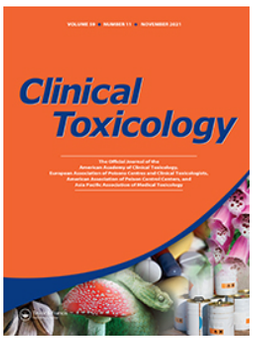

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Clinical experience with titrating doses of digoxin antibodies in acute digoxin poisoning. (ATOM-6)

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CLINICAL RESEARCH

Clinical experience with titrating doses of digoxin antibodies in acute digoxin poisoning. (ATOM-6)

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ABSTRACT

Introduction: For acute digoxin poisoning, it has been recommended to give bolus doses of 10–20 vials or potentially larger than needed doses calculated from dose ingested or the measured concentration. However, a recent revision of internal Poisons Information Centre guidelines prompted a change of our recommendations, specifically instead of large boluses, to use titrating repeated low doses of digoxin antibodies(Digoxin-Fab) based on bedside assessment of cardiac toxicity.

Methods: This is a prospective observational study of patients with acute digoxin poisoning identified through two Poisons Information Centres and three toxicology units. Patient demographics, signs and symptoms of digoxin toxicity, doses and response to Digoxin-Fab, free and bound serum digoxin concentrations. Outcomes were recorded and analysed.

Results: From September 2013 to September 2020, 23 patients with 25 presentations (median age 56 years, females 56%) were recruited. Median dose ingested was 13 mg(IQR: 9.5–25). Median heart rate (HR) was 41 beats/min before treatment. Initial median digoxin and potassium concentrations were 14.5 nmol/L (IQR: 10.9–20) [11.2 μg/L(IQR: 8.4–15.4)] and 5 mmol/L (IQR: 4.5–5.4 mmol/L), respectively. Gastrointestinal symptoms and acute kidney injury were present in 22 patients (88%) and 5 patients (20%), respectively. Four patients received an initial bolus dose of Digoxin-Fab of 5–20 vials. Twenty-one patients received repeated titrated doses (1–2 vials) of Digoxin-Fab and the median total dose was 4 vials (IQR: 2–7.5). Median maximal change in HR post-Digoxin-Fab was 19 beats/min. The median potassium concentration decrease post-Digoxin-Fab was 0.3 mmol/L. Total dose used in the titration group was 25% and 35% of the predicted doses based on the amount of digoxin ingested or measured serum concentration, respectively. Twelve had free digoxin concentrations measured. Free digoxin concentrations dropped to almost zero after any dose of Digoxin-Fab. Ten patients had a rebound of digoxin >2.6 nmol/L (2 μg/L). There were no deaths from acute digoxin toxicity.

Conclusions: The new practice of using small, titrated doses of Digoxin-Fab led to a considerable reduction in total usage and major savings. The clinical response to titrated doses was safe and acceptable in acute digoxin poisoning.

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Introduction

Acute digoxin poisoning is a rare presentation as most poisons centre would manage just a few acute digoxin poisoning per year [1]. Most previous case series of digoxin poisoning combine the results of acute and chronic digoxin poisoning [2–4], despite them being quite different clinical syndromes. People with chronic poisoning typically have multiple underlying illnesses, are prescribed multiple cardiotoxic medications and develop renal failure [5,6]. Deaths were not generally due to chronic digoxin toxicity, but were attributed to medical causes such as cardiac or respiratory failure, renal failure, sepsis or a combination of co-morbidities [6]. In contrast, acute digoxin poisoning typically involves deliberate ingestion of much larger doses by a generally healthier population and potentially requires a different management approach [7]. Pharmacokinetic modelling supported the use of less expensive and safer digoxin-Fab dosing strategies to manage acute digoxin poisoning [7].

The recommended doses of Digoxin-Fab in acute poisoning have previously been calculated from the amount required to bind half or all of the estimated digoxin body load [1,8–10], or to give empiric 10–20 vials Digoxin-Fab if the ingested dose is unknown [11]. However, Digoxin-Fab is expensive (US$750 per 40 mg vial during the study, currently up to US$1,000 per vial) and has a limited shelf life of about 3 years, making it difficult to stock adequate supplies if large doses are recommended. Using reported ingested dose will

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Supplemental data for this article can be accessed here.

generally overestimate required Digoxin-Fab doses [11]. This is because the bioavailability varies from 60 to 80%, and the use of activated charcoal and vomiting further reduces bioavailability [11]. Similarly, formulae using serum digoxin concentrations do not accurately reflect total digoxin burden when tissue distribution has not occurred [8], leading to over-estimation of the required Digoxin-Fab dose.

We developed a pharmacokinetic model for acute digoxin poisoning [7,11], and validated that this predicted concentrations well and that free digoxin concentration dropped to almost zero even with small doses of Digoxin-Fab, which could be repeated as required. We have shown that 1–2 vials of Digoxin-Fab (repeated if necessary) was an effective strategy in chronic toxicity [5] and this had become standard practice in Australia. From around 2015, we began to advise clinicians to also give titrated doses of Digoxin-Fab in patients with acute digoxin poisoning. In this observational study we report our favourable experience with switching to titrated doses in acute digoxin poisoning. We also provide clinical data restricted to acute digoxin poisonings; including measured free and total digoxin concentrations, Digoxin-Fab doses used and the clinical response to Digoxin-Fab.

Methods

This Digoxin Overdose and Response to Antibody (DORA) study (an arm of the Australian Toxicology Monitoring [ATOM] project) was a prospective observational study of patients with acute digoxin toxicity who have been administered Digoxin-Fab (by Phebra Pharmaceutical Company). Patients were recruited from September 2013 to September 2020 from calls to the New South Wales (NSW) and Queensland (QLD) Poisons Information Centre (PIC) and three toxicology units [Hunter Area Toxicology Service (HATS), South Eastern Sydney Toxicology Service (SEATS) and Princess Alexandra Toxicology Service (PATS)]. These units treat approximately 1000–2000 poisoning patients per year. The ATOM project has ethical approval from Human Research and Ethics Committees in NSW and QLD to cover all involved institutions and PIC.

Patients

Patients were recruited to the acute DORA study if they met the following inclusion criteria: a history of acute digoxin overdose, an elevated digoxin concentration (>2.6 nmol/L or 2 μg/L), and symptoms or signs attributable to digoxin toxicity. Consent was obtained from the patient or the next of kin if the patient could not sign a consent form. A standardised data form was used to enter patient information which included patient demographics (age, sex, weight), a brief past medical history, symptoms of digoxin toxicity (cardiac arrhythmias, gastrointestinal and neurological symptoms), current medications, clinical effects (heart rate [HR], blood pressure [BP]), laboratory investigations (digoxin concentration, potassium, creatinine), treatments (dose and timing of Digoxin-Fab) and outcomes (change in potassium concentration, HR and BP post Digoxin-Fab treatment). If body weight was not recorded, females were assumed to be 80 kg and males 85 kg in accordance with Australian epidemiological studies [12]. 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 samples were collected pre and post Digoxin-Fab administration from the patient, centrifuged and stored at −80 °C. The samples were analysed for total and free digoxin concentrations, as well as free digoxin antibody concentrations.

Free and bound digoxin concentration and Digoxin-Fab measurement in serum

Full details for the measurement of free and bound digoxin, as well as Digoxin-Fab have been published in a previous paper [5]. The lowest reportable limit is 0.2 nmol/L (0.15 μg/L) and is recorded as 0 if the result is <0.2 nmol/L (<0.15 μg/L). Free Digoxin-Fab (antibodies) concentration was measured by enzyme immunoassay using a modification of a previously developed assay for detection of horse derived antivenoms [13].

Analysis

Medians, interquartile ranges (IQR) and ranges are used to summarise continuous data. All graphical analysis was done in either Microsoft Excel or Prism 9.0.2 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com).

Results

From September 2013 to September 2020, there were 23 patients with 25 presentations of acute digoxin poisoning treated with Digoxin-Fab. Two patients had two separate admissions for acute digoxin toxicity. All but one patient was taking regular digoxin. They are numbered in chronological order from 1 to 25. Demographics of the 25 presentations are summarised. The median patient age was 56 years (IQR: 47–78) with a female predominance ($n = 14$; 56%). Body weight was documented in 20 patients (80%) with a median weight of 84 kg (IQR: 61–90).

Before treatment, the initial median HR was 41 beats/min (IQR: 35–54 beats/min) (Table 1). The median initial systolic BP was 120 mmHg (IQR: 109–146 mmHg) before Digoxin-Fab. Gastrointestinal symptoms with nausea and vomiting or abdominal pain were recorded in 22 patients. Slow atrial fibrillation was the commonest rhythm ($n = 16$), sinus bradycardia ($n = 9$), junctional bradycardia ($n = 6$), ventricular tachycardia/fibrillation ($n = 3$), complete heart block (n = 2), supraventricular tachycardia ($n = 2$), although many patients switched between rhythms (e.g., between various degree of atrio-ventricular block and sinus bradycardia).

The median reported ingested dose was 13 mg (IQR: 9.5–25 mg, range: 3.6–37.5). The median total digoxin

concentration was 14.5 nmol/L (IQR: 10.9–20, range: 7.9–52) [11.2 μg/L (IQR: 8.4–15.4, range: 6.1–40)] and was taken at a median time of 4 h (IQR: 3–6 h, range: 0.5–19.5) post-ingestion. The initial median potassium and creatinine concentrations were 5 mmol/L (IQR: 4.5–5.4 mmol/L, range: 4.1–6.7) and 75 μmol/L (8.5 mg/L) (IQR: 65–90 μmol/L) [7.4–10.2 mg/L], respectively. Five patients developed acute kidney injury on or during admission with elevated creatinine (range: 133–695 μmol/L) [15–78.6 mg/L]. The median length of stay was 4.5 days (range: 2–28 days) (Table 1).

Five patients also overdosed on beta-blockers or calcium antagonists, five patients co-ingested vasodilator drugs such as angiotensin converting enzyme inhibitors. One patient died after he was successfully managed for his acute digoxin poisoning from pseudomonas sepsis secondary to a urinary tract infection.

Treatment

Four of the first five patients received Digoxin-Fab boluses based on older guidelines (5, 10, 10, 20 vials). There was then universal adoption of the new dosing strategy with all subsequent patients given repeated titrated doses of Digoxin-Fab at the discretion of the physicians following discussion with toxicologists (Figure 1). The initial dose was usually 2 vials (2 patients had just 1 vial and 1 patient had 2.5 vials). The median total dose of Digoxin-Fab used for the 21 patients with titration was 4 vials (IQR: 2–7.5 vials; range: 1–17.5 vials). In the titration group, the total Digoxin-Fab dose used was 25% and 35% of the doses that would have been given based on the amount of digoxin ingested or measured serum concentration (Figure 1, Table 2). The median time for the administration of first and last dose of Digoxin-Fab for the entire cohort was 7 h (IQR: 4–13 h; range: 1.5–68 h) and 19 h (IQR: 13–38 h, range: 9–76 h) post-ingestion, respectively.

For the 25 patients, the median maximum change in HR after Digoxin-Fab was 19 beats/min (IQR: 13–29 beats/min) (Table 1, Supplementary Figure 1). The median heart rate post Digoxin-Fab was 65 beats/min (IQR: 58–72 beats/min). There was no change in median systolic blood pressure after Digoxin-Fab. The median change in potassium concentration was −0.3 mmol/L (IQR: +0.6 to −0.8 mmol/L). Digoxin-Fab was also effective in relieving gastrointestinal symptoms in all 22 patients who reported them. There were no adverse reactions recorded from the administration of Digoxin-Fab.

Other treatments included activated charcoal (9/25, 3 with repeated doses), and for the management of brady-arrhythmias: isoprenaline ($n = 2$), dobutamine ($n = 1$) and adrenaline ($n = 1$). These drugs were given either before or following Digoxin-Fab administration. One patient received treatment for hyperkalaemia with insulin and dextrose. Two patients received continuous veno-venous haemodialysis [CVVHD], one of them had acute kidney injury and it was not clear why the other received dialysis.

Table 1. Outcome of the patients with acute digoxin poisoning that were treated with Digoxin-Fab.

Acute digoxin poisoning	$N = 25$
Max median HR change (bpm)	19 (IQR: 13–29, range: −20 to 42)
Median HR before Digoxin-Fab (bpm)	41 (IQR: 35 to 54, range: 15 to 102)
Median HR post Digoxin-Fab (bpm)	65 (IQR: 58 to 72, range: 50 to 110)
Median K change (mmol/l)	−0.3 (IQR: +0.6 to −0.8, range: −1.3 to +0.9)
Median length of stay (days)	4.5 (IQR: 3–9, range: 2 to 28)
Fatality (%)	1* (4%)

*Patient was managed successfully from acute digoxin poisoning but died subsequently from urinary sepsis.

Free digoxin and Digoxin-Fab concentrations

Serum samples were available from 12 patients. Free digoxin concentrations decreased to almost zero following the administration of Digoxin-Fab regardless of the antibody dose used (Figure 2(a–c)). There was a rebound observed in the free digoxin concentrations in all 12 patients, ten of which were into the "toxic range" (>2.6 nmol/L or >2 μg/L).

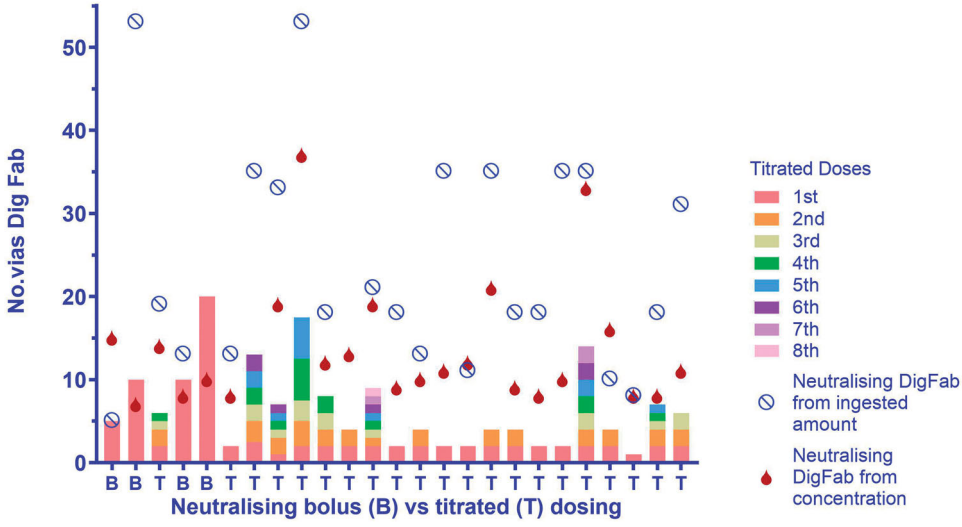

Figure 1. This is a bar graph that demonstrates the accumulated doses of Digoxin-Fab for each patient. Different colour bars for Digoxin-Fab represented different doses of Digoxin antibody given during hospital admissions in accordance with the time of administration (Patient 24 has an estimated digoxin concentration >12.6 nmol/L). The number of vials of Digoxin-Fab estimated based on digoxin dose and concentration are also plotted on the graph.

Table 2. Calculated and actual number of vials of Digifab used for patients.

Calculation using	Median no. vials for 4 patients with bolus doses	Median no. vials for the 21 patients with titrated doses	Total no. of vials for 25 patients	Total no. of vials for 21 patients with titrated doses
Ingested digoxin dose	13 (Range: 5–53)	19 (IQR: 14–35; Range: 8–53)	548	477
Serum digoxin conc (nmol/L)	9 (Range: 7–15)	12 (IQR: 9–19; range: 8–57)	385	344
Actual Digoxin-Fab used	10 (Range: 5–20)	4 (IQR: 2–7.5; range: 1–17.5)	166	121

Patient 1 and 5 had unknown amount of digoxin ingested, so they could not be used to calculate the Digoxin-Fab needed based on ingested dose.
Number of vials based on serum digoxin concentration = [serum conc (μg/L)/1000 (to convert to mg/L) × weight (kg) × 7 (typical Vd = 7 L/kg) × 2 (vials required/mg]].
Conversion of units of digoxin nmol/L to μg/L: nmol/L × 0.781 = μg/L.
In cases where body weight was not able to be obtained, females were assumed 80 kg and males 85 kg in accordance with Australian epidemiological studies [10].

The other two patients had bolus doses of 10 vials Digoxin-Fab, accounting for the lower non-toxic rebound free digoxin concentration (patient 2 & 4). Patient 3 had repeated titrated doses of Digoxin-Fab according to clinical symptoms which were primarily bradycardia, and this was shown to coincide with rebound free digoxin concentrations. Patient 5 had 20 vials of Digoxin-Fab but had persistent hypotension and acute kidney injury from co-ingestion of unknown amounts of amlodipine, carbamazepine, valsartan, hydrochlorothiazide and received inotropic support and haemodialysis. The free Digoxin-Fab in patient 5 dropped to zero after 30 h while the free digoxin concentration had a rebound to 10.9 nmol/L (8.4 μg/L) and remained elevated to 287 h post ingestion. Overall, the median time for the rebound free digoxin concentration to be above 2.6 nmol/L (2 μg/L) was 18 h (IQR: 14–28, range: 12–66 h) for those who had normal renal function and 103 h (IQR: 90–243, range: 88–287 h) for patients with acute kidney injury.

Patients who received bolus doses of Digoxin-Fab at 10–20 vials initially had excess free Digoxin-Fab (Figure 2(a)) that could not be utilised but still had a subsequent rebound in digoxin concentration.

Cost saving

Based on US$750 per vial, the potential savings for the titration group were US$267,000 and US$167,250, respectively by using titrated doses of Digoxin-Fab when compared with estimated doses based on ingestion dose or serum digoxin concentration (Table 2).

Discussion

Our experience suggests that the approach used in chronic poisoning of giving small titrated doses of Digoxin-Fab was readily accepted into practice and worked reasonably well [5]. In this study, with much larger median doses of digoxin acutely ingested and higher serum digoxin concentrations of 13 mg and 14.5 nmol/l (11.2 ng/L), respectively, the clinical responses to 2 vials of Digoxin-Fab with a median increase heart rate of 19 bpm were generally greater than the modest changes seen with chronic poisoning (Table 1, Supplementary Figure 1). Digoxin ingestion >10 mg or digoxin concentration >10 μg/L (13.6 nmol/L) are considered potentially fatal [10]. Other studies have reported similar or lower average doses ingested and serum digoxin concentrations, supporting the fact that our cohort have severe digoxin toxicity [1,10]. Previous studies often combine acute and chronic digoxin poisoning [2,3]. However, those studies reporting greater effectiveness of Digoxin-Fab had a greater proportion of acute poisoning [11].

The indication for Digoxin-Fab in most of our patients was brady-arrhythmias, consistent with the expected dose dependent node block and resulting reduction in heart rate [14]. This was also the variable that appeared to respond best to treatment. Hyperkalaemia ($K > 5.5$ mmol/L) is suggested to be a useful clinical marker for (acute) digoxin toxicity requiring treatment [2,15]. However, our study showed an initial median potassium concentration of 5 mmol/L with a small change of potassium concentration following the use of digoxin-Fab. We did not find potassium to be a very useful marker in this cohort of patients with acute digoxin toxicity. This could be because these patients presented early and were managed with decontamination using activated charcoal, and repeated titrated low doses of digoxin-Fab and this regime reduced the toxicity of digoxin.

The driving force behind the move to using smaller titrated doses of Digoxin-Fab was the very high cost of the antidote, its limited stocking in many hospitals, and the theoretical support for the possibility that lower doses may be equally effective. We recently simulated serum and tissue digoxin concentrations and response in a typical patient with acute digoxin poisoning and concluded that only a fraction of digoxin is in the central compartment and this can be neutralised by just 80 mg Digoxin-Fab [11]. This is because reversal of digoxin-induced Na^+K^+ATPase inhibition is dependent on the Digoxin-Fab concentration and the maximal effect is seen whenever the Fab: digoxin ratio is ≥1 [16]. In addition, digoxin has a direct and an indirect effect via the autonomic system on the sinus node and atrio-ventricular node which explained the predominance of brady-arrhythmia that can be reversed by Digoxin-Fab [17]. Digoxin-Fab is also effective in managing gastrointestinal symptoms such as vomiting because the emetic effect of digoxin is thought to be mediated by chemoreceptors located in the medulla rather than by direct irritant effect on the gut [17].

A lower dose of Digoxin-Fab increases the likelihood of an early rebound in free digoxin concentrations [18]. In the three patients who received a bolus dose of 10–20 vials Digoxin-Fab, two had minimal rebound. There are also case reports that showed a rebound in free digoxin in serum and urine despite giving large bolus doses of digoxin-Fab [4]. The third patient (patient 5) who received 20 vials had renal

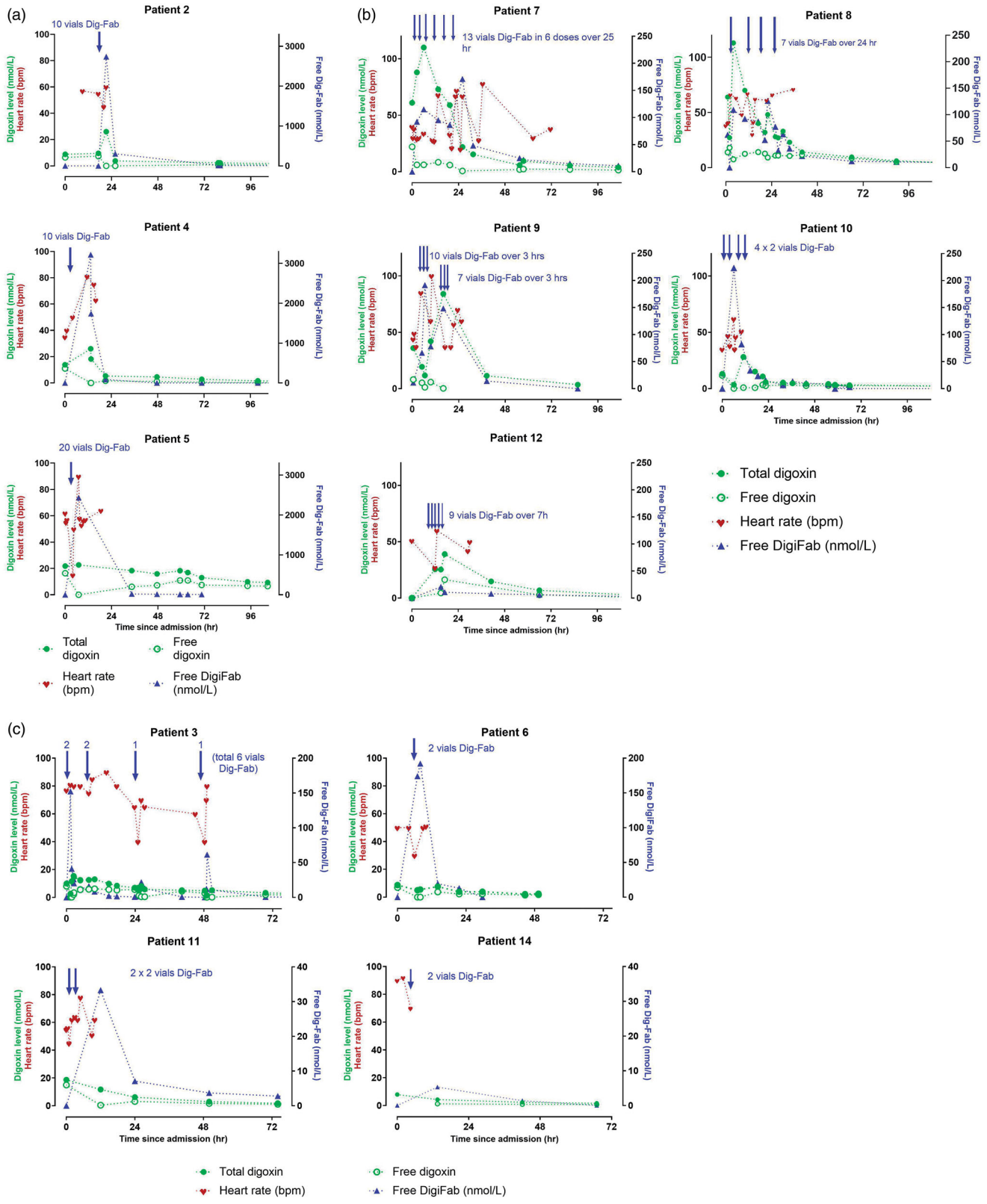

Figure 2. Graphical representations of total and free digoxin concentrations, free Digoxin-Fab concentrations and heart rate in 12 patients. Patient 5, 7 and 10 had acute kidney injury. The conversion factor for digoxin concentration is to divide nmol/L by 1.3 to convert to μg/L. (a) Patients who received bolus doses of Digoxin-Fab (DigFab). (b) Patients who received large titrated doses of Digoxin-Fab. (2c) Patients who received small titrated doses Digoxin-Fab.

failure and in fact had prolonged elevated free digoxin concentrations. This is consistent with the literature that showed patients with digoxin poisoning and renal failure have delayed elevation of serum digoxin concentrations in relation to the digoxin-Fab and have recurrence of digoxin toxicity [19]. Our study showed that of the other nine patients who had repeated titrated doses of Digoxin-Fab and free digoxin concentration measured, all nine had a rebound to toxic free

digoxin concentrations (>2.6 nmol/L or 2 μg/L). Many patients developed further symptoms or brady-tachy arrhythmias and were given further small, titrated doses of Digoxin-Fab to which they generally responded and no fatalities from acute poisoning occurred in this series. Previous guidelines have also stated that there is no point in measuring total digoxin concentration once Digoxin-Fab is administered. However, given the rebound in free digoxin seen even with the largest Digoxin-Fab doses, it may be worth measuring either free digoxin, or total digoxin concentration 24–36 h post Digoxin-Fab, especially if there are ongoing signs consistent with clinical toxicity. Most hospitals cannot measure free serum digoxin concentration and so treatment with further doses of Digoxin-Fab need to be based on recurrence of brady-tachy arrhythmias. In addition, the use of adjunctive treatment such as atropine, vasopressors (isoprenaline, adrenaline) or pacemakers [20] may also be used to manage patients with acute digoxin poisoning.

Our study demonstrated that physicians were willing to switch to a strategy of titrating small doses of Digoxin-Fab (2 vials) according to clinical parameters (HR <40 beats/min or ventricular tachyarrhythmia) rather than giving large bolus doses of Digoxin-Fab. The first advantage is the avoidance of using digoxin concentrations or pharmacokinetic formulae to determine patient specific doses of Digoxin-Fab. The second advantage is the considerable cost saving without compromising patient care. This has system wide implications. A titrated dosing strategy supports the concept of stocking fewer vials (e.g., 4 vials) across many hospitals. This will also reduce potential wastage in unused expired Digoxin-Fab stock. Currently few hospitals can afford stocking the "standard" 10–20 vials recommended to cover an acute digoxin overdose [21], which results in many hospitals not routinely stock Digoxin-Fab in NSW Australia [22].

A limitation of this study was the small number of patients in this study with acute digoxin poisoning. The heterogenous nature of the comorbid diseases/drugs in patients with acute digoxin toxicity is a universal limitation making it difficult to reliably determine the effects of Digoxin-Fab and predictors of response. In this regard a 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 Digoxin-Fab treatment, to augment the clinical evaluation.

Conclusion

The new practice of using 2 vial doses of Digoxin-Fab, repeated as clinically required, led to a considerable reduction in total usage of Digoxin-Fab and major savings. Only around a quarter of digoxin poisonings in this study required more than 10 vials of Digoxin-Fab, which would have been the minimum dose for most patients based on traditional guidelines. Lower doses of Digoxin-Fab reliably reduced free digoxin concentrations with an acceptable clinical response in most patients. This strategy will decrease antidote stock holding costs and may support wider availability of Digoxin-Fab.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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