digoxin dose was 125 μg (IQR: 125–250). Before treatment, the median HR was 49 beats/min (IQR: 35–69, range: 20–120). Slow atrial fibrillation (20; 55.6%) or junctional rhythm (6; 16.7%) was the commonest presenting rhythms. There were four patients who had a paced rhythm. The median initial systolic BP was 109 mmHg (range: 55–180) before giving anti-digoxin Fab. Gastrointestinal symptoms including nausea, vomiting, abdominal pain or diarrhoea were recorded in 22/35 patients (63%).

The initial median total digoxin concentration was 4.7 nmol/L (range: 2.3–11.2 nmol/L). Pearson correlation between initial digoxin concentration and HR was −0.184 ($p = 0.28$). The initial median potassium concentration was 5.3 mmol/L (IQR: 4.5–6.2, range: 2.9–9.2 mmol/L; Table 1). Thirty-one (86%) patients had renal impairment. The median creatinine was 228 μmol/L (IQR: 128–278, range: 90–770 μmol/L).

Twenty-four patients (67%) were also taking either beta-blockers or calcium channel blockers (non-dihydropyridine), 18 patients (50%) taking angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and 12 taking spironolactone (33%). These could have contributed to the bradycardia and hyperkalaemia, respectively (Table 1). Five patients died; in all cases they had major comorbid problems (Table 2).

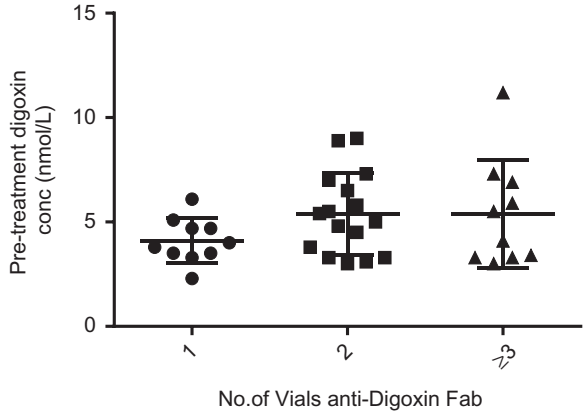

Figure 1. Scatter plot of the pre-treatment digoxin concentration (nmol/L) for each dosing group of anti-digoxin Fab with median and 25 and 75 percentile indicated: one vial (40 mg; 10 patients), two vials (80 mg; 16 patients), and three or more vials (120–400 mg; 10 patients). Conc: concentration.

Treatment

Ten patients received one vial (40 mg), 16 patients received two vials (80 mg), and 10 patients received three or more vials of anti-digoxin Fab (120–400 mg). The initial median total

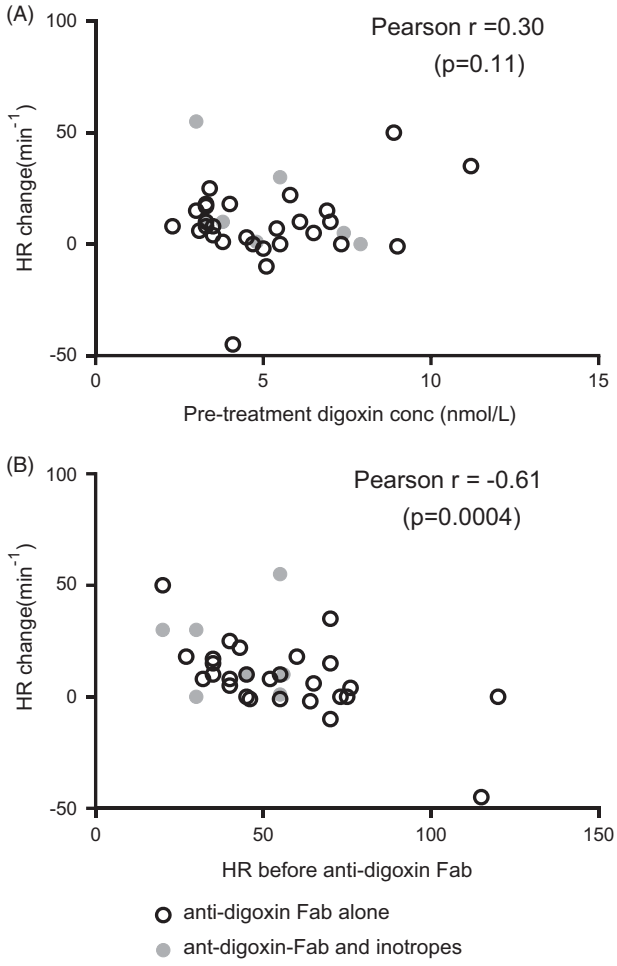

Figure 2. The relationship between change of HR (A) and pre-treatment digoxin concentration (B) and initial heart rate (HR) in 36 patients. There were seven patients who were also managed with inotropes and showed a more substantial improvement of HR in most of them (represented by grey circles). The Pearson correlations exclude patients receiving treatment with inotropes. Anti-dig Fab: anti-digoxin Fab; Pearson r: Pearson correlation.

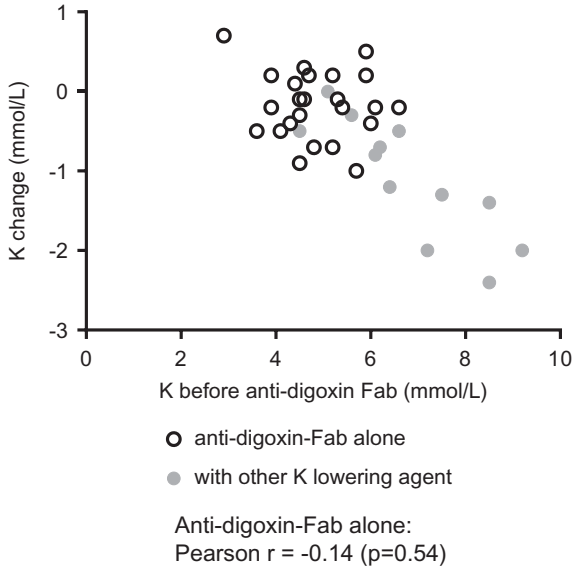

Figure 3. The change in potassium versus initial potassium concentration. There were 12 patients who were treated with potassium lowering agents and showed more substantial changes in potassium concentration (marked by grey circles). K: potassium; Pearson r: Pearson correlation.

digoxin concentrations measured at the treating hospital were 3.9 (range: 2.3–6.1), 5.2 (range: 3.0–9.0), 4.8 (range: 3.0–11.2) nmol/L for 1, 2, ≥3 vials of anti-digoxin Fab, respectively (Figure 1).

The median change in HR after anti-digoxin Fab was 8 beats/min (IQR: 0.5–17.5). Pearson correlation between initial digoxin concentration and change of HR, initial digoxin concentration and change of potassium were 0.13 ($p = 0.44$) (Figure 2(A)) and 0.21 ($p = 0.21$), respectively. There was a median change of 4.5 beats/min for one vial; 10 beats/min for two vials; and 17.3 beats/min for three vials or more of anti-digoxin Fab. There were seven patients who were also treated with inotropes such as adrenaline or noradrenaline, isoprenaline or dopamine given either prior or following digoxin antibody and helped to improve HR in most of these patients (Figure 2(A,B)). There was no change in systolic BP after anti-digoxin Fab (109 mmHg [55–180] and 110 mmHg [70–170]). The median decrease in potassium was 0.3 mmol/L (IQR: 0–0.8) and there was no relationship with anti-digoxin Fab dose. There were 12 patients who were treated with potassium lowering agents such as sodium bicarbonate, insulin dextrose, salbutamol or resonium and these patients showed a more substantial change in potassium concentration (Figure 3). Anti-digoxin Fab was effective in relieving gastrointestinal symptoms in all 22 patients who reported them. Three patients received continuous veno-venous haemodialysis (CVVHD) for renal failure.

Adverse effects occurring shortly after anti-digoxin Fab were observed but not clearly attributable to anti-digoxin Fab. Two patients were documented to have ventricular tachycardia (VT) following the administration of anti-digoxin Fab when free digoxin concentrations were almost zero (one had a serum potassium of 7.2 mmol/L). One patient developed rapid atrial fibrillation following anti-digoxin Fab but was also on an isoprenaline infusion and later diagnosed with sick sinus syndrome. One patient had sinus tachycardia and one had worsening heart failure, requiring treatment with frusemide.

Free digoxin and anti-digoxin Fab concentrations

Samples were available from 32 patients for the measurement of free digoxin and free anti-digoxin Fab. Free digoxin concentrations decreased to almost zero following the administration of anti-digoxin Fab regardless of the antibody dose used. The median free digoxin concentration was 3.8 nmol/L (range: 1.6–8.2) before and 0 nmol/L (range: 0–1.2) after the administration of anti-digoxin Fab (Figure 4). The median free anti-digoxin Fab concentration post administration was 3 mg/L (65 nmol/L) (IQR: 0.8–5.1; range: 0.3–9.8 mg/L), 7 mg/L (150 nmol/L) (IQR: 2.7–15; range: 0.8–26.3 mg/L), 18.5 mg/L (398 nmol/L) (IQR: 5.3–35.5; range: 0.2–57.8 mg/L) for 1, 2, and ≥3 vials, respectively.

There was a rebound observed in the free digoxin concentration in 25 patients, and nine of these had a rebound greater than 2 nmol/L. The median peak rebound digoxin concentration measured was 1.3 nmol/L (IQR: 0.3–2.2; range: 0–6.3 nmol/L), detected at a median of 28 h (IQR: 16–48.5; range: 10–106 h) after the administration of anti-digoxin Fab.

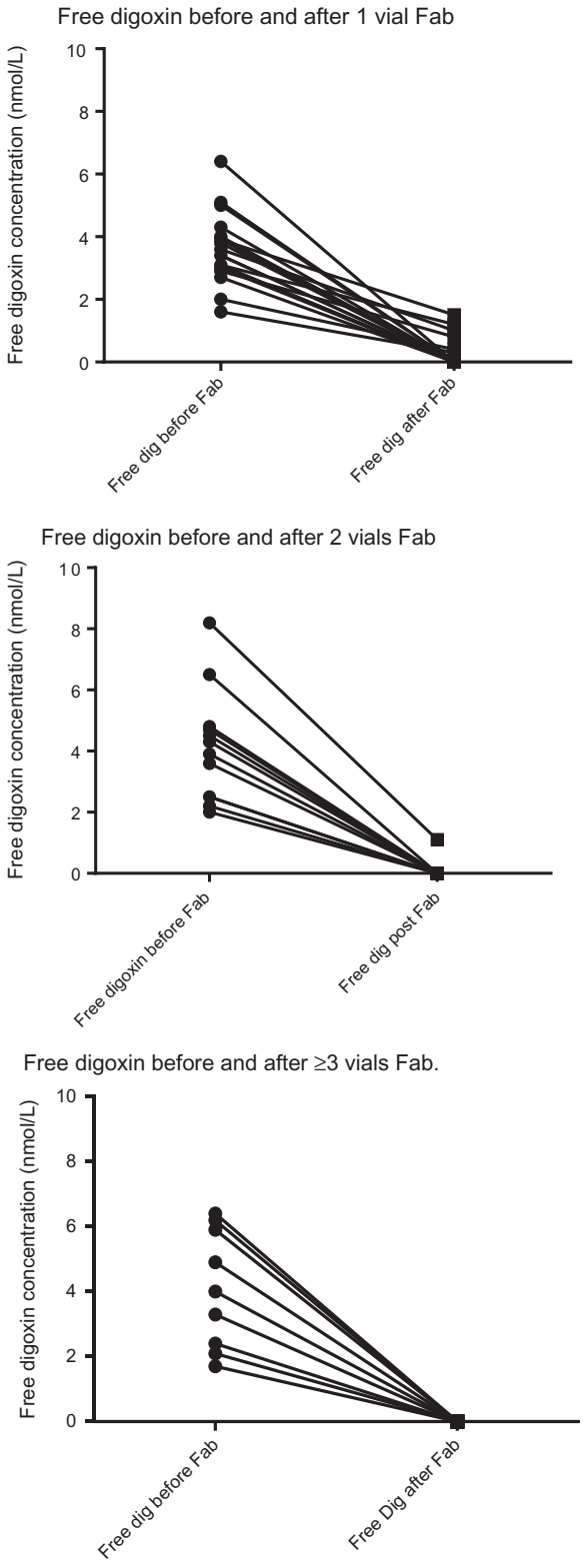

Figure 4. Free digoxin concentration before and after anti-digoxin Fab for each different dosing group: 1 vial, 2 vials or ≥3 vials. Free digoxin concentration represents digoxin that is not bound to plasma protein or anti-digoxin Fab. Fab: anti-digoxin Fab.

The median rebound free digoxin concentrations were 1.2, 0.9 and 0.9 nmol/L in the groups receiving 1, 2 and ≥3 vials of anti-digoxin Fab, respectively. The rebound in free digoxin concentration coincided with low or undetectable concentrations of anti-digoxin Fab. The median time for those who developed a peak rebound free digoxin concentration >2 nmol/L ($n = 9$) was 15 h (IQR: 8–18; range: 6–20 h). There were two patients in the one vial group, six patients in the two vials group and one patient in the ≥3 vials group who had a peak rebound free digoxin concentration >2 nmol/L but none of these patients received further doses of anti-digoxin Fab or developed significant clinical sequelae attributable to digoxin toxicity. Eight out of nine of these patients survived to discharge from hospital. The patient who died had a rebound of free digoxin concentration to 3.0 nmol/L 43 h after anti-digoxin Fab (not treated at this time with further anti-digoxin Fab). This patient had not shown any signs of improvement after the initial anti-digoxin Fab treatment, and had many other explanations for a fatal outcome.

Five other patients were given repeated doses of anti-digoxin Fab because they did not have a clinical response to the initial anti-digoxin Fab but the measured free digoxin concentrations were almost zero before the repeated dose of antibodies were administered.

Discussion

In this series, the patient demographics were typical of chronic digoxin poisoning.[17] The majority of patients were old, had heart disease and renal impairment, and presented with bradyarrhythmias or slow atrial fibrillation. This observational study supported the hypothesis that anti-digoxin Fab was efficacious in rapidly reducing the free digoxin concentration to almost zero following administration in the majority of cases (Figure 4). However, this did not translate into a major clinical response. There was only a median change of HR of eight beats per minutes following the administration of anti-digoxin Fab (Figure 2(A,B)). There was only a weak association between initial digoxin concentration and change of HR initial potassium and change of potassium if no additional treatment such as inotropes or potassium lowering agents were given (Pearson correlation 0.3 and 0.14, respectively). If digoxin toxicity was the cause for hyperkalaemia and bradycardia, then binding digoxin with antibody should produce a significant change in HR or potassium. This finding is not consistent with a study which showed that digoxin can cause a dose dependent reduction in HR.[18] This may be explained by the fact that many patients (67%) were also taking rate control medications to slow down their ventricular rate such as beta-blockers and calcium antagonists. These could be contributing to the bradyarrhythmias and explain the lack of reversibility with anti-digoxin Fab.

Many previous studies appearing to report greater effectiveness of anti-digoxin Fab have combined the presentation of results from acute and chronic digoxin poisoning.[19,20] Moreover, it is common for there to be just a global determination that there was (or was not) some sort of positive response to anti-digoxin Fab as evaluated by the treating physicians. This might not only be potentially biased, but also combines a range of outcomes of different magnitude and very different importance. We found a universal response for those with gastrointestinal symptoms but objective cardiac

effects and hyperkalaemia response were less impressive. Another smaller retrospective series of chronic digoxin poisoning, found only 3/14 patients had improvement in "cardiac toxicity" 4 h post administration of anti-digoxin Fab.[21]

The simplest interpretation of our and other studies is that in patients diagnosed with "chronic digoxin toxicity" the comorbid illnesses and other drugs rather than digoxin are driving much of the cardiac manifestations and the underlying risk of death. Other studies have also reported very high mortality (171 patients, 24%) not attributable to the failure of anti-digoxin Fab therapy (i.e., indicating that the authors decided that the patients died from other comorbidities).[20] Hyperkalaemia ($K > 5.5$ mmol/L) is a clinical marker for (acute) digoxin toxicity requiring treatment.[19,22] This criterion may not be useful in chronic toxicity for several reasons. Our study did not show a significant change in potassium concentration following the use of anti-digoxin Fab. Further, the overwhelming majority had other explanations for hyperkalaemia including both renal failure and drugs interfering with the homeostatic mechanisms for excretion of potassium through the renin/angiotensin/aldosterone axis.

If anti-digoxin Fab is used, the use of lower doses may be equally effective. We recently simulated serum and tissue digoxin concentrations and response in a typical patient with chronic digoxin poisoning and concluded that only a fraction of digoxin is in the central compartment and this can be neutralised by just 40 mg anti-digoxin Fab.[9] Reversal of digoxin-induced Na^+K^+ATPase inhibition is dependent on the anti-digoxin Fab concentration but the maximal effect is seen whenever the Fab:digoxin ratio is ≥ 1.[23] Our data showed that patients who received ≥ 2 vials anti-digoxin Fab have excess free antibodies suggesting two vials were sufficient to bind up most digoxin in the central compartment of patients with chronic digoxin toxicities. Another case study supported our data and showed just two vials anti-digoxin Fab were sufficient to rapidly bind all free digoxin in the circulation.[24]

A lower dose of anti-digoxin Fab increases the likelihood of an early rebound of free digoxin concentrations.[25] Our study showed only a minority of patients had a rebound to toxic free digoxin concentrations following low dose anti-digoxin Fab and most of these did not develop any haemodynamic or cardiac compromise. These results are no worse than when higher doses of anti-digoxin Fab are given. A study of 14 chronic toxicity patients with renal failure (mean creatinine of 380 μmol/L) and digoxin concentrations >3.2 nmol/L, showed that despite giving half to full neutralisation dose (median: 120 mg; range: 32–180 mg), the rebound peak free digoxin concentration was 1.7 nmol/L at about 77 h post anti-digoxin Fab administration.[26] This suggests that larger doses do not necessarily prevent rebound. They would be expected to delay its onset (which will be when the anti-digoxin Fab is eliminated), but this may not be useful as monitoring for rebound toxicity might need to be continued for longer.

A limitation of this study was the small number of patients who had high digoxin concentrations (>5 nmol/L, $n = 15$); the effectiveness of anti-digoxin Fab needs to be further studied in this group. The heterogeneous nature of the comorbid diseases/drugs in patients with chronic digoxin toxicity is a universal limitation making it difficult to determine the effects of anti-digoxin Fab and predictors of response. In this regard, the strength of our study was that we deliberately collected a set of objective pharmacokinetic and pharmacodynamic parameters closely linked to the time before and after treatment to augment the clinical evaluation.

Conclusion

This study supported our hypothesis that one to two vials of anti-digoxin Fab was adequate to bind all free digoxin in the central compartment and that subsequent rebound in the free digoxin concentrations in a small number of patients was not associated with worsening clinical effects. Gastrointestinal effects responded well. However, the only objective cardiac effects of treatment were a small increase in HR (median increase 8 bpm) and a slight decrease in potassium concentration (median decrease 0.3 mmol/L); further, some other treatments may have contributed to this modest response. Numerous other factors contribute to bradycardia, hyperkalaemia and renal failure in these patients, making it often difficult to observe any clinically relevant effectiveness. Treatment of these contributory factors may be more important than giving anti-digoxin Fab. Further research is required to determine if there is a subgroup of patients with higher digoxin concentrations or other indicators of digoxin toxicity, where anti-digoxin Fab may be beneficial. Our study suggests that in chronic toxicity one or two vials of anti-digoxin Fab appear to be sufficient to achieve the same objective effects as larger doses.

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Disclosure statement

The authors report no declarations of interest.

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