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Pharmacological treatment of cardiac glycoside poisoning

Darren M. Roberts,[1,2] Gamini Gallapatthy,[3] Asunga Dunuwille[3] & Betty S. Chan[4]

[1]Medical School, Australian National University, Canberra, ACT, Australia, 2603, [2]Drug Health Clinical Services, Royal Prince Alfred Hospital, Camperdown, NSW, Australia, 2050, [3]Cardiology, National Hospital of Sri Lanka, Colombo, Sri Lanka and [4]Clinical Toxicology and Emergency Medicine, Prince of Wales Hospital, Randwick, NSW, Australia

Correspondence
Dr Darren Roberts, Medical School, Australian National University, The Canberra Hospital, Yamba Drive, Garran, ACT, 2605, Australia.
Tel.: +61 (2) 6244 2222
Fax: +61 (6) 6244 4627
E-mail: darren.roberts@anu.edu.au

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Cardiac glycosides are an important cause of poisoning, reflecting their widespread clinical usage and presence in natural sources. Poisoning can manifest as varying degrees of toxicity. Predominant clinical features include gastrointestinal signs, bradycardia and heart block. Death occurs from ventricular fibrillation or tachycardia. A wide range of treatments have been used, the more common including activated charcoal, atropine, β-adrenoceptor agonists, temporary pacing, anti-digoxin Fab and magnesium, and more novel agents include fructose-1,6-diphosphate (clinical trial in progress) and anticalin. However, even in the case of those treatments that have been in use for decades, there is debate regarding their efficacy, the indications and dosage that optimizes outcomes. This contributes to variability in use across the world. Another factor influencing usage is access. Barriers to access include the requirement for transfer to a specialized centre (for example, to receive temporary pacing) or financial resources (for example, anti-digoxin Fab in resource poor countries). Recent data suggest that existing methods for calculating the dose of anti-digoxin Fab in digoxin poisoning overstate the dose required, and that its efficacy may be minimal in patients with chronic digoxin poisoning. Cheaper and effective medicines are required, in particular for the treatment of yellow oleander poisoning which is problematic in resource poor countries.

Source, epidemiology and importance

Cardioactive steroids are naturally-occurring compounds identified in various plant and animal species (see examples in Table 1. There is much structural diversity, being subclassified on the basis of the aglycone steroid moiety, whereby those with a five-membered lactone ring are called cardenolides while those with a six-membered lactone ring are called bufadenolides [1]. Ouabain and bufadenolides are structurally similar to compounds found in humans, probably of adrenal origin, that are elevated in pre-eclampsia, hypertension and chronic kidney disease [2, 3]. Many cardioactive steroids are bound to sugars so are referred to as cardiac glycosides and these are the major type associated with poisoning, so cardiac glycoside will be the term used throughout this review.

Unfortunately, poisoning due to cardiac glycosides is a world-wide phenomenon. This reflects the long-standing and widespread therapeutic use of digitalis glycosides, particularly digoxin, but also epidemic and sporadic poisoning with oleander plants. For example, in the US alone, thousands of cases of cardiac glycoside poisoning were referred to US Poison Control Centers in 2013 and the majority were treated in a healthcare facility [4]. Digoxin poisoning may follow intercurrent illnesses and/or prescribing or dispensing errors, and accidental or intentional poisoning.

Yellow oleander and common oleander are found throughout the tropics and subtropics [5]. Yellow oleander poisoning is a major public health issue in some regions of Sri Lanka and India [6, 7]. Ingestion of seeds (yellow oleander) or oleander leaves can be associated with severe poisoning and death. Treatment is complicated due to variability in toxic threshold, diagnostic tests, delayed onset of toxicity (particularly in the case of yellow oleander), requirement for hospital transfer and availability of efficacious and affordable treatments [5].

Pharmacokinetics

Individual cardiac glycosides vary widely in their pharmacokinetic properties, despite similarities in structure [8]. The pharmacokinetics of digoxin vary, including

Table 1

Selected sources of cardiac glycosides

Scientific name	Common name	Selected cardioactive steroids	Steroid subclassification
Antiaris toxicaria		Antiarin	Cardenolide
Asclepias sp.	Milk weed		Cardenolide
***Cascabela thevetia* or *Thevetia peruviana* (previously *T. neriifolia*)**	Yellow oleander	Thevetin A and B, peruvoside, neriifolin, thevetoxin, ruvoside, theveridoside	Cardenolide
Cerbera odallam	Sea mango	Cerberin	Cardenolide
Calotropis gigantea	Crown flower		Cardenolide
Convallaria majalis	Lily of the valley	Convallarin, convallamarin, convallatoxin	Cardenolide
***Digitalis sp* (including *D. lanata* and *D. purpurea*)**	Foxglove	Digoxin, digitoxin	Cardenolide
Drimia maritima (Urginea maritima)	Squill	Glucoscillarene A, proscillaridine A, scillarene A, scilliglaucoside and scilliphaeoside	Bufadenolide
Homo sapiens	Human beings	Marinobufagenin, ouabain	Bufadenolide and cardenolide
***Kalanchoe* sp**			Bufadenolide
Nerium oleander	Common oleander	Oleandrin, folineriin, adynerin, digitoxigenin	Cardenolide
Rhinella marina	Cane toad	Bufalin, marinobufagenin, telocinobufagin	Bufadenolide
Strophanthus sp		Ouabain (g–strophanthin)	Cardenolide

absorption (can relate to the formulation [9]), duration of distribution (2–6 h) and elimination half-life (mean 40 h, range 20–50 h), and elimination is predominantly renal [10]. The onset of digoxin's effect is delayed by approximately 6 h, which reflects the time for distribution to a peripheral compartment and/or time-dependent binding to the Na^+-K^+-ATPase [11]. In acute poisoning, the initial serum digoxin concentration may be very high and will not reflect the total body burden because full distribution has not occurred. Digitalis cardiac glycosides are thought to undergo enterohepatic recycling, given that multiple doses of activated charcoal (MDAC) increase clearance (discussed later). For example, the mean elimination half-life of digitoxin is long at 7.5 days which reflects extensive enterohepatic recirculation [10].

Compared with ingestion of yellow oleander extract, the pharmacokinetic profile of digoxin cross-reacting substances following intentional ingestion of the seed is erratic with prolonged absorption (extending beyond 50 h post-ingestion in some) which dominates the concentration–time profile. The apparent terminal half-life is also highly variable, with a median time of 42.9 h. The number of seeds ingested correlates poorly with the area under the concentration–time curve or severity of cardiotoxicity, suggesting variability in bioavailability [8].

There are limited pharmacokinetic data on other cardiac glycosides in humans.

Mechanism of action and toxicity

It is generally considered that cardiac glycosides have an identical mechanism of action, which has largely been described using digoxin and ouabain. However, there may be differences in action between individual cardiac glycosides [2] and this may influence toxicity or response to treatment. For example insulin appears to reverse the effect of digoxin but not ouabain on Na^+-K^+-ATPase, which may be due to different binding regions [12].

Cardiac glycosides inhibit the Na^+-K^+-ATPase on cardiac and other tissues, causing intracellular retention of Na^+, followed by increased intracellular Ca^{2+} concentrations through the effect of the Na^+-Ca^{2+} exchanger. The elevated intracellular Ca^{2+} concentration promotes inotropy and bradycardia, and the intracellular accumulation of Na^+ and Ca^{2+} causes partial membrane depolarization which increases automaticity and ventricular ectopy. Digoxin also increases vagal tone, contributing to bradycardia and impaired conduction through the atrio-ventricular node, and may block voltage-gated Na^+ channels. Other actions are also reported, including endocytosis of Na^+-K^+-ATPase and activation of intracellular signal transduction mechanisms [3, 13].

Clinical features of poisoning

The predominant features of acute poisoning include gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhoea), hyperkalaemia, generalized weakness, drowsiness and, importantly, cardiotoxicity (bradycardia and heart block, dysrhythmias). These may appear within a few hours of acute poisoning. Vision changes, including green/yellow discolouration, have been reported rarely following chronic digoxin poisoning [6, 14–18]. However, other electrolyte abnormalities may be noted in patients with chronic poisoning due to concomitant conditions and medications [19].

The most common cardiac abnormality in poisoning is sinus bradycardia. ECG changes in therapeutic dosing

(or mild poisoning) include flattening or inversion of the T wave and depression of the ST segment. Moderate poisoning manifests as prolonged PR interval (first degree heart block) or sinus bradycardia. Severe poisoning manifests as second or third degree heart block due to inhibition of the atrioventricular node. Sinus arrest or exit block are also reported. Deaths occur due to ventricular fibrillation resistant to electrical cardioversion or asystolic arrest [6, 14–19].

In a series of intentional yellow oleander poisoning, 56% of 162 patients with intentional self-poisoning developed dysrhythmias requiring treatment [15]. Reflecting the pharmacokinetics discussed above, the time course for progression and resolution of cardiotoxicity was variable. For example, one patient remained in sinus rhythm for 72 h before developing second degree heart block, while another had a serious dysrhythmia at 92 h [14, 15]. However, the majority of deaths occurred within 24 h [20].

Atrial fibrillation, ventricular ectopics and tachycardias are also reported from digoxin, particularly chronic poisoning which may also relate to pre-existing cardiac disease or electrolyte disturbances from concomitant diuretic therapy or intercurrent illnesses [16–18].

Outcomes

Previously, it was reported that mortality from digitalis compounds was up to 20% and severe toxicity may not occur until 24 h post-admission for digoxin, or up to 5 days for digitoxin poisonings [18]. Mortality was reported to be lower following introduction of Fab antibody fragments [18] and has been even lower in recent times [4]. The case fatality for yellow oleander poisoning is up to 10% in patients presenting to tertiary centres [21] but as low as 3% at secondary care hospitals [15, 20]. Multiple factors may contribute to this difference in outcome, including referral criteria, treatments and resources.

Management of poisoning

The management of patients with suspected or known cardiac glycoside poisoning is complicated by the variable time course in toxicity, unpredictable dose–response relationship, and requirement for interhospital transfers and expensive or invasive treatments.

Given the structural similarity of the cardiac glycosides, treatments are frequently extrapolated from digitalis poisoning. However, in recent years, there have been an increasing number of clinical trials assessing yellow oleander poisoning. Currently, randomized controlled trials are only available for yellow oleander poisoning, so data supporting recommendations for poisoning with other cardiac glycosides including digoxin is of low quality [22].

Overview and risk assessment

A risk assessment regarding the likelihood of developing toxicity, and planning treatment, should be conducted in all patients with acute poisoning. In the case of cardiac glycoside poisoning this can be complicated due to variability in the toxic dose, and in the case of yellow oleander there is also variability in the onset of toxicity as discussed above. For example, death has occurred after ingestion of one or two yellow oleander seeds, while other patients have survived after consuming 10 or more seeds without requiring pacing or anti-digoxin Fab [6, 8, 14, 21]. In the case of digoxin, ingestion exceeding 10 mg is often reported to be associated with severe toxicity and death in the absence of treatment, but outcome data supporting this are limited and confounded by treatment received.

Where possible, patients with acute poisoning should be admitted to a critical care area for continuous cardiac monitoring, investigations and consideration of treatment. Because of the risk of a delayed onset of significant dysrhythmias from yellow oleander, it may be necessary to monitor such patients for up to 72 h post-ingestion. Toxicity from digoxin poisoning usually manifests within 6 h of the last dose, whether this follows acute or chronic poisoning.

If a patient is asymptomatic, the ECG does not show brady- or tachyarrhythmias, potassium is within the reference range and digoxin concentration is less than 2.3 ng ml^{-1} (3 nmol l^{-1}) then the risk of developing poisoning is low and the patient can be medically cleared.

Key treatments for consideration are gastro-intestinal decontamination, treatment of nausea and bradycardia, and for severe dysrhythmias, administration of anti-digoxin Fab or temporary cardiac pacing.

Risk stratification and treatment are largely guided by investigations.

Biochemistry Hyperkalaemia is a manifestation of cardiac glycoside poisoning, and although a higher potassium concentration is associated with increased risk, the relationship between potassium concentration and cardiotoxicity is poorly defined. In acute digoxin exposures, when present, hyperkalaemia is a hallmark of poisoning [23]. In chronic digoxin poisoning, there are many confounders that could contribute towards hyperkalaemia such as renal failure, concurrent use of angiotensin blocking agents or spironolactone [24]. In the case of yellow oleander, while hyperkalaemia is associated with toxicity, a mean concentration of 5.4 mmol l^{-1} was noted in severe cardiotoxicity while 4.3 mmol l^{-1} was found in mild cardiotoxicity. Significant variability within each group (including hypokalaemia) reduces its reliability [14].

Digoxin assay In digoxin exposures, higher plasma digoxin concentrations are associated with more severe poisoning, but there are no specific criteria for diagnosing a patient as being poisoned. For example, symptoms of toxicity were noted in some patients with digoxin concentrations less than 2 ng ml^{-1} (2.6 nmol l^{-1}), but not others with a digoxin concentration exceeding 2 ng ml^{-1} (2.6 nmol l^{-1}) [19]. Distribution kinetics, as discussed above, are a possible contributor to this poor correlation.

Most digoxin assays are based on ELISA platforms which can cross react with similar structures, so this can be utilized for determining if non-digoxin cardiac glycosides (e.g. from oleander) are present [1, 8]. However, the reported 'digoxin concentration' may not correlate with toxicity because it reflects an unknown proportion of several cardiac glycosides with differing potency and cross-reactivity. Further, recent ELISA platforms cross-react to a lesser extent than earlier platforms so they may be less useful for measuring non-digoxin cardiac glycosides. Communication with the laboratory may provide valuable insights into the extent of cross-reactivity with the assay they use, including information regarding whether it has been tested against positive controls from non-digoxin sources.

Decontamination

A single dose of activated charcoal 50–100 g should be administered to all patients with acute ingestion of a potentially toxic exposure, regardless of the time of ingestion. Although clinical trials have not confirmed the efficacy of this approach, this recommendation is based on pharmacokinetic data (see above, and enhanced elimination below), and the safety of activated charcoal.

Yellow oleander has a prolonged absorption phase and while some advocate the use of gastric lavage [15, 21], there is no evidence to support its use and it could potentially delay the administration of activated charcoal which is likely to be more effective in preventing prolonged absorption.

Electrolyte abnormalities

Treatment of hyperkalaemia is controversial, largely due to limited data. Given the mechanism of action of cardiac glycosides the extent of elevation is broadly considered to reflect the severity of poisoning, but there are exceptions as discussed previously.

Insulin may interact directly with Na^+-K^+-ATPase, altering the effect of digoxin as well as correcting hyperkalaemia by driving potassium into cells. Compared with control, there was a marked improvement in survival with less cardiotoxicity in rats administered insulin-dextrose and a difference in potassium (approximately 7.0 mmol l^{-1} *vs.* 4.5 mmol l^{-1}, depending on the model) [25]. Further, the apparent protective effect of insulin on Na^+-K^+-ATPase activity may depend on the type of cardiac glycoside due to differences in the subunit of Na^+-K^+-ATPase to which the cardiac glycoside binds [12].

Hypokalaemia may be noted in patients with cardiac glycoside poisoning, relating to either excessive diarrhoea or vomiting or medications such as diuretics. Hypokalaemia should be corrected since it increases cardiotoxicity from digitalis with therapeutic dosing [16]. Deaths have been reported in hypokalaemic patients with yellow oleander poisoning.

Exogenous calcium to 'stabilize' the myocardium in hyperkalaemia is commonly recommended in other settings. Theoretically, given that the intracellular concentration of calcium is elevated in cardiac glycoside poisoning, administration of calcium may increase toxicity and animal data have reported increased toxicity including death, which may relate to sustained cardiac contraction also known as 'stone heart'. However, case reports have not noted complications from intravenous calcium [26] and a study in pigs with digoxin poisoning reported that intravenous calcium chloride 10 mg kg^{-1} did not change mortality [27]. Other resources advise that calcium should be given [28], should not be given [29] or may be harmful [30]. At present, the benefit or toxicity of exogenous calcium for the treatment of hyperkalaemia in the case of cardiac glycoside poisoning is poorly defined and our practice is not to use it, in particular due to the availability of treatments that decrease potassium (e.g. anti-digoxin Fab, insulin-dextrose).

Antidotes

Therapeutic options to treat cardiac glycoside toxicity include pharmacological antagonists of bradycardia, reversal of Na^+-K^+-ATPase inhibition or enhanced elimination of the cardiac glycoside. Up to 40% of patients with severe cardiotoxicity from yellow oleander may revert to sinus rhythm after a number of hours without specific treatment, but it is not possible to determine in which patients this will occur [14, 15]. Spontaneous resolution from acute digoxin poisoning is less commonly reported, but the majority reported in the literature are treated so data are limited. The role of antidotes for treatment of chronic digoxin poisoning is less clear. Key antidotes are discussed below and listed in Table 2.

Atropine Atropine antagonizes cardiac glycoside vagal activation, increasing heart rate and observational data suggest a benefit [15, 31]. Doses of 0.6–1 mg are used first line, but doses as high as 2–3 mg have been used for persistent bradycardia, e.g. less than 40 beats min^{-1} accompanied by hypotension. Although larger doses have been used [15, 21], these may be associated with an anticholinergic delirium which requires sedatives and close nursing care. Hyperthermia can be hazardous in hot, non-air conditioned wards [14, 15, 21]. In Sri Lanka, it is used as a bridging treatment prior to temporary pacing.

Table 2

Summary of treatments for cardiac glycoside poisoning, in addition to supportive treatment

Indications	Treatment	Dose	Use in practice
Known, or potential for, toxicity	Multiple doses of activated charcoal	50 g loading followed by 25 g every 2–4 h for 24 h, but other regimens have also been used.	Unknown, but appears to be common, in particular for yellow oleander poisoning.
Hyperkalaemia, renal failure, bradycardia not responding to atropine, or ventricular arrhythmia.	Anti-digoxin Fab	Two vials (80 mg) incremental dose according to clinical response in acute digoxin poisoning [29]. One vial (40 mg) in chronic digoxin poisoning, repeat if required in 1 h [29]. 20–30 vials (800–1200 mg) in acute yellow oleander poisoning [33]	In practice there is wide variability in treatment thresholds and dosages for digoxin poisoning [42]. Not usually available for use developing countries due to cost.
Hyperkalaemia	Intravenous insulin and dextrose	50 ml 50% dextrose followed by 10 units short acting insulin i.v.	Unknown for digoxin poisoning, but in Sri Lanka, it is frequently used for $K^+ > 6$ mmol l^{-1}.
Bradycardia	Intravenous atropine	0.5–1 mg i.v.	Commonly, as a bridge to other treatments
Bradycardia (and perhaps hyperkalaemia)	Intravenous isoproterenol (isoprenaline) [16] or oral salbutamol		Unknown, except for Sri Lanka where it is used after temporary pacing.
Bradycardia and conduction block	Temporary cardiac pacing	According to usual guidelines	Its use in clinical practice outside of Sri Lanka is unknown, but in the case of digoxin use is thought to be limited in developed countries due to use of anti-digoxin Fab.

Anti-digoxin Fab Anti-digoxin Fab has a high binding affinity for digoxin, removing it from Na^+-K^+-ATPase, thereby reducing toxicity. Because anti-digoxin Fab may also bind to other cardiac glycosides, similar to the principles discussed in relation to the digoxin immunoassay, they have been utilized for treatment of toxicity from non-digoxin cardiac glycosides, notably yellow oleander.

Data on anti-digoxin Fab in digitalis poisoning are limited to observational data, so the efficacy and indications for anti-digoxin Fab are uncertain [22]. Case series have reported benefits from anti-digoxin Fab, but data regarding the response in acute or chronic poisoning are conflicting [32]. Recent observational data support an effect in acute poisoning, but a clinically meaningful effect in chronic poisoning has been questioned [24]. Here, while anti-digoxin Fab was found to be efficacious in binding the free digoxin in the central circulation, it appeared to be minimally effective in alleviating cardiac toxicities in chronic digoxin poisoning. Patients diagnosed with chronic 'digoxin poisoning' generally have significant co-morbid diseases such as renal and/or cardiac failure and are medicated with drugs such as β-adrenoceptor blockers and calcium antagonists. The lack of response to Fab in such cases suggests these other factors could drive much of the cardiac manifestations and risk of death. Outcomes can be favourable in patients with chronic 'digoxin poisoning' without treatment with Fab and further case controlled studies are needed to further support these observations.

Data also support outcomes of acute digoxin poisoning without use of anti-digoxin Fab. A case series of 147 patients (mean 10.1 mg, median 7.5 mg, range 1.25–37.5 mg) in a centre without access to anti-digoxin Fab, of whom 70% had nausea/vomiting, 52% had ECG changes and 43% had indications for anti-digoxin Fab, mortality was low at 1.4% [33]. The mean digoxin concentration was 4.3 μg l^{-1} (5.5 nmol l^{-1}) from 73 patients, which was much lower than expected from the reported dose. This suggests that not all cases of acute digoxin overdose require anti-digoxin Fab, nor should anti-digoxin Fab dose be calculated based on ingested dose. In contrast, a higher mortality (7.6%) was noted in a case series of acute and chronic digoxin and digitoxin poisoning despite Fab being used first line [34]. Further, a retrospective case-controlled study of chronic digoxin poisoning did not observe a beneficial effect of anti-digoxin Fab on mortality [35].

The optimal dose of anti-digoxin Fab for digoxin poisoning is also not established. Approaches to dosing regimens are variable, many incorporate whether it is acute or chronic poisoning, the ingested dose, and/or aim for half to full neutralization based on serum digoxin concentration [10]. Recently, dosing regimens based on much lower initial doses have been proposed, with 40 mg (one vial) for chronic poisoning and 80 mg (two vials) for acute poisoning. These can be repeated after 60 min if inadequate response or recurrence, or earlier if there is a clinical deterioration [32]. Larger doses, including that which will achieve full neutralization, can be used if the patient is peri-arrest.

An RCT ($n = 66$) in yellow oleander poisoning showed an early improvement in cardiac rhythm and hyperkalaemia from anti-digoxin Fab, prompting early termination of the trial. It was not powered to detect a change in mortality and no deaths were noted [36].

Dosing is generally higher in yellow oleander poisoning because of an inability to quantify adequately the body burden based on blood tests (in contrast to digoxin) and perhaps lower cross-reactivity. A dose–response study associated with the above-mentioned RCT recommended dosage of 1200 mg [36], but subsequent data suggest that 800 mg i.v. may also be effective [37, 38].

Temporary cardiac pacing

Uncontrolled data suggest that temporary cardiac pacing is associated with more complications and deaths than anti-digoxin Fab, and it does not reverse hyperkalaemia. For example a retrospective series noted failure of pacing to prevent life threatening dysrhythmia in 23% of cases, compared with 8% for Fab [18, 39]. However, these data are decades old so the extent to which they generalize to current treatments is unclear. Insertion of the pacing wire may also trigger ventricular fibrillation. Other potential limitations of temporary cardiac pacing are logistics, including procedural expertise and facilities that are often unavailable in rural regions and developing countries, requiring interhospital transfer of the patient and the associated delay in treatment may be associated with death [15, 21, 36].

Electrical cardioversion

Electrical cardioversion is generally ineffective for patients with malignant ventricular dysrhythmias from yellow oleander poisoning. Experience with digitalis poisonings is similar, where it has been recommended that electrical cardioversion should be reserved for cases with ventricular dysrhythmias refractory to other treatments using low energy levels (e.g. 20–100 J) [16, 40].

Enhanced elimination

MDAC are recommended for toxic exposures to digoxin because of pharmacokinetic data. For example, MDAC increased the clearance of intravenous digoxin in volunteers by 47% in one study [41], MDAC decreased the apparent elimination half-life by nearly 50% in patients with chronic digoxin poisoning [42], but in another study this was only significant if there was impaired kidney function [43]. MDAC doubled the clearance of intravenous digitoxin in volunteers [43].

In yellow oleander poisoning, a RCT (n = 401) noted that MDAC reduced mortality in yellow oleander poisoning compared with single dose activated charcoal (SDAC) [21]. However, a subsequent larger RCT which included yellow oleander poisoning (n = 1647) noted a non-significant trend in improved outcomes with MDAC [20]. There were differences in MDAC regimen between these studies but this was not considered to have had a significant effect on the results. Of note, a pharmacokinetic sub-study of the latter RCT suggested a similar increase in apparent clearance of cardiac glycosides from SDAC or MDAC, compared with no activated charcoal [8].

Taken together, it appears reasonable to administer MDAC, although it should not be used in preference to other treatments. Activated charcoal is safe but should not be administered to patients with an unprotected airway or ileus, for example due to atropine treatment.

Data do not support the role of extracorporeal treatments such as dialysis in cardiac glycoside poisoning [44].

Other treatments

A range of other treatments have been trialled, but data supporting an effect are limited and their use in routine clinical practice appears uncommon, or data are limited to animal studies. These include anticalin [45], fructose-1, 6-diphosphate (FDP; CAS 488-69-7) [46, 47], β-adrenoceptor agonists (isoprenaline or salbutamol) and magnesium for which evidence are limited. An anticalin with a high binding affinity for digoxin reduced the free plasma concentration of digoxin and toxicity in rats [45]. Anticalins are a non-biological alternative to anti-digoxin Fab, but data in humans are currently lacking. FDP is a relatively cheap drug that increases ATP production and stimulates Na^+-K^+-ATPase activity, and is currently being assessed for the treatment of yellow oleander poisoning. Others have been trialled including phenytoin and lignocaine, the rationale and evidence for which are limited.

Conclusions

Although there are a range of options available for the treatment of cardiac glycoside poisoning, their efficacy is poorly defined and this appears to influence their use in practice. More data are required to clarify the optimal treatment of cardiac glycoside poisoning, including the evaluation of lower priced medicines that can be used in resource poor countries. Research priorities include improved understanding of the dose–response of cheaper treatments such as insulin-dextrose in humans. Further, data of more novel and non-biological antidotes such as FDP and anticalin in humans with cardiac glycoside poisoning are of interest.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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