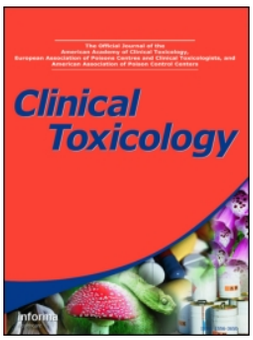

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CLINICAL RESEARCH

Clinical outcomes from early use of digoxin-specific antibodies versus observation in chronic digoxin poisoning (ATOM-4)

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ABSTRACT

Introduction: In our previous study on chronic digoxin poisoning, there was a minor improvement after treatment with digoxin-specific antibody (digoxin-Fab). We hypothesised patients with elevated digoxin concentrations may derive little benefit from digoxin-Fab because their presenting complaint was more closely related to their multiple co-morbidities. We aimed to compare the outcome of patients who were initially treated with digoxin-Fab with those that received supportive care.

Method: Patients were prospectively recruited to the study if they had an elevated digoxin concentration, signs or symptoms of toxicity thought to be from digoxin. Patients who were initially managed with digoxin-Fab were compared with those not initially receiving digoxin-Fab (observation group). Patients presented with ventricular arrhythmias before initial assessment were excluded from the analysis. Primary outcome was mortality. Secondary outcomes were length of stay (LOS), change in heart rate (HR) and potassium concentration.

Results: From September 2013 to January 2018, 128 patients were recruited of which 78 (61%) received initial digoxin-Fab. Digoxin-Fab and supportive care groups had an initial median heart rate of 46 (range: 20–120) vs 52 bpm (range: 29–91) ($p = .06$), systolic blood pressure of 110 mmHg (range: 65–180) vs 125 mmHg (range: 90–184) ($p = .009$), respectively. Digoxin concentrations 4.4 nmol/L (range: 3.3–9) vs 4.2 (range: 2–11.2) ($p = .42$) and potassium concentrations 5.4 mmol/L (range: 3–11) vs 5.1 mmol/L (range: 3.5–8.2) ($p = .33$) were similar. Median dose of digoxin-Fab used was 1.5 vials (IQR: 1–2). There were 9 (12%) deaths in the Fab group compared to 7 (14%) in those treated with supportive care (risk difference −2.5%; 95% CI: −14 to 9%; $p = .68$). The median LOS was six days in both groups. Mean changes in potassium concentration [-0.5 ± 0.1 vs. -0.4 ± 0.1 mmol/L; difference −0.1 (95% CI: −.02, 0.4), $p = .70$] and HR within 4 h [8 ± 1 vs. 7 ± 3 bpm; difference −1.0 (95% CI: −6.7, 4.8), $p = 0.74$] were similar in the two groups.

Conclusions: This study did not appear to show any benefit from the routine use of digoxin-Fab in patients thought to have chronic digoxin poisoning. These patients have multiple co-morbidities that may be contributing to their clinical features, other treatments are often equally effective.

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Digoxin poisoning; digoxin-Fab; overdose; digoxin-specific antibody

Introduction

Digoxin has been recommended for use in the management of atrial fibrillation and heart failure [1]. However, its efficacy has been questioned especially in the context of a narrow therapeutic range [2,3]. While there has been a decline in use, the diagnosis of digoxin toxicity remains common [3] and a United States National Database recorded 22,600 cases of digoxin toxicity over a 5-year period from 2007 to 2011 [4]. Most patients are elderly, have atrial fibrillation and/or congestive cardiac failure, but also other co-morbidities such as diabetes and hypertension. They are also on multiple medications including beta-blockers, calcium antagonists and diuretic agents. Digoxin toxicity is typically precipitated by acute kidney injury and/or drug interactions.

Digoxin-Fab has been available since the 1970s to treat patients with digoxin toxicity [5,6]. It has become very expensive in recent years and now costs approximately US$750 per vial. Around a quarter of people with a diagnosis of digoxin toxicity receive Fab treatment [3]. However, it is unclear to what extent digoxin accounts for clinical features manifested by patients with an elevated digoxin concentration. Elevated digoxin concentrations are expected in patients who have multiple organ failure from any cause [7]. In a previous study, we showed that 1–2 vials of digoxin-specific Fab (digoxin-Fab) in patients with chronic digoxin poisoning rapidly led to zero free serum digoxin concentrations;

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Supplemental data for this article can be accessed here.

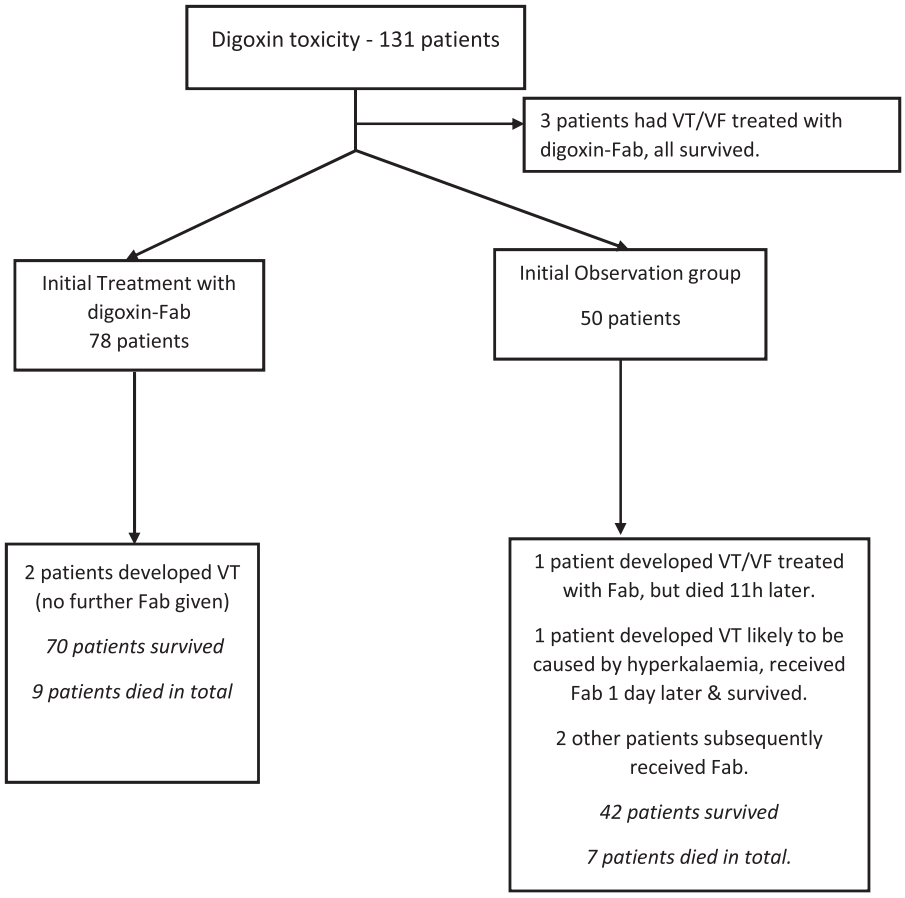

Figure 1. Flow chart of all the digoxin toxicity patients.

but had only a modest effect on heart rate and no effect on blood pressure or other features [8,9].

This prospective observational study aims to further assess the clinical response of patients to digoxin-Fab in chronic digoxin poisoning by comparing a group of patients that initially received Fab with a group that did not initially receive Digoxin-Fab; assessing mortality, length of stay (LOS), and change of potassium and heart rate (HR) over time.

Methods

Design and setting

This study is a sub-group of the Australian TOxicology Monitoring project (ATOM-4). We prospectively recorded data from patients with chronic digoxin toxicity. Patients were recruited from three toxicology units in Australia and calls to the New South Wales (NSW) and Queensland (QLD) Poisons Information Centre (PIC). The ATOM project has ethical approval from Human Research and Ethics Committees in NSW and QLD to cover all involved institutions and PIC. The three toxicology units are the Hunter Area Toxicology Service (HATS), South Eastern Area Toxicology Service (SEATS) and Princess Alexandra Hospital (PAH). These units are based in NSW and QLD and treat a high volume of poisoning patients per year (HATS: 900 admissions, SEATS: 1000 consults and admissions, PAH: 2200 admissions). The SEATS, HATS and PAH have ethical approval from their respective local ethics committee for the ATOM study.

Selection of participants

Patients were included in the study if they met the inclusion criteria, an elevated digoxin concentration (>2.6 nmol/L or 2 μg/L) and/or symptoms or signs thought to be attributable to digoxin toxicity such as bradycardia, cardiac arrhythmia or hyperkalaemia. Some of these patients were managed with digoxin-Fab while others were not. This study includes the 36 patients who were treated with digoxin-Fab and recruited to the DORA study in ATOM-1 [8]. Patients were excluded from the study if they had acute or acute on chronic digoxin poisoning. Those with ventricular tachyarrhythmia on presentation were also excluded as all such patients should be immediately treated with digoxin-Fab. The decision to administer digoxin-Fab was determined by the treating team in the hospital either before or after consultation with the clinical toxicologist on call. Consent was obtained from patient or next of kin to have access to medical records. A standardised data form was used to enter patient information which included patient demographics (age, sex and weight), past medical history, symptoms of digoxin toxicity (cardiac arrhythmias, ECG changes, gastrointestinal and neurological symptoms), current medications such as spironolactone, diuretics, angiotensin antagonists, beta-blockers or calcium antagonists, clinical effects (HR, blood pressure

Table 1. Baseline characteristics of patients according to whether they received initial digoxin-specific fab for chronic digoxin toxicity.

Chronic digoxin poisoning	Patients initially treated with digoxin specific Fab $n = 78$	Patients were observed with expectant treatment $n = 50$	p-Value
Median age (yrs)	80 (72–87; 53–97)	81 (73–85; 53–97)	0.64
No. Female (%)	50 (64%)	29 (58%)	0.58
No. patients on BB or CCA (%)	53 (67%)	32 (65%)	0.35
No. patients on angiotensin antagonists (%)	40 (51%)	20 (41%)	0.28
No. patients on spironolactone (%)	24 (30)	15 (31)	1
No. patients on diuretics (%)	25 (32)	27 (55)	0.02
No. patients with gastrointestinal symptoms (%)	44 (56)	20 (41)	0.1
Digoxin dose (μg/day)*	125 (125–250, 62.5–750)	125 (125–250; 62.5–375)	0.09
Initial HR per min*	46 (35–61; 20–120)	52 (43–65; 29–91)	0.06
Initial SBP (mmHg)*	110 (99–134, 65–180)	125 (105–150, 90–184)	0.009
Initial digoxin conc (nmol/L)*	4.4 (3.3–5.6; 1.9–11.2)	4.2 (3.3–5.1; 2.1–9)	0.42
Initial K conc (mmol/L)*	5.4 (4.5–6.1; 3–11)	5.1 (4.6–5.5; 3.5–8.2)	0.33
Initial Cr (μmol/L)*	224 (132–309; 70–770)	194 (133–240; 84–647)	0.33

BB: beta-blockers; CCA: calcium channel antagonists; HR: heart rate; SBP: systolic blood pressure; K: potassium; Cr: Creatinine.
Data are shown as n (%) or * median (IQR, range).

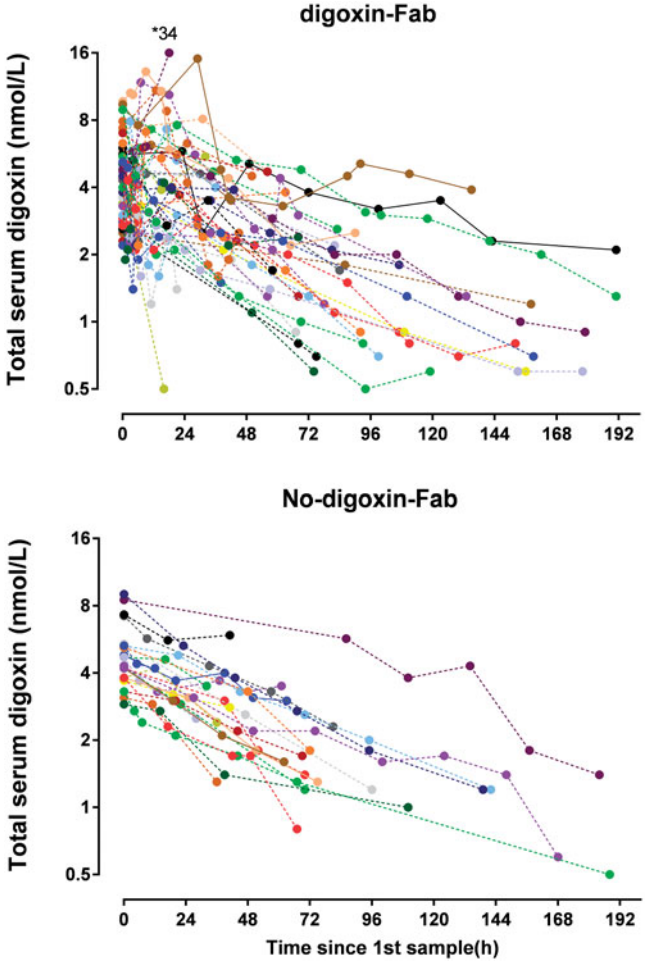

Figure 2. Digoxin concentrations versus time in the digoxin-Fab and observed groups for patients who had at least three digoxin levels recorded. In the digoxin-Fab group, there were a few patients (solid line) who had late rebound of digoxin concentrations suggested that there were redistribution of free digoxin from the tissue. One patient (*) had a total digoxin concentration up to 34 nmol/L 19 h after first blood sample.

[BP]), laboratory investigations (digoxin concentration, potassium, creatinine in serum or plasma), treatment (dose and timing of digoxin specific Fab), LOS and outcome. Medical records were requested from the hospital if additional clinical information was needed to complete the data form.

Outcomes

The primary outcome was the number of deaths that occurred in each group. Secondary outcomes were the LOS, the change in HR within 4 h, and the change in potassium concentration with time.

Data analysis

Descriptive data were reported as proportions and percentages. Medians, interquartile ranges (IQR) and ranges were used to summarise continuous data. Continuous variables were compared using paired t-tests to compare HR and potassium concentrations before and after Fab treatment and Mann-Whitney test or Fisher's exact test to compare the group that received Fab with the observed group and analysed as per intention to treat. General Linear Model was used to determine if there were any differences in the change of HR and K with time between the group who received digoxin-Fab and the observed group. Hodges-Lehmann estimator was used to calculate the confidence intervals on the difference in outcome such a HR and K change. All statistical analysis was performed in Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and Prism (GraphPad Software, San Diego, CA, www.graphpad.com). A $p < .05$ value was considered statistically significant.

Results

From September 2013 to January 2018, there were 128 patients who met inclusion criteria; 78 (61%) of these received initial digoxin-Fab treatment (Figure 1). Baseline characteristics of patients were similar in the two groups except for SBP, 110 mmHg (range: 58–97) for the Fab and 125 mmHg (range: 53–97) for the observed group (Table 1).

Digoxin concentrations were plotted against time for patients who had at least three digoxin levels recorded for the digoxin-Fab and observed group (Figure 2). Patients who received digoxin-Fab had higher initial total digoxin concentrations (bound and free) and some showed late rebound in

Table 2. Outcome of the patients initially treated with digoxin-Fab vs those initially observed.

Chronic digoxin poisoning	Initial digoxin-Fab $n = 78$	Initial observation $n = 50$	Difference (95% CI)	p-Value
Mean HR change within 4 h (bpm)	8 ± 1	7 ± 3	−1.0 (−6.7, 4.8)	0.74
Mean K change (mmol/L)	−0.5 ± 0.1	−0.4 ± 0.1	−0.1 (-0.2, 0.4)	0.70
Median length of stay (days)	6 (IQR 3–11; range 1–43)	6 (IQR 3–10; range 1–32)	0 (−1, 2)	0.51
Fatality (%)	9 (11%)	7 (14%)	3.0 (−8.8, 14.9)	0.68

HR: heart rate; K: potassium; ± Standard error of the mean; IQR: inter-quarter range; CI: confidence interval.

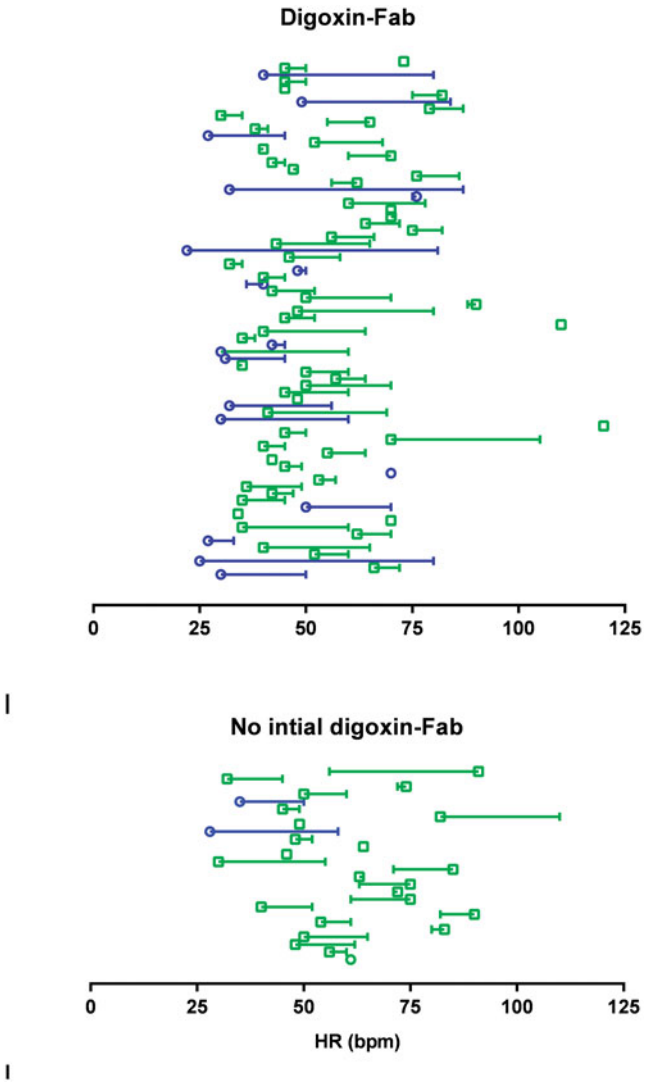

Figure 3. Change of heart rate with time in the digoxin-Fab and observed group. Square represented initial heart rate and attached line indicated change Circle indicated initial heart rate and attached line indicated change in a patient who was treated for bradycardia such as isoprenaline or atropine.

digoxin concentrations from redistribution. The median number of vials of digoxin-Fab used was 1.5 vials (IQR: 1–2, range: 0.5–10). In the observed group, patients showed lower initial total digoxin concentrations when compared with the digoxin-Fab group and have minimal late rebound of digoxin concentrations.

Outcomes

There were 9 (12%) deaths in those treated with digoxin-Fab compared to 7 (14%) in those not receiving treatment (risk difference −2.5%; 95% CI: −14 to 9%; $p = .68$). In the observed group, one patient developed ventricular tachycardia and fibrillation that was attributed to digoxin toxicity and was treated with digoxin-Fab but died from hypoxic brain damage 11 h after a prolonged cardiac arrest. The other six deaths were attributed to other medical causes (Supplementary Table 1). The median length of stay was six days for both groups ($p = .51$). There were minimal differences in the change in HR or K in the two groups (Table 2). The mean HR increase after the administration of digoxin-Fab was 8 ± 1 bpm, similar to the 7 ± 3 bpm seen over the same period of time in the observed group (Table 2). There was no significant effect of Fab group on HR change after adjusting for baseline HR, $F(1,102) = 0.39$, $p = .54$. The mean K change was −0.5 ± 0.1 mmol/L for the digoxin-Fab and −0.4 ± 0.1 mmol/L for the observed group (Table 2). There was no significant effect of Fab group on K change after adjusting for baseline K, $F(1, 101) = 0.04$, $p = .85$. This was despite the fact that patients who received digoxin-Fab were also more likely to receive other concurrent treatment for bradycardia (22% vs. 6%) (Figure 3) and hyperkalaemia (35% vs. 16%) (Figure 4).

Ventricular arrhythmias were noted in two patients in each group (Figure 1 and Supplementary Table 2). In the Fab group, two patients had transient VT post-Fab treatment and recovered. In the observed group, four patients subsequently received digoxin-Fab, 2 with ventricular tachyarrhythmia and two with persistent bradycardia (for unclear reasons).

There were three patients with digoxin toxicity who were not included in the analysis (Figure 1). They had recurrent episodes of VT/VF on initial assessment and were treated with digoxin-Fab. They also had hyperkalaemia and underlying cardiac diseases (Supplementary Table 2).

Discussion

Our study showed that outcomes for patients diagnosed with digoxin toxicity were similar in those who did and did not receive initial digoxin-Fab. The baseline characteristics of the observed and Fab treatment groups were similar (Table 1). There were a few patients in the Fab treatment group who had late rebound of digoxin concentration (96,120 h) due to redistribution (Figure 2). Since digoxin-Fab has a shorter half-life than digoxin, it was likely that these were free digoxin concentrations but none of the patients required further dosing of digoxin-Fab. More patients in the digoxin-Fab group received concurrent treatment for bradycardia (22% vs. 6%) and hyperkalaemia (35% vs. 16%), suggesting that digoxin-Fab did not decrease the need for other treatments, and also perhaps indicating that the use of digoxin-Fab was by clinicians who favoured action over observation and supportive care (Table 1).

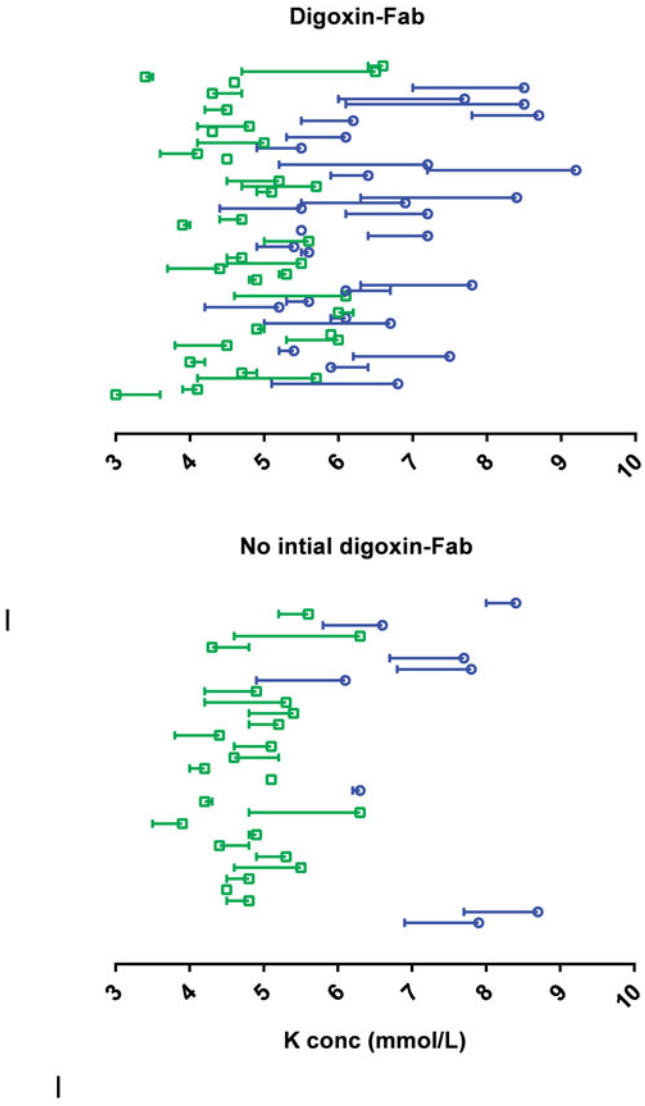

Figure 4. Change of potassium with time in the digoxin-Fab and observed (no initial digoxin-Fab) group. Square represented initial potassium concentration and attached line indicated change. Circle indicated initial potassium concentration and attached line indicated change in a patient who was treated for hyperkalaemia such as insulin dextrose or sodium bicarbonate.

The similar heart rate response regardless of the use of digoxin-Fab may be partly explained by the bradycardia being caused by effects of beta-blockers or calcium antagonists which were taken concurrently by about two-thirds of the patients in the group (Table 1). Similarly, the modest change of potassium with digoxin-Fab indicated that hyperkalaemia could be explained by other factors such as concomitant use of angiotensin converting enzymes or receptor inhibitors, spironolactone and renal failure. These co-morbidities and medications made it difficult to utilise hyperkalaemia as a marker of digoxin toxicity. Conversely, renal failure was the usual precipitant for digoxin toxicity as digoxin is largely excreted by the kidneys. Hence, the symptoms thought to be consistent with digoxin toxicity in patients with elevated digoxin concentrations are more likely multifactorial and less likely to be caused by digoxin.

Previous studies on digoxin poisoning have claimed that the use of digoxin-specific Fab can potentially reduce mortality or reduce the length of stay [5,10]. However, our study observed similar mortality in the groups that did and did not receive digoxin-Fab and there was no difference in the LOS. One previous study has also reported a higher in-hospital mortality rate for those receiving digoxin-Fab when compared with an observed group (14% vs. 6%) [4]. This study also showed no statistical significant difference in the LOS between the Fab treatment and the observed group (8.9 vs. 6.6 days) [4]. Further, they reported the cost was considerably higher in the Fab treatment group. However, the patients in this study who did and did not receive digoxin-Fab were not very similar and it is likely that differences related to the multiple co-morbidities including renal failure, dehydration, sepsis and cardiac failure.

Regarding limitations, we were constrained by the nature of being an observational study. This affected the uniformity of data involving the serial collection of bloods for digoxin and potassium concentrations. While it was recommended to monitor serial digoxin, potassium and creatinine concentrations, there was a slight variation with regard to the time when the blood samples were collected. In addition, this is a heterogenous group of patients with multiple co-morbidities and taking various medications and the treatment was determined by the clinicians and clinical toxicologists. However, the observed group has shown similar baseline demographics with the digoxin-Fab group and hence this enabled us to determine if digoxin-Fab was effective in managing chronic digoxin toxicity. Finally, the sample size was not large (78 in the Fab and 50 in the observed group) and hence we cannot rule out a Type 2 error.

Conclusions

This study suggests routine initial use of digoxin-Fab in patients with chronic digoxin poisoning did not appear to reduce the mortality, LOS or change in HR or potassium concentration with time. The decision to treat with digoxin-Fab should not be solely dependent on serum digoxin concentration but rather clinical parameters such as HR, ECG rhythm, electrolytes and renal function [9]. There were similar and modest changes in heart rate and potassium in the digoxin-Fab and observed group. Supportive treatment is vital in managing these patients who have multiple co-morbidities, and it is likely other comorbidities and supportive treatments are more important in determining outcomes than management of the elevated digoxin concentration.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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