

# UC San Diego

## UC San Diego Previously Published Works

### Title

Extracorporeal treatment for poisoning to beta-adrenergic antagonists: systematic review and recommendations from the EXTRIP workgroup.

### Permalink

<https://escholarship.org/uc/item/8776m2gn>

### Journal

Critical Care (UK), 25(1)

### Authors

Bouchard, Josée  
Shepherd, Greene  
Hoffman, Robert  
[et al.](#)

### Publication Date

2021-06-10

### DOI

10.1186/s13054-021-03585-7

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>


Peer reviewed

RESEARCH

Open Access



# Extracorporeal treatment for poisoning to beta-adrenergic antagonists: systematic review and recommendations from the EXTRIP workgroup

Josée Bouchard<sup>1</sup> , Greene Shepherd<sup>2</sup>, Robert S. Hoffman<sup>3</sup>, Sophie Gosselin<sup>4,5,6</sup>, Darren M. Roberts<sup>7,8</sup>, Yi Li<sup>9</sup>, Thomas D. Nolin<sup>10</sup>, Valéry Lavergne<sup>1</sup> and Marc Ghannoum<sup>1,11\*</sup> on behalf of the EXTRIP workgroup

## Abstract

**Background:**  $\beta$ -adrenergic antagonists (BAAs) are used to treat cardiovascular disease such as ischemic heart disease, congestive heart failure, dysrhythmias, and hypertension. Poisoning from BAAs can lead to severe morbidity and mortality. We aimed to determine the utility of extracorporeal treatments (ECTRs) in BAAs poisoning.

**Methods:** We conducted systematic reviews of the literature, screened studies, extracted data, and summarized findings following published EXTRIP methods.

**Results:** A total of 76 studies (4 in vitro and 2 animal experiments, 1 pharmacokinetic simulation study, 37 pharmacokinetic studies on patients with end-stage kidney disease, and 32 case reports or case series) met inclusion criteria. Toxicokinetic or pharmacokinetic data were available on 334 patients (including 73 for atenolol, 54 for propranolol, and 17 for sotalol). For intermittent hemodialysis, atenolol, nadolol, practolol, and sotalol were assessed as dialyzable; acebutolol, bisoprolol, and metipranolol were assessed as moderately dialyzable; metoprolol and talinolol were considered slightly dialyzable; and betaxolol, carvedilol, labetalol, mepindolol, propranolol, and timolol were considered not dialyzable. Data were available for clinical analysis on 37 BAA poisoned patients (including 9 patients for atenolol, 9 for propranolol, and 9 for sotalol), and no reliable comparison between the ECTR cohort and historical controls treated with standard care alone could be performed. The EXTRIP workgroup recommends against using ECTR for patients severely poisoned with propranolol (strong recommendation, very low quality evidence). The workgroup offered no recommendation for ECTR in patients severely poisoned with atenolol or sotalol because of apparent balance of risks and benefits, except for impaired kidney function in which ECTR is suggested (weak recommendation, very low quality of evidence). Indications for ECTR in patients with impaired kidney function include refractory bradycardia and hypotension for atenolol or sotalol poisoning, and recurrent torsade de pointes for sotalol. Although other BAAs were considered dialyzable, clinical data were too limited to develop recommendations.

**Conclusions:** BAAs have different properties affecting their removal by ECTR. The EXTRIP workgroup assessed propranolol as non-dialyzable. Atenolol and sotalol were assessed as dialyzable in patients with kidney impairment, and

\*Correspondence: marcghannoum@gmail.com

<sup>1</sup> Research Center, CIUSSS du Nord-de-L'île-de-Montréal, Hôpital du Sacré-Coeur de Montréal, University of Montreal, Montreal, QC, Canada  
Full list of author information is available at the end of the article



© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

the workgroup suggests ECTR in patients severely poisoned with these drugs when aforementioned indications are present.

**Keywords:** Beta-blockers, ECLS, Hemodialysis, Hemoperfusion, Overdose, Intoxication

## Introduction

Poisoning from  $\beta$ -adrenergic antagonists (BAAs), also referred as  $\beta$ -blockers, can result in bradycardia, hypotension, dysrhythmias, and cardiogenic shock. Treatment is primarily supportive, but in severe cases high-dose insulin euglycemic therapy, vasopressors, and extracorporeal life support (ECLS) may be required. Extracorporeal treatments (ECTRs) are mentioned as part of the management of BAA poisoning, although their place remains uncertain and controversial [1]. The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Additional file 1). Its mission is to provide recommendations on the use of ECTRs in poisoning (<http://www.extrip-workgroup.org>) [2–5]. We present EXTRIP's systematic review and recommendations for the use of ECTR in patients with BAA poisoning.

## Clinical pharmacology and toxicokinetics

BAAs are among the most commonly prescribed drugs for the prevention and treatment of cardiovascular disease [6, 7]. BAAs bind to  $\beta$ -adrenergic receptors, thereby competitively inhibiting the binding of epinephrine and norepinephrine to these receptors, and impairing conduction and contraction. Aside from their relatively small molecular size, BAAs have considerable heterogeneity regarding their physicochemical characteristics and pharmacokinetics (Table 1). For example, labetalol, propranolol, and carvedilol have a large volume of distribution, extensive protein binding, substantial hepatic metabolism, negligible renal clearance, and do not require dose modification in chronic kidney disease (CKD), whereas sotalol, nadolol, and atenolol have opposite characteristics. Additionally, their different properties influence their clinical effect; these include selectivity to the  $\beta$ -1 adrenergic receptors (e.g., metoprolol > propranolol),  $\alpha$ -adrenergic antagonist activity (e.g., carvedilol, labetalol), intrinsic sympathomimetic activity (e.g., acebutolol, pindolol), membrane-stabilizing activity (MSA) from sodium channel blockade (e.g., propranolol, acebutolol, and labetalol), central nervous system (CNS) depression (e.g., propranolol), and Class III antidysrhythmic effect because of antagonism of potassium channels (e.g., sotalol). For several commercialized BAAs, intravenous and/or sustained-release forms are available.

In overdose, a prolonged absorption phase, saturation of enzymatic biotransformation, and poison-induced impairment of blood flow to organs may all contribute to a prolonged apparent elimination half-life, which has been described for propranolol [8], metoprolol [9, 10], atenolol [11], and sotalol [12–14] although this finding is inconsistent [15–18]. Protein binding does not appear to be modified in supratherapeutic concentrations [19, 20].

## Overview of toxicity

Over the last 5 years, the number of BAA exposures reported to the United States National Poison Data System has increased [21], and is associated with 3.9% of fatal poisonings [21]. In 2019, 11,166 single ingredient BAA exposures were reported in the US including 19 fatalities [21]. Manifestations of BAA poisoning range from asymptomatic bradycardia to cardiogenic shock and death [22–25]. Cardiovascular symptoms usually appear within 2 h of ingestion and are unlikely to occur in an asymptomatic patient after 6 h from ingestion for immediate-release formulations [22, 26, 27], 8 h for sustained-release formulations, and 12 h for sotalol [12, 23, 24, 28]. Decreased consciousness and bronchospasm may occur after these periods, even with normal blood pressure and electrocardiogram [26, 29]. Other manifestations of poisoning from BAAs include hyperkalemia and hypoglycemia [30, 31]. Highly lipophilic drugs, like propranolol, penetrate the blood–brain barrier causing delirium, coma, and seizures [27, 30, 32, 33]. Sotalol, which also possesses potassium efflux channel blocking properties, causes QT interval prolongation and severe ventricular dysrhythmias, including torsade de pointes [12, 32, 34, 35]. In overdose, receptor selectivity is lost, leading to overlapping manifestations among BAAs [36, 37].

Some publications report a linear or threshold relationship between dose and outcome [32, 37]. For specific BAAs, a positive correlation was noted for propranolol [27, 32, 36], sotalol [32], atenolol [32], metoprolol [32, 38], carvedilol [39], and talinolol [36]. Unintentional exposures and inadvertent ingestions in young children rarely cause severe toxicity due to the smaller doses involved, although exceptions are reported [40, 41]. Quantification assays for BAAs are rarely available to guide clinical decisions, and concentrations correlate poorly with the development of symptoms [42–44], except for sotalol [45–48].

Fatalities from BAA ingestions are more likely if co-ingested with cardioactive drugs, such as calcium

**Table 1** Physicochemical properties and pharmacokinetics of immediate-release  $\beta$ -adrenergic antagonists

Drug	MW (Da)	Protein binding (%)	V <sub>D</sub> (L/kg)		F (%)	T <sub>max</sub> (h)		Endogenous T <sub>1/2</sub> (h)		Renal CL (mL/min), Normal GFR		Therapeutic range (mg/L)	References
			Normal	GFR		CKD	Normal GFR	ESKD	Normal GFR	ESKD	Normal GFR		
Acebutolol	336	10–25	1.5–2.5	N/A	35–50	2.0–4.0	4–10&	600–800	N/A	150–300	0.2–2	[19, 68, 69, 80, 138–148]	
Alprenolol	249	80–90	2.5–3.5	N/A	5–15	1.0–2.0	2–4	800–1000	N/A	50	0.03–0.15	[149–152] [153]	
Atenolol	266	0–5	1.0–1.2		50–60	3.0–3.5	5–8	140–180	20	120–140	0.1–1.5	[11, 20, 73, 78, 79, 85, 90, 105, 118, 124, 148, 154–163]	
Betaxolol	344	50	4.5–6.0	5.0–6.5	75–90	2.5–4.0	14–16	220–270	100–150	50	0.005–0.05	[86, 148, 164–168]	
Bisoprolol	325	30	2.0–3.0		90	1.5–2.5	9–12	200–250	50	120–150	0.01–0.1	[93, 98, 148, 169–175]	
Bopindolol	381	N/A	1.8–2.0	N/A	70	1.0–2.0	4–6	350–400	N/A	N/A	0.001–0.015	[148, 176–180]	
Carteolol	292	10–30	4	N/A	85	2.0	5–7	650	N/A	250	0.01–0.1	[148, 181–183]	
Carvedilol	405	98	1.5–2.5	N/A	20–30	1.0–3.0	6–7	600	5	5	0.02–0.2	[96, 148, 184–190]	
Celiprolol	379	25	4–5	N/A	30–70	2.0–4.0	5–7	900–1000	N/A	180–220	0.05–0.5	[191–193] [148, 194–200]	
Cetamolol	310	N/A	3.5	2.5	N/A	2.5–3.0	7	420*	150	100–150	0.01–0.1	[201–203]	
Esmolol	295	55	2.0–3.5		Not applicable		0.2	10,000–15,000		100–200	0.15–2	[95, 148, 204, 205]	
Labetalol	328	50	5.0–9.0		20–30	0.5–1.5	3–10	1200–2000		20	0.03–0.3	[92, 206–212] [94, 148, 213]	
Medroxalol	372	N/A	10–15	N/A	30–50	2–3	7–15	1000–1100	N/A	80–100	N/A	[213–215]	
Mepindolol	262	55	5.7**	N/A	N/A	1.4	3–6	650**	N/A	0**	0.007–0.07	[88, 148, 216, 217]	
Metipranolol	309	70	3–4	N/A	40–50	0.5–2.0	2.5–3.0	1100–1300	N/A	120–150	0.02–0.1	[97, 148, 218–221]	
Metoprolol	267	10	3.0–4.0	N/A	40–60	1.5–2.0	3–5	800–1200		100	0.03–0.5	[222–225] [9, 73, 82, 106, 148, 226–230]	
Nadolol	309	15–25	1.5–2.0	N/A	30	2.8	10–15	120–250	30	80–120	0.01–0.25	[75, 89, 148, 231–234]	
Nebivolol	405	98	9–12		Variable	1–3	10–15	800–1000		30	0.001–0.05	[148, 235–241]	
Oxprenolol	265	80–85	0.8–1.2	0.8	35–50	0.5–1.5	1–2	600–750	550	10	0.05–0.3	[84, 148, 242–252]	
Penbutolol	291	90–95	0.5–1.0	N/A	90	1.0–2.0	15–20	300–600	N/A	5	0.01–0.3	[253] [148, 254–262]	
Pindolol	248	40–55	1.3–2.3	1.6–1.8	50–90	0.5–1.5	3–5	450–550	180–240	150–250	0.02–0.15	[148, 263–269]	
Practolol	266	57	1.5	N/A	90–100	2–5	10–13	135	20	100–120	1.5–5	[65, 67, 148, 270–274]	
Prenalterol	225	5	2.5–3.5	N/A	25–35	0.5–2.5	1.5–2.5	800–1400	N/A	200–800	0.01–0.04	[275–282]	
Propranolol	259	85–95	3.0–5.0		20–50	1.5–2.0	3–5	800–1200		5	0.02–0.3	[20, 66, 70, 74, 154, 230, 283–300] [73, 87, 131, 148, 301, 302]	
Sotalolol	272	0	1.3–1.5		90	2.5–3.5	5–9	120–160	20–25	80–120	0.5–3	[71, 83, 303–307] [13, 15, 115, 148, 303, 306, 308–310]	
Talinolol	363	60**	3.0–3.5		55	2.5–3.5	10–12	320–380		150–200	0.04–0.15	[99, 104, 107, 148, 311–313]	

**Table 1** (continued)

Drug	MW (Da)	Protein binding (%)	V <sub>D</sub> (L/kg)		F (%)	T <sub>max</sub> (h)		Endogenous T <sub>1/2</sub> (h)		Endogenous CL (mL/min)		Renal CL (mL/min), Normal GFR	Therapeutic range (mg/L)	References
			Normal GFR	CKD		Normal GFR	ESKD	Normal GFR	ESKD	Normal GFR	ESKD			
Timolol	316	10	2.0–2.5	N/A	60	1.3–2.0	3–5	450–580	N/A	100	0.005–0.1	[300, 314–317] [72, 148, 315]		
Tolamolol	316	90	1.2–1.8	N/A	N/A	1–3	2–3	1100	N/A	N/A	N/A	[318–320]		

MW: Molecular weight; V<sub>D</sub>: Volume of distribution; F: bioavailability; T<sub>max</sub>: Time to maximum concentration; T<sub>1/2</sub>: elimination half-life; CL: Clearance; N/A: Not available

\* Not adjusted for bioavailability, \*\* No reference from primary data (taken from reviews)

& conflicting data, perhaps due to non-sensitive assays which included measurement of metabolites in early reports [68, 69]

Total body clearance and volume of distribution were obtained from intravenous data. If these data were unavailable but reported for oral data (i.e., as V/F or CL/F), then values were adjusted for bioavailability

This systematic review has taken the liberty to review all BAAs for which data exist, even if some are not currently commercially available

channel blockers [22, 32, 37, 49]. In cohorts of severe BAA poisoning, reported mortality rates range between 0 and 13% [21–23, 25, 32, 50–52].

Management of BAA poisoning is primarily supportive [1]. Although outside the scope of this review, standard care includes gastrointestinal decontamination, atropine, inotropes and vasopressors, temporary cardiac pacing, glucagon, intravenous calcium, high-dose euglycemic hyperinsulinemia, and extracorporeal life support (ECLS) [1, 53–57].

## Methods

The workgroup developed recommendations following the EXTRIP methodology previously published [3] with modifications, updates, and clarifications. PRISMA statement was followed for reporting items of the presented systematic review of the literature. The full methods are presented in the online Additional file 1.

The search strategy used was as follows: [(dialysis or hemodialysis or haemodialysis or hemoperfusion or haemoperfusion or plasmapheresis or plasmapheresis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or plasma exchange or CRRT or CVV\* or CKRT or exchange transfusion) and (beta block\* or beta-adrenergic or acebutolol or alprenolol or atenolol or betaxolol or bisoprolol or bopindol or carteolol or carvedilol or celiprolol or cetamolol or esmolol or labetalol or medroxalol or mepindol or metipranolol or metoprolol or nadolol or nebivolol or oxprenolol or penbutolol or pindolol or practolol or prenalterol or propranolol or sotalol or talindolol or talinolol or timolol or tolamolol)].

## Results

Results of the literature search are presented in Fig. 1.

In the final analysis, 76 studies were included for qualitative analysis, including 4 in vitro experiments [58–61], 2 animal experiments [62, 63], 1 pharmacokinetic simulation study [64], 37 pharmacokinetic studies [65–101], and 32 case reports/series [13, 15, 35, 102–130]. No comparative studies or randomized controlled trials were identified.

### Summary of evidence

#### Dialyzability

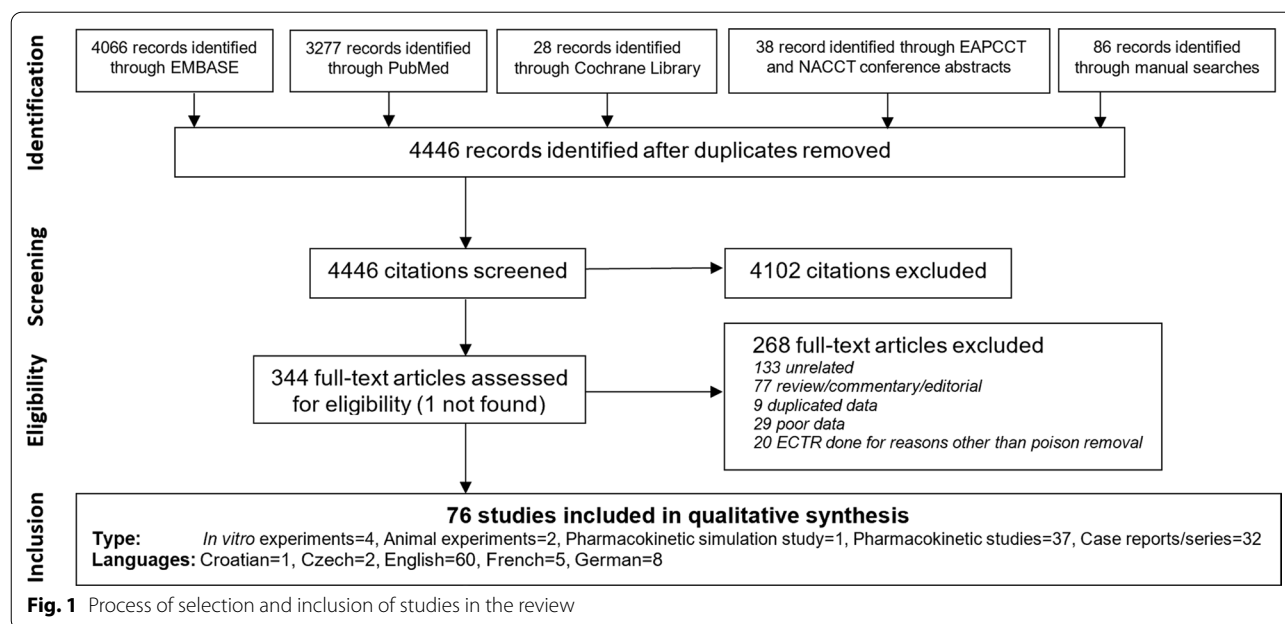
Because of the large heterogeneity in BAAs pharmacokinetics, no a priori overall estimation of dialyzability can be generalized for this entire drug class. Half-lives and clearances of BAAs obtained during ECTR are summarized in Table 2. Pharmacokinetic or toxicokinetic data related to ECTR were available for a total of 334 patients. Ninety percent of the pharmacokinetic articles were published prior to 1992. Although these older reports had

robust methods, with several subjects and serial samplings of BAAs concentrations in blood and dialysate, they must be interpreted with caution as they may not reflect current hemodialysis technology. With improved blood and effluent flows and better catheters and filters, these data are expected to be more favorable. For example, atenolol clearance by ECTR has tripled in 30 years [78, 101], bisoprolol clearance has doubled in 20 years [98, 101], and nadolol clearance has increased by 50% in 5 years [75, 89].

When measured from dialysate collection, the amount of BAA removed divided by the reported ingested dose during hemodialysis (when adjusted for a 6-h treatment and bioavailability) was 24% for atenolol [101], 18% for bisoprolol [101], ≈0% for carvedilol [101], 0.5% for labetalol [92], 3.3% for metoprolol [101], 50% for practolol [67], ≈0% for propranolol [70], and 4.6% for talinolol [99].

Data for continuous kidney replacement therapy (CKRT) are sparse: in 3 cases of atenolol overdose, CKRT removed between 8 and 25% of total body burden adjusted for a 6-h period [120, 123, 128], with atenolol clearance ranging from 20 to 48 mL/min. In one sotalol overdose, CKRT clearance was estimated as 53 mL/min [122]. These clearances are considerably inferior to those achievable during high-efficiency intermittent hemodialysis (Table 2). There is limited evidence for hemoperfusion and therapeutic plasma exchange (TPE), which can remove BAAs with extensive protein binding. This appears true for propranolol in vitro [59, 61] and in vivo [102, 131], although its high volume of distribution and high hepatic clearance substantially limit its dialyzability. Hemoperfusion in 2 patients with talinolol overdoses yielded clearances of 100–120 mL/min [104, 107] but this represented <20% of ingested dose, due to its large volume of distribution. As for penbutolol, in vitro data show little to no effect from hemoperfusion and only a minor and slow effect from TPE [60]. For BAAs with limited protein binding, hemoperfusion would not be expected to surpass diffusive or convective techniques as confirmed in one case of metoprolol overdose in which measured clearance [106] was comparable to that obtained during hemodialysis [101]. As expected, dialyzability of BAAs by peritoneal dialysis was consistently poor, with inconsequential impact on pharmacokinetics, i.e., approximately 6% of atenolol was removed in 24 h [90], 0.1% of labetalol in 72 h [92], and the peritoneal clearance of betaxolol only represented 7.5% of total clearance [86].

An increase in serum/blood concentrations was often observed following ECTR, often referred as “rebound,” in both pharmacokinetic studies [67, 76, 83, 92] and toxicokinetic reports [13, 15, 105, 107, 115, 118, 124]. The



median increase in concentration was 15% and occurred independently of volume of distribution.

Table 3 presents grading of dialyzability with the level of evidence, as defined by EXTRIP criteria (Additional file 1). The grading and level of evidence for hemodialysis was assessed as: *Dialyzable* for atenolol, nadolol, practolol, and sotalol; *Moderately dialyzable* for acebutolol, bisoprolol, and metipranolol; *Slightly dialyzable* for metoprolol and talinolol; *Not dialyzable* for betaxolol, carvedilol, labetalol, mepindolol, propranolol, and timolol. Some publications report that metoprolol may be dialyzable based on achievable clearance of 80–120 mL/min [101]. However, this only represents a small proportion of total body clearance (regardless of genetic polymorphism of clearance pathways), resulting in removal of <10% of an ingested dose. Because of its high endogenous clearance and volume of distribution, propranolol will not be removed meaningfully by ECTR modalities.

Although extracorporeal clearance of BAAs is independent of kidney function, its relative impact compared to total body clearance will increase for some BAAs as kidney function declines. This can be illustrated graphically (Fig. 2): for example, a hemodialysis clearance of 120 mL/min will represent 46% of total clearance for atenolol in a patient with normal kidney function (endogenous clearance = 140 mL/min) compared to 86% in an anuric patient (endogenous clearance 20 mL/min). Comparatively, ECTR clearance will have very little impact on enhancing total clearance of propranolol, regardless of kidney function. These estimates are considered conservative for several BAAs including sotalol, practolol,

nadolol, and betaxolol, as the ECTR data are at least 30 years old [67, 83, 86, 89]. Limited data exist for esmolol but even when assuming an optimal hemodialysis plasmatic clearance of 300 mL/min, this would represent less than 2% of total clearance [95].

Only 7 patients that could be assessed for dialyzability grading had normal kidney function, and only two reports were identified for a BAA (sotalol) whose grading may differ depending on kidney function [13, 15]. For these two cases, dialyzability was assessed as “*Dialyzable*” for one case of hemodialysis and “*Moderately dialyzable*” for one case of hemoperfusion-hemodialysis in series.

**Clinical data**

Among case reports and case series, the panel acknowledged variability in methodological quality and lack of reporting of critical information [132]. The evidence for a clinical effect of ECTR in BAA poisoning was available for 37 patients (acebutolol = 4, atenolol = 9, carvedilol = 1, metoprolol = 1, propranolol = 9, sotalol = 9, talinolol = 4), 16 of which had impaired kidney function (Table 4). All included patients were self-poisoned, except 6 dosing errors in end-stage kidney disease (ESKD) (atenolol = 1, sotalol = 5). Bradycardia and hypotension requiring vasopressors and/or inotropes were ubiquitous features for all BAAs except for propranolol and sotalol (predominant features for sotalol were ventricular dysrhythmias).

As reflected by changing trends in the management of BAA poisoning over almost 40 years, treatments were very heterogeneous. In particular, only eight patients



**Table 2** Half-life and clearance of  $\beta$ -adrenergic antagonists during extracorporeal treatments

Drug	ECTR		T <sub>1/2</sub> (Hours)				Clearance (mL/min)				References	
	ECTR	n	During ECTR		Endogenous		ECTR		Endogenous			
			Median	Range	Normal GFR	ESKD	Median	n	Range	Normal GFR		ESKD
Acebutolol	HD	7	6.1 (Met=7.2)	2.2-7	4-10	4-10	45 (Met=33.6)	12	30.5-55.1	600-800	N/A	[68, 69, 80, 109, 113]
	HF-HP	1	0.3				151	1				
Atenolol	HD	48	4.6	0.5-17.8	5-8	5-100	119.5	25	18-311	140-180	20	[73, 76, 78, 79, 85, 90, 91, 100, 101, 105, 118, 123, 124, 128]
	CKRT	2	22	14.5-29.5			47	3	19.9-48			
Betaxolol	HD+HP	1	3.4				N/A					
	PD	17	23	19.2-34	14-16	25-35	2.6	7	1.3-3.7	220-270	100-150	[86]
Bisoprolol	HD	16	7.8	6.4-9.6	9-12	25-35	17.5 ± 0.7	12				
	PD	3	23.6	20.8-26.4	6-7	6-7	11.7 ± 1.2	12	30.5-70	200-250	50	[93, 98, 101]
Carvedilol	HD	8	4.6	4.1-5.3	0.2	0.2	12.1	14	12.1-38.6	600		[96, 101]
	HD	6	0.12 ± 0.1				Met=76.8 ± 39.1	6		10,000-15,000		[95]
Esmolol	PD	6	0.13 ± 0.1				Met=2.7 ± 0.5	6				
	HD	7	1.8	0.6-3.8	3-10	10-12	37.4	14	25.7-97	1200-2000		[92, 94]
Labetalol	PD	8	13.1 ± 6.3				1.9 ± 1.7	8				
	HD	2	3.0		3-6	3-6	31	2		650	N/A	[88]
Mepindolol	HD	8	1.4 ± 0.5		2.5-3.0	2.5-3.0	N/A			1100-1300	N/A	[97]
	HD	8	2.9 (Met=5)	2.3-3	3-5	3-5	101	8		800-1200		[73, 101, 106]
Nadolol	HP	1	2.2				96.1	1				
	HD	6	3.5	3.0-8.5	10-15	30-45	82	15	46.4-102	120-250	30	[75, 89]
Oxprenolol	HD	3	Met=5.6		1-2	60-80	N/A			600-750	550	[84]
	HD	14	14 (Met=5)	8-30	10-13	60-80	> 100*	6		135	20	[65, 67]
Practolol	HP	3	5.6	4.9-8.9	3-5	3-5	189	2	188-191	800-1200		[66, 70, 73, 74, 87, 102]
	HD	23	3.4	1.5-8			9.4	11	3.8-26.5			
Sotalol	TPE	1	1.2				N/A					
	HD	9	7	3.5-9.5	5-9	35-60	80	3	67-80	120-160	20-25	[13, 15, 71, 83, 108, 115, 122]
Timolol	HP+HD	1	2.8				N/A					
	CKRT	1	18				53.1	1				
Talinolol	HD	2	N/A		10-12	20-25	28	7		320-380		[99, 104, 107]
	HP	2	3.3	2.7-3.8			109	2	96-121			
Timolol	HD	2	3.8	2.3-5.2	3-5	3-5	N/A			450-580	N/A	[72]

Legend: HD, Hemodialysis; HP, Hemoperfusion; HF, Hemofiltration; TPE, therapeutic plasma exchange; PD, Peritoneal dialysis; CKRT, Continuous kidney replacement therapy; ECTR, Extracorporeal treatment; ESKD, End-stage kidney disease; Met, metabolite; GFR, Glomerular filtration rate; N/A, Not available; n, number

In order to make data consistent and comparable for analysis, some transformations were performed (if necessary); half-lives were calculated graphically; clearances were calculated from removal data; when both clearance from arterio-venous differences and dialysate collections were provided, these were averaged; in some cases, clearance reported by some authors were calculated by using blood flows and plasma concentrations which may lead to overestimations [13, 98, 109], and so were recalculated

\* Reported dialysate flow assumed to be > 300 mL/min



**Table 3** Final toxicokinetic grading according to EXTRIP criteria

Drug	PK/TK grading	Number of patients						Final grading and level of evidence
		HD	PD	CKRT	HP	TPE	HP-HD	
Acebutolol	Dialyzable	1, MET = 2						HD: Moderately dialyzable, D* HD (MET): Moderately dialyzable, C
	Moderately dialyzable	1, MET = 1						
	Slightly dialyzable	1, MET = 1						
	Not dialyzable							
Atenolol	Dialyzable	24						HD: Dialyzable, A CKRT: Slightly dialyzable, C HD-HP: Moderately dialyzable, D PD: Not dialyzable, B
	Moderately dialyzable	1		1			1	
	Slightly dialyzable			2				
	Not dialyzable		7					
Betaxolol	Dialyzable							HD: Not dialyzable, B PD: Not dialyzable, C
	Moderately dialyzable							
	Slightly dialyzable							
	Not dialyzable	12	6					
Bisoprolol	Dialyzable	5						HD: Moderately dialyzable, B
	Moderately dialyzable	14						
	Slightly dialyzable							
	Not dialyzable							
Carvedilol	Dialyzable							HD: Not dialyzable, B
	Moderately dialyzable							
	Slightly dialyzable							
	Not dialyzable	8						
Labetalol	Dialyzable							HD: Not dialyzable, B PD: Not dialyzable, C
	Moderately dialyzable							
	Slightly dialyzable							
	Not dialyzable	17	8					
Mepindolol	Dialyzable							HD: Not dialyzable, C
	Moderately dialyzable							
	Slightly dialyzable	1						
	Not dialyzable	1						
Metipranolol	Dialyzable							HD: Moderately dialyzable, C
	Moderately dialyzable	4						
	Slightly dialyzable							
	Not dialyzable							
Metoprolol	Dialyzable	M = 2						HD: Slightly dialyzable, B HD (MET): dialyzable, C HP: Slightly dialyzable, D (Normal GFR)
	Moderately dialyzable							
	Slightly dialyzable	8			1 (Normal GFR)			
	Not dialyzable							
Nadolol	Dialyzable	6						HD: Dialyzable, B
	Moderately dialyzable							
	Slightly dialyzable							
	Not dialyzable							
Oxprenolol	Dialyzable	MET = 3						HD (MET): Dialyzable, C
	Moderately dialyzable							
	Slightly dialyzable							
	Not dialyzable							
Practolol	Dialyzable	14						HD: Dialyzable, B
	Moderately dialyzable							
	Slightly dialyzable							
	Not dialyzable							

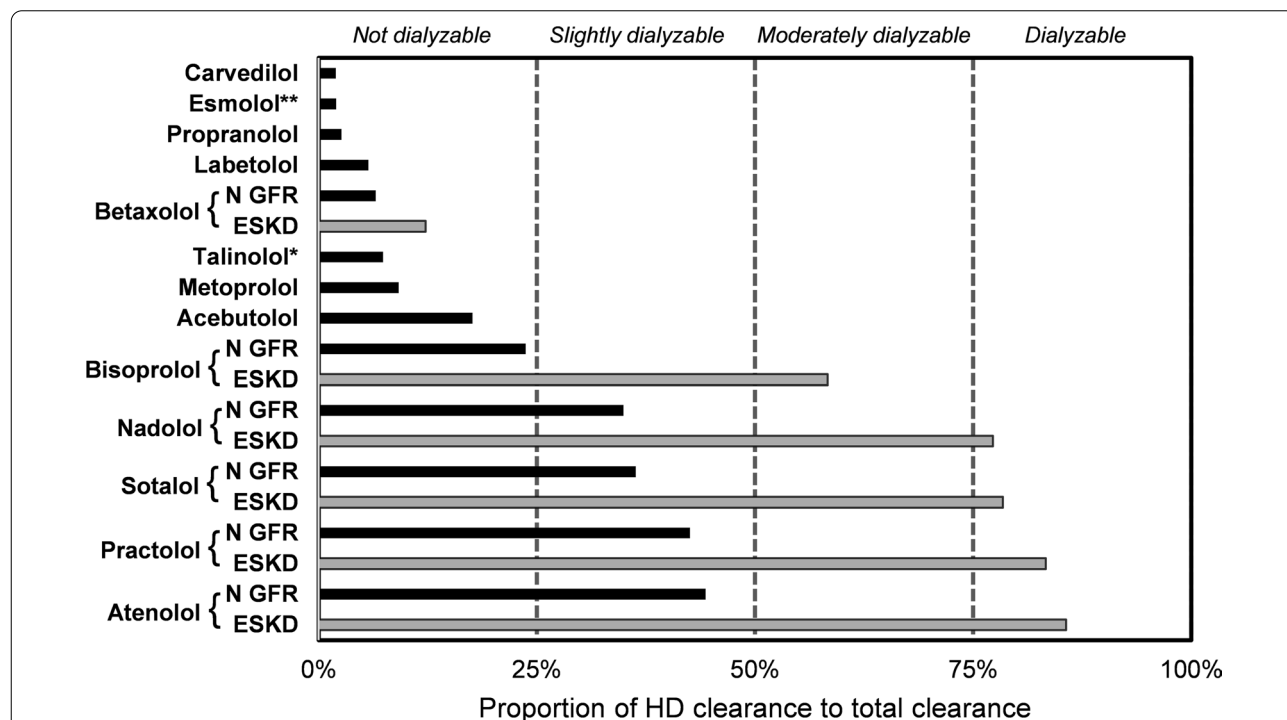
**Table 3** (continued)

Drug	PK/TK grading	Number of patients						Final grading and level of evidence
		HD	PD	CKRT	HP	TPE	HP-HD	
Propranolol	Dialyzable	1, MET = 2						HD: Not dialyzable, A HD (MET): Dialyzable, C HP: Slightly dialyzable, D (Normal GFR)
	Moderately dialyzable	2				1**		
	Slightly dialyzable				2 (Normal GFR)			
Sotalol	Dialyzable	6, 1 (Normal GFR)						HD: Dialyzable, B HD: Dialyzable, D (Normal GFR) CKRT: Slightly dialyzable, D HD-HP: Moderately dialyzable, D (Normal GFR)
	Moderately dialyzable	1				1 (Normal GFR)		
	Slightly dialyzable			1				
Talinolol	Dialyzable							HD: Slightly dialyzable, B HP: Slightly dialyzable, C (Normal GFR)
	Moderately dialyzable							
	Slightly dialyzable	8			2 (Normal GFR)			
Timolol	Dialyzable							HD: Not dialyzable, D
	Moderately dialyzable							
	Slightly dialyzable	1						
	Not dialyzable	1						

MET, Metabolites; PK, Pharmacokinetics TK, Toxicokinetics; HD, Hemodialysis; HP, Hemoperfusion; PD, Peritoneal dialysis; CKRT, Continuous kidney replacement therapy; TPE, Therapeutic plasma exchange; HD-HP, hemodialysis and hemoperfusion in series; GFR, Glomerular filtration rate

\* 6 additional patients would be rated as “dialyzable” but the assay was non-specific and likely measured parent drug and metabolites, so the result is uninterpretable [69]

\*\* Based on half-life comparison, a criterion considered unreliable for poisons with a high Vd like propranolol, so not graded



**Fig. 2** Proportion of hemodialysis clearance relative to total clearance. Legend: GFR: Glomerular filtration rate, ESKD: End-stage kidney disease, HD: Hemodialysis. \*These are conservative estimations, as ECTR clearances would likely be higher if performed today. \*\*based on endogenous clearance of 12,000 mL/min. For carvedilol, esmolol, propranolol, labetalol, talinolol, metoprolol, and acebutolol, it is assumed the ratio would apply regardless of kidney function

**Table 4** Summary of clinical findings of patients receiving extracorporeal treatments for  $\beta$ -adrenergic antagonist removal

	Acebutolol (n = 4)	Atenolol (n = 9)	Carvedilol (n = 1)	Metoprolol (n = 1)	Propranolol (n = 9)	Sotalol (n = 9)	Talinolol (n = 4)
<i>Patient characteristics</i>							
Age, years	20 (17–27)	45 (28–74)	21	49	31 (15–49)	66 (44–78)	21 (20–47)
Men, %	0	56	0	0	44	78	50
ESKD, %	0	11	0	0	0	44	0
<i>Poisoning information</i>							
Intentional overdose, %	100	89	100	100	100	44	100
Dose if acute ingestion, g	8.4 (4.8–12)	4.5 (2.5–10)	1.8	0.5	3.1 (0.6–5.0)	8.0 (7.2–14.4)	2.5 (1.5–5.0)
Peak concentration, mg/L	14 (10–18)	14 (2.5–70)	0.6	2.8	1.5 (0.04–3)	17 (2.5–65)	5.5 (5.0–6.1)
Time from ingestion to admission, hours	2 (2–2)	6.5 (2–8)		0.8	2 (1–8)	2.5 (1–4)	6 (2–8)
<i>Signs/Symptoms/Labs</i>							
Coma, %	100	89	100	100	50	100	75
Altered consciousness, %	100	100	100	100	83	100	75
Bradycardia, %	100	100	100	100	100	50	100
Severe dysrhythmia, %	25	0	100	0	33	100	25
Hypotension, %	100	100	100	100	75	89	100
QRS complex duration, msec	260	128 (98–160)	N/A	N/A	104	120 (104–140)	420
Prolonged QRS complex duration, %	100	43	0	0	N/A	25	50
QT interval duration, msec	N/A	440 (400–448)	N/A	N/A	N/A	618 (509–880)	440
Prolonged QT interval, %	N/A	17	N/A	N/A	N/A	100	25
Acute kidney injury, %	100	87.5	100	0	0	38	0
Serum glucose, mmol/L	14.7	7.7 (2.2–19.2)	8.3	N/A	10.7	4.4 (1.4–7.4)	N/A
Serum bicarbonate, mmol/L	16	19 (10.8–21)	N/A	N/A	20 (15–25)	17	N/A
Serum lactate, mmol/L	1.9	4.6 (1.8–9.3)	4.7	N/A	7.6 (1.9–13.2)	1.9	N/A
Serum potassium, mmol/L	3.2	4.3 (< 0.8–8.5)	5.9	N/A	4.2 (3.7–4.7)	5.1 (3.8–7.1)	N/A
<i>Other treatments</i>							
Gastric lavage, %	25	44	0	0	67	22	75
Activated charcoal, %	75	56	0	100	50	11	25
Vasopressors/ inotropes, %	100	100	100	100	50	75	75
Mechanical ventilation, %	100	100	0	100	17	75	75
Atropine, %	100	56	0	100	67	22	25
Lipid emulsion, %	0	11	0	0	16	0	0
Pacemaker, %	100	44	100	100	33	88	50
High-dose insulin euglycemic therapy, %	0	67	0	0	33	0	0
Glucagon, %	75	100	100	100	83	33	25
Extracorporeal life support (ECLS), %	25	22	100	0	0	0	0
<i>Extracorporeal treatments</i>							
Hemodialysis, n	1	3	0	0	0	6	0
TPE, n	0	0	1	0	2	0	0
CKRT, n	0	3	0	0	0	1	0
More than 1 ECTR, n	0	2	0	0	0	0	0
HF-HP, n	1	0	0	0	0	0	0
HD-HP, n	1	1	0	0	3	1	1
HP, n	1	0	0	1	4	0	3
<i>Outcome</i>							
Death, %	0	11	0	0	11	11	50
Sequelae, %	25	11	0	0	N/A	11	N/A
Length of stay, days	30 (7–49)	22 (12–32)	23	N/A	6 (5–32)	20	N/A
Length of ICU stay, days	2 (2–2)	9.5 (1.5–28)	8	3	8.5 (4–13)	3 (2–6)	N/A
Length of life-threatening dysrhythmia	N/A	N/A	N/A	N/A	56	16 (12–120)	N/A
Length of prolonged QT interval, msec	N/A	N/A	N/A	N/A	N/A	37 (30–120)	N/A
Length of bradycardia/hypotension, hours	25 (24–26)	48 (20–168)	120	18	67 (24–70)	36	9

**Table 4** (continued)

Results presented as medians and range. No range is presented when the number of values is one. When specific data was not reported, this was not included in the incidence

ESKD, end-stage kidney disease; TPE, therapeutic plasma exchange; CKRT, continuous renal replacement therapy; ECTR, extracorporeal treatment; HF-HP, hemofiltration-hemoperfusion; HD-HP, hemodialysis and hemoperfusion in series; HP, hemoperfusion; ICU, intensive care unit; N/A, Not available

received high-dose insulin euglycemic therapy and four patients received ECLS, treatments now considered likely to improve outcome [1]. For these reasons, it was difficult to determine a benefit from ECTR. Three patients died of cardiogenic shock [102, 103, 108], one of irreversible brain injury [107], and one of multiorgan failure after four weeks, despite marked improvement post-ECTR [105]. The overall mortality for the cohort was 13.5%.

For sotalol, resolution of dysrhythmias/torsade de pointes was rapid with intermittent hemodialysis, often occurring during or just after treatment [13, 15, 35, 115, 116, 121], while this was more protracted with slower techniques like peritoneal dialysis (PD) [114] or CKRT [122]. For atenolol (n=9), when hemodialysis was used, an increase in blood pressure was noted after the first treatment, with one exception [129]. Again, apparent improvement was slower with CKRT [120, 127, 128]. Dysrhythmias recurred in two patients, within two hours of ECTR cessation, requiring another session [13, 15]. Although nine patients were reported for propranolol, the clinical impact of ECTR could only be analyzed in two patients: one improved slowly after hemoperfusion [125] while the other improved after TPE but had recurrence of hypotension shortly after [130]. For acebutolol, four patients were described, three of which improved during ECTR [109, 113, 117], while this was uncertain in one patient who received hemoperfusion [112]. In all four patients of talinolol poisoning, hemoperfusion was employed alone or in combination with hemodialysis, and two of them died [103, 107]. There was only one patient described for carvedilol [126] and metoprolol [106], which were difficult to interpret because of the co-ingested calcium channel blockers in both cases. No ECTR-associated complications were described in the cohort.

In summary, clinical improvement from ECTR was generally noted with BAAs considered dialyzable such as atenolol and sotalol when high-efficiency ECTRs were used, whereas this was questionable with other BAAs or when techniques with lower efficiency were used.

To further measure the effect of ECTR, outcomes of the ECTR cohort were compared to historical controls not receiving ECTRs (Table 5). Unfortunately, this analysis is severely hampered by the small numbers of reported patients, the variability in treatments provided and the heterogeneity of populations compared. For example, historical controls reported to poison control

centers are expected to have more benign features than those included in the ECTR cohort. Overall, the mortality of patients receiving ECTRs for BAA poisoning was greater than those reported in historical controls, including one cohort of critically ill patients [23]. Aside from mortality, the only outcome that could be compared to assess the benefit of ECTR was the median duration of QT interval prolongation in sotalol poisoning, which was 37 h [IQR 33.5, 78.5] for the ECTR cohort (median maximal QTc interval=140% of normal) versus 75 h [IQR 57, 87.5] in one historical cohort (median maximal QTc interval=172%) [12]. However, this analysis is underpowered. With regard to harms and costs, the use of ECTR is associated with an increased risk of catheter- and ECTR-related complications and added costs which will vary depending on the choice of technique and the geographical location [133]. It is possible that ECTR may exacerbate hypotension in some cases despite the absence of net ultrafiltration, although the incidence of this risk and its magnitude are unknown.

## Discussion

### Recommendations

As per EXTRIP methods, the workgroup only voted on BAAs for which the number of patient clinical reports were sufficient. Although there were 4 reports for acebutolol and talinolol, they were not considered to be of sufficient quality to permit elaborations of recommendations.

### General statements and indications for ECTR

#### Propranolol

- In patients severely poisoned with propranolol, we *recommend against* performing ECTR in addition to standard care rather than standard care alone (strong recommendation, very low quality evidence).

#### Atenolol

- In patients severely poisoned with atenolol and kidney impairment\*, we *suggest* performing ECTR in addition to standard care rather than standard care alone when refractory bradycardia and hypotension is present (weak recommendation, very low quality evidence)
- In patients severely poisoned with atenolol and normal kidney function, we *make no recommendation*

**Table 5** Extracorporeal treatments + standard care versus standard care in  $\beta$ -adrenergic antagonists poisoning (evidence profile table)

Quality assessment		Summary of findings						Importance			
Drug	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECTR + standard care	Standard care (controls)	Impact	Quality	
Mortality All $\beta$ -adrenergic antagonists <sup>a</sup> n = 10	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	13.5% (5/37)	ICU data 8.2% (9/110) admitted in 1 ICU 2002–9 [23] PCC and hospital data 3.8% (63/1678) 0/858: German PCC 2001–11 single-substance [32] 1/11: children, self-harm [50] 2/73: 1 hospital 1993–7 [37] 0/40: 1 hospital 1966–80 [25] 4/280: 2 PCCs 1992–8, [22] 60/416: US PCCs 2017–19, at least major effect [21, 51, 52]	Comparable mortality between the ECTR group and the control group admitted to ICU (risk difference = 53 more deaths per 1000 patients in the ECTR group (with a 95% CI from 68 less to 175 more deaths per 1000))	⊕○○○ VERY LOW	CRITICAL
Propranolol <sup>f</sup> n = 5	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	11.1% median dose 3.1 g (1/9)	Ranging from 0 to 2.1% 0/41 German PCC 2001–11 single substance median dose 0.4–0.5 g [32] 7/339 UK PCC 2017–18, median dose 0.6 g [321] 0/50: 1 hospital 1993–7 mean dose 1.3 g [37] 0/18 1979–1985 mean dose 1.6 g [36]	Groups not comparable	⊕○○○ VERY LOW	CRITICAL
Sotalolol <sup>g</sup> n = 3	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	11.1% median 8.0 g (1/9)	Overall = 0% 0/31: German PCC 2001–11 single substance [32] 0/6: Case in Finland 1977–1980, mean dose 5.7 g [12]	Groups not comparable	⊕○○○ VERY LOW	CRITICAL

**Table 5** (continued)

Quality assessment		Summary of findings							Importance		
Drug	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECTR + standard care	Standard care (controls)	Impact	Quality	
Atenolol <sup>h</sup> n = 3	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	11.1% median 4.5 g (1/9)	Overall = 0% (0/48; German PCC 2001–11, single substance, median dose 0.5–0.8 g [32] 0/10; 1 hospital 1993–7 mean dose 2.0 g [37])	Groups not comparable	⊕○○○ VERY LOW	CRITICAL
Duration of QT interval prolongation											
Sotalolol <sup>i</sup> n = 4	Observational studies	Very serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	Publication bias strongly suspected <sup>e</sup>	Median = 37 h [33.5, 78.5] 3 pts, median 8 g	Median = 75 h [57, 87.5] 6 pts median dose 6.2 g 1977–80 [12]	No formal comparison possible due to the small sample size of the ECTR group	⊕○○○ VERY LOW	IMPORTANT
Serious complications of catheter insertion <sup>j</sup>											
n = 5 <sup>k</sup>	Observational studies	Not serious	Not serious <sup>l</sup>	Not serious <sup>m</sup>	Not serious <sup>n</sup>	Strong association <sup>o</sup>	Rate of serious complications of catheter insertion varies from 0.1% to 2.1%	≈ 0	Absolute effect is estimated to be varying from 1 to 21 more serious complications per 1000 patients in the ECTR group	⊕⊕⊕○ MODERATE	CRITICAL
Serious complications of ECTR <sup>p</sup>											
n = 4 <sup>t</sup>	Observational studies	Not serious	Not serious	Not serious	Not serious	Strong association <sup>r</sup>	Rate of serious complications of ECTR varies according to the type of ECTR performed from 0.005% (HD and CKRT), to 0.6% (TPE) and up to 1.9% (HP)	≈ 0	Absolute effect is estimated to be varying from > 0 to 19 more serious complications per 1000 patients in the ECTR group depending of the type of ECTR performed	⊕⊕⊕○ MODERATE	CRITICAL

**Table 5** (continued)

<p>ECRT: Extracorporeal treatments, IHD: Intermittent hemodialysis, TPE: Therapeutic plasma exchange, CKRT: Continuous kidney replacement therapy, HP: Hemoperfusion, Pts = patients, PCC: Poison control center</p> <p><sup>a</sup> Requirement for extracorporeal life support; <sup>b</sup> Length of requirement of vasopressors; <sup>c</sup> Length of hospital stay; <sup>d</sup> Length of ICU stay; <sup>e</sup> "Sequelae" were outcomes ranked important or critical although no data were reported in the control group, so no comparison with the ECTR group could be performed</p> <p><sup>a</sup> Includes our systematic review of the literature on ECTR (37 patients from 32 case reports or case series) and 9 cohorts on standard care alone in <math>\beta</math>-adrenergic antagonists. No exclusion was based on the presence of co-ingestants or interventions</p> <p><sup>b</sup> Case reports published on effect of ECTR. Uncontrolled and unadjusted for confounders such as severity of poisoning, co-ingestions, supportive and standard care, and co-interventions. Confounding-by-indication is inevitable since ECTR was often attempted after other therapies had failed</p> <p><sup>c</sup> ECTR and standard care performed may not be generalizable to current practice (literature pre-dating 2000)</p> <p><sup>d</sup> Few events in small sample size, optimal information size criteria not met</p> <p><sup>e</sup> Publication bias is strongly suspected due to the study design (case reports published in toxicology either report very severe poisoning with/without impressive recovery with treatments attempted)</p> <p><sup>f</sup> Includes our systematic review of the literature on ECTR (9 case reports) and 4 cohorts on standard care alone in propranolol poisoning</p> <p><sup>g</sup> Includes our systematic review of the literature on ECTR (9 case reports) and 2 cohorts / case series on standard of care alone in sotalol poisoning</p> <p><sup>h</sup> Includes our systematic review of the literature on ECTR (9 case reports) and 2 cohorts on standard of care alone in atenolol poisoning</p> <p><sup>i</sup> Includes our systematic review of the literature on ECTR (3 case reports) and 1 case series on standard of care alone in sotalol poisoning</p> <p><sup>j</sup> For venous catheter insertion: serious complications include hemothorax, pneumothorax, hemomediastinum, hydrothorax, subcutaneous emphysema retroperitoneal hemorrhage, embolism, nerve injury, arteriovenous fistula, tamponade, and death. Hematoma and arterial puncture were judged not serious and thus excluded from this composite outcome. Deep venous thrombosis and infection complications were not included considering the short duration of catheter use</p> <p><sup>k</sup> Based 5 single-arm observational studies: 2 meta-analyses comparing serious mechanical complications associated with catheterization using or not an ultrasound, which included 6 RCTs in subclavian veins [322] and 11 in internal jugular veins [323]; 2 RCTs comparing major mechanical complications of different sites of catheterization [324, 325]; one large multicenter cohort study reporting all mechanical complications associated with catheterization [326]. Rare events were reported from case series and case reports</p> <p><sup>l</sup> Not rated down for inconsistency since heterogeneity was mainly explained by variation in site of insertion, use of ultrasound, experience of the operator, populations (adults and pediatric), urgency of catheter insertion, practice patterns, and methodological quality of studies</p> <p><sup>m</sup> Not rated down for indirectness since cannulation and catheter insertion was judged similar to the procedure for other indications</p> <p><sup>n</sup> Not rated down for imprecision since wide range reported explained by inconsistency</p> <p><sup>o</sup> The events in the control group are assumed to be zero (since no catheter is installed for ECTR); therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95%CI which included the null value and all observed complications occurred in a very short timeframe (i.e., few hours)</p> <p><sup>p</sup> For IHD and CKRT: serious complications (air emboli, shock, and death) are exceedingly rare. Minor bleeding from heparin, transient hypotension, and electrolytes imbalance were judged not serious. For HP, serious complications include severe thrombocytopenia, major bleeding, and hemolysis. Transient hypotension, hypoglycemia, hypocalcemia, and thrombocytopenia were judged not serious. For TPE, serious complications include citrate toxicity, severe allergic reaction, arrhythmia, and vasovagal reaction. Hypotension, hypocalcemia, and urticaria were judged as not serious. All non-serious complications were excluded from this composite outcome</p> <p><sup>q</sup> IHD/CKRT: Based on 2 single-arm studies describing severe adverse events per 1000 treatments in large cohorts of patients [327, 328]. TPE: Based on the 2 most recent one-arm studies reporting potential life-threatening adverse events [329, 330]. HP: Based on 2 small single-arm studies in poisoned patients [331, 332]. Rare events were reported in case series and case reports</p> <p><sup>r</sup> Assuming that patients in the control group would not receive any form of ECTR, the events in the control group would be zero; therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95%CI which included the null value and all observed complications occurred in a very short timeframe (i.e., few hours)</p>
--



for or against performing ECTR in addition to standard care rather than standard care alone (no recommendation, very low quality evidence)

### Sotalol

- In patients severely poisoned with sotalol and kidney impairment\*, we suggest performing ECTR in addition to standard care rather than standard care alone when refractory bradycardia and hypotension and/or recurrent torsade de pointes is present (weak recommendation, very low quality of evidence)
- In patients severely poisoned with sotalol with normal kidney function, we make no recommendation for or against performing ECTR in addition to standard care rather than standard care alone (no recommendation, very low quality evidence).
- In patients severely poisoned with sotalol, we suggest against performing ECTR solely based on the QT interval (weak recommendation, very low quality evidence).

\*“Kidney impairment” was defined as stage 3B, 4, or 5 CKD (i.e., eGFR < 45 mL/min/1.73m<sup>2</sup>) or AKI as KDIGO stage 2 or 3 AKI. In the absence of a baseline serum creatinine concentration, kidney impairment was defined as an eGFR < 45 mL/min/1.73m<sup>2</sup> in adults; and in children with no baseline creatinine, the use of KDIGO criteria of AKI stage 2 and 3 after imputing a baseline serum creatinine using the Schwartz 2009 formula assuming 120 mL/min/1.73m<sup>2</sup> of “normal” eGFR. The presence of oligo/anuria unresponsive to fluid resuscitation should be considered as impaired kidney function, regardless of serum creatinine concentration (See supplemental section)

### Rationale

Severe BAA poisoning can lead to bradycardia and hypotension refractory to vasopressors and inotropes, occasionally causing death [57]. Assuming all other priority therapeutic measures are in place to mitigate BAA toxicity including involvement of a clinical toxicologist, the workgroup considered the use of ECTR for severe poisoning due to propranolol, atenolol, and sotalol.

Propranolol has a short half-life and a high endogenous clearance independent of kidney function. These attributes added to extensive protein binding make this drug non-dialyzable regardless of the ECTR used. Although the data were limited, ECTR did not appear to accelerate clinical recovery and the mortality from ECTR cases was higher than historical controls. For these reasons, the workgroup recommended against ECTR for propranolol poisoning (Median: 1.0/Upper quartile: 1.0/Disagreement index: 0.0).

Atenolol and sotalol both have endogenous clearances (and elimination half-lives) that are highly dependent on kidney function. The contribution of ECTR in patients with kidney impairment is considerable. The greater the impairment in kidney function, the greater the relative toxicokinetic effect of ECTR. Both are considered to be “Dialyzable” in patients with kidney impairment. Although the number of cases is small, clinical improvement from sotalol and atenolol poisoning appears to coincide with initiation of ECTR, especially when high efficiency techniques are used. It is conceivable that relevant patient-important outcomes (PIOs), such as length of vasopressor requirement, long-term sequelae, and mortality would be reduced with ECTR in this population. In patients who already have vascular access in place, the risk associated with insertion is already taken into account, so the risk-benefit ratio is even lower. The workgroup suggested ECTR in patients with impaired kidney function for both atenolol (Median: 7.0 / Lower quartile: 4.0 / Disagreement index: 0.59) and sotalol (Median: 7.0 / Lower quartile: 4.0 / Disagreement index: 0.59); the workgroup nevertheless acknowledged that the initiation of ECTR, even without net ultrafiltration, might exacerbate hemodynamic instability and may not be possible to perform. The benefit of ECTR is theoretically less for patients poisoned with atenolol or sotalol and normal kidney function, even if the addition of ECTR can approximately double total clearance; the duration of toxicity is expected to be much shorter in this population. For these reasons, the workgroup considered that, at the time of writing, the benefits and harms were balanced with considerable knowledge gaps and made no recommendation for patients poisoned with atenolol or sotalol and normal kidney function.

A major consideration for sotalol is its ability to cause QT prolongation, which is uncommon with other BAAs and can lead to life-endangering torsade de pointes, a poor prognostic indicator in sotalol poisoning. Obviously, the workgroup is not advocating ECTR for the treatment of torsade de pointes, as ECTR would not be technically feasible. However, recurrent torsade de pointes is indicative of severity and of a role for ECTR initiation. For non-recurrent torsades, ECTR is not justified. In the literature, there is no clear QTc duration cut-off which predicts torsade de pointes [134]. The risk of life-threatening cardiac events increases as the QTc gets longer than 500 ms [134, 135] and each 10-ms increase contributes to approximately a 5% to 7% exponential increase in risk. However, QT can be prolonged at therapeutic sotalol concentration. These findings support the recommendation of the workgroup not to perform ECTR solely based on QT prolongation.

Although monitoring of poison concentrations is useful in some settings, there remain too many uncertainties in the concentration-effect relationship to provide a threshold concentration for ECTR initiation in BAA poisoning. Hypotension and bradycardia are poorly related to atenolol concentrations [136], QT interval prolongation is correlated with sotalol concentrations but with considerable imprecision [45–48]. Further, only 7 out of 37 panelists had access to atenolol or sotalol assays and only 3 within 12 hours of it being ordered. Very few clinicians outside of large academic centers are likely to have access to BAA assays. The panel did recognize the value of a subtherapeutic concentration in excluding the need for ECTR. The panel emphasized that the indication for ECTR is likely to depend on the availability of ECLS, which should be instituted prior to ECTR assuming both are available in the same center, as it is simple to add a hemodialysis circuit to extracorporeal membrane oxygenation.

#### **Research gaps**

Additional pharmacokinetic data in ESKD patients are needed, especially during hemodialysis, for acebutolol (because of imprecision about sampling in studies), betaxolol, bopindolol, carteolol, cetamolol, nadolol, oxprenolol, pindolol, sotalol, and timolol. In addition, clinical cases of poisoning with toxicokinetic data of ECTR is required for acebutolol, atenolol, bisoprolol, metoprolol, nadolol and sotalol in patients with normal GFR or slightly impaired GFR.

Toxicokinetic/toxicodynamic relationships should better evaluate if serum concentrations can determine the utility of ECTR in clinical decision-making. Better prognostic markers on admission would also be useful to determine which subset of patients are most likely to benefit from ECTR.

The added value of ECTR to ECLS should be demonstrated. In patients with impaired kidney function, additional studies could help characterize if the transfer of an unstable patient for ECTR with or without ECLS could potentially be beneficial and within which timeframe this could be useful. If ECLS is unavailable in the initial center, studies could compare clinical outcomes associated with transfer for ECLS vs. hemodialysis alone at the initial center.

#### **Type of ECTR**

In patients severely poisoned with atenolol or sotalol requiring ECTR: when all modalities are available, *we recommend using intermittent hemodialysis* rather than any

other type of ECTR (strong recommendation, very low quality evidence).

#### **Rationale**

If ECTR is used for poison removal, then the most efficient modality at removing atenolol or sotalol should be selected, i.e., intermittent hemodialysis. In the rare circumstance that intermittent hemodialysis is unavailable but other techniques are, then hemoperfusion, CKRT, sustained low-efficiency dialysis (SLED), or prolonged intermittent renal replacement therapy (PIRRT) can be used, preferably the modality providing the best solute clearance and quickest to deliver. Although CKRT and other “slower” techniques such as SLED/PIRRT are often preferred for patients with hemodynamic compromise, this applies specifically to those requiring net ultrafiltration. It is therefore uncertain if CKRT or SLED/PIRRT would be better tolerated than intermittent hemodialysis in patients not requiring net ultrafiltration. It is acknowledged that all techniques may exacerbate hypotension to some extent for various causes including fluid and solute shifts, and electrolyte fluxes.

Regardless of technique, ECTR parameters should be optimized to enhance clearance (higher blood and effluent flows, filter/dialyzer with larger surface area) [137] and to reduce risk of hemodynamic compromise (priming of the ECTR circuit, lowering dialysate temperature, dialysate/replacement fluid without low potassium, calcium and magnesium concentrations, and minimizing net ultrafiltration).

Importantly, if dialysis is performed for sotalol poisoning, the input of a nephrologist is recommended to ensure that the serum magnesium concentration remains above 1 mmol/L and serum potassium concentration within 4.5–5 mmol/L to minimize the risk of dysrhythmias, including torsade de pointes. Magnesium may be added to the dialysate or administered intravenously to offset its elimination during ECTR.

#### **Research gap**

Data with hemoperfusion and high-cut off dialysis should be assessed in poisoning from highly protein-bound BAAs with reasonably low volume of distribution and plasma clearance such as penbutolol, oxprenolol, and carvedilol.

#### **Cessation of ECTR**

In patients severely poisoned with atenolol or sotalol requiring ECTR, *we recommend stopping ECTR based on clinical improvement* (strong recommendation, very low quality of evidence)

### Rationale

The indication to stop ECTR, once initiated, should be reliant on clinical indicators of improvement. These include appropriate heart rate and blood pressure for adequate end organ perfusion, weaning of ECLS, decreasing inotropic and vasopressor requirements, and sustained cessation of torsade de pointes if applicable. It is recognized that QT interval prolongation may persist even at therapeutic sotalol concentrations so the use of this target for cessation is not recommended. In addition, there is no predefined duration of ECTR to treat BAA poisoning as this will depend on the type and amount of BAA ingested, as well as the underlying kidney function in some cases. The workgroup suggested not to cease ECTR solely based on a target serum concentration, as safe thresholds are not well known, and assays are infrequently available to guide judgement.

Our work has several strengths. This is the first systematic review of the use of extracorporeal therapy in BAA poisoning. This systematic review summarizes the best evidence on the use of extracorporeal therapy in BAA poisoning using the most stringent guideline methodology (GRADE). No articles were rejected based on language or year of publication. It also provides clinical recommendations following a voting process using a two-round modified Delphi procedure from an international collaborative comprising recognized experts from various clinical specialties and resource settings. Limitations of the study are inherently associated with the quality of articles used for the drafting of recommendations. In many cases, details regarding these articles were of poor quality. There were insufficient data to draft recommendations on BAAs other than propranolol, atenolol, and sotalol due to the limited published evidence available; however, the workgroup acknowledged there was little clinical plausibility of a clinical benefit from ECTR for non-dialyzable BAAs such as betaxolol, carvedilol, esmolol, labetalol, mepindolol, and timolol.

### Conclusion

In conclusion, poisoning from BAAs can cause serious toxicity and death.  $\beta$ -adrenergic antagonists have different physicochemical properties and pharmacokinetics which will affect their removal by ECTR. The EXTRIP workgroup assessed propranolol as non-dialyzable. Atenolol as well as sotalol were assessed as dialyzable in patients with kidney impairment and the workgroup suggests ECTR in patients severely poisoned with these drugs when aforementioned indications are present.

### Abbreviations

BAA: Beta-adrenergic antagonists; CKD: Chronic kidney disease; CKRT: Continuous kidney replacement therapy; CL: Clearance; ECLS: Extracorporeal life support; ECTR: Extracorporeal treatments; ESKD: End-stage kidney disease; EXTRIP: The Extracorporeal Treatments In Poisoning workgroup; F: Bioavailability; GFR: Glomerular filtration rate; HD: Hemodialysis; HF: Hemofiltration; HP: Hemoperfusion; ICU: Intensive care unit; IHD: Intermittent hemodialysis; IQR: Interquartile range; Met: Metabolite; MW: Molecular weight; N/A: Not available; PCC: Poison control center; PD: Peritoneal dialysis; PIO: Patient-important outcomes; PK: Pharmacokinetics; Pts: Patients;  $T_{1/2}$ : Elimination half-life; TK: Toxicokinetics;  $T_{MAX}$ : Time to maximum concentration; TPE: Therapeutic plasma exchange;  $V_D$ : Volume of distribution.

### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-021-03585-7>.

**Additional file 1.** Detailed methods and glossary.

### Acknowledgements

We would like to acknowledge the valuable help of our dedicated translators, librarian, data extractors, and meeting secretary. Official translators were Alexandra Angulo, Alla Abbott, Anant Vipat, Andreas Betz, Angelina Kovaleva, Denise Gemmellaro, Ewa Brodziuk, Helen Johnson, Junzheng Peng, Marcela Covic, Nathalie Eeckhout, Rosie Finnegan, Salih Topal, and Vilma Etchard. The librarian was Elena Guadagno. Data extractors for EXTRIP-2 included Maria Rif, François Filion, Karine Mardini, Maria Rif, Tudor Botnaru, Elizabeth Koo, and Gabrielle Wilson. The meeting secretary was Brenda Gallant.

In addition to the authors of this manuscript, members of the EXTRIP Group include: Badria Alhatali, Kurt Anseeuw, Steven Bird, Ingrid Berling, Timothy E Bunchman Diane P Calello, Paul K Chin, Kent Doi, Tais Galvao, David S Goldfarb, Hossein Hassanian-Moghaddam, Lotte CG Hoegberg, Siba Kallab, Sofia Kebede, Jan T Kielstein, Andrew Lewington, Etienne M Macedo, Rob MacLaren, Bruno Megarbane, James B Mowry, Thomas D Nolin, Marlies E Ostermann, Ai Peng, Jean-Philippe Roy, Anitha Vijayan, Steven J Walsh, Anselm Wong, David M Wood, Christopher Yates, Josée Bouchard, Greene Shepherd, Robert S. Hoffman, Sophie Gosselin, Darren M. Roberts, Yi Li, Thomas D. Nolin, Valéry Lavergne and Marc Ghannoum.

### Authors' contributions

MG, SG, RSH, VL, TSN, YL, and DMR designed the study; JB, MG, and GS, carried out extractions; all authors participated in analysis and interpretation of data; JB, MG, GS, and VL made the tables and figures; all authors drafted and revised the paper; all authors provided intellectual content of critical importance to the work. All authors read and approved the final manuscript.

### Funding

EXTRIP received support consisting of an unrestricted grant of \$60,633 Canadian from the Verdun Research Fund (the institution of Marc Ghannoum) solely for the reimbursement of travel expenses for the in-person guideline meeting and payment to dedicated translators for retrieval and translation of foreign language articles. The funding source did not have a role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

### Availability of data and materials

The data underlying this article will be shared on reasonable request to the corresponding author.

### Declarations

#### Ethics approval and consent to participate

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

TDN reports personal fees from MediBeacon, CytoSorbents, and McGraw-Hill Education outside the submitted work. MG is a scholar of the Fonds de Recherche du Québec—Santé. DMR acknowledges support of St. Vincent's Centre for Applied Medical Research Clinician "Buy-Out" Program. AV reports consulting functions for NxStage, Astute Medical, and Boehringer-Ingelheim and speaker fees from Sanofi-Aventis. MO has received speaker honoraria and research funding from Fresenius Medical and Baxter and has had consulting functions for Nxstage and Baxter. All remaining authors have nothing to disclose.

**Author details**

<sup>1</sup>Research Center, CIUSSS du Nord-de-l'île-de-Montréal, Hôpital du Sacré-Coeur de Montréal, University of Montreal, Montreal, QC, Canada. <sup>2</sup>Division of Practice Advancement and Clinical Education, UNC Eshelman School of Pharmacy, Chapel Hill, NC, USA. <sup>3</sup>Division of Medical Toxicology, Ronald O. Perleman Department of Emergency Medicine, NYU Grossman School of Medicine, New York, NY, USA. <sup>4</sup>Centre Intégré de Santé et de Services Sociaux (CISSS) Montérégie-Centre Emergency Department, Hôpital Charles-Lemoyne, Greenfield Park, QC, Canada. <sup>5</sup>Department of Emergency Medicine, McGill University, Montreal, QC, Canada. <sup>6</sup>Centre Antipoison du Québec, Quebec, QC, Canada. <sup>7</sup>Departments of Renal Medicine and Transplantation and Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, NSW, Australia. <sup>8</sup>St Vincent's Clinical School, University of New South Wales, Sydney, NSW, Australia. <sup>9</sup>Emergency Department, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China. <sup>10</sup>Department of Pharmacy and Therapeutics, and Department of Medicine Renal-Electrolyte Division, University of Pittsburgh Schools of Pharmacy and Medicine, Pittsburgh, PA, USA. <sup>11</sup>Verdun Hospital, 4000 Lasalle Boulevard, Verdun, Montreal, QC H4G 2A3, Canada.

Received: 1 March 2021 Accepted: 26 April 2021

Published online: 10 June 2021

**References**

- Rotella JA, Greene SL, Koutsogiannis Z, Graudins A, Hung Leang Y, Kuan K, et al. Treatment for beta-blocker poisoning: a systematic review. *Clin Toxicol (Phila)*. 2020;1–41.
- Ghannoum M, Nolin TD, Lavergne V, Hoffman RS. Blood purification in toxicology: nephrology's ugly duckling. *Adv Chronic Kidney Dis*. 2011;18(3):160–6.
- Lavergne V, Nolin TD, Hoffman RS, Robert D, Gosselin S, Goldfarb DS, et al. The EXTRIP (Extracorporeal Treatments In Poisoning) workgroup: Guideline methodology. *Clin Toxicol*. 2012;50:403–13.
- Berling I, King JD, Shepherd G, Hoffman RS, Alhatali B, Lavergne V, et al. Extracorporeal Treatment for Chloroquine, Hydroxychloroquine, and Quinine Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup. *J Am Soc Nephrol*. 2020;31(10):2475–89.
- Wong A, Hoffman RS, Walsh SJ, Roberts DM, Gosselin S, Bunchman TE, et al. Extracorporeal treatment for calcium channel blocker poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)*. 2021;1–31.
- The 50 most commonly prescribed drugs in America and their average price 2020 [Available from: <https://www.drugreport.com/50-commonly-prescribed-drugs-in-america/>].
- WHO. WHO Model Lists of Essential Medicines 2019 [Available from: <https://www.who.int/medicines/publications/essentialmedicines/en/>].
- Ducret F, Zech P, Perrot D, Moskovtchenko JF, Traeger J. Deliberate self-overdose with propranolol. Changes in serum levels. *Nouv Presse Med*. 1978;7(1):27–8.
- Isbister GK, Ang K, Gorman K, Cooper J, Mostafa A, Roberts MS. Zero-order metoprolol pharmacokinetics after therapeutic doses: severe toxicity and cardiogenic shock. *Clin Toxicol*. 2016;54(9):881–5.
- Grass J, Steinwall J, Lindeman E. Prolonged elimination after massive overdose of metoprolol and amlodipine in a patient treated with extracorporeal life support (ECLS). *Clin Toxicol (Phila)*. 2018;56(6):528–9.
- Snook CP, Sigvaldason K, Kristinnsson J. Severe atenolol and diltiazem overdose. *J Toxicol Clin Toxicol*. 2000;38(6):661–5.
- Neuvonen PJ, Elonen E, Vuoremaa T, Laako M. Prolonged Q-T interval and severe tachyarrhythmias: common features in patients with sotalol overdose. *Clin Pharmacol Ther*. 1981;29(2):268.
- Singh SN, Lazin A, Cohen A, Johnson M, Fletcher RD. Sotalol-induced torsades de pointes successfully treated with hemodialysis after failure of conventional therapy. *Am Heart J*. 1991;121(2 Pt 1):601–2.
- Gustavsson CG, Vinge E, Norlander BO, Pantev E. Pharmacokinetic evaluation of a case of massive sotalol intoxication. *Ann Pharmacother*. 1997;31(7–8):856–9.
- Miethel R, Habel U, Schuster HP. 8 g sotalol self-poisoning treated with hemoperfusion/hemodialysis. *Intensivmedizin und Notfallmedizin*. 1996;33(1):47–51.
- DeLima LGR, Kharasch ED, Butler S. Successful pharmacologic treatment of massive atenolol overdose: sequential hemodynamics and plasma atenolol concentrations. *Anesthesiology*. 1995;83(1):204–7.
- Freestone S, Thomas HM, Bhamra RK, Dyson EH. Severe atenolol poisoning: treatment with prenalterol. *Hum Toxicol*. 1986;5(5):343–5.
- Page C, Hackett LP, Isbister GK. The use of high-dose insulin-glucose euglycemia in beta-blocker overdose: a case report. *J Med Toxicol*. 2009;5(3):139–43.
- Meffin PJ, Winkle RA, Peters FA, Harrison DC. Acebutolol disposition after intravenous administration. *Clin Pharmacol Ther*. 1977;22(5 Pt 1):557–67.
- Barber HE, Hawksworth GM, Kitteringham NR, Petersen J, Petrie JC, Swann JM. Protein binding of atenolol and propranolol to human serum albumin and in human plasma [proceedings]. *Br J Clin Pharmacol*. 1978;6(5):446P-P447.
- Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Brooks DE, Dibert KW, et al. 2019 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 37th Annual Report. *Clin Toxicol (Phila)*. 2020;58(12):1360–541.
- Love JN, Howell JM, Litovitz TL, Klein-Schwartz W. Acute beta blocker overdose: factors associated with the development of cardiovascular morbidity. *J Toxicol Clin Toxicol*. 2000;38(3):275–81.
- Megarbane B, Deye N, Malissin I, Baud FJ. Usefulness of the serum lactate concentration for predicting mortality in acute beta-blocker poisoning. *Clin Toxicol*. 2010;48(10):974–8.
- Hermanns-Clausen M, Desel H. Sotalol overdose: how dangerous is it? *Clin Toxicol*. 2002;40:350.
- Elkharrat D, Bismuth C. Acute intoxication by beta-blocking agents: No mortality in 40 cases Blocking of beta-adrenoreceptors may be an autolimited phenomenon. *Int J Clin Pharmacol Res*. 1982;2(3):207–10.
- Love JN. Beta blocker toxicity after overdose: when do symptoms develop in adults? *J Emerg Med*. 1994;12(6):799–802.
- Reith DM, Dawson AH, Epid D, Whyte IM, Buckley NA, Sayer GP. Relative toxicity of beta blockers in overdose. *J Toxicol Clin Toxicol*. 1996;34(3):273–8.
- Wax P, Erdman A, Chyka P, Keyes D, Caravati EM, Booze L, et al. beta-blocker ingestion: An evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol*. 2005;43(3):131–46.
- Weinstein RS. Recognition and management of poisoning with beta-adrenergic blocking agents. *Ann Emerg Med*. 1984;13(12):1123–31.
- Auzepy P, Boukara N, Richard C, Giudicelli JF. Acute poisoning caused by beta blockers in the adult. Apropos of 7 cases. *Ann Cardiol Angeiol (Paris)*. 1983;32(4):253–8.
- Gengo FM, Huntton L, McHugh WB. Lipid-soluble and water-soluble beta-blockers. Comparison of the central nervous system depressant effect. *Arch Intern Med*. 1987;147(1):39–43.
- Lauterbach M. Clinical toxicology of beta-blocker overdose in adults. *Basic Clin Pharmacol Toxicol*. 2019;125(2):178–86.
- Lifshitz M, Zucker N, Zalstein E. Acute dilated cardiomyopathy and central nervous system toxicity following propranolol intoxication. *Pediatr Emerg Care*. 1999;15(4):262–3.
- Cammu G, Geelen P, Baetens P, De Vos J, Demeyer I. Two cases of torsades de pointes caused by sotalol therapy. Resuscitation. 1999;40(1):49–51.

35. Gupta AK, Greller HA, Chan GM, Lee DC, Caraccio T, Mcguigan M, et al. Sotalol induced torsade de pointes and enhanced elimination with hemodialysis. *Clin Toxicol*. 2009;47(7):723.
36. Oltmanns G, Schwela H, Kulick B, Knappe J, Hausteil KO, Schmidt H. Acute beta blocker poisoning. *Zeitschrift für die Gesamte Innere Medizin und Ihre Grenzgebiete*. 1985;40(18):546–51.
37. Vucinic S, Jokovic D, Jovanovic D, Vucinic Z, Todorovic V. Factors influencing the degree and outcome of acute beta-blockers poisoning. *Vojnosanit Pregl*. 2000;57(6):619–23.
38. Hermanns-Clausen M, Sydow A, Desel H. Metoprolol overdoses - Clinical course in relation to ingested dose [German]. *Intensivmedizin und Notfallmedizin*. 2005;42(1):47–52.
39. Forrester MB. Pattern of adult carvedilol ingestions reported to poison control centers. *Clin Toxicol*. 2009;47(7):746–7.
40. Love JN, Howell JM, Klein-Schwartz W, Litovitz TL. Lack of toxicity from pediatric beta-blocker exposures. *Hum Exp Toxicol*. 2006;25(6):341–6.
41. Dommer P, Truitt CA, Brooks DE, LoVecchio F. Retrospective review of poison center data for unintentional beta-blocker and/or calcium channel blocker ingestions. *Clin Toxicol*. 2011;49(6):601.
42. M'Rad A, Blel Y, Essafi F, Foudhaili N, Ben Slimen A, Brahmi N, et al. Prognostic value of plasma concentration of acebutolol in acute poisoning. *Annals of Intensive Care Conference: French Intensive Care Society, International Congress Resuscitation*. 2016;6 (SUPPL. 1).
43. Love JN. Beta-blocker toxicity: a clinical diagnosis. *Am J Emerg Med*. 1994;12(3):356–7.
44. Frishman W, Jacob H, Eisenberg E, Ribner H. Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 8. Self-poisoning with beta-adrenoceptor blocking agents: recognition and management. *Am Heart J*. 1979;98 (6):798–811.
45. Neuvonen PJ, Elonen E, Tarssanen L. Sotalol intoxication, two patients with concentration-effect relationships. *Acta Pharmacol Toxicol (Copenh)*. 1979;45(1):52–7.
46. Wang T, Bergstrand RH, Thompson KA, Siddoway LA, Duff HJ, Woosley RL, et al. Concentration-dependent pharmacologic properties of sotalol. *Am J Cardiol*. 1986;57(13):1160–5.
47. Somberg JC, Preston RA, Ranade V, Molnar J. QT prolongation and serum sotalol concentration are highly correlated following intravenous and oral sotalol. *Cardiology*. 2010;116(3):219–25.
48. Darpo B, Karnad DR, Badilini F, Florian J, Garnett CE, Kothari S, et al. Are women more susceptible than men to drug-induced QT prolongation? Concentration-QTc modelling in a phase 1 study with oral rac-sotalol. *Br J Clin Pharmacol*. 2014;77(3):522–31.
49. Love JN, Enlow B, Howell JM, Klein-Schwartz W, Litovitz TL. Electrocardiographic changes associated with beta-blocker toxicity. *Ann Emerg Med*. 2002;40(6):603–10.
50. Eibs HG, Oberdisse U, Brambach U. Intoxication by beta-blockers in children and adolescents (author's transl). *Monatsschr Kinderheilkd*. 1982;130(5):292–5.
51. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Beuhler MC, Rivers LJ, et al. 2018 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report. *Clin Toxicol (Phila)*. 2019;57(12):1220–413.
52. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. *Clin Toxicol*. 2017;2018:1–203.
53. Johnson NJ, Gaieski DF, Allen SR, Perrone J, DeRoos F. A review of emergency cardiopulmonary bypass for severe poisoning by cardiotoxic drugs. *J Med Toxicol*. 2013;9(1):54–60.
54. Megarbane B, Deye N, Baud FJ. Extracorporeal life support for acute poisonings with cardiotoxicants [French]. *Resuscitation*. 2009;18(5):428–38.
55. Palatnick W, Jelic T. Emergency department management of calcium-channel blocker, beta blocker, and digoxin toxicity. *Emerg Med Pract*. 2014;16(2):1–19 (**quiz -20**).
56. Gaudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. *Br J Clin Pharmacol*. 2016;81(3):453–61.
57. Skoog CA, Engebretsen KM. Are vasopressors useful in toxin-induced cardiogenic shock? *Clin Toxicol*. 2017;55(4):285–304.
58. Daheb K, Lipman ML, Hildgen P, Roy JJ. Artificial neural network modeling for drug dialyzability prediction. *J Pharm Pharmaceut Sci*. 2013;16(5):665–75.
59. Heath A, Gabriëllsson M, Redgardh CG. Absorption of beta-adrenoceptor antagonists to Amberlite resin. *Br J Clin Pharmacol*. 1983;15(4):490–2.
60. Pauls A, Grigoleit HG, Von Herrath D, Schaefer K. Comparison of drug elimination by current methods of blood purification. *Blood Purif*. 1984;2(1):14–22.
61. Schneider T, Siegmund W, Franke G, Kraatz G, Scherber A. The binding of propranolol, dihydralazine and selected metabolites to adsorbent resins for hemoperfusion. *Pharmazie*. 1986;41(10):742–3.
62. Celardo A, Traina GL, Arboix M, Puigdemont A, Bonati M. Pharmacokinetic and pharmacodynamic modelling of atenolol in rabbits maintained on continuous peritoneal dialysis. *Eur J Drug Metab Pharmacokin*. 1987;12(1):41–8.
63. Traina GL, Celardo A, Arboix M, Bonati M. Experimental model for pharmacokinetic studies during continuous peritoneal dialysis in the rabbit. *J Pharmacol Methods*. 1986;15(2):133–41.
64. Gwilt PR. General equation for assessing drug removal by extracorporeal devices. *J Pharm Sci*. 1981;70(3):345–6.
65. Eastwood JB, Curtis JR, Smith RB. Pharmacodynamics of practolol in chronic renal failure. *BMJ*. 1973;4(5888):320–2.
66. Lowenthal DT, Briggs WA, Gibson TP, Nelson H, Cirkseña WJ. Pharmacokinetics of oral propranolol in chronic renal disease. *Clin Pharmacol Ther*. 1974;16(5 Part 1):761–9.
67. Harvengt C, Desager JP, Muschart JM, Tjandramaga YB, Verbeeck R, Verberckmoes R. Influence of the hemodialysis on the half-life of practolol in patients with severe renal failure. *J Clin Pharmacol*. 1975;15(8–9):605–10.
68. Roux A, Aubert P, Guedon J, Flouvat B. Study of acebutolol dialysis and pharmacokinetic data in patients with renal insufficiency undergoing hemodialysis. *Nouv Presse Med*. 1975;4(46 Suppl):3228–33.
69. Aubert P, Roux A, Flouvat B, Lucsko M, Chaignon M, Guedon J. Pharmacokinetics of acebutolol in renal failure. *J Urol Nephrol (Paris)*. 1976;82(9):799–804.
70. Bianchetti G, Graziani G, Brancaccio D, Morganti A, Leonetti G, Manfrin M, et al. Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clin Pharmacokin*. 1976;1(5):373–84.
71. Tjandramaga TB, Verbeeck R, Thomas J, Verbesselt R, Verberckmoes R, Schepper PJ. The effect of end-stage renal failure and haemodialysis on the elimination kinetics of sotalol. *Br J Clin Pharmacol*. 1976;3(2):259–65.
72. Lowenthal DT, Pitone JM, Affrime MB, Shirk J, Busby P, Kim KE, et al. Timolol kinetics in chronic renal insufficiency. *Clin Pharmacol Ther*. 1978;23(5):606–15.
73. Niedermayer W, Seiler KU, Wassermann O. Pharmacokinetics of antihypertensive drugs (atenolol, metoprolol, propranolol and clonidine) and their metabolites during intermittent haemodialysis in humans. *Proc Eur Dial Transplant Assoc*. 1978;15:607–9.
74. Flouvat B, Decourt S, Potaux L. Pharmacokinetics of propranolol in patients with chronic renal insufficiency undergoing hemodialysis. *Therapie*. 1979;34(1):63–72.
75. Herrera J, Vukovich RA, Griffith DL. Elimination of nadolol by patients with renal impairment. *Br J Clin Pharmacol*. 1979;7(Suppl 2):S227S–S231.
76. Rosseel MT, Bogaert MG, Christiaens M, Verpooten GA, De Broe ME. Plasma levels of atenolol after haemodialysis in patients with end stage renal disease. *Arch Int Pharmacodyn Ther*. 1979;239(1):176.
77. Bailey RR, Munn SR, Begg E. The pharmacokinetics of acebutolol in patients with renal functional impairment. *Aust N Z J Med*. 1980;10(1):124.
78. Flouvat B, Decourt S, Aubert P, Potaux L, Domart M, Goupil A, et al. Pharmacokinetics of atenolol in patients with terminal renal failure and influence of haemodialysis. *Br J Clin Pharmacol*. 1980;9(4):379–85.
79. Kirch W, Schafer M, Braun M. Single intravenous dose kinetics accumulation of atenolol in patients with impaired renal function and on hemodialysis. *Arch Toxicol Suppl*. 1980;4:366–9.
80. Roux A, Aubert P, Guedon J, Flouvat B. Pharmacokinetics of acebutolol in patients with all grades of renal failure. *Eur J Clin Pharmacol*. 1980;17(5):339–48.



81. Schneck DW, Pritchard JF, Gibson TP, Vary JE, Hayes AH Jr. Effect of dose and uremia on plasma and urine profiles of propranolol metabolites. *Clin Pharmacol Ther.* 1980;27(6):744–55.
82. Seiler KU, Schuster KJ, Meyer GJ, Niedermayer W, Wassermann O. The pharmacokinetics of metoprolol and its metabolites in dialysis patients. *Clin Pharmacokinet.* 1980;5(2):192–8.
83. Blair AD, Burgess ED, Maxwell BM, Cutler RE. Sotalol kinetics in renal insufficiency. *Clin Pharmacol Ther.* 1981;29(4):457–63.
84. Dayer P, Glasson P, Gorgia A, Balant L, Fabre J. Retention of metabolites of a beta-blocking drug, oxprenolol, in renal insufficiency. *Schweizerische medizinische Wochenschrift.* 1981;111(49):1915–8.
85. Kirch W, Kohler H, Mutschler E, Schafer M. Pharmacokinetics of atenolol in relation to renal function. *Eur J Clin Pharmacol.* 1981;19(1):65–71.
86. Bouchet JL, Pocheville M, Alsabbach M. Betaxolol pharmacokinetics in chronic renal failure, hemodialysis and CAPD [French]. *Nephrologie.* 1982;3(3):142.
87. Kawasaki T, Ueno M, Uezono K, Abe I, Kawazoe N, Omae T, et al. Blood levels of long-acting propranolol in normal subjects and patients with renal failure. *Fukuoka igaku zasshi = Hukuoka acta medica.* 1983;74(11):737–43.
88. Krause W, Kampf D, Fischer HC. Pharmacokinetics of mepindolol in patients with chronic renal failure. *Eur J Clin Pharmacol.* 1984;27(4):429–33.
89. Michaels RS, Duchin KL, Akbar S, Meister J, Levin NW. Nadolol in hypertensive patients maintained on long-term hemodialysis. *Am Heart J.* 1984;108(4 Pt 2):1091–4.
90. Salahudeen AK, Wilkinson R, McAlinsh J, Bateman DN. Atenolol pharmacokinetics in patients on continuous ambulatory peritoneal dialysis. *Br J Clin Pharmacol.* 1984;18(3):457–60.
91. Campese VM, Feinstein EI, Gura V, Mason WD, Massry SG. Pharmacokinetics of atenolol in patients treated with chronic hemodialysis or peritoneal dialysis. *J Clin Pharmacol.* 1985;25(5):393–5.
92. Halstenson CE, Opsahl JA, Pence TV, Luke DR, Sirgo MA, Plachetka JR, et al. The disposition and dynamics of labetalol in patients on dialysis. *Clin Pharmacol Ther.* 1986;40(4):462–8.
93. Payton CD, Fox JG, Pauleau NF, Boulton-Jones JM, Ioannides C, Johnston A, et al. The single dose pharmacokinetics of bisoprolol (10 mg) in renal insufficiency: the clinical significance of balanced clearance. *Eur Heart J.* 1987;8(Suppl M):15–22.
94. Gasparovic V, Milutinovic S, Plavsic F, Gjurasin M, Molnar V. Pharmacokinetics of labetalol in patients on hemodialysis. *Acta Med Jugosl.* 1988;42(2):141–5.
95. Flaherty JF, Wong B, La Follette G, Warnock DG, Hulse JD, Gambertoglio JG. Pharmacokinetics of esmolol and ASL-8123 in renal failure. *Clin Pharmacol Ther.* 1989;45(3):321–7.
96. Miki S, Masumura H, Kaifu Y, Yuasa S. Pharmacokinetics and efficacy of carvedilol in chronic hemodialysis patients with hypertension. *J Cardiovasc Pharmacol.* 1991;18(Suppl 4):S62–8.
97. Motan J, Mayer O, Spanel M. Kinetics of metipranolol in patients with chronic kidney failure and during hemodialysis. *Vnitř Lek.* 1991;37(3):285–92.
98. Kanegae K, Hiroshige K, Suda T, Iwamoto M, Ohta T, Nakashima Y, et al. Pharmacokinetics of bisoprolol and its effect on dialysis refractory hypertension. *Int J Artif Organs.* 1999;22(12):798–804.
99. Krueger M, Achenbach H, Terhaag B, Haase H, Richter K, Oertel R, et al. Pharmacokinetics of oral talinolol following a single dose and during steady state in patients with chronic renal failure and healthy volunteers. *Int J Clin Pharmacol Ther.* 2001;39(2):61–6.
100. Daheb K, Lecours JP, Lipman ML, Hildgen P, Roy JJ. Prediction of in vivo atenolol removal by high-permeability hemodialysis based on an in vitro model. *J Pharm Biopharmaceut Sci.* 2013;16(5):657–64.
101. Tieu A, Velenosi TJ, Kucey AS, Weir MA, Urquhart BL. beta-blocker dialyzability in maintenance hemodialysis patients: a randomized clinical trial. *Clin J Am Soc Nephrol CJASN.* 2018;13(4):604–11.
102. Stein G, Demme U, Sperschneider H, Funfstuck R, Werner R, Meier F, et al. Detoxication by hemoperfusion. *Z Gesamte Inn Med.* 1981;36(24):963–9.
103. Garrasch B, Presber G, Lindau K. Contribution to intoxication with beta-adrenergic blocking agents. [German]. *Anaesthesiologie und Reanimation.* 1983;8(5):279–86.
104. von Thielier H, Oltmanns G, Wehren JH. Hemoperfusion in acute talinolol intoxication. *Dt Gesundh-Wesen.* 1983;38:1459–61.
105. Bouffard Y, Ritter J, Delafosse B. Atenolol intoxication: Study of one case with plasmatic analysis [French]. *J Toxicol Med.* 1984;4(3):273–7.
106. Anthony T, Jastremski M, Elliott W, Morris G, Prasad H. Charcoal hemoperfusion for the treatment of a combined diltiazem and metoprolol overdose. *Ann Emerg Med.* 1986;15(11):1344–8.
107. Terhaag B, Grunert A, Richter K, Bahlmann G, Glaris A. Effectiveness of hemoperfusion in talinolol overdose—a case report. *Z Klin Med.* 1987;42:1463–6.
108. Perrot D, Bui-Xuan B, Lang J, Bouffard Y, Delafosse B, Faucon G, et al. A case of sotalol poisoning with fatal outcome. *J Toxicol Clin Toxicol.* 1988;26(5–6):389–96.
109. Lenga P, Odenthal HJ, Josephs W, Rawert B, Schilken P, Wiechmann HW. Treatment of an intoxication with acebutolol by hemoperfusion. Case report on a severe self poisoning. *Intensivmedizin und Notfallmedizin.* 1989;26(6):307–11.
110. Rostock G, Kinzel W. Concentrations of propranolol (Obsidan) in blood of patients with intoxications. *Zeitschrift für Klinische Medizin.* 1989;44(2):157–60.
111. Saitz R, Williams BW, Farber HW. Atenolol-induced cardiovascular collapse treated with hemodialysis. *Crit Care Med.* 1991;19(1):116–8.
112. Welch CD, Knoerzer RE, Lewis GS. Verapamil and acebutolol overdose results in asystole: intra-aortic balloon pump provides mechanical support. *J Extra-Corporeal Technol.* 1992;24(1):36–7.
113. Rooney M, Massey KL, Jamali F, Rosin M, Thomson D, Johnson DH. Acebutolol overdose treated with hemodialysis and extracorporeal membrane oxygenation. *J Clin Pharmacol.* 1996;36(8):760–3.
114. Tang S, Lo CY, Lo WK, Tai YT, Chan TM. Sotalol-induced torsade de pointes in a CAPD patient—successful treatment with intermittent peritoneal dialysis. *Perit Dial Int.* 1997;17(2):207–8.
115. van Uum SH, van den Merkhof LF, Lucassen AM, Wuis EW, Diemont W. Successful haemodialysis in sotalol-induced torsade de pointes in a patient with progressive renal failure. *Nephrol Dial Transplant.* 1997;12(2):331–3.
116. Stein H, Sirota R, Snipes E, Gronich J, Collins D. Acute hemodialysis for sotalol HCL intoxication (ASAIO Journal (March/April 1998) 44 (70A)). *ASAIO J.* 1998;44:70A.
117. Bergl Z, Simecek V. Protracted cardiopulmonary resuscitation in patient intoxicated with lethal dose of beta-blocker Sactal [Czech]. *Anesthesiologie a Neodkladna Pece.* 2000;11(2):83–4.
118. Salhanick SD, Wax PM. Treatment of atenolol overdose in a patient with renal failure using serial hemodialysis and hemoperfusion and associated echocardiographic findings. *Vet Hum Toxicol.* 2000;42(4):224–5.
119. Kolcz J, Pietrzyk J, Januszewska K, Procelewaska M, Mroczek T, Malec E. Extracorporeal life support in severe propranolol and verapamil intoxication. *J Intensive Care Med.* 2007;22(6):381–5.
120. Pfaender M, Casetti PG, Azzolini M, Baldi ML, Valli A. Successful treatment of a massive atenolol and nifedipine overdose with CVVHDF. *Minerva Anestesiol.* 2008;74(3):97–100.
121. Zebuda C, Majilesi N, Greller HA, Lee DC, Su MK, Chan GM. Sotalol-induced torsades de pointes treated with hemodialysis. *Clin Toxicol.* 2008;46(7):603.
122. Mulder VC, Oudemans-Van Straaten HM, Zandstra DF, Franssen EJ. Massive ingestion of cardiac drugs: toxicokinetic aspects of digoxin and sotalol during hemofiltration. *Clin Toxicol (Phila).* 2010;48(3):218–21.
123. Rona R, Cortinovis B, Marcolin R, Patroniti N, Isgr S, Marelli C, et al. Extracorporeal life support for near-fatal multi-drug intoxication: A case report. *Journal of Medical Case Reports.* 2011;5 (no pagination) (231).
124. Huang SH, Tirona RG, Ross C, Suri RS. Case report: atenolol overdose successfully treated with hemodialysis. *Hemodialysis International Symposium on Home Hemodialysis.* 2013;17(4):652–5.
125. Garg A, Panda S, Dalvi P, Mehra S, Ray S, Singh VK. Severe suicidal digoxin and propranolol toxicity with insulin overdose. *Indian J Crit Care Med.* 2014;18(3):173–5.
126. Koschny R, Lutz M, Seckinger J, Schwenger V, Stremmel W, Eisenbach C. Extracorporeal life support and plasmapheresis in a case of severe polyintoxication. *J Emerg Med.* 2014;47(5):527–31.
127. Sandeep P, Ram R, Sowgandhi N, Reddy SA, Katyarmal DT, Kumar BS, et al. Atenolol and amlodipine combination overdose managed with

- continuous venovenous hemodiafiltration: a case report. *Indian J Nephrol.* 2014;24(5):327–9.
128. Heise CW, Beutler D, Bosak A, Orme G, Loli A, Graeme K. Massive atenolol, lisinopril, and chlorthalidone overdose treated with endoscopic decontamination, hemodialysis, impella percutaneous left ventricular assist device, and ECMO. *J Med Toxicol.* 2015;11(1):110–4.
  129. Seegobin K, Maharaj S, Deosaran A, Reddy P. Severe beta blocker and calcium channel blocker overdose: Role of high dose insulin. *Am J Emerg Med.* 2018;36(4):736 e5–e6.
  130. Chen LW, Mao DR, Chen YS. Extracorporeal life support: the final “antidote” for massive propranolol overdose. *Hong Kong J Emerg Med.* 2019;26(2):118–23.
  131. Talbert RL, Wong YY, Duncan DB. Propranolol plasma concentrations and plasmapheresis. *Drug Intell Clin Pharm.* 1981;15(12):993–6.
  132. Lavergne V, Ouellet G, Bouchard J, Galvao T, Kielstein JT, Roberts DM, et al. Guidelines for reporting case studies on extracorporeal treatments in poisonings: methodology. *Semin Dial.* 2014;27(4):407–14.
  133. Bouchard J, Lavergne V, Roberts DM, Cormier M, Morissette G, Ghanoum M. Availability and cost of extracorporeal treatments for poisonings and other emergency indications: a worldwide survey. *Nephrol Dial Transplant.* 2017;32(4):699–706.
  134. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. *JAMA.* 2003;289(16):2120–7.
  135. Sauer AJ, Moss AJ, McNitt S, Peterson DR, Zareba W, Robinson JL, et al. Long QT syndrome in adults. *J Am Coll Cardiol.* 2007;49(3):329–37.
  136. Amery A, De Plaen JF, Lijnen P, McAinsh J, Reybrouck T. Relationship between blood level of atenolol and pharmacologic effect. *Clin Pharmacol Ther.* 1977;21(6):691–9.
  137. Bouchard J, Roberts DM, Roy L, Ouellet G, Decker BS, Mueller BA, et al. Principles and operational parameters to optimize poison removal with extracorporeal treatments. *Semin Dial.* 2014;27(4):371–80.
  138. Decourt S, Roux A, Baglin A, Domart M, Aubert P, Flouvat B, et al. Study of the binding of beta blockers to plasma proteins. *Therapeutic consequences.* *Acquis Med Recent.* 1977:181–94.
  139. Kaye CM, Kumana CR, Leighton M, Hamer J, Turner P. Observations on the pharmacokinetics of acebutolol. *Clin Pharmacol Ther.* 1976;19(4):416–20.
  140. Roux A, Henry JF, Fouache Y, Chau NP, Hervy MP, Forette F, et al. A pharmacokinetic study of acebutolol in aged subjects as compared to young subjects. *Gerontology.* 1983;29(3):202–8.
  141. Roux A, Flouvat B, Fouache Y, Bourdarias JP. Systemic bioavailability of acebutolol in man. *Biopharm Drug Dispos.* 1983;4(3):293–7.
  142. Collins RF. Pharmacokinetics of acebutolol. *Nouv Presse Med.* 1975;4(46 Suppl):3223–8.
  143. Roux A, Flouvat B, Chau NP, Letac B, Lucsko M. Pharmacokinetics of acebutolol after intravenous bolus administration. *Br J Clin Pharmacol.* 1980;9(2):215–7.
  144. Smith RS, Warren DJ, Renwick AG, George CF. Acebutolol pharmacokinetics in renal failure. *Br J Clin Pharmacol.* 1983;16(3):253–8.
  145. Wan SH, Koda RT, Maronde RF. Pharmacokinetics, pharmacology of atenolol and effect of renal disease. *Br J Clin Pharmacol.* 1979;7(6):569–74.
  146. Kirch W, Kohler H, Berggren G, Braun W. The influence of renal function on plasma levels and urinary excretion of acebutolol and its main N-acetyl metabolite. *Clin Nephrol.* 1982;18(2):88–94.
  147. Munn S, Bailey RR, Begg E, Ebert R, Ferry DG. Plasma and urine concentrations of acebutolol and its acetyl metabolite in patients with renal functional impairment. *N Z Med J.* 1980;91(658):289–91.
  148. Schulz M, Schmoldt A, Andresen-Streichert H, Iwersen-Bergmann S. Revisited: Therapeutic and toxic blood concentrations of more than 1100 drugs and other xenobiotics. *Crit Care.* 2020;24(1):195.
  149. Johansson R, Regardh CG, Sjogren J. Absorption of alprenolol in man from tablets with different rates of release. *Acta Pharm Suec.* 1971;8(1):59–70.
  150. Imamura H, Komori T, Ismail A, Suenaga A, Otagiri M. Stereoselective protein binding of alprenolol in the renal diseased state. *Chirality.* 2002;14(7):599–603.
  151. Alvan G, Lind M, Mellstrom B, von Bahr C. Importance of “first-pass elimination” for interindividual differences in steady-state concentrations of the adrenergic beta-receptor antagonist alprenolol. *J Pharmacokinetics Biopharm.* 1977;5(3):193–205.
  152. Bodin NO, Borg KO, Johansson R, Obianwu H, Svensson R. Absorption, distribution and excretion of alprenolol in man, dog and rat. *Acta Pharmacol Toxicol (Copenh).* 1974;35(4):261–9.
  153. Ablad B, Borg KO, Johansson R, Regardh CG, Solvell L. Combined pharmacokinetic and pharmacodynamic studies on alprenolol and 4-hydroxy-alprenolol in man. *Life Sci.* 1974;14(4):693–704.
  154. Decourt S, Roux A, Baglin A, Aubert P, Prinseau J, Flouvat B. Influence of protein binding on dialysis clearance of several beta-blocking agents in chronically hemodialysed patients. *Therapie.* 1982;37(6):635–40.
  155. Mason WD, Winer N, Kochak G, Cohen I, Bell R. Kinetics and absolute bioavailability of atenolol. *Clin Pharmacol Ther.* 1979;25(4):408–15.
  156. McAinsh J, Holmes BF, Smith S, Hood D, Warren D. Atenolol kinetics in renal failure. *Clin Pharmacol Ther.* 1980;28(3):302–9.
  157. Rubin PC, Scott PJ, McLean K, Pearson A, Ross D, Reid JL. Atenolol disposition in young and elderly subjects. *Br J Clin Pharmacol.* 1982;13(2):235–7.
  158. Kirch W, Schafer-Korting M, Mutschler E, Ohnhaus EE, Braun W. Clinical experience with atenolol in patients with chronic liver disease. *J Clin Pharmacol.* 1983;23(4):171–7.
  159. Buck ML, Wiest D, Gillette PC, Trippel D, Krull J, O’Neal W. Pharmacokinetics and pharmacodynamics of atenolol in children. *Clin Pharmacol Ther.* 1989;46(6):629–33.
  160. Fitzgerald JD, Ruffin R, Smedstad KG, Roberts R, McAinsh J. Studies on the pharmacokinetics and pharmacodynamics of atenolol in man. *Eur J Clin Pharmacol.* 1978;13(2):81–9.
  161. Brown HC, Carruthers SG, Johnston GD, Kelly JG, McAinsh J, McDevitt DG, et al. Clinical pharmacologic observations on atenolol, a beta-adrenoceptor blocker. *Clin Pharmacol Ther.* 1976;20(5):524–34.
  162. Sassard J, Pozet N, McAinsh J, Legheand J, Zech P. Pharmacokinetics of atenolol in patients with renal impairment. *Eur J Clin Pharmacol.* 1977;12(3):175–80.
  163. el-Yazigi A, Bouchama A, al-Abdely H, Yusuf A, Sieck JO. Impaired elimination of atenolol in a nephropathic patient with self-medication overdose. *J Clin Pharmacol.* 1993;33(5):450–2.
  164. Warrington SJ, Turner P, Kilborn JR, Bianchetti G, Morselli PL. Blood concentrations and pharmacodynamic effects of betaxolol (SL 75212) a new beta-adrenoceptor antagonist after oral and intravenous administration. *Br J Clin Pharmacol.* 1980;10(5):449–52.
  165. Ludden TM, Boyle DA, Gieseke D, Kennedy GT, Crawford MH, Ludden LK, et al. Absolute bioavailability and dose proportionality of betaxolol in normal healthy subjects. *J Pharm Sci.* 1988;77(9):779–83.
  166. Bianchetti G, Thiercelin JF, Thenot JP. Pharmacokinetics of betaxolol in middle aged patients. *Eur J Clin Pharmacol.* 1986;31(2):231–3.
  167. Stagni G, Davis PJ, Ludden TM. Human pharmacokinetics of betaxolol enantiomers. *J Pharm Sci.* 1991;80(4):321–4.
  168. Palminteri R, Assael BM, Bianchetti G, Gomeni R, Claris-Appiani A, Edefonti A, et al. Betaxolol kinetics in hypertensive children with normal and abnormal renal function. *Clin Pharmacol Ther.* 1984;35(2):141–7.
  169. Kirch W, Rose I, Demers HG, Leopold G, Pabst J, Ohnhaus EE. Pharmacokinetics of bisoprolol during repeated oral administration to healthy volunteers and patients with kidney or liver disease. *Clin Pharmacokinetics.* 1987;13(2):110–7.
  170. Leopold G, Pabst J, Ungethüm W, Buhning KU. Basic pharmacokinetics of bisoprolol, a new highly beta 1-selective adrenoceptor antagonist. *J Clin Pharmacol.* 1986;26(8):616–21.
  171. Hayes PC, Jenkins D, Vavianos P, Dagap K, Johnston A, Ioannides C, et al. Single oral dose pharmacokinetics of bisoprolol 10 mg in liver disease. *Eur Heart J.* 1987;8 Suppl M:23–9.
  172. Le Jeune C, Poirier JM, Cheymol G, Ertzbischoff O, Engel F, Hugues FC. Pharmacokinetics of intravenous bisoprolol in obese and non-obese volunteers. *Eur J Clin Pharmacol.* 1991;41(2):171–4.
  173. Cvan Trobec K, Grabnar I, Kerec Kos M, Vovk T, Trontelj J, Anker SD, et al. Bisoprolol pharmacokinetics and body composition in patients with chronic heart failure: a longitudinal study. *Eur J Clin Pharmacol.* 2016;72(7):813–22.
  174. Le Coz F, Sauleman P, Poirier JM, Cuhe JL, Midavaine M, Rames A, et al. Oral pharmacokinetics of bisoprolol in resting and exercising healthy volunteers. *J Cardiovasc Pharmacol.* 1991;18(1):28–34.
  175. Nikolic VN, Jevtovic-Stoimenov T, Velickovic-Radovanovic R, Ilic S, Deljanin-Ilic M, Marinkovic D, et al. Population pharmacokinetics of



- bisoprolol in patients with chronic heart failure. *Eur J Clin Pharmacol*. 2013;69(4):859–65.
176. MacDonald NJ, Grant AC, Rodger RS, Meredith PA, Elliott HL. The effect of renal impairment on the pharmacokinetics and metabolism of bopindolol. *Br J Clin Pharmacol*. 1991;31(6):697–700.
177. Aellig WH, Nuesch E, Engel G, Grevel J, Niederberger W, Rosenthaler J. Relationship between plasma concentrations and cardiac beta-adrenoceptor blockade—a study with oral and intravenous bopindolol. *Br J Clin Pharmacol*. 1986;21(1):45–51.
178. Platzer R, Galeazzi RL, Niederberger W, Rosenthaler J. Simultaneous modeling of bopindolol kinetics and dynamics. *Clin Pharmacol Ther*. 1984;36(1):5–13.
179. Wensing G, Branch RA, Humbert H, Ohnhaus EE, Kirch W. Pharmacokinetics after a single oral dose of bopindolol in patients with cirrhosis. *Eur J Clin Pharmacol*. 1990;39(6):569–72.
180. Holmes D, Nuesch E, Houle JM, Rosenthaler J. Steady state pharmacokinetics of hydrolysed bopindolol in young and elderly men. *Eur J Clin Pharmacol*. 1991;41(2):175–8.
181. Ishizaki T, Ohnishi A, Sasaki T, Kushida K, Horai Y, Chiba K, et al. Pharmacokinetics and absolute bioavailability of carteolol, a new beta-adrenergic receptor blocking agent. *Eur J Clin Pharmacol*. 1983;25(1):95–101.
182. Hasenfuss G, Schafer-Korting M, Knauf H, Mutschler E, Just H. Pharmacokinetics of carteolol in relation to renal function. *Eur J Clin Pharmacol*. 1985;29(4):461–5.
183. Lang W. Animal experimental studies on the pharmacokinetics of carteolol. *Arzneimittelforschung*. 1983;33(2a):286–9.
184. von Mollendorff E, Reiff K, Neugebauer G. Pharmacokinetics and bioavailability of carvedilol, a vasodilating beta-blocker. *Eur J Clin Pharmacol*. 1987;33(5):511–3.
185. Neugebauer G, Akpan W, Kaufmann B, Reiff K. Stereoselective disposition of carvedilol in man after intravenous and oral administration of the racemic compound. *Eur J Clin Pharmacol*. 1990;38(Suppl 2):S108–11.
186. Louis WJ, McNeil JJ, Workman BS, Drummer OH, Conway EL. A pharmacokinetic study of carvedilol (BM 14.190) in elderly subjects: preliminary report. *J Cardiovasc Pharmacol*. 1987;10(Suppl 11):S89–93.
187. Neugebauer G, Akpan W, von Mollendorff E, Neubert P, Reiff K. Pharmacokinetics and disposition of carvedilol in humans. *J Cardiovasc Pharmacol*. 1987;10(Suppl 11):S85–8.
188. Masumura H, Miki S, Kaifu Y, Kitajima W, Abe Y. Pharmacokinetics and efficacy of carvedilol in hypertensive patients with chronic renal failure and hemodialysis patients. *J Cardiovasc Pharmacol*. 1992;19(Suppl 1):S102–7.
189. Gehr TW, Tenero DM, Boyle DA, Qian Y, Sica DA, Shusterman NH. The pharmacokinetics of carvedilol and its metabolites after single and multiple dose oral administration in patients with hypertension and renal insufficiency. *Eur J Clin Pharmacol*. 1999;55(4):269–77.
190. Kramer BK, Röss KM, Erley CM, Rislis T. Pharmacokinetic and blood pressure effects of carvedilol in patients with chronic renal failure. *Eur J Clin Pharmacol*. 1992;43(1):85–8.
191. Hitzberger G, Takacs F, Pittner H. Pharmacokinetics of the beta adrenergic blocking substance celiprolol after single intravenous and oral administration in man. *Arzneimittelforschung*. 1983;33(1):50–2.
192. Riddell JG, Shanks RG, Brogden RN. Celiprolol. A preliminary review of its pharmacodynamic and pharmacokinetic properties and its therapeutic use in hypertension and angina pectoris. *Drugs*. 1987;34(4):438–58.
193. Caruso FS, Doshan HD, Hernandez PH, Costello R, Applin W, Neiss ES. Celiprolol: pharmacokinetics and duration of pharmacodynamic activity. *Br J Clin Pract Suppl*. 1985;40:12–6.
194. Schmidt P, Takacs F, Pittner H, Minar E, Balcke P, Zazgornik J, et al. Comparative pharmacokinetics of the beta-1 receptor blocker celiprolol after a single oral administration in subjects with healthy kidneys and in patients with impaired renal function. *Wien Klin Wochenschr*. 1985;97(18):729–32.
195. Norris RJ, Lee EH, Muirhead D, Sanders SW. A pharmacokinetic evaluation of celiprolol in healthy elderly volunteers. *J Cardiovasc Pharmacol*. 1986;8(Suppl 4):S91–2.
196. Hartmann C, Krauss D, Spahn H, Mutschler E. Simultaneous determination of (R)- and (S)-celiprolol in human plasma and urine: high-performance liquid chromatographic assay on a chiral stationary phase with fluorimetric detection. *J Chromatogr*. 1989;496(2):387–96.
197. Savale HS, Pandya KK, Gandhi TP, Modi IA, Modi RI, Satia MC. Plasma analysis of celiprolol by HPLC: a useful technique for pharmacokinetic studies. *J AOAC Int*. 2001;84(4):1252–7.
198. Lilja JJ, Backman JT, Laitila J, Luurila H, Neuvonen PJ. Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol. *Clin Pharmacol Ther*. 2003;73(3):192–8.
199. Lilja JJ, Juntti-Patinen L, Neuvonen PJ. Orange juice substantially reduces the bioavailability of the beta-adrenergic-blocking agent celiprolol. *Clin Pharmacol Ther*. 2004;75(3):184–90.
200. Lilja JJ, Niemi M, Neuvonen PJ. Rifampicin reduces plasma concentrations of celiprolol. *Eur J Clin Pharmacol*. 2004;59(11):819–24.
201. Skoutakis VA, Acchiardo SA, Carter CA, Ingebretsen CG, Klausner MA, Lee DK, et al. Pharmacokinetics of cetamolol in hypertensive patients with normal and compromised renal function. *J Clin Pharmacol*. 1988;28(5):467–76.
202. Coelho J, Schnelle K, Joubert L, Ventura D, Mullane J. Dynamics of beta-adrenoceptor blockade with cetamolol. *Br J Clin Pharmacol*. 1985;19(4):411–6.
203. Stern MD. Radioreceptor assay for serum levels of cetamolol, a new beta-adrenoceptor antagonist. *Clin Biochem*. 1984;17(3):162–5.
204. Sum CY, Yacobi A, Kartzinell R, Stampfli H, Davis CS, Lai CM. Kinetics of esmolol, an ultra-short-acting beta blocker, and of its major metabolite. *Clin Pharmacol Ther*. 1983;34(4):427–34.
205. Buchi KN, Rollins DE, Tolman KG, Achari R, Drissel D, Hulse JD. Pharmacokinetics of esmolol in hepatic disease. *J Clin Pharmacol*. 1987;27(11):880–4.
206. Martin LE, Hopkins R, Bland R. Metabolism of labetalol by animals and man. *Br J Clin Pharmacol*. 1976;3(4 Suppl 3):695–710.
207. Luke DR, Awni WM, Halstenson CE, Opsahl JA, Matzke GR. Bioavailability of labetalol in patients with end-stage renal disease. *Ther Drug Monit*. 1992;14(3):203–8.
208. McNeil JJ, Anderson AE, Louis WJ, Morgan DJ. Pharmacokinetics and pharmacodynamic studies of labetalol in hypertensive subjects. *Br J Clin Pharmacol*. 1979;8(Suppl 2):1575–S161.
209. Kanto J, Allonen H, Lehtonen A, Mantyla R, Pakkanen A. Clinical and pharmacokinetic studies on the alpha- and beta-blocking drug labetalol. *Ther Drug Monit*. 1980;2(2):145.
210. Daneshmend TK, Roberts CJ. The influence of food on the oral and intravenous pharmacokinetics of a high clearance drug: a study with labetalol. *Br J Clin Pharmacol*. 1982;14(1):73–8.
211. Nyberg G, Hansson R, Tietz F. Single-dose pharmacokinetics of labetalol in healthy young men. *Acta Med Scand Suppl*. 1982;665:67–73.
212. Abernethy DR, Schwartz JB, Plachetka JR, Todd EL, Egan JM. Comparison in young and elderly patients of pharmacodynamics and disposition of labetalol in systemic hypertension. *Am J Cardiol*. 1987;60(8):697–702.
213. Elliott HL, Meredith PA, Sumner DJ, Reid JL. Comparison of the clinical pharmacokinetics and concentration-effect relationships for medroxalol and labetalol. *Br J Clin Pharmacol*. 1984;17(5):573–8.
214. Haeghele KD, Jaillon P, Cheymol G, Alken RG, Schechter PJ, Koch-Weser J. Kinetics of medroxalol, a beta- and alpha-adrenoceptor antagonist. *Clin Pharmacol Ther*. 1983;34(6):785–91.
215. Keeley FJ, Weiner DL, Okerholm RA. Bioavailability of medroxalol in man. *Biopharm Drug Dispos*. 1983;4(4):305–9.
216. Bonelli J, Hitzberger G, Krause W, Wendt H, Speck U. Pharmacokinetics and pharmacodynamics of mepindolol sulphate. *Int J Clin Pharmacol Ther Toxicol*. 1980;18(4):169–76.
217. Borchard AC. Pharmacological properties of beta-adrenoceptor blocking drugs. *J Clin Basic Cardiol*. 1998;1(1):5–9.
218. Seyfried C, Ledermann H, Rennekamp H, L'Age M, Abshagen U. Pharmacokinetics of the beta-receptor blocker metipranolol in patients with liver cirrhosis (author's transl). *Dtsch Med Wochenschr*. 1982;107(1):21–6.
219. Abshagen U, Betzien G, Kaufmann B, Ende G. Pharmacokinetics of metipranolol in normal man. *Eur J Clin Pharmacol*. 1982;21(4):293–301.
220. Lapka R, Sechser T, Rejcholec V, Peterkova M, Votavova M. Pharmacokinetics and pharmacodynamics of conventional and controlled-release formulations of metipranolol in man. *Eur J Clin Pharmacol*. 1990;38(3):243–7.

221. Janku I, Perlik F, Tkaczykova M, Brodanova M. Disposition kinetics and concentration-effect relationship of metipranolol in patients with cirrhosis and healthy subjects. *Eur J Clin Pharmacol*. 1992;42(3):337–40.
222. Appelgren C, Borg KO, Elofsson R, Johansson KA. Binding of adrenergic beta-receptor antagonists to human serum albumin. *Acta Pharm Suec*. 1974;11(4):325–32.
223. Regardh CG, Borg KO, Johansson R, Johnsson G, Palmer L. Pharmacokinetic studies on the selective beta1-receptor antagonist metoprolol in man. *J Pharmacokinet Biopharm*. 1974;2(4):347–64.
224. Regardh CG, Jordo L, Ervik M, Lundborg P, Olsson R, Ronn O. Pharmacokinetics of metoprolol in patients with hepatic cirrhosis. *Clin Pharmacokinet*. 1981;6(5):375–88.
225. Regardh CG, Landahl S, Larsson M, Lundborg P, Steen B, Hoffmann KJ, et al. Pharmacokinetics of metoprolol and its metabolite alpha-OH-metoprolol in healthy, non-smoking, elderly individuals. *Eur J Clin Pharmacol*. 1983;24(2):221–6.
226. Richard J, Cardot JM, Godbillon J. Inter- and intra-subject variability of metoprolol kinetics after intravenous administration. *Eur J Drug Metab Pharmacokinet*. 1994;19(2):157–62.
227. Schaaf LJ, Campbell SC, Mayersohn MB, Vagedes T, Perrier DG. Influence of smoking and gender on the disposition kinetics of metoprolol. *Eur J Clin Pharmacol*. 1987;33(4):355–61.
228. Jordo L, Attman PO, Aurell M, Johansson L, Johnsson G, Regardh CG. Pharmacokinetic and pharmacodynamic properties of metoprolol in patients with impaired renal function. *Clin Pharmacokinet*. 1980;5(2):169–80.
229. Regardh CG, Johnsson G, Jordo L, Solvell L. Comparative bioavailability and effect studies on metoprolol administered as ordinary and slow-release tablets in single and multiple doses. *Acta Pharmacol Toxicol (Copenh)*. 1975;36(Suppl 5):45–58.
230. Regardh CG, Johnsson G, Jordo L, Lungborg P, Persson BA, Ronn O. Plasma concentrations and beta-blocking effects in normal volunteers after intravenous doses of metoprolol and propranolol. *J Cardiovasc Pharmacol*. 1980;2(6):715–23.
231. Patel L, Johnson A, Turner P. Nadolol binding to human serum proteins. *J Pharm Pharmacol*. 1984;36(6):414–5.
232. Dreyfuss J, Brannick LJ, Vukovich RA, Shaw JM, Willard DA. Metabolic studies in patients with nadolol: oral and intravenous administration. *J Clin Pharmacol*. 1977;17(5–6):300–7.
233. Dreyfuss J, Griffith DL, Singhvi SM, Shaw JM, Ross JJ Jr, Vukovich RA, et al. Pharmacokinetics of nadolol, a beta-receptor antagonist: administration of therapeutic single- and multiple-dosage regimens to hypertensive patients. *J Clin Pharmacol*. 1979;19(11–12):712–20.
234. Morrison RA, Singhvi SM, Creasey WA, Willard DA. Dose proportionality of nadolol pharmacokinetics after intravenous administration to healthy subjects. *Eur J Clin Pharmacol*. 1988;33(6):625–8.
235. Neves DV, Lanchote VL, Moyses Neto M, Cardeal da Costa JA, Vieira CP, Coelho EB. Influence of chronic kidney disease and haemodialysis treatment on pharmacokinetics of nebivolol enantiomers. *Br J Clin Pharmacol*. 2016;82(1):83–91.
236. Himmelmann A, Hedner T, Snoeck E, Lundgren B, Hedner J. Haemodynamic effects and pharmacokinetics of oral d- and l-nebivolol in hypertensive patients. *Eur J Clin Pharmacol*. 1996;51(3–4):259–64.
237. Cheymol G, Woestenborghs R, Snoeck E, Ianucci R, Le Moing JP, Naditch L, et al. Pharmacokinetic study and cardiovascular monitoring of nebivolol in normal and obese subjects. *Eur J Clin Pharmacol*. 1997;51(6):493–8.
238. Kamali F, Howes A, Thomas SH, Ford GA, Snoeck E. A pharmacokinetic and pharmacodynamic interaction study between nebivolol and the H2-receptor antagonists cimetidine and ranitidine. *Br J Clin Pharmacol*. 1997;43(2):201–4.
239. Lindamood C, Ortiz S, Shaw A, Rackley R, Gorski JC. Effects of commonly administered agents and genetics on nebivolol pharmacokinetics: drug-drug interaction studies. *J Clin Pharmacol*. 2011;51(4):575–85.
240. Briciu C, Neag M, Muntean D, Vlase L, Bocsan C, Buzoianu A, et al. A pharmacokinetic drug interaction study between nebivolol and paroxetine in healthy volunteers. *J Clin Pharm Ther*. 2014;39(5):535–40.
241. Briciu C, Neag M, Muntean D, Bocsan C, Buzoianu A, Antonescu O, et al. Phenotypic differences in nebivolol metabolism and bioavailability in healthy volunteers. *Clujul Med*. 2015;88(2):208–13.
242. Riess W, Huerzeler H, Raschdorf F. The metabolites of oxprenolol (Trasicor) in man. *Xenobiotica; the fate of foreign compounds in biological systems*. 1974;4 (6):365–73.
243. Dayer P, Glasson P, Balant L, Striberni R, Fabre FJ. Differential consequences of renal failure on the pharmacokinetics of oxprenolol and its main metabolite. *Eur J Drug Metab Pharmacokinet*. 1983;8(2):181–8.
244. Rigby JW, Scott AK, Hawksworth GM, Petrie JC. A comparison of the pharmacokinetics of atenolol, metoprolol, oxprenolol and propranolol in elderly hypertensive and young healthy subjects. *Br J Clin Pharmacol*. 1985;20(4):327–31.
245. Laethem ME, Lefebvre RA, Belpaire FM, Vanhoe HL, Bogaert MG. Stereoselective pharmacokinetics of oxprenolol and its glucuronides in humans. *Clin Pharmacol Ther*. 1995;57(4):419–24.
246. Mason WD, Winer N. Pharmacokinetics of oxprenolol in normal subjects. *Clin Pharmacol Ther*. 1976;20(4):401–12.
247. Bradbrook ID, John VA, Morrison PJ, Rogers HJ, Spector RG. Pharmacokinetic investigation of the absorption of oxprenolol from Oros delivery systems in healthy volunteers: comparison of in vivo and in vitro drug release. *Br J Clin Pharmacol*. 1985;19(Suppl 2):1635–S169.
248. Dawes CP, Kendall MJ, Welling PG. Bioavailability of conventional and slow-release oxprenolol in fasted and nonfasted individuals. *Br J Clin Pharmacol*. 1979;7(3):299–302.
249. Kendall MJ. Pharmacokinetics of oxprenolol in the elderly. *Am J Cardiol*. 1983;52(9):54D–D56.
250. Antonin KH, Bieck P, Scheurien M, Jedrychowski M, Malchow H. Oxprenolol absorption in man after single bolus dosing into two segments of the colon compared with that after oral dosing. *Br J Clin Pharmacol*. 1985;19(Suppl 2):1375–S142.
251. Dieterle W, Faigle JW, Kung W, Theobald W. The disposition and metabolism of 14C-oxprenolol.HCl in man. *Xenobiotica; the fate of foreign compounds in biological systems*. 1986;16 (2):181–91.
252. Koopmans R, Oosterhuis B, Karemaker JM, Wemer J, van Bostel CJ. The effect of oxprenolol dosage time on its pharmacokinetics and haemodynamic effects during exercise in man. *Eur J Clin Pharmacol*. 1993;44(2):171–6.
253. Gottschalk R, Sistovaris N. Protein binding studies of furosemide and penbutolol. *Arzneimittelforschung*. 1985;35(6):899–902.
254. Aguirre C, Rodriguez-Sasiain JM, Calvo R. Decrease in penbutolol protein binding as a consequence of treatment with some alkylating agents. *Cancer Chemother Pharmacol*. 1994;34(1):86–8.
255. Bernard N, Cuisinaud G, Pozet N, Zech PY, Sassard J. Pharmacokinetics of penbutolol and its metabolites in renal insufficiency. *Eur J Clin Pharmacol*. 1985;29(2):215–9.
256. Giudicelli JF, Richer C, Chauvin M, Idrissi N, Berdeaux A. Comparative beta-adrenoceptor blocking effects and pharmacokinetics of penbutolol and propranolol in man. *Br J Clin Pharmacol*. 1977;4(2):135–40.
257. Muller FO, Hundt HK, Bromley PA, Torres J, Vanderbeke O. Single and divided doses of penbutolol. *Clin Pharmacol Ther*. 1979;25(5 Pt 1):528–35.
258. Ochs HR, Hajdu P, Greenblatt DJ. Pharmacokinetics and dynamics of penbutolol in humans: evidence for pathway-specific stereoselective clearance. *Klin Wochenschr*. 1986;64(14):636–41.
259. Spahn H, Kirch W, Hajdu P, Mutschler E, Ohnhaus EE. Penbutolol Pharmacokinetics: the influence of concomitant administration of cimetidine. *Eur J Clin Pharmacol*. 1986;29(5):555–60.
260. Brockmeier D, Hajdu P, Henke W, Mutschler E, Palm D, Rupp W, et al. Penbutolol: pharmacokinetics, effect on exercise tachycardia, and in vitro inhibition of radioligand binding. *Eur J Clin Pharmacol*. 1988;35(6):613–23.
261. Vedin JA, Wilhelmsson C, Maass L, Peterson LE. Pharmacodynamic and pharmacokinetic study of oral and intravenous penbutolol. *Eur J Clin Pharmacol*. 1983;25(4):529–34.
262. Luo X, Lei Y, He L, Liu W, Li M, Ran L, et al. No influence of CYP2D6\*10 genotype and phenotype on the pharmacokinetics of nebivolol in healthy Chinese subjects. *J Clin Pharm Ther*. 2015;40(5):561–5.
263. Galeazzi RL, Gugger M, Weidmann P. beta blockade with pindolol: differential cardiac and renal effects despite similar plasma kinetics in normal and uremic man. *Kidney Int*. 1979;15(6):661–8.
264. Gugler R, Herold W, Dengler HJ. Pharmacokinetics of pindolol in man. *Eur J Clin Pharmacol*. 1974;7(1):17–24.

265. Lavene D, Weiss YA, Safar ME, Loria Y, Agorus N, Georges D, et al. Pharmacokinetics and hepatic extraction ratio of pindolol in hypertensive patients with normal and impaired renal function. *J Clin Pharmacol*. 1977;17(8–9):501–8.
266. Juma FD. Pharmacokinetics of pindolol in Kenyan Africans. *Eur J Clin Pharmacol*. 1983;25(3):425–6.
267. Chau NP, Weiss YA, Safar ME, Lavene D, Georges DR, Milliez PL. Pindolol availability in hypertensive patients with normal and impaired renal function. *Clin Pharmacol Ther*. 1977;22(5 Pt 1):505–10.
268. Guerret M, Cheymol G, Aubry JP, Cheymol A, Lavene D, Kiechel JR. Estimation of the absolute oral bioavailability of pindolol by two analytical methods. *Eur J Clin Pharmacol*. 1983;25(3):357–9.
269. Stone WJ, Walle T. Massive propranolol metabolite retention during maintenance hemodialysis. *Clin Pharmacol Ther*. 1980;28(4):449–55.
270. Bodem G, Chidsey CA. Pharmacokinetic studies of practolol, a beta adrenergic antagonist, in man. *Clin Pharmacol Ther*. 1973;14(1):26–9.
271. Bodem G, Grieser H, Eichelbaum M, Gugler R. Pharmacokinetics of practolol in renal failure. *Eur J Clin Pharmacol*. 1974;7(4):249–52.
272. Kaye CM, Kumana CR, Franklin DA, Baker LR. A study of practolol elimination in all grades of chronic renal failure. *Int J Clin Pharmacol Biopharm*. 1975;12(1–2):83–8.
273. Tilstone WJ, Semple PF, Boyle JA. Proceedings: The renal clearance of practolol in man. *J Pharm Pharmacol*. 1974;26(Suppl):66P–P67.
274. Giudicelli JF, Tillement JP, Boissier JR. Beta-adrenergic activity compared in vitro and in vivo and protein fixation. *J Pharmacol*. 1973;129–36.
275. Graffner C, Hoffmann KJ, Johnsson G, Lundborg P, Ronn O. Pharmacokinetic studies in man of the selective beta 1-adrenoceptor agonist, prenalaterol. *Eur J Clin Pharmacol*. 1981;20(2):91–7.
276. Ronn O. Pharmacokinetics of prenalaterol in healthy subjects and patients with congestive heart failure. *Acta Med Scand Suppl*. 1982;659:89–98.
277. Dahlstrom U, Graffner C, Jonsson U, Hoffmann KJ, Karlsson E, Lagerstrom PO. Pharmacokinetics of prenalaterol after single and multiple administration of controlled release tablets to patients with congestive heart failure. *Eur J Clin Pharmacol*. 1983;24(4):495–502.
278. Jennings G, Bobik A, Oddie C, Hargreaves M, Korner P. Cardioselectivity of prenalaterol and isoproterenol. *Clin Pharmacol Ther*. 1983;34(6):749–57.
279. Sainsbury EJ, Fitzpatrick D, Ikram H, Nicholls MG, Espiner EA, Ashley JJ. Pharmacokinetics and plasma-concentration-effect relationships of prenalaterol in cardiac failure. *Eur J Clin Pharmacol*. 1985;28(4):397–403.
280. Ronn O, Graffner C, Johnsson G, Jordo L, Lundborg P, Wikstrand J. Haemodynamic effects and pharmacokinetics of a new selective beta 1-adrenoceptor agonist, prenalaterol, and its interaction with metoprolol in man. *Eur J Clin Pharmacol*. 1979;15(1):9–13.
281. Ronn O, Fellenius E, Graffner C, Johnsson G, Lundborg P, Svensson L. Metabolic and haemodynamic effects and pharmacokinetics of a new selective beta 1-adrenoceptor agonist, prenalaterol, in man. *Eur J Clin Pharmacol*. 1980;17(2):81–6.
282. Klein G, Wirtzfeld A, Bozler G, Ronn O, Graffner C. Compartment model of prenalaterol. *Acta Med Scand Suppl*. 1982;659:99–107.
283. Evans GH, Shand DG. Disposition of propranolol. VI. Independent variation in steady-state circulating drug concentrations and half-life as a result of plasma drug binding in man. *Clin Pharmacol Ther*. 1973;14(4):494–500.
284. Wood AJ, Vestal RE, Spannuth CL, Stone WJ, Wilkinson GR, Shand DG. Propranolol disposition in renal failure. *Br J Clin Pharmacol*. 1980;10(6):561–6.
285. Olanoff LS, Walle T, Walle UK, Cowart TD, Gaffney TE. Stereoselective clearance and distribution of intravenous propranolol. *Clin Pharmacol Ther*. 1984;35(6):755–61.
286. Cheymol G, Poirier JM, Barre J, Pradalier A, Dry J. Comparative pharmacokinetics of intravenous propranolol in obese and normal volunteers. *J Clin Pharmacol*. 1987;27(11):874–9.
287. Straka RJ, Lalonde RL, Pieper JA, Botorff MB, Mirvis DM. Nonlinear pharmacokinetics of unbound propranolol after oral administration. *J Pharm Sci*. 1987;76(7):521–4.
288. Walle T, Walle UK, Cowart TD, Conradi EC. Pathway-selective sex differences in the metabolic clearance of propranolol in human subjects. *Clin Pharmacol Ther*. 1989;46(3):257–63.
289. Sowinski KM, Lima JJ, Burlew BS, Massie JD, Johnson JA. Racial differences in propranolol enantiomer kinetics following simultaneous i.v. and oral administration. *Br J Clin Pharmacol*. 1996;42(3):339–46.
290. Lowenthal DT, Mutterperl R. The pharmacokinetics (PK) of multiple dose (MD) propranolol (P) in chronic renal disease (CRD). *Clin Pharmacol Ther*. 1976;19(1):111.
291. Johnson JA, Burlew BS. Racial differences in propranolol pharmacokinetics. *Clin Pharmacol Ther*. 1992;51(5):495–500.
292. Wood AJ, Carr K, Vestal RE, Belcher S, Wilkinson GR, Shand DG. Direct measurement of propranolol bioavailability during accumulation to steady-state. *Br J Clin Pharmacol*. 1978;6(4):345–50.
293. Weiss YA, Safar ME, Chevillard C, Frydman A, Simon A, Lemaire P, et al. Comparison of the pharmacokinetics of intravenous dl-propranolol in borderline and permanent hypertension. *Eur J Clin Pharmacol*. 1976;10(6):387–93.
294. Castleden CM, George CF. The effect of ageing on the hepatic clearance of propranolol. *Br J Clin Pharmacol*. 1979;7(1):49–54.
295. Jackman GP, McLean AJ, Jennings GL, Bobik A. No stereoselective first-pass hepatic extraction of propranolol. *Clin Pharmacol Ther*. 1981;30(3):291–6.
296. Venter CP, Joubert PH, Strydom WJ. Comparative pharmacokinetics of intravenous propranolol in black and white volunteers. *J Cardiovasc Pharmacol*. 1985;7(2):409–10.
297. Arends BG, Bohm RO, van Kemenade JE, Rahn KH, van Baak MA. Influence of physical exercise on the pharmacokinetics of propranolol. *Eur J Clin Pharmacol*. 1986;31(3):375–7.
298. Bowman SL, Hudson SA, Simpson G, Munro JF, Clements JA. A comparison of the pharmacokinetics of propranolol in obese and normal volunteers. *Br J Clin Pharmacol*. 1986;21(5):529–32.
299. Cid E, Mella F, Lucchini L, Carcamo M, Monasterio J. Plasma concentrations and bioavailability of propranolol by oral, rectal, and intravenous administration in man. *Biopharm Drug Dispos*. 1986;7(6):559–66.
300. Wilson TW, Firor WB, Johnson G, Holmes GI, Tsianco MC, Huber PB, et al. Timolol and propranolol: bioavailability, plasma concentrations, and beta blockade. *Clin Pharmacol Ther*. 1982;32(6):676–85.
301. Chidsey CA, Morselli P, Bianchetti G, Morganti A, Leonetti G, Zanchetti A. Studies of the absorption and removal of propranolol in hypertensive patients during therapy. *Circulation*. 1975;52(2):313–8.
302. Olanoff LS, Walle T, Cowart TD, Walle UK, Oexmann MJ, Conradi EC. Food effects on propranolol systemic and oral clearance: support for a blood flow hypothesis. *Clin Pharmacol Ther*. 1986;40(4):408–14.
303. Anttila M, Arstila M, Pfeffer M, Tikkanen R, Vallinkoski V, Sundquist H. Human pharmacokinetics of sotalol. *Acta Pharmacol Toxicol (Copenh)*. 1976;39(1):18–28.
304. Poirier JM, Jaillon P, Lecocq B, Lecocq V, Ferry A, Cheymol G. The pharmacokinetics of d-sotalol and d, l-sotalol in healthy volunteers. *Eur J Clin Pharmacol*. 1990;38(6):579–82.
305. Salazar DE, Much DR, Nichola PS, Seibold JR, Shindler D, Slugg PH. A pharmacokinetic-pharmacodynamic model of d-sotalol Q-Tc prolongation during intravenous administration to healthy subjects. *J Clin Pharmacol*. 1997;37(9):799–809.
306. Sundquist H, Anttila M, Simon A, Reich JW. Comparative bioavailability and pharmacokinetics of sotalol administered alone and in combination with hydrochlorothiazide. *J Clin Pharmacol*. 1979;19(8–9 Pt 2):557–64.
307. Uematsu T, Kanamaru M, Nakashima M. Comparative pharmacokinetic and pharmacodynamic properties of oral and intravenous (+)-sotalol in healthy volunteers. *J Pharm Pharmacol*. 1994;46(7):600–5.
308. Blair AD, Cutler RE, Lam FY. Pharmacokinetics of sotalol in humans with normal and varying degrees of renal function. *Clin Res*. 1980;28(1):68A.
309. Dumas M, d'Athis P, Besancenot JF, Chadoint-Noudeau V, Chalopin JM, Riffe G, et al. Variations of sotalol kinetics in renal insufficiency. *Int J Clin Pharmacol Ther Toxicol*. 1989;27(10):486–9.
310. Sundquist HK, Anttila M, Forsstrom J, Kasanen A. Serum levels and half-life of sotalol in chronic renal failure. *Ann Clin Res*. 1975;7(6):442–6.
311. Trausch B, Oertel R, Richter K, Gramatte T. Disposition and bioavailability of the beta 1-adrenoceptor antagonist talinolol in man. *Biopharm Drug Dispos*. 1995;16(5):403–14.

312. Haustein KO, Fritzsche K. On the pharmacokinetics of talinolol, a new beta 1-receptor blocking agent. *Int J Clin Pharmacol Ther Toxicol.* 1981;19(9):392–5.
313. Terhaag B, Palm U, Sahre H, Richter K, Oertel R. Interaction of talinolol and sulfasalazine in the human gastrointestinal tract. *Eur J Clin Pharmacol.* 1992;42(4):461–2.
314. Ishizaki T, Tawara K, Oyama Y, Nakaya H. Clinical pharmacologic observations on timolol. I. Disposition and effect in relation to plasma level in normal individuals. *J Clin Pharmacol.* 1978;18(11–12):511–8.
315. Else OF, Sorenson H, Edwards IR. Plasma timolol levels after oral and intravenous administration. *Eur J Clin Pharmacol.* 1978;14(6):431–4.
316. Vedin JA, Kristianson JK, Wilhelmsson CE. Pharmacokinetics of intravenous timolol in patients with acute myocardial infarction and in healthy volunteers. *Eur J Clin Pharmacol.* 1982;23(1):43–7.
317. El-Rashidy R. Estimation of the systemic bioavailability of timolol in man. *Biopharm Drug Dispos.* 1981;2(2):197–202.
318. Faulkner JK, Stopher DA, Walden R. Pharmacokinetic and pharmacological studies with tolamolol in man. *Br J Clin Pharmacol.* 1975;2(5):423–8.
319. Routledge PA, Davies DM, Rawlins MD. Pharmacokinetics of tolamolol in the treatment of hypertension. *Eur J Clin Pharmacol.* 1977;12(3):171–4.
320. Balant L, Gorgia A, Marmy A, Tschopp JM. [Clearance concept applied to pharmacokinetics: 2. Experience with tolamolol (beta-blocking agent) in renal insufficiency (author's transl)]. *Nephrologie.* 1980;1 (4):177–82.
321. Williams HA, Henke D, Elamin MEMO, Sandilands EA, Thomas SHL, Thompson JP, et al. Can poisons centre data inform safer prescribing? A pilot review of propranolol exposures reported to the UK National Poisons Information Service (NPIS). *Clin Toxicol.* 2019;57(6):453.
322. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF. Ultrasound guidance versus anatomical landmarks for subclavian or femoral vein catheterization. *Cochrane Database Syst Rev.* 2015;1:CD011447.
323. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF. Ultrasound guidance versus anatomical landmarks for internal jugular vein catheterization. *Cochrane Database Syst Rev.* 2015;1:CD006962.
324. Parienti JJ, Mongardon N, Megarbane B, Mira JP, Kalfon P, Gros A, et al. Intravascular complications of central venous catheterization by insertion site. *N Engl J Med.* 2015;373(13):1220–9.
325. Shin HJ, Na HS, Koh WU, Ro YJ, Lee JM, Choi YJ, et al. Complications in internal jugular vs subclavian ultrasound-guided central venous catheterization: a comparative randomized trial. *Intensive Care Med.* 2019;45(7):968–76.
326. Bjorkander M, Bentzer P, Schott U, Broman ME, Kander T. Mechanical complications of central venous catheter insertions: A retrospective multicenter study of incidence and risks. *Acta Anaesthesiol Scand.* 2019;63(1):61–8.
327. Wong B, Zimmerman D, Reintjes F, Courtney M, Klarenbach S, Dowling G, et al. Procedure-related serious adverse events among home hemodialysis patients: a quality assurance perspective. *Am J Kidney Dis.* 2014;63(2):251–8.
328. Tennankore KK, d’Gama C, Faratro R, Fung S, Wong E, Chan CT. Adverse technical events in home hemodialysis. *Am J Kidney Dis.* 2015;65(1):116–21.
329. Mokrzycki MH, Kaplan AA. Therapeutic plasma exchange: complications and management. *Am J Kidney Dis.* 1994;23(6):817–27.
330. Sutton DM, Nair RC, Rock G. Complications of plasma exchange. *Transfusion.* 1989;29(2):124–7.
331. Yang X, Xin S, Zhang Y, Li T. Early hemoperfusion for emergency treatment of carbamazepine poisoning. *Am J Emerg Med.* 2018;36(6):926–30.
332. Shannon MW. Comparative efficacy of hemodialysis and hemoperfusion in severe theophylline intoxication. *Acad Emerg Med.* 1997;4(7):674–8.

### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

