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RESEARCH ARTICLE

Extracorporeal treatment for digoxin poisoning: systematic review and recommendations from the EXTRIP Workgroup

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ABSTRACT

Background: The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup was formed to provide recommendations on the use of extracorporeal treatments (ECTR) in poisoning. Here, we present our results for digoxin. **Methods:** After a systematic literature search, clinical and toxicokinetic data were extracted and summarized following a predetermined format. The entire workgroup voted through a two-round modified Delphi method to reach a consensus on voting statements. A RAND/UCLA Appropriateness Method was used to quantify disagreement, and anonymous votes were compiled and discussed in person. A second vote was conducted to determine the final workgroup recommendations. **Results:** Out of 435 articles screened, 77 met inclusion criteria. Only *in-vitro*, animal studies, case reports and case series were identified yielding a very low quality of evidence for all recommendations. Based on data from 84 patients, including six fatalities, it was concluded that digoxin is slightly dialyzable (level of evidence = B), and that ECTR is unlikely to improve the outcome of digoxin-toxic patients whether or not digoxin immune Fab (Fab) is administered. Despite the lack of robust clinical evidence, the workgroup recommended against the use of ECTR in cases of severe digoxin poisoning when Fab was available (1D) and also suggested against the use of ECTR when Fab was unavailable (2D). **Conclusion:** ECTR, in any form, is not indicated for either suspected or proven digoxin toxicity, regardless of the clinical context, and is not indicated for removal of digoxin-Fab complex.

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Introduction

The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Supplement 1) aiming to provide recommendations on the use of extracorporeal treatments (ECTRs) in poisoning (www.extrip-workgroup.org). Rationale, background, objectives, complete methodology, and many toxin-specific recommendations are already published.[1–13] The following presents the workgroup's systematic review and clinical recommendations regarding the use of ECTR in patients with digoxin poisoning.

Pharmacology

Digoxin is a cardiac glycoside derived from the foxglove plant that is used for the treatment of heart failure and for rate

control of supraventricular dysrhythmias.[14] Its mechanism of action is through inhibition of the myocardial Na⁺-K⁺-ATPase pump.[14]

The molecular mass of digoxin is 781 Da and it is approximately 20 to 30% protein bound (Table 1). In therapeutic doses, 60 to 80% of orally administered digoxin is absorbed. Absorption and subsequent distribution are usually complete within 6 h but may be delayed for as long as 34 h after large ingestions.[15] The volume of distribution (V_D) of digoxin is large (6.2 ± 2.6 L/kg); less than 0.5% of the total body burden of digoxin is located in the blood, while the highest tissue concentrations are found in the heart and kidney, although skeletal muscle represents the largest single store in the body.[16,17] In patients on chronic digoxin therapy, the V_D decreases as kidney function declines.[18] In patients with normal kidney function, digoxin is predominantly excreted unchanged by the kidneys (60–70%), and to a lesser extent is cleared by hepatic hydroxylation. Elimination is biphasic, with a

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 Supplemental data for this article can be accessed here.

Table 1. Digoxin physicochemical and toxicokinetic data.

Molecular mass	781 Da
Volume of distribution	6.1 ± 2.6 L/kg
Protein binding	20–30%
Oral bioavailability	60–80%
Therapeutic range	0.5–2.0 ng/mL (0.6–2.6 nmol/L) for rate control 0.5–0.8 ng/mL (0.6–1.0 nmol/L) for heart failure
Toxic serum concentrations	>2.0 ng/mL (2.6 nmol/L)
Toxic exposure	>2–3 mg (adult), >2 mg (child)
Life threatening dose	>5–10 mg (adult), >4 mg (child)

distribution half-life of approximately 2 h and a terminal elimination half-life that averages 44.1 ± 6.0 h.[19] The effect of overdose on the elimination rate of digoxin is controversial, being reported as shortened, prolonged, or unchanged.[15,20,21] Most cases of overdose report a prolongation of the initial distribution half-life, possibly representing continued absorption, and variable effects on the terminal elimination half-life. The therapeutic concentration range of digoxin is between 0.5 and 2.0 ng/mL (0.6–2.6 nmol/L), although a range between 0.5 and 0.8 ng/mL (0.6–1.0 nmol/L) is generally preferred as it is effective in heart failure patients and minimizes toxicity.[16,22] Eighty-seven percent of patients with evidence of toxicity have serum digoxin concentrations greater than 2.0 ng/mL (2.6 nmol/L).[23] Toxicity may occur at lower digoxin concentrations in the setting of hypokalemia, hypercalcemia, or hypomagnesemia.[24–26]

Digoxin immune Fab (Fab), used for severe digoxin toxicity, has a molecular mass of 46,200 Da and a V_D of 0.4 L/kg. After administration of Fab, free digoxin serum concentrations drop to near zero within 1 to 2 min, while total serum digoxin concentrations increase by a factor of 8–20 and up to 33 in patients with normal or impaired kidney function, respectively.[21,27] Peak total serum digoxin concentrations occur in less than 12 h but may be prolonged for up to 30 h in patients with severely impaired kidney function. The elimination half-life of Fab in patients with normal kidney function is 16 to 30 h, but increases to an average of 98 h in those with severely impaired kidney function.[23,28] After Fab administration, a rebound of free digoxin peaks between 3.5 and 24 h, although peaks at 41 to 129 h (average: 88 h) may occur in patients with severely impaired kidney function.[27,28] After digoxin-immune Fab is administered, serum digoxin concentrations are no longer useful since they represent both free and inactive Fab-bound digoxin unless free digoxin concentrations are measured by incorporating equilibrium dialysis or ultrafiltration in the assay.[24,29]

Other digitalis compounds including digitoxin, beta-methyl-digoxin, and acetyldigoxin share the same basic mechanism of action with digoxin, but differ in some aspects. Because digitoxin has a smaller volume of distribution and longer elimination half-life than digoxin, the following systematic review and recommendations may not be applicable.[16] Beta-methyl-digoxin and acetyldigoxin result from modifications of the aglycone side chain of digoxin in an effort to enhance absorption. Acetyldigoxin is deacetylated in the intestinal wall and absorbed into the body primarily as digoxin.[30] About 50% of beta-methyl-digoxin is demethylated in the liver to digoxin.[31] As such, the recommendations that follow for

ECTR should also apply to acetyldigoxin and beta-methyl-digoxin.

Overview of digoxin poisoning

There were 3761 toxic exposures to cardiac glycosides reported by US poison control centers in 2013; one-third of which had at least a moderate outcome as defined by the National Poison Data System (including 26 deaths).[32] The therapeutic use of digoxin is also independently associated with an increased mortality when used both in new onset atrial fibrillation for rate control [hazard ratio 1.26 (95% CI 1.23–1.29, $p < 0.001$)] and in heart failure [hazard ratio 1.72 (95% CI 1.25–2.36)].[33,34]

The toxic effects of digoxin are an extension of its therapeutic mechanism of action; inhibition of cardiac cell membrane-bound $\text{Na}^+\text{-K}^+$ ATPase resulting in decreased intracellular potassium and excessive intracellular sodium and calcium accumulation, producing delayed after depolarizations, which lead to triggered dysrhythmias.[14,35] Toxic doses of digoxin can produce nearly any type of dysrhythmia including atrial and ventricular premature depolarizations, ventricular fibrillation, and ventricular tachycardia.[35,36] Overall, patients without previous cardiac disease develop sinus bradycardia with varying degrees of AV block and supraventricular dysrhythmias.[35] Death occurs usually from asystole associated with a high-degree heart block and resistance to electrical pacing. Patients with existing heart disease develop exacerbations of pre-existing dysrhythmias, AV block, and ventricular dysrhythmias. In this population, death is commonly due to ventricular fibrillation. Pediatric patients generally exhibit sinus bradycardia or first or second-degree AV block as toxicity, although life-threatening cardiac events are also reported.[37]

Management of patients with digoxin toxicity may include the prevention of further exposure, and symptomatic treatment with correction of electrolyte abnormalities, antiarrhythmic therapy (phenytoin, lidocaine, magnesium sulfate) and transcutaneous electrical pacemaker support if deemed safe and appropriate.[36,38,39] In acute toxicity, gastrointestinal decontamination may be important due to the possibility of delayed absorption. In addition, care should be taken in the interpretation of serum digoxin concentrations in acute overdose because of the slow distribution of digoxin into the tissues. Even during normal therapeutic dosing, serum concentrations that are obtained during the distribution phase result in “supratherapeutic” serum concentrations. Therefore, serum concentrations determined 6 to 8 h after ingestion are a better estimation of total body stores. However, in the presence of a patient with overt signs of toxicity, digoxin concentration should be obtained immediately and interpreted with an understanding of the time of the last dose.

In patients with severe digoxin toxicity, the use of digoxin-specific Fab antibodies is the preferred method of reversing cardiac and non-cardiac toxicity. Digoxin immune Fab rapidly binds circulating digoxin, making it unavailable for binding at membrane receptors. A rapid release of digoxin from receptor sites in the heart then results, which is immediately bound and inactivated by circulating digoxin immune Fab. Release of digoxin from $\text{Na}^+\text{-K}^+$ -ATPase normalizes sodium, potassium, and

calcium concentrations in the heart, resulting in restoration of normal conduction and rhythm. Seventy-five percent of patients treated with Fab typically show evidence of clinical response within 1 h, with complete resolution of cardiac toxicity within 4 h.[40] A recent review of digoxin-specific Fab use reported response rates of from 50 to 90% in the three largest case series published, totaling 430 acute and 1308 chronic poisonings.[41] Higher response rates were reported for acute poisoning and cases with more severe toxicity.

Multiple-dose activated charcoal (MDAC) enhances elimination of digoxin in animals and healthy volunteer studies,[42–44] as well as one randomized controlled study of another cardiac glycoside oleandrin.[45] MDAC for cardiac glycosides toxicity is not currently recommended in the latest position statement from the joint European and American Clinical Toxicology societies.[46] For this therapy to be most effective, it should be started early in toxicity prior to the drug fully distributing to extravascular tissues. Hemodialysis and/or hemoperfusion are not generally thought to be effective for digoxin poisoning because of the large V_D of digoxin.[47–50] Despite this, cases of ECTR for digoxin removal continue to be published today [51–54] and some authors continue to support its use.

Methods

Predetermined methodology, incorporating guidelines from The Appraisal of Guidelines for Research and Evaluation (AGREE) [55] and Grading of Recommendations Assessment, Development and Evaluation (GRADE) [56] were used and are described in detail elsewhere.[2] The primary literature search was conducted on 12 July 2012 in Medline, EMBASE, and the Cochrane library (Review and Central). The literature search was updated on 15 November 2014 following the same methodology as described below; the new articles and summarized data were submitted to every participant who then amended their votes.

The search strategy was as follows: (digoxin OR digitalis OR lanoxin) AND (toxicity OR poison* OR intoxication OR overdos*) AND (hemoperfusion OR haemoperfusion OR hemofiltration OR haemofiltration OR hemodialysis OR haemodialysis OR hemodiafiltration OR haemodiafiltration OR dialysis OR plasmapheresis OR plasmaphaeresis OR plasma exchange OR exchange transfusion OR CRRT).

A manual search of conference proceedings of the European Association of Poisons Centres and Clinical Toxicologists and North American Congress of Clinical Toxicology Annual Scientific Meetings (2002–2014), and Google Scholar was performed, as well as the bibliography of each article obtained during the literature search. Clinical cases where ECTR was only used for uremia, electrolyte/acid-base correction, fluid overload, or a combination of these were excluded. The clinical use of ECTR as reviewed by EXTRIP was either primary removal of digoxin by ECTR or elimination enhancement of digoxin-Fab complex when Fab was given.

A subgroup of EXTRIP completed the literature search, reviewed each article, extracted data, and summarized findings. The epidemiologist and the members of the subgroup determined the level of evidence assigned to each clinical recommendation (Supplement 2). Dialyzability was determined based on criteria listed in Table 2. The potential benefit of the procedure was weighed against its cost, availability, alternative treatments, and its related complications. All these information were submitted to the entire workgroup for consideration, along with structured voting statements based on a pre-determined format.

The strength of recommendations was evaluated by a two-round modified Delphi method for each proposed voting statement (online supplement 4) and RAND/UCLA Appropriateness Method was used to quantify disagreement between voters.[57] Anonymous votes with comments were sent to the epidemiologist who then compiled and returned them to each participant. The workgroup met in person to exchange ideas and debate statements. A second vote was later conducted and these results were used in determining the core EXTRIP recommendations.

Results

Results of the literature search are presented in Figure 1.

From the initial 435 studies obtained, 77 distinct articles met the inclusion criteria. Of these, data were extracted from a total of 10 *in-vitro*/animal experiments,[58–67] 52 case reports and case series (for a total of 81 patients),[51–53,67–115] one uncontrolled descriptive cohort (three patients),[116] and 16 pharmacokinetic studies of digoxin on patients receiving ECTR (75 patients).[66,117–131] No randomized controlled trials or comparative studies were identified.

Table 2. Criteria of dialyzability.

Dialyzability ^a	Primary criteria % Removed ^b	Alternative criteria 1 $CL_{\text{ECTR}}/CL_{\text{TOT}}$ (%)	Alternative criteria 2 $T_{1/2 \text{ ECTR}}/T_{1/2}$ (%)	Alternative criteria 3 $RE_{\text{ECTR}}/RE_{\text{TOT}}$ (%) ^c
D, Dialyzable	>30	>75	<25	>75
M, Moderately dialyzable	>10–30	>50–75	>25–50	>50–75
S, Slightly dialyzable	≥3–10	≥25–50	≥50–75	≥25–50
N, Not dialyzable	<3	<25	>75	<25

^aApplicable to all modalities of ECTR, including hemodialysis, hemoperfusion, hemofiltration.

^bCorresponds to % removal of ingested dose or total body burden in a 6-h ECTR period.

^cMeasured during the same period of time.

These criteria should only be applied if measured or calculated (*not reported*) endogenous half-life is >4 h (otherwise, ECTR is considered not clinically relevant). Furthermore, the primary criteria is preferred for poisons having a large V_D (>5 L/kg).

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CL_{ECTR} : Extracorporeal Clearance, CL_{TOT} : Total Clearance, $T_{1/2 \text{ ECTR}}$: Extracorporeal Half-life, RE_{ECTR} : Extracorporeal Drug Removal, RE_{TOT} : Total Drug Removal.

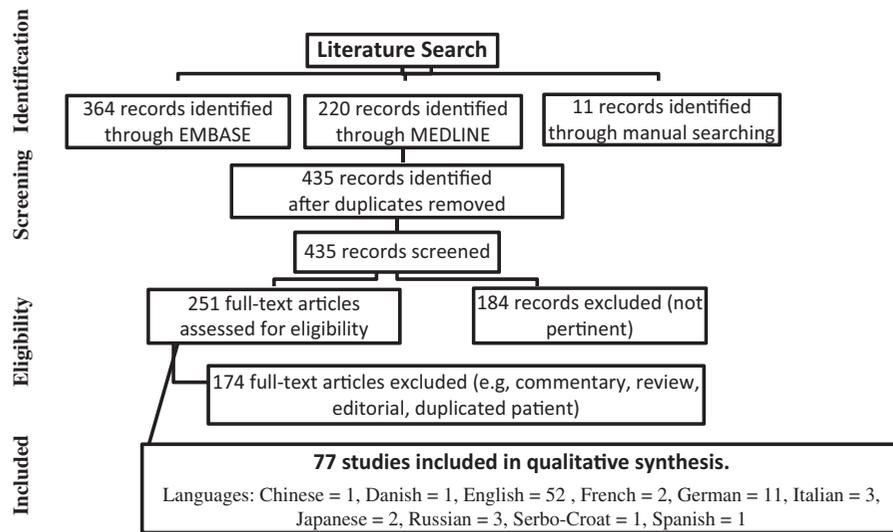


Figure 1. Flow diagram 15 November 2014.

Clinical results

The majority of the data evaluating the clinical impact of ECTR in digoxin poisoning is comprised of case reports and case series. For this reason, the level of evidence was determined to be *very low* for all clinical recommendations.

Demographic data, clinical presentation, treatments given and the outcome of the 81 patients reported from case reports and case series are presented in Table 3. Poisonings were differentiated between acute (i.e. after an unintentional or intentional massive ingestion or injection of digoxin), and chronic poisonings (i.e. toxicity resulting from subacute exposure, inappropriate dosing, a reduction in kidney function, or a combination of any). Poisonings were further separated between those cases that received Fab and those that did not. Among the 66 patients in whom Fab was not given,[51–53,66,67,83–114,116,132] 52 (79%) showed improvement during ECTR. In some cases, there was dramatic correction in cardiac rhythm,[83,94,95,99,132] while others reported improvement only for minor signs of toxicity. The 66 patients included the three from the descriptive cohort in addition to the 63 patients in Table 3.[116]

Extracorporeal treatments following Fab administration has been used to attempt to eliminate the Fab-digoxin complex and prevent/reverse toxicity associated with rebound of free digoxin in patients with impaired kidney function. We identified 18 such cases. Most were asymptomatic after administration of Fab and remained so after ECTR.[68–82] In three other cases, toxic symptoms had either not completely resolved with Fab or reappeared after Fab and disappeared following therapeutic plasma exchange.[70,72,79] In only one case did therapeutic plasma exchange appear to correct the cardiac abnormalities alone.[79] In the others, the text was unclear regarding the administration of additional digoxin-specific Fab or the timing of the clinical improvement.[72]

Reported complications during ECTR included the predictable decrease and reversible reduction of platelets and leucocytes that is reported regardless of the toxin involved.[99,105,111] It is important to note that in early

reported cases, ECTR exacerbated digoxin toxicity if the serum potassium decreased too much during the treatment.[133,134]

Dialyzability

When raw data were available, amount removed and percentage removed were calculated by the primary reviewer using standard methods as reported previously.[2] When possible, data were pooled with either the geometric mean (95% CI) or arithmetic mean (95% CI) values reported.

Table 4 summarizes the relevant metrics of ECTR for the various techniques studied. When hemodialysis was used, regardless of the clearance obtained, estimated removal was invariably low compared to ingested dose or total body removal; in one case of poisoning, 0.116 mg digoxin was recovered over 8 h, which was estimated at 0.15% of the dose ingested or 2.3% of the amount in the body with 5 mg estimated to have been absorbed.[93] One dated pharmacokinetic study on 9 dialysis-dependent patients reported a mean clearance of 8 mL/min (range: 3–17 mL/min) and recovery of 3% of the ingested dose during ECTR,[117] while another later study performed on 12 chronic ESRD patients showed a mean digoxin clearance of 19.5 ± 1.8 mL/min with an estimated removal of only 3.8% of the total body load.[123] Although most of these studies were performed using outdated dialysis filters, results would not change significantly even when using a high surface area membrane and higher blood flows.

In a pharmacokinetic simulation of digoxin removal, hemoperfusion for a period of 4 h with a clearance of 100 mL/min removed less than 7% of the amount of digoxin in the body, regardless of the time after the dose that hemoperfusion is started.[128] A pharmacokinetic study with charcoal hemoperfusion performed during initial redistribution when maximal removal should be expected only showed removal of 6% of the dose administered over 4 h.[130] Although extraction ratios with hemoperfusion are usually more impressive than with hemodialysis for similar blood flow rates,[121] the same limitations to dialyzability, namely a very large V_D , apply for hemoperfusion. Clearance was available for 28 patients

Table 3. Clinical data of included patients in case reports.

	Did not receive Fab (N = 63)		Received Fab (N = 18)	
	Acute (n = 37)	^a Chronic (n = 26)	Acute (n = 5)	^a Chronic (n = 13)
Patient demographics				
Mean age (years)	39 (range 0–83)	67 (range 24–98)	65 (range 46–79)	64 (range 0–89)
Sex (% male)	23.1%	54.5%	75%	75%
Mean weight (kg)	21 (range 0.2–50)	58 (range 46–72)	150	57 (range 3–99)
Poisoning exposure				
Mean quantity digoxin ingested (milligrams)	25.1 (range 2–200)		15.7 (range 7.1–30)	
Mean peak digoxin concentration (pre-Fab) (ng/mL)	12.4 (range 3.6–52)	4.5 (range 0.8–16)	19.6 (range 8.8–35.6)	7.6 (range 3.6–36)
Clinical symptoms and signs				
Mean peak serum potassium (mmol/L)	5.9 (range 3.7–13.5)	5.2 (range 3.6–7)	4.6 (range 4.2–5.1)	5.0 (range 2.8–6.5)
Altered consciousness (n)	7 (26%)	5 (23%)	1 (20%)	3 (25%)
Blurred vision (n)	3 (11%)	4 (18%)	0 (0%)	0 (0%)
Nausea/vomiting (n)	17 (63%)	9 (41%)	3 (60%)	1 (8%)
Dysrhythmia (n)	25 (93%)	20 (91%)	5 (100%)	12 (100%)
Other treatments used				
Decontamination (n)	13 (35%)		2 (40%)	
Mean Fab dose (mg)			720 (range 260–1040)	249 (range 6–1240)
ECTR used				
Charcoal HP (n)	15 (41%)	3 (12%)	1 (20%)	0 (0%)
Resin HP (n)	6 (16%)	6 (23%)	0 (0%)	0 (0%)
HP unknown type (n)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
HP coated with Fab (n)	3 (8%)	7 (27%)	0 (0%)	0 (0%)
HP/HD or HP + HD (n)	4 (11%)	5 (19%)	0 (0%)	0 (0%)
HD (n)	3 (8%)	1 (4%)	0 (0%)	5 (39%)
PD (n)	0 (0%)	0 (0%)	0 (0%)	2 (15%)
CRRT (n)	0 (0%)	3 (12%)	1 (20%)	0 (0%)
TPE (n)	4 (11%)	0 (0%)	3 (60%)	3 (23%)
ET (n)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
More than 1 ECTR (n)	0 (0%)	1 (4%)	0 (0%)	3 (23%)
Outcome				
Fatalities (n)	3 (8%)	1 (4%)	0 (0%)	2 (15%)

^aThose where unclear were assumed chronic.

CRRT: Continuous Renal Replacement Techniques, ECTR: Extracorporeal treatment, ET: Exchange transfusion, Fab: Digoxin Immune Fab, HP: Hemoperfusion, HD: Hemodialysis, PD: Peritoneal dialysis, TPE: Therapeutic plasma exchange.

Table 4. Aggregate human toxicokinetic parameters for digoxin.

Technique/Sorbent	CL _{ECTR} (mL/min)		% Ingested dose removed		% Body load removed	
	Mean	N	Mean	N	Mean	N
HD (pharmacokinetic) [117,122]	15.7 (14.4, 17.0)	23	3.5% (2.4, 4.7)	21	3.1% (1.7, 4.6)	4
HP (toxicokinetic simulation) [128]	N/A	1	0.15%*	1	2.3%*	1
HP (pharmacokinetic, charcoal) [121,130]	58.2 (57.0, 59.4)	7	N/A	–	7.9% (6.7, 9.2)	7
HP-HD (Charcoal Various) [91,99,114,132]	44.6 (42.6, 46.7)	4	0.2%, 0.2%*	2	2.5% (–0.8, 5.8)	3
HP (Amberlite XAD-4) [67,90,94,95]	144.1 (142.5, 145.8)	8	2.6%*	1	14.8% (13.4, 16.3)	6
HP (APAMB) [105]	44.2 (42.7, 45.8)	11	1.9% (0.1, 3.8)	3	3.0% (1.5, 4.5)	11
HP (Charcoal, coated) [51,86,88,91,104,132]	51.0 (49.3, 52.7)	6	0.7% (–1.0, 2.5)	4	1.9% (–0.6, 4.3)	4
HP (Charcoal, other) [106,107]	83.3 (82.1, 84.4)	4	N/A	–	0.8%, 3.1%*	2
HP (Hemoresin) [83]	126.8 (125.5, 128.3)	3	1.0% (–3.6, 5.6)	3	7.9% (6.8, 9.0)	3
HP (Styrene divinylbenzene copolymer) [108]	100.9*	1	N/A	–	8.1%*	1
CRRT [97,102]	11.2*	1	N/A	–	2.7%, 0.5%*	2
PD [117]	7.0	14	<3.0 to 5.3%	14	N/A	–
ET [127]	N/A	–	0.45 to 3.4%	4	N/A	–

CL_{ECTR}: Extracorporeal clearance; CRRT: Continuous renal replacement therapy; ET: Exchange Transfusion; HD: Hemodialysis; HP: Hemoperfusion; PD: Peritoneal Dialysis; HP-HD: Hemoperfusion and Hemodialysis in series.

*For n = 1 and n = 2, individual value(s) reported.

during hemoperfusion and averaged 71.4 mL/min (95% CI 70.1, 72.7 mL/min) with a range of 13.0 to 293.0 mL/min.[51,67,83,86,88,90,91,95,104,105,107,116,132] In general, blood clearance increased as blood flow to the dialyzer increased and varied by type of hemoperfusion sorbent used.

The average amount of digoxin removed adjusted to a 6 h hemoperfusion was 0.0712 mg [95% CI 0.0618, 0.0807 mg] with

a range of 0.0096 to 0.6624 mg in the 27 patients for which data were available.[51,67,83,86,88,91,95,104,105,107,108,116] The fraction of the ingested dose removed averaged 1.5% (95% CI 0.7, 2.2%), ranging from 0.04% to 3.5% in the 11 patients where it was reported.[51,67,83,86,88,91,105] The percent of body load removed averaged 4.1% (95% CI 2.5, 5.6%), ranging from 0.4 to 26.9% in the 25 cases in which it was

estimated,[51,83,86,88,91,95,104,105,107,108] These results are similar to those reported in non-toxic patients. The nine cases that reported using a combination of hemoperfusion and hemodialysis showed similar clearances, absolute amount removed, percentages of digoxin removed, and percent of cases with a rebound to hemoperfusion alone. Clearances and amount removed tended to be higher with hemoperfusion using Amberlite XAD-4 resin membranes.

Rebound in digoxin concentrations were reported after hemoperfusion in 16 cases,[51,83,86,88,91,94–96,106,109] while 17 cases reported no rebound and no information was available for 13 cases. One case had increasing concentrations during hemoperfusion.[108] In 11 out of the 17 cases of no rebound, hemoperfusion was performed using a membrane coated with digoxin antibodies, which is not currently commercially available.[105]

Peritoneal dialysis was not reported in overdose patients due to prior studies showing poor dialyzability with therapeutic use; mean clearances of 8 mL/min; and recovery of less than 3% of ingested dose was reported in one study of 14 patients,[117] while clearances of 2.3 to 3.1 mL/min and removal of between 7.8 and 24 μ g total over 24 h were reported in continuous ambulatory peritoneal dialysis.[120] One author reported peritoneal dialysis removal between 3.0 and 5.3% of the amount ingested in three children aged 3 weeks, 11.5 months, and 5 years.[129]

There were 12 digoxin-toxic cases reporting therapeutic plasma exchange, 7 after Fab use and 5 without Fab use. Only three cases, where Fab was used, had information on the amount of digoxin removed. They will be discussed in the section on ECTR after Fab administration. Exchange transfusion was performed in four patients and only removed 0.45 to 3.4% of the administered dose.[127] One study reported 5.2 to 20.5% removal of an intramuscular dose of digoxin in two infants, 1.5 h after administration, by exchange transfusion; rebound was noticed in both infants.[119]

Of the two cases using continuous renal replacement therapy (CRRT), only one had toxicokinetic data showing a clearance of 11.2 mL/min. The amounts removed per hour for the two patients were 0.00131 and 0.000016 mg, or 2.7 and 0.5% of the estimated total body load eliminated over 21 and 72 h, respectively. Rebound was not reported in one case and did not occur in the other. Pharmacokinetic studies in patients on CRRT showed similar results, with clearances of 36.7 ± 6.6 mL/min for a flat plate RP-6 device and 19.5 ± 2.3 mL/min for using a polysulfone membrane Amicon D 30/Fresenius AV 600 device.[124,125] The total amount of digoxin removed was 0.014 mg over 4 h.[125]

Removal of digoxin after digoxin-specific Fab administration

The molecular mass of digoxin-specific Fab complexes (46,200 Da) surpasses the cut-off of most dialyzers, hemofilters, and adsorption columns. Although the potential therapeutic benefit of high molecular weight cut-off dialyzers and liver support therapies is promising, they have not yet been tested for removal of digoxin-specific Fab complexes.

Therapies performed to remove digoxin after administration of digoxin-specific Fab are presented in Table 5. Continuous veno-venous hemofiltration with a cellulose triacetate filter using a blood flow of 220 mL/min and a ultrafiltration rate of 4000 mL/h. was estimated to remove 7% of the ingested digoxin dose over five days.[75] One case of hemoperfusion and one case of hemodialysis had no usable data.[74,135] One case using peritoneal dialysis showed negligible removal of digoxin in the dialysate (0.004 mg/L free digoxin and 0.00125–0.00132 mg/L total digoxin).[68] The other case using peritoneal dialysis showed a clearance of 0.98 ± 0.23 mL/min for total digoxin, 5.83 ± 1.51 mL/min for free digoxin, and 0.22 ± 0.07 mL/min for Fab.[71] The total amount removed during peritoneal dialysis was 0.1019 mg total digoxin, 0.075 mg free digoxin, and 3.74 mg Fab over four days. Approximately, 8.4% of the estimated digoxin load (0.76%/24 h) was removed by peritoneal dialysis. Three cases had therapeutic plasma exchange performed, two with some usable data. One study using a 4L procedure reported total digoxin amounts removed of >0.040 mg during the first therapeutic plasma exchange, 0.40 mg during the second therapeutic plasma exchange, and 0.009 mg during the third exchange.[72] Another group reported 0.032 and 0.100 mg total digoxin removed using plasma exchanges of 4 and 5 L, representing 0.9% of the amount ingested.[82] In all cases, dialyzability would be graded as “Not dialyzable”, except for one study where therapeutic plasma exchange removed 0.250 mg over one 90 min session, which may be explained by modifications of digoxin toxicokinetics following Fab administration.[70] There were 14 cases reported in which some type of ECTR was performed after digoxin-specific Fab was administered; data could be extracted in six. None of the reported therapies (CRRT, peritoneal dialysis, therapeutic plasma exchange) cleared either digoxin or the digoxin-Fab complex to any significant degree as shown in Table 5. The available evidence indicates that ECTR does not effectively remove the digoxin-Fab complex.

Clinical recommendations

General statement

We recommend not to perform ECTR in severe digoxin poisoning when Fab is administered (1D) and we suggest not to perform ECTR when Fab is not administered (2D) (Table 7).

Rationale

Digoxin-specific Fab is an effective treatment that can reverse toxic effects of cardiac glycosides rapidly. From the above analysis, digoxin is at best, slightly removable by high-efficiency ECTRs.

The arguments put forward by advocates for ECTR in digoxin poisoning are usually the following [95,99]:

- The V_D of digoxin in patients with impaired kidney function is smaller, and these are the patients who may most benefit from ECTR because of lower endogenous clearance.

Table 5. Toxicokinetics of digoxin and digoxin-Fab complex after Fab administration.

	Patient	Digoxin exposure	Peak digoxin concentration (pre-Fab) (ng/mL)	Dose of Fab administered	ECTR	Digoxin removed	Digoxin-Fab removed
Mulder et al. [75]	75 yo, M	7.1 mg	16	360 mg	CRRT	0.5 mg in 5 days	Not significant
Berkovitch et al. [68]	Newborn, F	0.170 mg over 5 days	7.1	6 mg	PD	0.0023 mg in 14 h	Not measured
Caspi et al. [71]	64 yo, M	Chronic OD	3.6	80 mg	PD	0.10 mg in 11 days	3.7 mg in 11 days
Caputo et al. [70]	89 yo, M	Chronic OD	7.8	480 mg	TPE		0.25 mg in 90 min
					HDF		0.01 mg in 240 min
Chillet et al. [72]	70 yo, M	1.000 mg in 4 days	4.4	160 mg (day 4) 160 mg (day 5)	TPE	>0.040 mg (day 4) >0.0398 mg (day 5) 0.0085 mg (day 9)	Not measured
Zdunek et al [82]	46 yo, M	12.5 mg	21	560 mg (day 1) 440 mg (day 2)	TPE	0.03 mg (day 2) 0.1 mg (day 3)	Not measured

CRRT: continuous renal replacement therapy; ECTR: Extracorporeal Treatments; Fab: Digoxin Immune Fab; HD: Hemodialysis; HDF: Hemodiafiltration; OD: Overdose; PD: Peritoneal Dialysis; TPE: Therapeutic plasma exchange.

Table 6. Pharmacokinetic/Toxicokinetic grading for individual patients.

	GRADING	HD	CRRT	HP	HP-HD	PD	HDF	TPE	ET
Toxicokinetic patients	D: Dialyzable							1	
	MD: Moderately Dialyzable			2					
	SD: Slightly Dialyzable			7					
	ND: Not Dialyzable	1	4	8	2	2	1	3	
Pharmacokinetic patients	D: Dialyzable								
	MD: Moderately Dialyzable								
	SD: Slightly Dialyzable	21		2					1
	ND: Not Dialyzable	4				22			5

CRRT: Continuous renal replacement therapy; ET: Exchange Transfusion; HDF: Hemodiafiltration; HD: Hemodialysis; HP: Hemoperfusion; HP-HD: Hemoperfusion-Hemodialysis in series; PD: Peritoneal Dialysis; TPE: Therapeutic plasma exchange.

Table 7. Executive summary of recommendations.**General statement**

ECTR is not recommended in severe digoxin poisoning if Fab is administered (1D)

ECTR is not suggested in severe digoxin poisoning if Fab is not administered (2D)

Indications for ECTR

ECTR is not recommended in any of the following situations (1D):

- A suspected digoxin ingestion alone regardless if Fab is administered
- An elevated digoxin serum concentrations alone regardless if Fab is administered
- Cardiovascular disturbances if Fab is administered
- Serum potassium > 6.0 mmol/L

For removal of digoxin immune Fab complex in a patient with no clinical toxicity and impaired kidney function ECTR is not suggested in any of the following situations (2D):

- Cardiovascular disturbance if Fab is not administered
- Serum potassium between 6.0 and 7.0 mEq/L

For removal of digoxin immune Fab complex in a patient with clinical toxicity and impaired kidney function No agreement for ECTR was reached in the following situation:

- Serum potassium > 7.0 mmol/L

Choice of ECTR

- Neither intermittent hemodialysis nor hemoperfusion are suggested in severe digoxin poisoning (2D)
- Other ECTR modalities are not recommended for severe digoxin poisoning (1D)
- Therapeutic plasma exchange is not recommended to remove the digoxin immune Fab complex in patients with impaired kidney function (1D)

ECTR: Extracorporeal treatments; Fab: Digoxin Immune Fab.

- Small removal of digoxin from the central compartment may result in significant decreases in myocardial digoxin concentrations, and may have clinical significance.
- Within 6 h after a massive ingestion, digoxin has not yet fully distributed in tissue and so may be more amenable to ECTR removal.
- Digoxin-specific Fab are not always available and are expensive, usually more than ECTR.

Although digoxin is a relatively large molecule compared to other pharmaceuticals (781 Da), its molecular mass and low

protein binding would not be obstacles to its clearance by modern-day ECTRs. The major limiting factor to its dialyzability is the large V_D , in that post-distribution, most of total body digoxin burden is located in the tissues, outside the blood compartment where ECTR purification occurs.

There are specific caveats in the pharmacokinetic and toxicokinetic assessment of dialyzability of large V_D poisons using usual parameters: reductions of plasma concentrations and measurement of apparent plasma half-life during ECTR are unreliable because of the massive rebound of tissue digoxin

that would be expected following ECTR. Similarly, reliance of plasmatic or whole blood clearance by ECTR is imprecise because they only correlate with removal from the blood compartment. A high plasma clearance over short durations of time (i.e. as occurs during intermittent hemodialysis) will not result in significant removal of total body stores. For example, in some reports, clearance of digoxin was greater than 100 mL/min [94] and reduction in apparent serum half-life above 90%,[94,99,111] yet the percent of ingested dose removed during a 6-h ECTR procedure was usually less than 5%. Unfortunately, authors still erroneously equate high clearance rates and high extraction ratios with significant removal of digoxin.[52,94,99] While high-dose CRRT for extended periods of time may lead to substantial removal, there are no data available currently to confirm this.

As mentioned above, dialyzability criteria based on clearance and half-life of digoxin are unreliable. A preferable way to grade dialyzability is by using the Primary Criteria, i.e. quantifying digoxin from extruded column or by dialysate/effluent/ultrafiltrate collection and comparing it to ingested/injected amount or by total body stores in a 6-h period.[2,7] A table summarizing mean clearance and removal in the pharmacokinetic studies identified is available in online supplement 3, while Table 6 shows the dialyzability grading for included individual patients, based on the Primary Criteria defined by EXTRIP.[2] In those articles that satisfied the Primary Criteria, all confirm very small amounts of digoxin removed. Considering the factors above and following the results presented in Table 6, the workgroup agreed with the following statement: "Digoxin is slightly dialyzable (level of evidence = B)".

Although most of literature reviewed was dated, results would not be expected to be significantly altered had more modern and efficient technology been used (higher blood flows, larger catheters, higher efficiency filters). Again, the limiting factor is the large V_D of digoxin and not extraction by the filter or adsorbent column.

There were many confounding factors in the published cases, including medical conditions, such as acute kidney injury, chronic kidney disease, congestive heart failure, atrial fibrillation, hypertension, and diabetes. In addition, many other therapeutic modalities were used, including intubation, mechanical ventilation, antidysrhythmics, vasoactive substances, and pacemakers. The actual contribution of ECTR to the overall outcome was impossible to determine. It is very likely that significant publication bias exists as only six deaths were reported in the 81 cases (7%), while the National Poison Data System of the American Association of Poison Control Centers routinely reports mortality ranging between 10 and 17% in cases of severe cardiac glycoside overdoses.[136] Alternatively, improvement in these cases where ECTR was used may be attributed to correction of acidosis or other metabolic derangements.

Conversely, it is not impossible that ECTR may provide some real benefit. Although not applicable to humans, clinical data in animal experiments suggest that ECTR improves outcome: in one animal experiment, all dogs hemoperfused with a digoxin-antibody column survived while those who were either not hemoperfused or hemoperfused through beads lacking anti-digoxin did not,[60,61] although this benefit is likely explained

by an effect of the antibody and not the ECTR. In an additional animal experiment of eight digoxin-poisoned dogs with ventricular tachycardia, the group that underwent charcoal hemoperfusion 30 min after the onset of dysrhythmias had a significantly shorter duration of toxicity compared to the control group (137 vs. 204 min, $p < 0.05$), despite the relatively low amount of digoxin removed.[62] The improvement during ECTR may also infer that redistribution of a critical amount of digoxin away from receptor sites may occur during ECTR. In the above animal study, myocardial tissue-to-serum digoxin ratios were 51.3% in controls compared to 33.2% after hemoperfusion suggesting that even after equilibration, tissue digoxin concentrations are lower.[62] However, recent data suggests that the kinetics and inotropic response to digoxin are mediated by a mixture of two receptor sub-types: a low affinity/high capacity/slow dissociation binding site (R_1) and a high affinity/low capacity/fast dissociation binding site (R_2), which account for 89 and 11% of the total number of α -2 isoform Na^+/K^+ ATPase receptors responsible for digoxin-induced inotropy.[137] In higher doses, it appears that the R_1 receptors predominate in digoxin's pharmacodynamic activity, suggesting that since digoxin slowly dissociates from the R_1 sites, efforts to ameliorate toxicity by enhanced elimination would be blunted by the slow dissociation.

It is possible that the distribution of digoxin into tissues may afford an opportunity for ECTR to remove more digoxin if performed within the first 6 to 8 h after an acute ingestion prior to the onset of toxicity. There are little data to examine the possibility offered by this early clinical scenario. We identified six cases that received ECTR within 8 h after ingestion.[52,86–88,90,91] Gradual improvement was reported in these patients over hours to days, and the impact of ECTR on this improvement was difficult to assess. In two studies, quantified removal was 0.010 mg in 6 h, and 0.157 mg in 4 h, and 0.157 mg in 4 h in another.[86,91] It is therefore impossible to confirm the benefit to attempt enhanced elimination if ECTR is performed soon after ingestion and it may be impractical in many cases due to delayed initial presentation or the technical requirements for prompt initiation of ECTR. Although the workgroup suggested to not perform ECTR in situations where a patient would not have access to Fab, some participants nonetheless considered this a potential option in those patients who were severely poisoned if they presented shortly after an acute exposure and ECTR was immediately available.

Evidence of clinical improvement may indicate that redistribution of a critical amount of digoxin away from receptor sites may be achieved during ECTR as discussed above, although actual amount removed was always $< 25\%$ of the dose ingested or total body load. However, the pharmacokinetics and pharmacodynamics of digoxin at the receptor site argue against this hypothesis.[137]

Although comparison with ECTR is unavailable, clinical improvement with Fab is more readily apparent than what is described in published reports using ECTR and justifies its higher cost. Despite the concerns of rebound of free digoxin in plasma in patients with impaired kidney function who have received Fab, the elimination of the complex by ECTR is at present unsatisfactory and perhaps unnecessary.

With these considerations, the workgroup strongly voted against ECTR when Fab was available: 26 out of 27 participants voted against ECTR, while 1 voted as neutral (median vote = 1, upper quartile = 1, and disagreement index = 0). There was slightly more support for ECTR when Fab was not administered: 16 out of 27 participants voted against ECTR, 6 had a neutral stance, and 5 voted for ECTR in this case (median vote = 3, upper quartile = 4.5, and disagreement index = 0.4). The reason for the modestly increased support for ECTR in this scenario was the high mortality associated with severe digoxin toxicity and the lack of other efficacious therapeutic alternatives. The workgroup nevertheless agreed that the clinical benefit demonstrated in reports is likely anecdotal and possibly related by correction of associated electrolyte abnormalities. Until an ECTR can show promising total body removal of digoxin, a clinical benefit in a human trial or positive cost-benefit superiority of ECTR over Fab, the workgroup advocated against ECTR regardless of the indication.

Indications for ECTR

The workgroup was unable to support any indication for ECTR in severe digoxin poisoning, aside from the usual accepted circumstances where ECTR is applied (e.g. acute kidney injury, hyperkalemia that persists after Fab administration, fluid overload). Table 7 summarizes the conditions associated with digoxin poisoning considered in its deliberations.

Cessation of ECTR

Since it was determined that ECTR was never indicated for digoxin removal, the parameters for the cessation of ECTR were considered irrelevant.

Choice of ECTR

Since ECTR was not considered useful in severe digoxin poisoning, we suggested to neither use intermittent hemodialysis nor hemoperfusion (2D), and recommended to use none of the other ECTRs (1D). As mentioned, digoxin-Fab complexes can only be removed by therapeutic plasma exchange, albeit very slowly, and so was not recommended even in patients with impaired kidney function (1D). In case of recrudescence toxicity in dialysis-dependent patients, Fab can be re-administered, and is preferable to therapeutic plasma exchange which is expensive, carries more risk than hemodialysis (e.g. hypersensitivity reactions, hypocalcemia, citrate toxicity), [138,139] and not as widely available.

Conclusion

The workgroup recommends not performing ECTR for digoxin poisoning, regardless of whether the preferred treatment, digoxin-specific Fab, is available or not. Although at the present time, the workgroup suggested against the use of ECTR shortly after a massive exposure to digoxin when Fab is not available, we acknowledge that this might require further study especially in acute overdose when Fab is not available.

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