

REVIEW ARTICLE

# Digoxin-specific antibody fragments in the treatment of digoxin toxicity

B. S. H. CHAN<sup>1,3</sup> and N. A. BUCKLEY<sup>2,3</sup>

<sup>1</sup>Department of Emergency Medicine, Clinical Toxicology Unit, Prince of Wales Hospital, NSW, Australia

<sup>2</sup>Pharmacology, Sydney Medical School, University of Sydney, Sydney, Australia

<sup>3</sup>New South Wales Poisons Information Centre, NSW, Australia

**Context.** Digoxin-specific antibody fragments (digoxin-Fab) are widely regarded as a safe and effective treatment for the management of acute and chronic digoxin poisoning. Calculated equimolar doses of digoxin-Fab are high, very expensive, and infrequently used. **Objective.** To review the pharmacology, efficacy, effectiveness, indications, safety and the dosage of digoxin-specific antibody fragments. **Methods.** Pubmed, Embase, Medline and Cochrane were searched from 1946 to May 2013 using the terms digoxin, digoxin-specific Fab, and digoxin antibody. **Pharmacology and kinetics of digoxin and digoxin-Fab.** Digoxin acts via inhibition of Na<sup>+</sup>/K<sup>+</sup> ATPase. It has a narrow therapeutic index. Digoxin has 60–80% bioavailability, a mean plasma half-life of 40 h and a volume of distribution (Vd) of 5–10 L/kg and low protein binding (20%). A 40-mg vial of digoxin-Fab (DigiFab) binds 0.5 mg digoxin. Digoxin-Fab has a mean plasma half-life of 19–30 h and a Vd of 0.4 L/kg. The half-lives of both digoxin and digoxin-Fab are prolonged in renal failure to over 100 h. **Efficacy and effectiveness of digoxin-Fab.** There were no randomised clinical trials examining the use of digoxin-Fab for acute or chronic digoxin poisonings. Ten case series with a total of 2,080 patients have reported on the use of digoxin-Fab in digoxin poisoning. In three large case series of 430 acute and 1308 chronic poisonings, response rates to digoxin-Fab vary from 80–90% to 50%. The time for reversal of digoxin toxicity is reported to be 30–45 min. Studies with pharmacokinetic data showed that free digoxin concentration fell to almost zero within a few minutes following the administration of digoxin-Fab. Digoxin-Fab was used more frequently in acute than chronic digoxin poisoning with a higher reported success rate when used in acute overdose. It is sometimes recommended to use full neutralisation doses (based on serum concentration × Vd or ingested dose). It has also been proposed to use half this dose. **Indications for digoxin-Fab.** Patients who have life-threatening tachy-bradyarrhythmias, hyperkalaemia (>6 mmol/L) or haemodynamic instability with an elevated digoxin concentration (>2 µg/L or 2.6 nmol/L). The lowest effective digoxin-Fab dosing regimen has not been established. **Safety of digoxin-Fab.** Adverse events such as exacerbation of heart failure, increased ventricular rate and hypokalaemia are uncommon (<10%). Recrudescence of digoxin toxicity and allergic reactions are infrequent. **Digoxin-Fab dosing in acute poisoning.** Digoxin load based on ingested dose will generally overestimate digoxin-Fab doses as bioavailability is 60–80%, and further reduced by vomiting and activated charcoal. Digoxin load based on concentration also will be overestimated when the concentration is taken before distribution is complete (around 6 h). Much smaller doses of digoxin-Fab can eliminate the digoxin in the central compartment (Vd ≈ 55 L). In imminent cardiac arrest, it may be justified to give a full neutralising dose. Otherwise, based on pharmacokinetic modelling, it is recommended to give 80 mg bolus digoxin-Fab, repeated as required according to clinical parameters because the onset of clinical response is usually rapid. Most patients would be expected to require a total of less than half of the calculated neutralising dose using this strategy. **Digoxin-Fab dosing in chronic poisoning.** Even if digoxin load is estimated following distribution (>6 h), excessive neutralisation doses may still be calculated because of variation in Vd due to equations failing to account for lean body weight, age and renal failure. In practice, it is suggested to give 40 mg (1 vial) digoxin-Fab at a time and repeat after 60 min if patient is still symptomatic, sooner if patient is clinically unstable. In general, 40–120 mg (1–3 vials) should be sufficient. **Conclusions.** Digoxin-Fab is safe and indicated in all patients with life-threatening arrhythmias and an elevated digoxin concentration. However, calculated full neutralising doses of digoxin-Fab are expensive and may not be required. In acute poisoning, a small bolus of 80 mg, repeat if necessary, titrated against clinical effect, is likely to achieve equivalent benefits with much lower total doses. With chronic poisoning, it may be simplest to give 40 mg (1 vial) digoxin-Fab at a time and repeat after 60 min if there is no response.

**Keywords** Pharmacokinetics; Acute poisoning; Chronic overdose; Antidote

## Context

Digoxin is used for the management of congestive cardiac failure and long-term rate control for atrial fibrillation.

However, it has a narrow therapeutic index. Recent evidence has led to the therapeutic range being reduced from around 0.8–2 µg/L (1–2.6 nmol/L) to 0.5–0.8 µg/L (0.6–1.0 nmol/L) for the management of heart failure.<sup>1</sup> Despite this, in a recent study, digoxin toxicity was the third most common adverse drug event leading to hospitalisation in patients aged over 65.<sup>2</sup> The risk of digoxin toxicity is also high immediately post hospitalisation, perhaps as a result of adjustment of medication dose and drug interactions.<sup>3</sup>

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Address correspondence to Dr. Betty S. H. Chan, Department of Emergency Medicine, Clinical Toxicology Unit, Prince of Wales Hospital, Barker St, Randwick 2031, NSW, Australia. Tel: + 61439601068. E-mail: bettyshchan@gmail.com

Digoxin-specific antibodies, prepared from sheep antiserum, were introduced in 1967 as an immunoassay for digoxin in human serum.<sup>4</sup> In 1976, Smith and colleagues<sup>5</sup> first successfully treated a patient who had ingested digoxin 22.5 mg with digoxin-specific antibody fragments (digoxin-Fab) after conventional therapy failed. Since then digoxin-Fab has been widely recommended and used. It has not been established in clinical trials that this improves outcomes, but reported mortality rates from digoxin toxicity have improved from 20–30%<sup>6–8</sup> to as low as 5–8% following the introduction of digoxin-Fab.<sup>9</sup> As reported rates of use of digoxin-Fab are lower than this difference, it is likely that many other factors have contributed to this apparent change. Digoxin-Fab has also been effective in managing other cardiac glycoside poisonings such as oleander,<sup>10–13</sup> toad venom,<sup>14</sup> Chinese herbal medicines like Chan Su,<sup>15</sup> Dan Shen and Lu-Shen-Wan.<sup>16</sup> While there is some preliminary experimental evidence that other treatments, such as glucose–insulin infusions<sup>17</sup> and fructose diphosphate,<sup>18</sup> show favourable cardiovascular effects in acute cardiac glycoside poisoning, the mainstay of treatment remains judicious use of digoxin-Fab with supportive care. This review will concentrate on the use of digoxin-Fab in digoxin poisoning and will not cover in detail its use in toxicity from other cardiac glycosides or other treatment modalities in digoxin poisoning.

Except in life-threatening situations, digoxin-Fab is used infrequently for digoxin poisoning, rates varying from 3.9 to 5.8%.<sup>19</sup> In 2013, the price increased from about US\$380 to US\$750 per vial and potentially it has become less cost-effective in managing digoxin poisoning. Many cardiologists and emergency physicians are reluctant to use digoxin-Fab unless the poisoning is deemed life threatening with tachy–bradyarrhythmias.<sup>20</sup> In acute digoxin poisoning, there is evidence to suggest that antibody treatment is effective but the recommended dosages are not standardised in the literature. There is a potential to overtreat patients with the number of vials of digoxin-Fab based on dose ingested or serum concentrations that do not reflect the total body burden.<sup>21</sup> On the other hand, the indications for managing chronic digoxin poisoning are less well defined. In chronic toxicity, the diagnosis is not always clear and patients often have cardiac and renal diseases. Clinical features may be due to many other factors that would not respond to digoxin-Fab. The recommended equimolar dose also varies because it depends on the assumption used for the volume of distribution (Vd). In addition, as most patients have been prescribed digoxin for therapeutic purposes, adverse events may result if all digoxin in the body is neutralised.

## Objective

To review the pharmacology, efficacy, effectiveness, indications, safety and the dosage of digoxin-Fab. On the basis of the reviewed data, to propose a regimen of administering digoxin-Fab to patients with digoxin poisoning based on pharmacokinetic principles.

## Methods

We reviewed Pubmed, Embase, Medline and Cochrane from 1946 to May 2013 searching for terms digoxin, digoxin-specific Fab, digoxin antibody to review the pharmacology, efficacy and effectiveness, indications, dosage and safety of digoxin-Fab. These searches elicited 5317 citations. Case reports without pharmacokinetic results were excluded; 140 citations were found to be relevant. There have been no randomised clinical trials on digoxin poisoning. There is a randomised trial demonstrating effectiveness of digoxin-Fab in managing severe arrhythmias caused by yellow oleander self-poisoning.<sup>11</sup> However, dosing recommendations for this indication are not relevant to digoxin as yellow oleander contains different cardiac glycosides.<sup>11</sup> There are several case series on acute and chronic digoxin poisoning treated with digoxin-Fab,<sup>7,22,23</sup> but these provide little or no data to support dosing strategies.

### Pharmacology and kinetics of digoxin and digoxin-Fab

Digoxin is a cardiac glycoside with a molecular weight of 780 Da (g/mol). Bioavailability is between 60 and 80%<sup>6,24</sup> and the plasma half-life is between 20 and 50 h (mean 40 h).<sup>25,26</sup> It has a large volume of distribution of 5–10 L/kg with extensive tissue distribution and low protein binding (20%). It is predominantly renally excreted. In the elderly, the apparent clearance (Cl/F) and volume of distribution (V/F) are both reduced to about 9 L/h (relative standard error (RSE) 18%) and 420 L (RSE 12%), respectively.<sup>27</sup> The half-life is prolonged in patients with renal failure and is reported to be between 68 and 177 h.<sup>28,29</sup>

Digoxin is a weak positive inotrope that acts via inhibition of Na<sup>+</sup>–K<sup>+</sup> ATPase.<sup>30</sup> ATPase inhibition results in an increase in intracellular Na<sup>+</sup>, which in turn causes an increase in intracellular Ca<sup>2+</sup> via the Na<sup>+</sup>–Ca<sup>2+</sup> exchanger. Life-threatening digoxin toxicity is believed to be due to excessive intracellular calcium, which can result in delayed after depolarisations manifesting as increased automaticity and ectopic beats, atrial or ventricular arrhythmias, ventricular tachycardia or fibrillation. Digoxin also has effects on the parasympathetic system, increasing vagal stimulation to the sinus and atrio-ventricular (AV) node, slowing the heart rate and conduction through the AV node.

At low plasma concentrations, digoxin acts as a sympatholytic agent for patients with cardiac failure. The optimal serum digoxin concentration is 0.5–0.8 µg/L for the management of cardiac failure with a left ventricular ejection fraction less than or equal to 45%. This is based on the Digitalis Investigation Group (DIG) trial, in which high serum digoxin concentrations were associated with a slightly increased mortality rate.<sup>31</sup> A serum digoxin concentration of 1.2 µg/L or higher was associated with a hazard ratio (HR) of 1.16 (95% CI, 0.96–1.39) when compared with placebo (HR: 1); in contrast, the hazard ratio was 0.80 (95% CI, 0.68–0.94) for serum digoxin concentrations of 0.5–0.8 µg/L.

Digoxin is a substrate for P-glycoprotein which is located in the small intestine, bile ducts and kidneys. Potent inhibitors of P-glycoprotein such as clarithromycin, quinidine, verapamil and amiodarone reduce renal tubular secretion and increase gut absorption resulting in an increase in serum digoxin concentration.<sup>32</sup> Drug interactions may cause a greater risk of digoxin toxicity in elderly patients who are more likely to have renal impairment and are commonly treated with multiple cardiac medications.

Digoxin-Fab is a monovalent immunoglobulin with a molecular weight of 46,000 Da; its half-life is between 19 and 30 h.<sup>22</sup> Digoxin-Fab is removed by both renal clearance and hepatic metabolism. The half-life is prolonged in the elderly to over 90 h<sup>33,34</sup> and in renal failure to greater than 130 h.<sup>35,36</sup> In a study of 16 patients who were treated with digoxin-Fab, the total body clearance was linked linearly to a decrease in renal clearance and increase in age.<sup>26</sup> It has a small Vd: 0.4 L/kg. It has 100–1000 times higher affinity than Na<sup>+</sup>/K<sup>+</sup> ATPase for digoxin. Each vial of DigiFab (38–40 mg of Fab) binds approximately 0.5 mg digoxin. In a pilot study of 11 patients, the unbound plasma digoxin concentration fell to almost 0 within a few minutes following the administration of digoxin-Fab.<sup>23</sup> In addition, digoxin-Fab increases renal clearance of digoxin by 20–30%, providing both toxicokinetic and toxicodynamic benefits.<sup>37</sup>

There is some evidence to suggest that there is uncoupling of the digoxin and antibody complex in the kidney. The digoxin-Fab fragments are filtered through the glomeruli and reabsorbed in the proximal tubules while digoxin is excreted.<sup>37</sup> However, there is no evidence that there is dissociation of the digoxin and antibody complex in the intravascular system.<sup>38</sup> Toxicity is likely to be determined by the free digoxin concentration, and therefore, molar ratios of digoxin to digoxin-Fab.<sup>33,39</sup> Digoxin-Fab has very high affinity for digoxin and so the free digoxin concentration would be low in the presence of unbound antibody.

Digoxin-Fab binds to intravascular digoxin rapidly and may also diffuse into the interstitial space.<sup>40</sup> Reduced free serum digoxin generates a concentration gradient which promotes digoxin redistribution back from the membrane receptors.<sup>41</sup> In acute ingestion, the time course for reversal of digoxin toxicity by digoxin-Fab is reported to be within 30–45 min,<sup>42,43</sup> even when half or less of the ingested dose has been neutralised with digoxin-Fab.<sup>44</sup> There is a 10- to 20-fold rise in the total measured digoxin concentration (which includes the Fab-digoxin complex) following the administration of digoxin-Fab for over 32 h, suggesting prolonged and continuous re-distribution of digoxin from the tissue to the plasma.<sup>23</sup>

In contrast, free digoxin concentrations remain low for a considerable period of time (up to 152 h following a bolus dose of digoxin-Fab).<sup>45</sup> While free digoxin concentrations consistently decrease rapidly following Fab therapy,<sup>22,33,42,46–50</sup> there can be a rebound in plasma unbound digoxin concentrations 12–24 h later in patients with normal renal function.<sup>33</sup> Furthermore, the elimination half-life of both digoxin and digoxin-Fab is significantly increased in

renal failure and this may delay the rebound in patients with renal insufficiency.<sup>46</sup> All the above factors support measuring clinical improvement with electrocardiographic changes rather than total plasma digoxin concentrations. This can be assisted by concentration monitoring only if the laboratory is capable of measuring free digoxin concentrations.<sup>39</sup>

### *Efficacy and effectiveness of digoxin-Fab*

There are 10 case series of digoxin poisoning (Table 1). In the three largest case series,<sup>7,22,23</sup> there were a total of 430 acute and 1308 chronic poisonings (Table 2). Symptoms of toxicity such as nausea and vomiting should manifest within a few hours of acute ingestion of digoxin.<sup>5</sup> These features may then be followed by cardiac arrhythmias and haemodynamic instability. Response rates to digoxin-Fab varied from 80–90%<sup>22,23</sup> to as low as 50%.<sup>7</sup> Higher response rates were reported in those series with more treatments of acute poisonings and more severe (and perhaps more specific) toxic manifestations. Interpretation of response rates in chronic versus acute poisoning however is complicated by very different rates of use, for example, 2.6% with chronic toxicity versus 41% with acute poisoning.<sup>51</sup>

There are different thresholds for diagnosis and variation in baseline toxicity which make it difficult to interpret response rate. For example, in one case series of 29 children (18 acute, 11 chronic poisonings), the mean serum digoxin concentration was 13.8 µg/L (range: 3–>100 µg/L), with 55% of patients also having underlying cardiac problems. All developed severe cardiac arrhythmias and 93% responded to digoxin-Fab with a median time of 90 min.<sup>23</sup> In contrast, another paediatric study included 41 children with ‘acute poisoning’ from three paediatric hospitals. However, there were no life-threatening arrhythmias in this group. There was a delay of up to 18 h post ingestion in the development of ECG abnormalities in seven patients with serum digoxin concentration >2 µg/L, but none of these abnormalities were life threatening. The serum digoxin concentrations were much lower (range 0.2–11.6 µg/L) and no patients had any underlying cardiac diseases. Hence, the two studies have very different baseline toxicities and outcome and are difficult to compare.

It has been suggested to use half of the calculated doses of digoxin-Fab based on serum concentrations or ingested dose.<sup>52</sup> However, acute and chronic poisonings are quite different in terms of patient characteristics such as age, cardiovascular diseases and co-morbidity and digoxin distribution in tissues. In the acute group, the serum concentration does not reflect the tissue concentrations until absorption and distribution are complete. Thus, the body burden and required digoxin-Fab dose can be greatly overestimated if the serum digoxin concentration is multiplied by the volume of distribution prior to this time. Reported digoxin dose may also be misleading as a guide to the need for digoxin-Fab. For example, in one case series<sup>53</sup> despite a median reported digoxin overdose of 7.5 mg, only 12% (17/147) of patients had life-threatening arrhythmias. On the other hand, in chronic digoxin poisoning, digoxin is mostly in the tissue



**Table 1.** A summary of case series published on digoxin poisoning.

| Publications  | Methodology  | Results  | Comment  |
|---|--|--|--|
| Smith et al. <sup>62</sup> This was incorporated in the study by Antman. <sup>23</sup>                                  | Smith et al. <sup>62</sup> conducted a prospective multicentre study on 26 patients with life-threatening arrhythmias or hyperkalaemia who failed conventional therapy. Of these, 20 patients had refractory ventricular tachycardia, 9 had ventricular fibrillation and 19 high-grade atrioventricular block with bradycardia (< 50/min), 4 had first- or second-degree block, 3 had sinus arrest or SA block and 5 had supraventricular tachycardia, 10 patients had hyperkalaemia > 5.6 mmol/L. | Four patients were treated after prolonged hypotension and shock and died from end organ failure. One patient died from recurrent ventricular arrhythmias after an inadequate dose of digoxin-Fab. Twenty-one patients (81%) responded well with reversal of cardiac rhythm disturbances and hyperkalaemia. There were no obvious adverse effects, but the authors cannot exclude the withdrawal of inotropic effect from digoxin as a contributing factor to the persistent shock of the four patients who had died.  | Digoxin-Fab was effective in managing life-threatening arrhythmias caused by digoxin poisoning.  |
| Smolarz et al. <sup>22</sup>  | A prospective review of 34 patients (31 digoxin, 3 digitoxin) from Germany, 27 of whom were suicidal ingestions, 3 were accidental and 4 were iatrogenic, they were treated with digoxin-Fab for severe digoxin poisoning resulting in life-threatening arrhythmias. This includes high-grade atrioventricular conduction disorders, multifocal ectopic beats, ventricular tachycardia and relapsing ventricular fibrillation.   | There were 32 patients (94%) who were successfully treated for life-threatening arrhythmias. The mean serum digoxin concentrations were 12.2 µg/L (range 3.4–29 µg/L). Most patients received 480 mg (range 240–800 mg). Arrhythmias disappeared between 0.5 and 13 h (mean 3.2 h) post Fab infusion. There were two deaths but thought not to be related to the digoxin toxicity. In those in whom free digoxin concentrations were measured, there was a rapid fall of free digoxin concentration and a marked rise of total digoxin concentration. There was simultaneous increase of excretion of bound digoxin in the urine.  | This study suggests that digoxin-Fab is effective in managing life-threatening arrhythmias especially in the setting of acute poisoning. It is difficult to be certain that the digoxin-Fab resolved arrhythmias after 3 h. This study used equimolar dose of digoxin-Fab as per mean digoxin concentration.   |
| Wenger et al. <sup>63</sup>   | A prospective study conducted in 20 hospitals in USA. There were 28 acute ingestions, 5 accidental and 30 chronic poisonings. Equimolar doses of digoxin-Fab were given based on the body load.  | The average serum digoxin concentration was reported to be > 14 µg/L. The digoxin-Fab dose averaged 520 mg (range 4–1600 mg). Toxicity was reversed within 30 min and there were no adverse events. There were 7 of the 63 patients excluded from the study and 6/7 died. The author explained patients either did not receive an adequate dose (two patients) or were pre-terminal (three patients) or had wrong diagnosis (two patients). Of the remaining 56 patients, 53 responded to digoxin-Fab. One patient died from recrudescence of digoxin toxicity due to an inadequate dose of digoxin-Fab. In the six patients in whom free digoxin concentration was measured, digoxin concentration dropped to 0 within a few minutes after digoxin-Fab administration.  | It would be worthwhile to find out more details regarding the two patients who died after having an inadequate dose of digoxin-Fab.  |
| Antman et al. <sup>64</sup> This study included the data from Smith et al. <sup>5</sup> and Wenger et al. <sup>63</sup> | A prospective multicentre study in USA Hospitals with 150 patients who had potentially life-threatening digoxin toxicity. The dose was designed to be equimolar to dose ingested or serum digoxin concentration.   | There were 75 patients (50%) who have chronic poisoning and 74 (50%) patients with acute poisoning. There were complete resolution of all symptoms in 119 patients (80%), 14 patients have partial response (10%) and 15 patients showed no response. The authors suggested that the reasons for partial or no response were wrong diagnosis (18 patients) or inadequate dose (2 patients) or patients already <i>in extremis</i> before treatment (7 patients). The median digoxin concentration was 10.4 nmol/L (8 µg/L) and the median digoxin-Fab dose was 200 mg (range: 120–480 mg). The median time to response was 19 min with 75% responded by 60 min. The median time to complete response was 88 min. The mortality rate was 29% (43/150). The majority of patients that died were thought to be caused by other medical illnesses. Free serum digoxin concentrations were measured in 11 patients and it dropped to zero concentration within 1–2 min while the total digoxin concentration rose to 10- to 20-fold higher than those before treatment. | This study was conducted over a 12-year period in multiple centres. The protocol was changed during this period from a 2-h to a 30-min infusion. This study suggested that digoxin-Fab is effective in patients with life-threatening symptoms of digoxin toxicities. The high mortality rate of 29% suggested that patients with digoxin toxicities often have co-existing multi-system dysfunction that ultimately determines the outcome. |

(Continued)

**Table 1.** (Continued)

| Publications                 | Methodology   | Results  | Comment  |
|------------------------------|---|--|--|
| Woolf et al. <sup>65</sup>   | This study combined two paediatric studies into the report. There were 29 patients from the multicentre study with severe cardiac toxicity. <sup>23</sup> Another 28 patients came from a post-marketing surveillance study of the safety and efficacy of digoxin-Fab which is a voluntary reporting system. <sup>7</sup> | Almost 90% of patients in both groups had partial or total resolution of cardiac arrhythmias. There was a fatality rate of 23% but the authors did not attribute the deaths to digoxin. Hypokalaemia was reported in 1 patient. There were no reports of allergic reaction or heart failure. There were 3 patients who had recurrence of cardiac conduction defects requiring a repeat dose of Fab fragments.  | This study combined two different studies with different inclusion criteria and methodology and did not provide much data in the study other than previously published reports. It did not clarify the cause of deaths in the study.   |
| Hickey et al. <sup>7</sup>   | This is a post-marketing surveillance observation study of 717 patients over a 2-year period who received digoxin-Fab from 487 hospitals. Of these, 508 patients were due to chronic poisoning (71%). The data were collected from treating physicians using questionnaires.  | The median dose digoxin-Fab used was 120 mg (range 8–1,600 mg). The median digoxin concentration for acute ingestion was between 9 and 11 µg/L and between 4 and 5 µg/L for chronic poisoning. Of these, 47 patients received < 50% of the estimated dose, 69 had 50% to < 75%, 155 received 75% to < 100% and 359 greater or equal to a full neutralising dose. There was a complete response in 357 (50%) patients, 172 patients (24%) had partial response and 89 patients (12%) had no response. Twenty patients (3%) developed recurrence of toxicity (5 recurred within 12 h, 11 recurred within 3 days, 4 between 5 and 11 days). Author suggests the risk of recrudescence when < 50% of the estimated dose of digoxin-Fab (8.5%) was given. In this study, 171 patients (24%) died, none attributed to digoxin-Fab. | There were only 618 patients who can be evaluated for responses as data were missing in 14% of patients. The basis of the neutralising dose is not shown in the paper. There could be reporting bias regarding response and adverse events by the treating physicians. This paper reported a lower response rate when compared with the Antman paper, possibly due to a higher proportion of chronic poisoning in this group. Of the 20 patients considered to have recrudescence of digoxin toxicity, the independent reviewer only agreed that 2 patients had probable recrudescence of digoxin toxicity, one of them received less than 50% of the estimated dose of digoxin-Fab. Similar to the Antman study, the 24% mortality rate suggested that this was a group of patients who have multiple co-morbidities. |
| Ujhelyi et al. <sup>46</sup> | Prospective observational study of 14 patients with an elevated digoxin concentration (> 2.5 µg/L), symptoms of digoxin toxicity and chronic renal failure who received digoxin-Fab.  | Following the administration of digoxin-Fab, the total digoxin concentration increases rapidly to a mean 40 µg/L. The half-life of total digoxin concentration was 118 h. The free digoxin concentration dropped rapidly following Fab therapy but rebounded later in patients with end-stage renal failure when compared with other patients that have mild renal impairment (127 h vs 55 h). Recrudescence of digoxin toxicity was suspected in three patients but only one has an elevated free digoxin concentration of 1.2 µg/L.  | This is a pharmacokinetic study which demonstrates that digoxin-Fab quickly binds to digoxin. Digoxin-Fab complex has a shorter half-life than digoxin particularly in patients with renal failure and can cause a delay rebound of free digoxin resulting in recrudescence of toxicity. There were three patients who were suspected to have recrudescence of cardiac toxicities. One did not respond to a second dose of digoxin-Fab, while the other two patients improved without any intervention. While there is a possibility of recurrence of cardiac toxicity in patients with end-stage renal failure, it is likely to be a rare event.  |

(Continued)

Table 1. (Continued)

| Publications   | Methodology  | Results   | Comment  |
|--|--|---|--|
| Lapostolle et al. <sup>8</sup> This study probably included data from Taboulet et al. <sup>6</sup> | Retrospective review of 838 patients with an elevated digoxin or digitoxin concentration (digoxin > 1.85 µg/L or digitoxin > 23 µg/L) in 20 hospitals in France. Chronic poisoning occurred in 722 patients (86%). The aims were to identify factors associated with the use of digoxin-Fab and compare acute with chronic poisonings. | Digoxin-Fab was given to 48/116 (41%) patients who had acute poisoning and 19/722 (2.6%) patients with chronic poisoning. The serum digoxin/digitoxin concentrations were statistically higher in the digoxin-Fab treated group than the non-treated group ( $p < 0.0001$ ). There were 120 deaths (4 were treated with digoxin-Fab). Mortality rate was higher in the chronic group when compared with the acute group (16% vs 5%). Mortality rate was lower in Fab treated group than untreated patients (6% vs 15%, $p < 0.005$ ).   | There were a lot of missing data with clinical data not available from 299 patients (26%). The chronic poisoning group was older (> 55 years) (96% vs 51%, $p < 0.0001$ ) with more patients having cardiac disease when compared with the acute group (99% vs 54%, $p < 0.0001$ ). This is not a randomised study and patients who were terminally ill with other co-morbidities were not given digoxin-Fab in view of poor prognosis. The authors did not investigate the cause of deaths, and therefore, it is difficult to attribute the high mortality rate to be due to patients not receiving digoxin-Fab.  |
| Bilbault et al. <sup>9</sup>   | A prospective observational study of 20 patients (4 acute and 16 chronic poisonings) who had life-threatening cardiac arrhythmias or hyperkalaemia were treated with digoxin-Fab 160 mg. A second 160-mg dose was given if the patient remained symptomatic.   | The median digoxin concentrations were 8.4 and 4.5 µg/L for the acute and chronic poisoning group, respectively. In the acute poisoning group, three out of four patients responded to 160 mg Digidot <sup>™</sup> . In the chronic group, 11/16 patients responded to 160 mg Digidot <sup>™</sup> . Hence, 70% patients required only one dose of digoxin-Fab (160 mg). There were three deaths from the chronic poisoning group but only one was thought to be related to digoxin toxicity (5%). Using this regime, 10 vials were saved in the acute group but 3 vials were overprescribed for the chronic group. | In this study, the calculated median dose required to neutralise digoxin burden in the acute and chronic digoxin poisoning would have been 320 mg and 160 mg Digidot <sup>™</sup> , respectively. The data suggests that acute digoxin poisoning does not require complete neutralisation on the basis of the serum concentration or ingested dose. In the chronic group, 160 mg Digidot <sup>™</sup> would have been adequate in neutralising the digoxin body burden in most of the cases. The follow-up period was 6 h post administration of digoxin-Fab and this may be too short to see if there is a recrudescence of toxicity especially in patients with renal failure. |
| Schaeffer et al. <sup>66</sup>   | A retrospective review of 14 patients with life-threatening digoxin toxicities with serum digoxin concentrations greater than 2 µg/L (2.6 µmol/L). There were 12 patients who had bradycardia (HR < 45/min), 1 had third-degree heart block and 1 had asystole.  | In this study, not all 14 patients had evaluable data. Cardiotoxicity improved in seven of nine evaluable patients within 24 h and another two patients were thought to improve by 72 h. Two adverse reactions occurred, which resolved with conventional treatment. The authors cannot determine the efficacy of the digoxin-Fab in three patients.  | This study demonstrated the limitations of a retrospective study in which multiple data were missing.  |

(Continued)

Table 1. (Continued)

| Publications                      | Methodology   | Results  | Comment   |
|-----------------------------------|---|--|---|
| Sanaei-Zadeh et al. <sup>53</sup> | A retrospective study of 147 patients with single acute digoxin poisoning. 22 were chronic users. No digoxin-Fab was available. | The median age was 23 years. The median ingested dose was 7.5 mg (range 1.25–37.5 mg) and the median time from ingestion to presentation was 4 h. The mean digoxin concentration was 4.3 µg/L. There were 17 patients who were considered to have life-threatening dysrhythmias (12%). Of 63 patients (43%) who had indications for treatment with digoxin-Fab, 2 patients died. There were no correlation found between chronic users and toxicities. | The patients in this study with acute digoxin poisoning have a relatively low serum digoxin concentration despite a reported high ingested dose and hence the low mortality rate. However, only 73 patients have digoxin concentrations performed which made it difficult to know if the other 74 patients have only mild poisoning or not. Early presentation to hospital and decontamination may explain the low lethality in this case series. The paper does pose the question of whether digoxin-Fab should be administered on the basis of reported ingested dose only. |

Table 2. Response to digoxin-Fab.

| Author                                   | Smolarz et al. <sup>22</sup> | Antman et al. <sup>23</sup> | Hickey et al. <sup>7</sup>  |
|--|------------------------------|-----------------------------|-----------------------------|
| Total no. of patients                    | 34                           | 148                         | 717                         |
| Acute                                    | 30 (88%)                     | 75 (51%)                    | 209 (29%)                   |
| Chronic                                  | 4 (12%)                      | 74 (49%)                    | 508 (71%)                   |
| Median/mean digoxin concentration (µg/L) | 12.2                         | 8                           | 9–11 (acute), 4–5 (chronic) |
| Median/mean digoxin-Fab (mg)             | 480                          | 200                         | 120                         |
| Complete response (%)                    | 32 (94%)                     | 119 (80%)                   | 357 (50%)                   |
| Partial response                         | –                            | 14 (10%)                    | 172 (24%)                   |
| No response (%)                          | –                            | 15 (10%)                    | 89 (12%)                    |
| Deaths (%)                               | 2 (6%)                       | –                           | 171 (24%)                   |

and full neutralisation may not be optimal as digoxin is needed to manage the cardiac conditions.

The concept of giving a loading dose followed by an infusion was proposed based on pharmacokinetic studies of 17 patients.<sup>40</sup> Most of these patients had acute poisonings and were successfully treated with 320–480 mg digoxin-Fab infused between 0.5 and 7 h. The study proposed that a loading dose of 160 mg followed by an infusion of 0.5 mg/min was adequate to bind digoxin that sequestered into the serum from the tissue during the first 8 h. This regimen was estimated to achieve a greater efficiency of digoxin-Fab with the percentage of bound-Fab increasing from 48 to 70% and a lower total digoxin-Fab dose.

Another case report showed that a smaller bolus dose followed by an infusion of digoxin-Fab can be used successfully. A patient ingested 10 mg methyl digoxin with a serum digoxin concentration of 7.4 µg/L (9.5 µmol/L) 23 h post ingestion.<sup>21</sup> He was treated with a small loading dose of 80 mg digoxin-Fab followed by 30 mg/h for 10 h. The free serum digoxin concentration went down to near zero during the digoxin-Fab infusion and then slowly rebounded to a concentration below 2 µg/L (2.6 µmol/L), peaking after 55 h. The total digoxin-Fab dose was 60% of the regimen that would otherwise have been used.

In some cases, free digoxin reappeared in the serum 8–12 h after beginning the treatment.<sup>40</sup> However, this amount of digoxin redistributed from the tissues may not necessarily be elevated or cause cardiac toxicity. For example, in a patient with chronic digoxin poisoning and ventricular tachycardia, single dose of 120 mg digoxin-Fab (3 vials) reduced the serum unbound digoxin concentration close to zero from 5.8 µg/L for at least 152 h and patient remained clinically stable.<sup>45</sup>

There is a greater potential for the free serum digoxin concentration to rebound at a much later time in patients with chronic renal failure that are treated with digoxin-Fab because the half-lives of digoxin and digoxin-Fab are much longer. For example, in one study of 14 patients that had normal renal function and were treated with digoxin-Fab, rebound took place within 12–24 h, but occurred up to 130 h later in patients with renal impairment and end-stage renal failure.<sup>38,46</sup> However, there were only three patients who were suspected to have recrudescence of cardiac toxicity.



One was treated with a second dose of digoxin-Fab without any improvement and later was shown to have free digoxin concentrations of zero after both the first and the second dose of digoxin-Fab. The other two patients improved without any intervention. Hence, with calculated 'neutralising' doses, recrudescence of cardiac toxicity is a rare event even in patients with chronic renal failure.

### Indications for digoxin-Fab

There is general agreement that digoxin-Fab is indicated in patients with life-threatening tachy-bradyarrhythmias, hyperkalaemia ( $>6$  mmol/L) or haemodynamic instability with concentrations (e.g. digoxin  $>2$   $\mu\text{g/L}$  or  $>2.6$  nmol/L) that support digoxin may be a contributing cause.<sup>9</sup> It is also generally stated that digoxin-Fab is *not* indicated for asymptomatic patients with an elevated serum digoxin concentration. However, there is no consensus as to whether it is useful or should be used for other less serious and non-specific toxicity such as gastrointestinal symptoms or increased automaticity. It is clear that such symptoms may be attributable to digoxin toxicity and may resolve with discontinuation of digoxin. Furthermore, the higher the digoxin concentration, the more likely the symptoms are to resolve with discontinuation.<sup>54</sup> Increased 'automaticity' (e.g. ventricular ectopics, or supraventricular tachyarrhythmias) and AV-block and those with multiple symptoms were most likely to improve with digoxin cessation and it is *likely* that digoxin-Fab would accelerate the rate of improvement of these symptoms. However, the cost-effectiveness of treating non-life-threatening digoxin toxicity is drawn into question due to the increased cost of digoxin-Fab and multiple co-morbidities of these patients.

There are very few studies that have carefully measured free and bound digoxin concentrations before and after the use of digoxin-Fab.<sup>33</sup> As a result, there are no current data to establish the lowest effective digoxin-Fab dosing regimen. Digoxin has a very large Vd of 5–10 L/kg, and distribution/redistribution occurs over several hours to days and is best described with a two-compartment model.<sup>55</sup> Most of the digoxin in the body is outside the central compartment and not immediately available for binding. Thus, even a very small loading dose of digoxin-Fab (40–80 mg; 1–2 vials) will generally rapidly drop the free serum digoxin concentration to zero.<sup>21,29,40</sup> Any excessive digoxin-Fab will be partly wasted (eliminated in urine). In a two-compartment pharmacokinetic model derived in volunteers, the mean central and peripheral compartments were estimated to be 55 L ( $V_c$ ) and 330 L ( $V_p$ ), respectively for digoxin.<sup>56</sup> The parameters in this model are also broadly in agreement with other studies.<sup>29</sup>

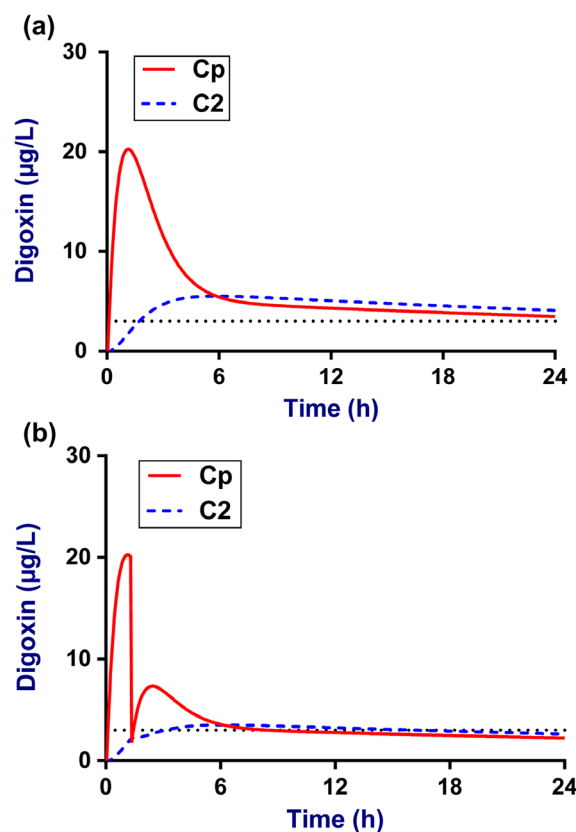
Using these pharmacokinetic parameters, we explored the advantages of a titrated digoxin-Fab dosing regimen:<sup>56</sup>

- Central compartment digoxin load: serum digoxin concentration ( $\mu\text{g/L}$ )  $\times$  55 L;
- Peripheral compartment digoxin load: serum digoxin concentration ( $\mu\text{g/L}$ )  $\times$  330 L;
- Rate constant for redistribution ( $k_{21}$ ) = 0.12/h,  $k_{12}$  = 0.76/h,  $k_{10}$  = 0.29/h.

### Digoxin-Fab in acute poisoning

Acute poisoning presents several problems with regard to estimating the amount of digoxin requiring neutralisation. The bioavailability of digoxin varies from 60 to 80%; hence, one can overestimate the digoxin-Fab dose if it is based on the ingested dose. In addition, vomiting or administration of activated charcoal may further reduce the amount of digoxin absorbed.

Figure 1 shows a simulated graph of digoxin concentrations in the central and peripheral compartment following a small overdose of digoxin with an early high concentration. If the serum digoxin concentration is used to calculate the dose, and less than 6 h or so have elapsed from the time of ingestion, then digoxin will not have completely distributed. Multiplying the digoxin concentration by the average volume of distribution may substantially overestimate the amount of digoxin present. Further, volume of distribution is variable and thus up to a 2-fold error may come from this calculation. After some digoxin-Fab is administered, the total digoxin (bound and unbound) concentration is increased and this

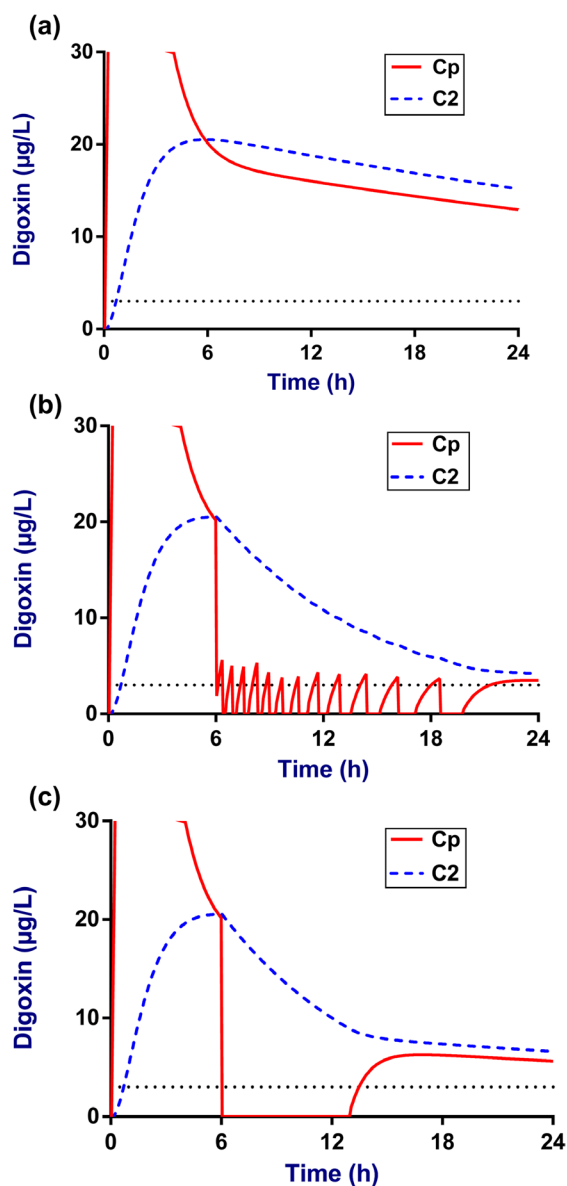


**Fig. 1.** A simulated graph of free digoxin concentrations in the central and peripheral compartment following an overdose of digoxin 3.5 mg (a) and after treatment with digoxin-Fab 80 mg (b) administered 2 h later. If the calculation of digoxin-Fab dose is based on the peak concentration in the distribution phase, then it will be estimated to be 800 mg. In this simulated model, digoxin-Fab 40 or 80 mg given during the distribution phase would have brought the digoxin concentration down significantly by 6 h. A two-compartment model has been used with the following parameters:  $F = 0.8$ ,  $K_a = 1$ ,  $K_{21} = 0.12/\text{h}$ ,  $K_{12} = 0.76/\text{h}$ ,  $K_{10} = 0.15/\text{h}$ ,  $V_c = 55$  L,  $Cl = 7.5$  L/h.<sup>56</sup> The dotted line is at 3  $\mu\text{g/L}$ .  $C_p$  = central compartment,  $C_2$  = peripheral compartment.



cannot be used to guide dosing strategy unless free digoxin can be measured. However, clinical response and ECG changes can be measured.

Figure 2 demonstrates a simulated graph of digoxin concentrations in the central and peripheral compartment following a large overdose of digoxin with a high serum concentration at 6 h. Giving a large bolus of digoxin-Fab would bring the digoxin concentration to zero but will



**Fig. 2.** A simulation of free digoxin concentrations in the central and peripheral compartment of a patient who had taken an acute overdose of digoxin 13 mg (a). (b) The outcome of giving repeated small bolus doses of digoxin-Fab that are titrated against clinical response (with toxicity appearing with concentrations of  $> 3 \mu\text{g/L}$ ). (c) Treatment with a large bolus dose of digoxin-Fab calculated to half neutralise the digoxin load (based on both the ingested dose and the 6 h concentration). There is a late rebound at  $> 12$  h with a peak free digoxin concentration subsequently of over  $6 \mu\text{g/L}$ . A two-compartment model has been used with the following parameters:  $F = 0.8$ ,  $K_a = 1$ ,  $K_{21} = 0.12/\text{h}$ ,  $K_{12} = 0.76/\text{h}$ ,  $K_{10} = 0.15/\text{h}$ ,  $V_c = 55 \text{ L}$ ,  $Cl = 7.5 \text{ L/h}$ .<sup>56</sup> The dotted line is at  $3 \mu\text{g/L}$ . Cp = central compartment, C2 = peripheral compartment.

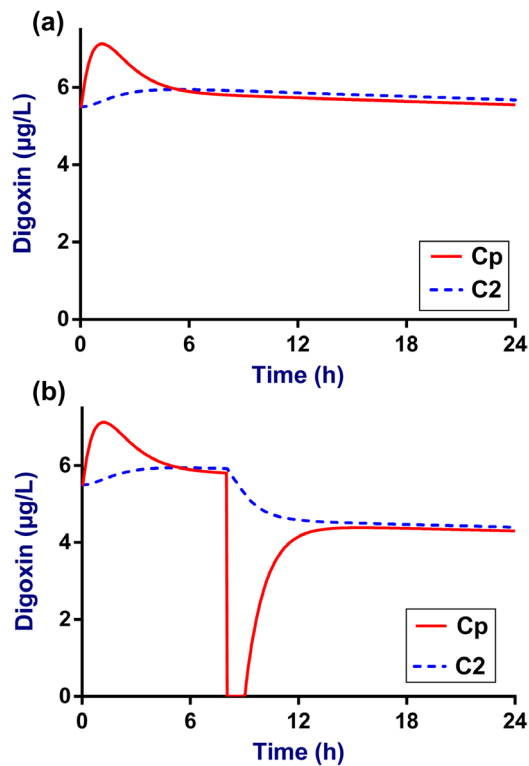
rebound at a later time following re-distribution. In such a scenario, it would be more efficient to give small repeated bolus doses of digoxin-Fab according to clinical response. This will provide a safe and more cost-effective approach to acute digoxin poisoning.

In the presence of life-threatening toxicity (e.g. high potassium or arrhythmias), the amount that can neutralise the digoxin in the central compartment can be estimated from the concentration ( $\mu\text{g/L}$ ) multiplied by 55 (the  $V_c$  in L). If a concentration is not available, some assumptions can be applied. A serum digoxin concentration greater than  $20 \mu\text{g/L}$  ( $= 26 \mu\text{mol/L}$ ) is rarely reported in acute overdose, and based on the above formula this would require 80 mg (2 ampoules) digoxin-Fab to neutralise the amount of digoxin in the central compartment. This is likely to be substantially lower than the 20 vials (costing around US\$15,000) suggested in the product information.

A case study demonstrated that a single infusion of 80 mg digoxin-Fab was adequate to manage an acute overdose with a serum digoxin concentration of  $15.4 \text{ nmol/L}$  ( $12 \mu\text{g/L}$ ).<sup>33</sup> An 82-year-old patient (45.7 kg) took an acute overdose 6 h previously and had a measured creatinine clearance of  $32 \text{ mL/min}$ . A full neutralising dose would have been calculated to be 8 vials (320 mg). The study measured digoxin-Fab as well as free and bound digoxin concentrations and showed that the free digoxin concentration dropped to zero within an hour. *In vitro*, the maximal effect is observed when the digoxin-Fab:digoxin ratio is equimolar and the addition of excess antibodies does not have a greater effect in reversing  $\text{Na}^+/\text{K}^+$  ATPase inhibition.<sup>41</sup> Pharmacokinetic simulations suggest that 40–80 mg (1 or 2 vials) of digoxin-Fab is sufficient to neutralise the amount of digoxin in the central compartment in most acute overdoses. The onset of clinical benefit should be apparent within 60 min. Further doses could be given based on clinical parameters such as ECG findings, haemodynamic status and potassium concentrations. Most patients should respond to half or less of the neutralising dose. If only low titrated doses of digoxin-Fab are given recrudescence (if it occurs) will occur quickly (within 6 h), so in principle this should reduce the required duration of monitoring for recrudescence of symptoms (potassium, ECG, and free digoxin concentrations, if available) from what is commonly suggested, i.e. 48 h, and even longer if there is renal failure. Altered dosing recommendations are based on case reports and pharmacokinetic data and should be validated with further clinical studies with toxicokinetic data. Due to these uncertainties, in the event of cardiac arrest, it would be reasonable to give a full neutralising dose.

### Digoxin-Fab dosing in chronic toxicity

Figure 3 shows a simulated graph of chronic digoxin poisoning. This graph demonstrates that the calculated digoxin-Fab dose can be overestimated if the digoxin concentration is measured before distribution takes place. In addition, there are several methods suggested to ‘calculate’ the total body burden. Although these methods appear similar, they can produce quite disparate results. Table 3 demonstrates



**Fig. 3.** A simulated graph of free digoxin concentrations in the central and peripheral compartment of a patient with chronic digoxin poisoning who had a trough digoxin concentration of 5.5 µg/L (a). At time 0, the patient takes a further dose of digoxin 250 µg. As in acute poisoning, if blood is taken before distribution is complete, the digoxin load will be overestimated (the modelled body burden is 2 mg). (b) Treatment with digoxin-Fab 40 mg at 8 h post last dose of digoxin. A two-compartment model has been used with the following parameters:  $F = 0.8$ ,  $K_a = 1$ ,  $K_{21} = 0.12/h$ ,  $K_{12} = 0.76/h$ ,  $K_{10} = 0.02/h$ ,  $V_c = 55 L$ ,  $Cl = 1 L/h$ .<sup>56</sup> The dotted line is at 3 µg/L. Cp = central compartment, C2 = peripheral compartment. Note in this model the clearance is only 1 L/h (simulating severe renal impairment).

how common methods used can overestimate (or occasionally underestimate) the amount of digoxin-Fab required to completely neutralise digoxin body load by almost 2-fold in patients with different lean body mass.

Yet, in chronic digoxin poisoning, it has generally been observed that 1–3 vials is usually sufficient to neutralise the body burden.<sup>6</sup> Empirically many people give 1 vial at a time and then assess the clinical response with further vials at roughly 60-min intervals if no response. Response to smaller doses may be due to a combination of factors: complete neutralisation is not required, the real digoxin body burden is not as large as estimated with usual methods, the cardiac effects are reversed rapidly but distribution back from the peripheral tissues is slow and there is also ongoing elimination during this time.

Overestimates of digoxin body burden may be further compounded by the fact that the volume of distribution is much reduced in renal failure, which is often a precipitating factor in the elderly.<sup>57</sup> A study showed that the volume of distribution is estimated to be 5.8 L/kg in subjects with normal renal function, while in patients with renal impairment it is about 3.6 L/kg. This can make a huge difference when calculating the total body burden of a renal impaired patient as shown in Table 4.<sup>29</sup> Hence, we recommend giving 1 vial (40 mg) at a time and observe for clinical response. If none is observed after 60 min, a second ampoule of digoxin-Fab may be administered, to neutralise digoxin re-distributing from the peripheral compartment. This time frame is suggested because previous studies showed that digoxin-Fab should work within 30–45 min of administration. If this regimen fails to improve symptoms, an alternative diagnosis should be considered.

### Safety of digoxin-Fab

Adverse events attributable to Fab such as exacerbation of heart failure, increased ventricular response in atrial fibrillation, or hypokalaemia are uncommon, reported to be < 10%, and are generally not serious (Table 5).<sup>23</sup> 'Allergic' reactions are also rare. In one large series, allergic reactions occurred in 0.8% (6/717) of patients.<sup>7</sup> Allergic reactions were more common in patients with a history of atopy or asthma.<sup>58</sup> Recrudescence of digoxin toxicity occurred in only 2.8% (20/717) of patients. In this study, the calculated digoxin-Fab

**Table 3.** Estimation of the digoxin body load for a 10 µg/L concentration.

| Patient                               | Most likely real Vd (L) | True total body burden (mg) | Method 1 (mg) | Method 2 (mg) |
|---------------------------------------|-------------------------|-----------------------------|---------------|---------------|
| Frail 50 kg M (58% lean body wt.)     | 290                     | 2.9                         | 5             | 3.5           |
| Obese 100 kg F (48% lean body wt.)    | 480                     | 4.8                         | 5             | 7             |
| Muscular 100 kg M (65% lean body wt.) | 650                     | 6.5                         | 5             | 7             |

This table shows estimates for a 10 µg/L concentration in a 50-kg frail elderly man, a 100-kg overweight woman and a 100-kg muscular man.<sup>67</sup> These are contrasted with physiological estimates based on the Vd being 10 times calculated lean body mass.<sup>68,69</sup> The scenarios demonstrate that these methods could easily overestimate the amount of digoxin-Fab required to completely neutralise digoxin body load by almost 2-fold.

Method 1: Estimate digoxin load by multiplying serum digoxin (µg/L) × 0.5 to give mg body burden [OR serum digoxin (nmol/L) × 0.4] (method 1). This makes an assumption that the volume of the distribution and body weight are the same for all patients.

Method 2: Estimate digoxin load by multiplying serum digoxin concentration (µg/L) × weight × average Vd (7 L/kg). To convert molar units (nmol/L) to mass units (µg/L) multiply by 0.78. Failure to do this step will overestimate body burden by about 25–30%.

The Heitmann equation is used to calculate the lean body weight of the frail elderly man and the lean body weight equation is used to calculate the other two scenarios, with an adjustment of 10%.<sup>68</sup> It is assumed that a frail 50-kg 75-year-old man has a BMI of 27, an obese 100-kg woman has a BMI of 35, and a muscular 100-kg man has a BMI of 25.

**Table 4.** Estimation of the total body burden with a serum digoxin concentration of 10 µg/L in normal and renal impaired patients.

|                                     | Vd in a 70-kg patient (L) | True body burden (mg) | Method 1 (mg) | Method 2 (mg) |
|-------------------------------------|---------------------------|-----------------------|---------------|---------------|
| Patients with normal renal function | 406                       | 4                     | 5             | 4.9           |
| Patients with renal impairment      | 252                       | 2.5                   | 5             | 4.9           |

This table showed that the two methods would have overestimated digoxin-Fab requirements by 2-fold due to the reduced volume of distribution in patients with renal failure.

Method 1: serum digoxin concentration (µg/L) × 0.5 to give mg body burden [OR serum digoxin (nmol/L) × 0.4].

Method 2: serum digoxin concentration (µg/L) × weight × average Vd (7 L/kg).

dose was estimated based on serum digoxin concentration and body weight or the dose ingested for acute overdose. Only four patients (8.5%) who received less than 50% of the calculated digoxin-Fab dose were thought to have recrudescence of digoxin toxicity. However, this finding was disputed by an independent cardiologist who attributed only one patient's deterioration as probably due to recrudescence of digoxin toxicity.<sup>7</sup>

### Cost considerations of digoxin-Fab

There is little dispute that digoxin-Fab is effective in managing life-threatening toxicity. It is also therefore cost-effective in Western countries with lower cost per life-year saved than many other commonly funded treatments.<sup>59</sup> When digoxin-Fab is used to treat patients without life-threatening toxicity, there may be offsetting cost savings from reduced use of other medical resources (reduced length of stay, laboratory monitoring, and other treatments such as pacemakers). The mean length of stay in the hospital in patients with digoxin toxicity is typically 2–5 days.<sup>60</sup> The higher the initial digoxin concentration, the greater the length of stay and all other costs of admission.

In a simulated cost analysis, digoxin-Fab use was associated with increased costs but also reduced the length of stay by 1.5 days.<sup>61</sup> Those with higher serum digoxin concentrations and severe renal impairment were responsible for most of the longer length of stay in the group not treated with digoxin-Fab. While this study suggested treating patients with non-life-threatening toxicity and associated renal failure may result in substantial cost savings to the health care system, the cost of digoxin-Fab has nearly doubled (from US\$424 to US\$750 per ampoule) since this study was completed. The bed cost has certainly

increased since the study. In addition, patients may require hospitalisation for the management of the underlying causes for digoxin toxicity such as renal failure. Hence, the cost-effectiveness would be dependent on the bed cost and the number of vials of digoxin-Fab used for patients with digoxin toxicity.

### Conclusions

Digoxin-Fab is safe and effective in patients with life-threatening toxicity such as bradyarrhythmia, ventricular arrhythmia and hyperkalaemia. Clinical benefit is less clear in non-life-threatening toxicity but it may reverse other manifestations such as increased automaticity and gastrointestinal symptoms, improve patient comfort and also shorten length of stay. Patients with higher concentrations and/or moderate to severe renal impairment are those most likely to benefit. The cost-effectiveness of digoxin-Fab is a balance between its increasing price and the daily costs of hospital stay in such patients. More efficient dosing strategies may also substantially improve the cost-effectiveness of digoxin-Fab. With acute ingestion, 40–80 mg (1–2 vials) will neutralise digoxin in the central compartment. The dose may be repeated if there is no clinical response. In cardiac arrest, a full neutralising dose may be justified. In most patients with chronic toxicity, titration with slow infusions of single vials (40 mg) of digoxin-Fab will drop the serum unbound digoxin concentration to zero and result in a clinical response; this approach should in most cases substantially reduce the total doses used. However, further pharmacokinetic studies are needed to clarify the indications, refine the optimal effective and cost-effective dosing regimen for digoxin-Fab in acute and chronic digoxin poisoning.

**Table 5.** Adverse reactions to digoxin-Fab.

|  | Smolarz et al. <sup>22</sup> | Antman et al. <sup>23</sup> | Hickey et al. <sup>7</sup> | Ujhely et al. <sup>46</sup> |
|--|------------------------------|-----------------------------|----------------------------|-----------------------------|
| Total number of patients in each study           | 34                           | 150                         | 717                        | 14                          |
| Allergic reaction                                | 0                            | 0                           | 6                          | 0                           |
| Hypokalaemia                                     | 0                            | 6                           | 2                          | 0                           |
| Heart failure/rapid ventricular rate             | 4                            | 4                           | 14                         | 5                           |
| Recrudescence of toxicities                      | 0                            | 0                           | 20                         | 3                           |
| Others   | 0                            | 4                           | 10                         | 0                           |
| Total number of patients with adverse events (%) | 4 (11.8%)                    | 14 (9.3%)                   | 52 (7.3%)                  | 8 (5.7%)                    |



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## Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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