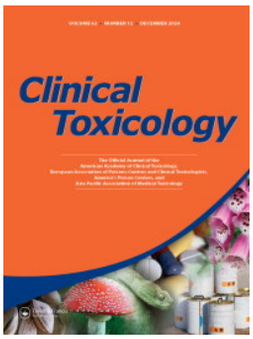

Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ictx20

A prospective study of acute propranolol overdose defining dose thresholds of severe toxicity (ATOM – 9)

Katherine Z. Isoardi, Angela L. Chiew, Cuong Do, Michael Humphreys, Ahmead Mustafa, Michael S. Roberts & Geoffrey K. Isbister

To cite this article: Katherine Z. Isoardi, Angela L. Chiew, Cuong Do, Michael Humphreys, Ahmead Mustafa, Michael S. Roberts & Geoffrey K. Isbister (10 Dec 2024): A prospective study of acute propranolol overdose defining dose thresholds of severe toxicity (ATOM – 9), Clinical Toxicology, DOI: 10.1080/15563650.2024.2435397

To link to this article: https://doi.org/10.1080/15563650.2024.2435397

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2024.2435397

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH

A prospective study of acute propranolol overdose defining dose thresholds of severe toxicity (ATOM – 9)

Katherine Z. Isoardi[a,b,c,d], Angela L. Chiew[e,f,g], Cuong Do[a], Michael Humphreys[a,b,c], Ahmead Mustafa[h], Michael S. Roberts[h,i] and Geoffrey K. Isbister[d,e,j]

[a]Clinical Toxicology Unit, Princess Alexandra Hospital, Brisbane, Australia; [b]Queensland Poisons Information Centre, Queensland Children's Hospital, Brisbane, Australia; [c]Faculty of Medicine, University of Queensland, Brisbane, Australia; [d]Clinical Toxicology Research Group, University of Newcastle, Newcastle, Australia; [e]NSW Poisons Information Centre, Sydney Children's Hospital, Sydney, Australia; [f]Clinical Toxicology Unit, Prince of Wales Hospital, Sydney, Australia; [g]School of Medicine, University of New South Wales, Sydney, Australia; [h]UniSA Clinical and Health Sciences, University of South Australia, Adelaide, Australia; [i]Frazer Institute, University of Queensland, Translational Research Institute, Brisbane, Australia; [j]Department of Clinical Toxicology, Calvary Mater Newcastle, Newcastle, Australia

ABSTRACT

Introduction: Propranolol is a beta-adrenoceptor blocking drug with sodium channel-blocking properties that can cause life-threatening toxicity in overdose. Limited research defines dose thresholds of toxicity. We aimed to investigate propranolol overdose and dose thresholds for severe toxicity.

Material and methods: This is a prospective series of patients with acute propranolol overdose ≥360 mg from August 2014 to December 2023 enrolled through the Australian TOxicology Monitoring (ATOM) collaboration. Severe toxicity was defined as seizure, coma, inotrope therapy, electrocardiographic evidence of sodium channel blockade, or cardiac arrest.

Results: There were 209 presentations in 165 patients (median age 30 years [range 15–80 years]; 117 females, 71%). The median reported dose ingested was 1,000 mg (IQR: 600–2,000 mg; range 360–16,000 mg). Co-ingestion occurred in 155 (74%) patients, most commonly involving benzodiazepines (n = 52). Bradycardia (heart rate <50 beats/min) occurred in 41 (20%), and hypotension (systolic blood pressure <90 mmHg) in 88 (42%). Severe toxicity occurred in 51 patients (24%), with 17 (8%) having a seizure and 29 (14%) developing coma. Forty-one (20%) received inotropes, including 31(15%) who were given epinephrine and 20 (10%) high-dose insulin. Electrocardiographic evidence of sodium channel blockade occurred in 16 (8%). Seven (3%) had a cardiac arrest (reported dose range 2,400–16,000 mg), with two deaths following the ingestion of propranolol 4,000 mg and 16,000 mg. The median length of stay was 17 h (IQR: 11–32 h). In 79 patients who ingested only propranolol, the lowest reported propranolol dose for hypotension was 400 mg and for bradycardia, 800 mg. The lowest reported dose for severe toxicity was propranolol 2,000 mg. In those ingesting propranolol only, 17 of 32 (53%) patients who ingested ≥2,000 mg had severe toxicity.

Discussion: Severe toxicity was common, occurring in a quarter of all propranolol overdoses and half of the isolated propranolol ingestions (≥2,000 mg). The outcome was usually favourable with good supportive care, even in severe toxicity.

Conclusion: The dose threshold for severe toxicity in isolated propranolol overdose appeared to be 2,000 mg.

ARTICLE HISTORY
Received 6 August 2024
Revised 21 November 2024
Accepted 22 November 2024

KEYWORDS
Beta-adrenoceptor blocking drug; bicarbonate; overdose; propranolol; sodium channel blockade

Introduction

Propranolol is a non-selective beta-adrenoceptor blocking drug with sodium channel blocking properties that can cause life-threatening toxicity in overdose. Its membrane-stabilizing activity is associated with an increased risk of neurological and cardiovascular toxicity compared to other beta-adrenoceptor blocking drugs [1, 2]. Severe toxicity is characterized by coma, seizure, cardiogenic shock and broad-complex dysrhythmias [3].

This heightened toxicity profile is particularly concerning as propranolol is a common beta-adrenoceptor blocking drug taken in overdose [1, 4]. In one large series of over 50,000 exposures from America's Poisons Centers® due to beta-adrenoceptor blocking drugs, propranolol was the most frequent, accounting for 44% of referrals [4]. Unlike other beta-adrenoceptor blocking drugs, propranolol has multiple indications outside of the cardiovascular setting. Propranolol is also used in the management of migraine, essential tremor, anxiety, and post-traumatic stress disorder [5]. These broad indications are likely an important driver of increasing propranolol prescriptions and overdose over the last two decades [6, 7]. Furthermore, patients prescribed propranolol for psychiatric indications are more likely to take overdoses, so

CONTACT Katherine Z. Isoardi katherine.isoardi@health.qld.gov.au Clinical Toxicology Unit, Princess Alexandra Hospital, 199 Ipswich Rd., Woolloongabba, Queensland 4102, Australia.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/15563650.2024.2435397.

increased availability in this group is problematic. Between 2007 and 2017, annual propranolol prescriptions in the United Kingdom have risen by 41%, while the rate of propranolol overdose has increased by more than 200% [8].

There is limited research defining dose thresholds of toxicity following propranolol overdose. A small series of 28 presentations that focussed on seizures found that six of the nine patients (66%) ingesting propranolol ≥2,000 mg had seizures compared to only two of 19 (11%) in the group ingesting <2,000 mg [1]. In a more recent series of 41 presentations [9] there appeared to be a threshold dose above which people became symptomatic. This study [9] could not comment on severe toxicity as it was limited by only three presentations having a poisoning severity score of 3 (severe toxicity).

We aimed to investigate propranolol overdose to better characterize its clinical features in overdose and attempt to define dose thresholds for severe toxicity.

Material and methods

Study design, setting and participants

This study is part of the multi-centre Australian TOxicology Monitoring (ATOM) collaboration. We prospectively recruited patients from three participating clinical toxicology units (Princess Alexandra Hospital, Brisbane, Calvary Mater Newcastle Hospital and Prince of Wales Hospital, Sydney), as well as the Queensland and New South Wales Poisons Information Centres. In Australia, propranolol is only available through the Pharmaceutical Benefits Scheme as an immediate-release preparation (10 mg and 40 mg). Both tablet sizes are dispensed in bottles containing 100 tablets. A slow-release preparation of 160 mg is available, but only as a private prescription with no government subsidy.

Patients who reported ingesting an acute overdose of greater than or equal to propranolol 360 mg during the period 1 August 2014 to 31 December 2023 were included in the study. This minimum dose was chosen as it is more than twice the defined daily dose of propranolol (160 mg). Patients <14 years of age or those in police or correctional service custody were excluded from enrolment.

Data collection

A preformatted data form (Supplementary Figure 1) was completed prospectively by the treating clinician and emailed to the study team. Data were then abstracted from this data form by a single abstractor (CD), with patient medical records being used to supplement any data that were missing. A scanned copy of the electrocardiograph (ECG) in each case was interpreted by one of three clinical toxicologists in the study team (KI, AC, GI) to determine QRS complex duration and terminal R wave height. The treating clinician, data form abstractor and clinical toxicologists in the study team were not blinded to the aims of the study. In a subgroup of patients in whom serum was collected and stored for drug assays, a propranolol concentration was performed using a liquid chromatography-tandem mass spectrometer assay with a validated concentration range of 3 µg/L to 2,000 µg/L (full methods in Supplementary Figure 2). No other blood concentrations were performed.

Data from all patients were collated on a Microsoft® Excel datasheet detailing demographics (age, sex, propranolol prescribed and, if so, the indication), exposure details (dose, time of ingestion, co-ingestions), clinical effects (heart rate, blood pressure, Glasgow Coma Scale [GCS], dysrhythmia, seizure), investigations (ECG, blood gas analysis, propranolol concentration), treatment (activated charcoal, intravenous fluids, inotropes [defined as inotrope, chronotrope or vasopressor therapy], intubation, electrical pacing, sodium bicarbonate, intravenous lipid emulsion), complications (acute kidney injury, aspiration, cardiac arrest), discharge location, and length of stay.

Electrocardiographic evidence of sodium channel blockade was defined as being present if the QRS complex duration was ≥120 ms and a significant terminal R wave (>3mm tall or R:S > 0.7) was present. Given therapeutic beta-adrenoreceptor blockade may produce a heart rate <60 beats/min [10], we defined bradycardia as a heart rate <50 beats/min. Hypotension was defined as a systolic blood pressure <90 mmHg. Acute kidney injury was defined using the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guideline [11]. Severe toxicity was defined as the occurrence of seizure, coma, inotrope therapy, sodium channel blockade, or cardiac arrest. We did not consider bradycardia or hypotension not receiving inotrope therapy to represent severe toxicity, as patients improved with minimal intervention.

Analysis

Descriptive statistics were used with median, interquartile range (IQR), and ranges used to describe continuous data. The association between the dose of propranolol ingested and serum concentration was assessed with Pearson's correlation coefficient. Comparison of proportions between groups was performed using Fisher's exact test, with 95% confidence intervals (95% CI) around proportions calculated using the Wilson score interval. All analyses and figures were performed using GraphPad Prism for Mac Version 10.1.1.

Ethical considerations

All patients recruited to the Australian TOxicology Monitoring (ATOM) collaboration provided consent to be included in the study. The Australian TOxicology Monitoring (ATOM) collaboration has ethical approval from the respective New South Wales and Queensland Human Research and Ethics Committees (HREC/12/POWH/165, HREC/14/QRCH/105). All three clinical toxicology units have ethical approval to include de-identified data from patient medical records in observational research (HREC/14/QPAH/308, HREC/12/184: LNR/12/POW/355, HREC/05/03/09/3.11).

Results

There were 209 presentations in 165 patients. There were 117 females (71%) with a median age of 30 years (IQR: 23–44 years;

range 15–80 years; Table 1). The reported median dose ingested was 1,000 mg (IQR: 600–2,000 mg; range 360–16,000 mg). All patients ingested the immediate-release preparation of propranolol. Co-ingestion occurred in 155 (74%) patients, most commonly involving benzodiazepines (52, 25%). Propranolol concentrations were available in 29 presentations. There was a moderately strong correlation between the dose of propranolol ingested and the peak serum concentration ($r = 0.66$; $P < 0.001$; Figure 1). Vomiting following ingestions was documented in 21 (10%) presentations. Activated charcoal was given in 74 (35%) presentations at a median of 2.1 h post-ingestion (IQR: 2.0–2.8 h; range 0.7–15.2 h). No patients received whole bowel irrigation. Bradycardia occurred in 41 (20%) presentations, and hypotension in 88 (42%). Dysrhythmias, in addition to sinus bradycardia, were first-degree atrioventricular block in 45 (22%), a junctional rhythm in one patient and an idioventricular rhythm in one patient.

Table 1. Baseline characteristics of 209 propranolol overdose presentations.

Characteristic	
Patients, *n*	165
Female, *n* (%)	117 (71)
Median age, years (range)	30 (15-80)
Representations, *n*	44
Median number of representations, *n* (range)	1 (1-10)
Prescribed propranolol, *n* (%)	139 (84)
Indication for propranolol	
Anxiety, *n* (%)	75 (36)
Migraine, *n* (%)	24 (11)
Tremor, *n* (%)	11 (5)
Other mental health indications,† *n* (%)	11 (5)
Cardiovascular indication, *n* (%)	6 (3)
Varices, *n* (%)	2 (1)
Restless legs, *n* (%)	2 (1)
Hyperthyroidism, *n* (%)	1 (<1)
Sweating, *n* (%)	1 (<1)
Unknown, *n* (%)	6 (3)
Reported co-ingestions *n* (%)	130 (62)
Benzodiazepines, *n* (%)	52 (25)
Ethanol, *n* (%)	50 (24)
Antipsychotics, *n* (%)	39 (19)
Over-the-counter analgesics, *n* (%)	27 (13)
Selective serotonin reuptake inhibitor, *n* (%)	24 (11)
Serotonin noradrenaline reuptake inhibitor, *n* (%)	16 (8)
Opioids, *n* (%)	16 (8)
Cardiovascular drug, *n* (%)	1 (<1)

†Other mental health indications include depression, bipolar affective disorder, insomnia, anorexia nervosa, alcohol use disorder, and post-traumatic stress disorder.

Severe toxicity occurred in 51 patients (24%). Seventeen patients (8%; reported dose range 1,000–16,000 mg) had a seizure. Coma occurred in 29 patients (14%; reported dose range 800–16,000 mg), and 16 of these also co-ingested sedating agents. Inotropes were used in 41 (20%; reported dose range 480–16,000 mg) presentations, epinephrine in 31 (15%) and high-dose insulin euglycaemic therapy in 20 (10%) patients. Electrocardiographic evidence of sodium channel blockade occurred in 16 patients (8%; reported dose range 2,400–16,000 mg). Sodium bicarbonate was administered to 28 (13%) patients with a median dose of 100 mmol (IQR: 100–250 mmol; range 50–500 mmol). Most cases (11/16) had only a modestly prolonged QRS complex duration of 120 ms (Table 3). Nine of these patients received sodium bicarbonate therapy with a median dose of 175 mmol (IQR: 100–225 mmol; range 50–400 mmol). There were five presentations with a more prolonged QRS complex duration ranging from 160 ms

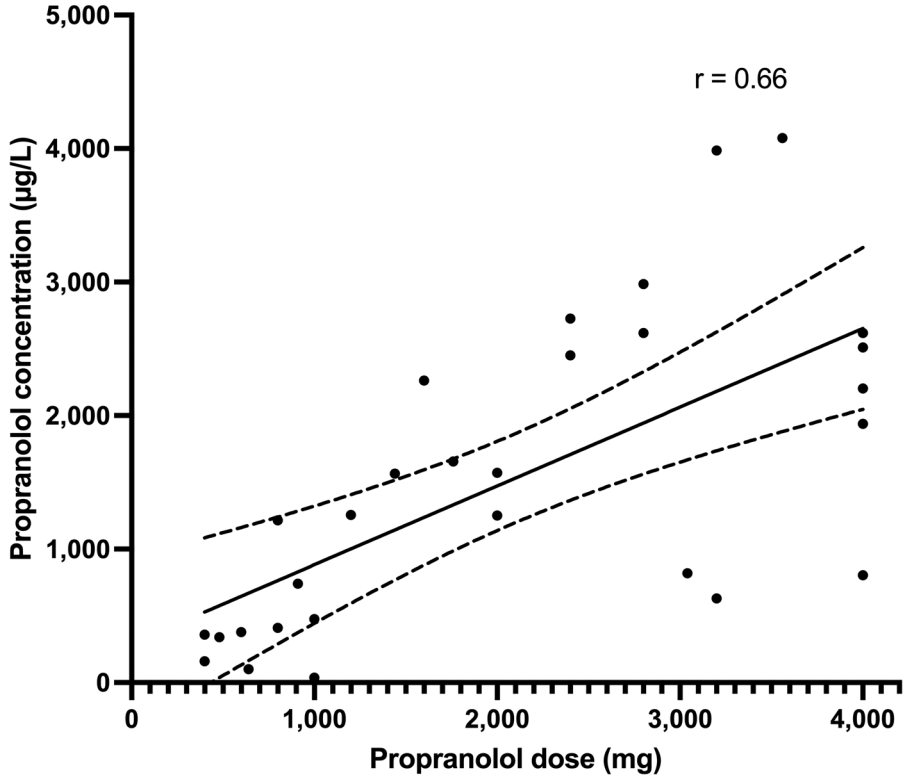

Figure 1. The association of peak propranolol concentration (µg/L) with reported dose ingested (mg) in 29 presentations where analytical sampling was performed. Dotted lines indicate 95% confidence intervals of the slope.

Table 2. Clinical features and treatment of propranolol overdose, including all 209 presentations and 79 isolated propranolol ingestions.

	All propranolol presentations ($n = 209$)	Propranolol only ingestions ($n = 79$)
Reported median dose (IQR) [range]	1,000 mg (600–2,000 mg) [360–16,000 mg]	1,100 mg (700–2,600 mg) [360–5,360 mg]
Reported median number of tablets taken (interquartile range)	60 (30–97)	70 (40–92)
Clinical features		
Bradycardia (%)	41 (20)	12 (15)
Hypotension (%)	88 (42)	32 (41)
Seizure (%)	17 (8)	12 (15)
Coma (%)	29 (14)	13 (16)
ECG evidence of sodium channel blockade (%)	16 (8)	9 (11)
Cardiac arrest (%)	7 (3)	4 (5)
Death (%)	2 (1)	0
Treatment		
Activated charcoal (%)	74 (35)	39 (49)
Crystalloid (%)	75 (31)	52 (63)
Inotropes (%)	41 (20)	16 (20)
Epinephrine (%)	31 (15)	14 (18)
High-dose insulin euglycaemic therapy (%)	20 (10)	8 (10)
Norepinephrine (%)	14 (7)	5 (6)
Isoprenaline (%)	5 (2)	2 (3)
Metaraminol (%)	4 (2)	2 (3)
Glucagon (%)	1 (<1)	0
Vasopressin (%)	1 (<1)	0
Endotracheal intubation (%)	34 (16)	14 (18%)
Sodium bicarbonate (%)	28 (13)	14 (18%)
median dose, mmol (range)	100 (50–550)	100 (100–400)
Intravenous lipid emulsion (%)	2 (1)	1 (1)
Electrical pacing (%)	1 (<1)	0

Table 3. Features of propranolol overdose presentations with ECG evidence of sodium channel blockade (QRS complex duration ≥120 ms and terminal R wave ≥3 mm or R:S ≥0.7) listed in decreasing order from presentation with longest QRS complex duration.

Reported ingested dose (mg)	Seizure	pH	QRS complex duration (ms)	Terminal R wave height (mm)	R:S ratio	Sodium bicarbonate dose given (mmol)	Hours post-ingestion of resolution†
16,000	No	7.18	200	3	3.0	500	‡
4,000	No	7.18	200	6	3.0	500	8.3
3,560	Yes	‡	200	4	0.8	350	3.8
6,000	Yes	6.76	180	6	1.5	250	2.6
2,400	Yes	6.80	160	3	1.0	250	‡
5,800	No	7.27	120	3	0.4	0	2.7
5,360	Yes	7.25	120	3	0.4	0	5.5
4,000	No	7.29	120	3	0.8	50	2.1
4,000	Yes	7.16	120	3	0.8	200	6.9
4,000	No	7.41	120	4	1.3	150	1.5
4,000	Yes	7.47	120	2	1.0	400	5.0
4,000	Yes	7.30	120	4	0.6	100	2.0
4,000	No	7.24	120	3	1.0	100	3.6
3,800	No	7.18	120	3	0.6	0	‡
3,200	Yes	7.10	120	6	1.2	200	3.4
2,800	No	7.26	120	3	1.0	300	‡

†Time when first ECG was performed which did not demonstrate evidence of sodium channel blockade, ‡not available.

to 200 ms. All were associated with acidaemia (pH range: 6.75–7.18) and received doses of sodium bicarbonate therapy ranging from 250–500 mmol (Table 2). Widening of the QRS complex was relatively short-lived, resolving within 8 h irrespective of whether sodium bicarbonate was given (Table 3; Figure 2). Seven patients (3%; reported dose range 2,400–16,000 mg) had a cardiac arrest. There were 46 intensive care unit admissions, and the median length of stay was 17 h (IQR: 11–32 h). There were two deaths following ingestions of propranolol 4,000 mg and 16,000 mg.

The first, a 35-year-old woman, who was prescribed propranolol 80 mg twice daily for migraine, was found to be in cardiac arrest following the ingestion of propranolol 4,000 mg (100 tablets of 40 mg) with baclofen 1,000 mg, fluoxetine 560 mg, temazepam 250 mg, paracetamol 5,000 mg and codeine 300 mg. She had a prolonged period of resuscitation in the pre-hospital setting, receiving epinephrine 10 mg and sodium bicarbonate 50 mmol prior to return of circulation after approximately 40 min. Her initial ECG had a QRS complex duration of 200 ms with evidence of sodium channel blockade (Figure 2). Her haemodynamics improved rapidly over the next hour, but she later became unsupportable due to multi-organ failure consistent with a profound hypoxic insult, and she died on day 2. The serum propranolol concentration in blood taken one hour following her cardiac arrest during the Coroner's post-mortem was 11 mg/L (reference range 0.02–0.3 mg/L), while the baclofen concentration was 9 mg/L (reference range 0.08–0.4 mg/L).

The second, a 64-year-old man weighing 110 kg, prescribed propranolol 80 mg daily for anxiety, ingested propranolol 16,000 mg (400 tablets of 40 mg) with oxycodone modified-release 1,800 mg. He had stockpiled four bottles of

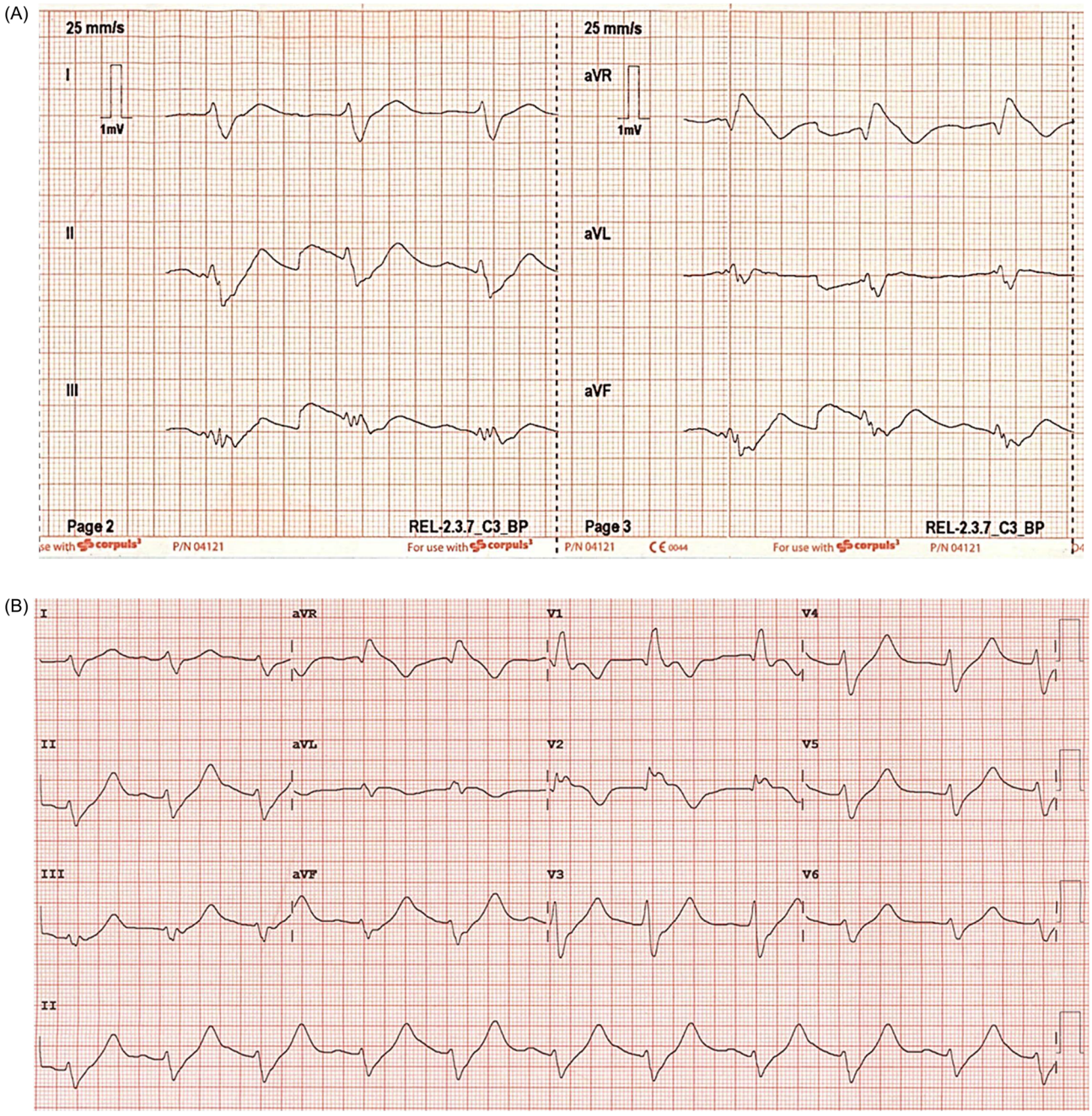

Figure 2. (A) Example of ECG evidence of sodium channel blockade with progression of QRS complex widening over time in a patient ingesting propranolol 4,000 mg approximately 80 min prior to suffering an out-of-hospital cardiac arrest. The patient was found unresponsive by paramedics with pulseless electrical activity and received 40 min of advanced cardiac life support with epinephrine 10 mg and sodium bicarbonate 50 mmol prior to return of spontaneous circulation. Pre-hospital electrocardiograph (limb leads only) after return of spontaneous circulation approximately 2 h post-ingestion, QRS complex duration was 200 ms, pH unknown. The patient was administered sodium bicarbonate 250 mmol by the paramedics en route to hospital. (B) Electrocardiograph on arrival at hospital approximately 3 h post-ingestion, QRS complex duration was 200 ms with pH 7.18. The patient received sodium bicarbonate 200 mmol.

propranolol 40 mg tablets in anticipation of overdose. He received naloxone 1,600 mg intramuscularly by ambulance staff and presented to a rural hospital at an unclear time post-ingestion with a GCS of 14, a heart rate of 70 beats/min and blood pressure of 88/55 mmHg. His arrival ECG had a QRS complex duration of 110 ms with no terminal R wave in aVR. He deteriorated over 60 min with progressive bradycardia and hypotension, then had a seizure precipitating an asystolic cardiac arrest 70 min following presentation. He had a prolonged period of resuscitation, receiving epinephrine 9 mg, sodium bicarbonate 500 mmol, glucagon 4 mg, insulin 200 U, and intravenous lipid emulsion 250 mg, prior to return of circulation after 60 min. The ECG following the return of circulation showed a QRS complex duration of 200 ms with a 3 mm terminal R wave in aVR (R:S ratio of 3). He was transferred to a tertiary hospital, arriving 6 h after the initial presentation with a heart rate of 80 beats/min (paced), blood pressure of 138/70 mmHg on epinephrine 100 µg/min and a glucagon infusion of 4 mg/h. His inotropic support was weaned over the subsequent 24 h. He sustained an unsurvivable hypoxic brain injury and was palliated on day 6. The serum propranolol concentration taken

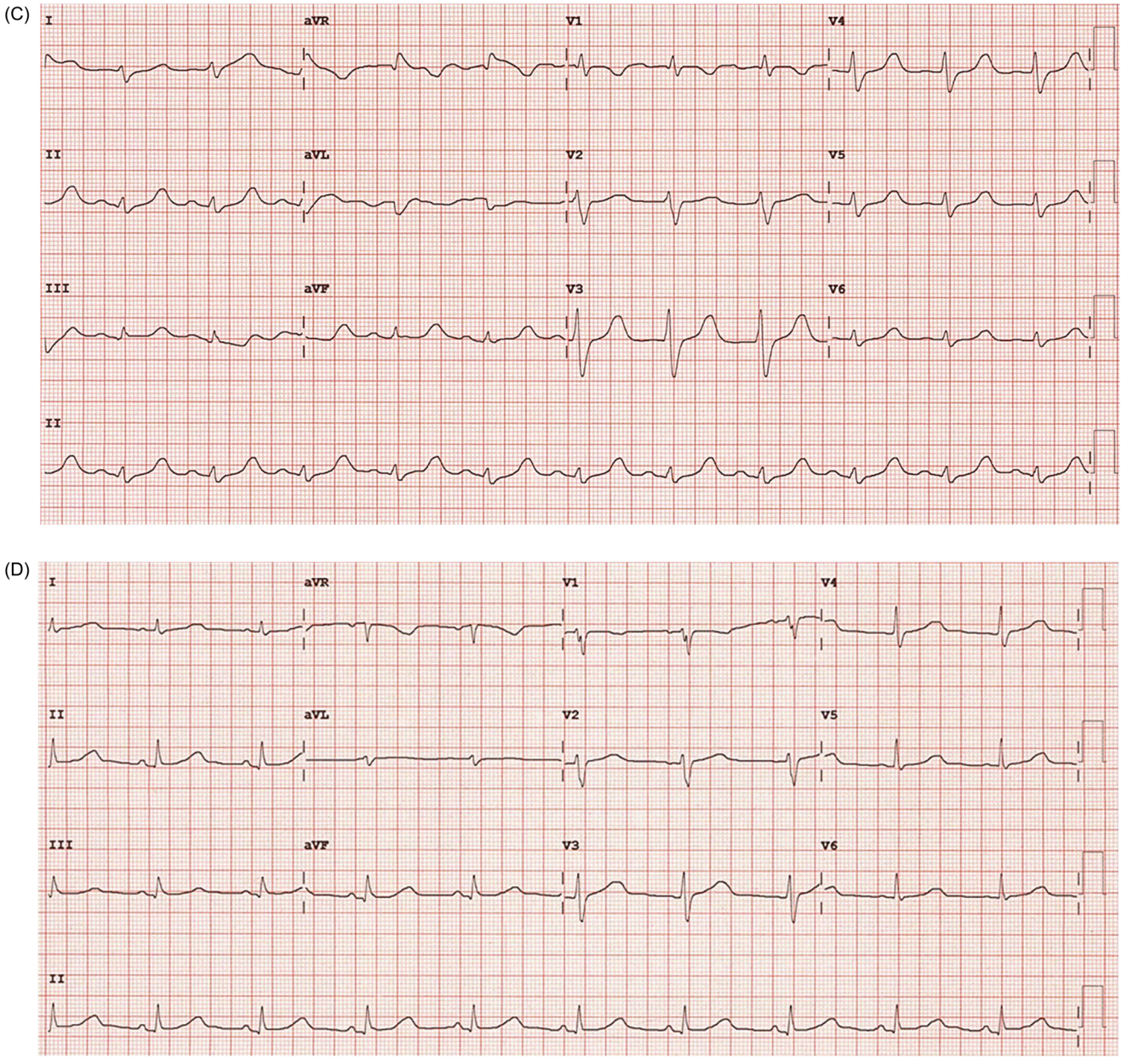

Figure 2. (C) Electrocardiograph 16 min after arrival at hospital, QRS complex duration was 170 ms, pH 7.31. No further sodium bicarbonate given. (D) Electrocardiograph 8 h post-ingestion, QRS complex duration was 120 ms, pH 7.37.

on arrival at the rural hospital 1 h before the initial cardiac arrest was 2 mg/L.

Isolated propranolol ingestions

There were 79 patients who did not co-ingest drugs apart from ethanol. Ethanol was reported as a co-ingestant in 25 of 79 of these ingestions. The reported median propranolol dose in this group was 1,100 mg (IQR: 700–2,600 mg; range 360–5,360 mg). Activated charcoal was given to 39 of 79 (49%) patients at a median time of 2.0 h (IQR: 1.4–3.1 h) post-ingestion. Twelve (15%) patients developed bradycardia, and 32 (41%) had hypotension. The lowest reported propranolol doses following which bradycardia or hypotension occurred were 800 mg and 400 mg, respectively.

Severe toxicity occurred in 17 (22%) patients ingesting propranolol alone. Seizures occurred in 12 patients (15%) at a median of 1.2 h post-ingestion (range 0.5–3.9 h). Seizures were significantly more common in the patients ingesting only propranolol compared to those who co-ingested other agents (15% ingested only propranolol versus 4% who co-ingested other agents; $P = 0.007$). Coma occurred in 13 patients (16%), two of whom reportedly co-ingested ethanol, 16 (20%) received inotropes, nine (11%) had ECG evidence of sodium channel blockade, and four (5%) had a cardiac arrest (Table 2).

The lowest reported dose for severe toxicity (coma, seizure, or inotrope use) was 2,000 mg, and for ECG evidence of sodium channel blockade or cardiac arrest (Figure 3A) was 2,400 mg. Of the 32 patients who ingested only propranolol in a dose ≥ 2,000 mg, 17 had one feature of severe toxicity (95% CI: 36–69%). There were no cases of severe toxicity in patients ingesting only propranolol <2,000 mg (95% CI: 0–8%). Patients with neurotoxicity (coma or seizure) all had accompanying

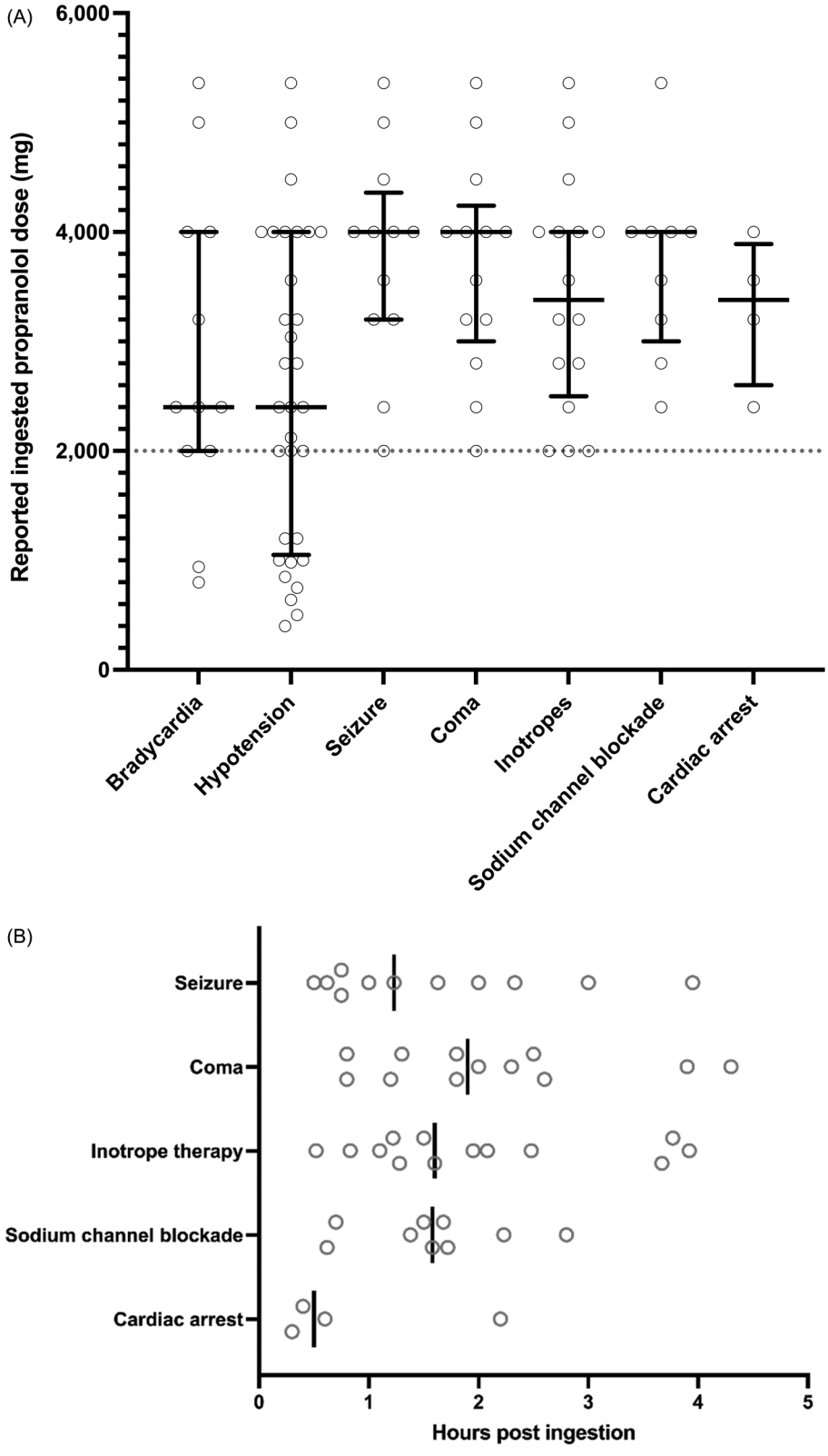

Figure 3. (A) The reported dose ingested in 79 patients with isolated propranolol overdoses for each clinical effect or complication is displayed as a scatter plot with the median reported dose represented by a horizontal line. Bradycardia was defined as a heart rate <50 beats/min, hypotension as a systolic blood pressure <90 mmHg and coma as a Glasgow Coma Scale <9. (B) Time until severe toxicity occurred in 79 patients with isolated propranolol overdose displayed as a scatter plot with the median time of onset represented by a solid vertical line.

haemodynamic instability and received inotropes except for one patient with both coma and seizure who had a heart rate of 54 beats/min and systolic blood pressure of 83 mmHg that responded to crystalloid therapy. The median time until severe toxicity occurred was 2 h, with the onset of at least one sign of toxicity occurring within 4 h for all patients who developed severe toxicity (Figure 3B). The length of stay of patients with severe toxicity was 53 h (IQR: 28–91 h).

Discussion

We found that severe toxicity was common following propranolol overdose, occurring in approximately one-quarter of patients in this series. Severe toxicity occurred early, with a median onset within 2 h of patients taking propranolol alone, and all of the patients with severe toxicity developed at least one feature within 4 h post-ingestion (Figure 3B). The dose threshold for patients ingesting propranolol alone with severe toxicity appeared to be 2,000 mg, with severe toxicity unlikely to occur below this threshold (95% CI: 0–8%). Widening of the QRS complex was uncommon and did not appear to respond rapidly to the administration of sodium bicarbonate. Even in large propranolol ingestions, the outcome was usually favourable with good supportive care.

Severe toxicity was common in this series, which has important implications given the increasing prescriptions of propranolol and signals towards rising harm [6]. Most patients taking a propranolol overdose ingested their own prescribed medication, with the commonest prescribed indication being anxiety. It has been suggested that primary care providers should be mindful of the increased risk of propranolol in overdose and avoid prescribing formulations >10 mg to those in a vulnerable cohort [7]. The 2,000 mg dose threshold for severe toxicity in this study is the same as that reported by Reith et al. [1] for an increased risk of seizure. The strength of our study is that it is larger than others, and we could estimate the dose threshold for severe toxicity in isolated propranolol ingestions, whereas in a previous study [1], 61% of patients co-ingested other agents. The overall rate of seizures (17/209, 8%) was lower in our study compared to that of Reith and colleagues [1] (8/28, 29%). This may reflect that the primary co-ingestant in our series was a benzodiazepine. It is important to note that seizures did occur at lower doses of propranolol (minimum reported dose 1,000 mg) in patients that co-ingested other agents.

An interesting finding in the study was that co-ingestants were other psychotropic medications, rather than other cardiac medications, which is again indicative of the population now being prescribed propranolol. This is reassuring and reflects the good outcomes in this study because other beta-adrenoceptor blocking drugs and highly toxic cardiac medications, such as calcium-channel blockers, are often co-ingested with other cardiovascular medications, increasing the toxicity [12]. In addition, the common co-ingestion of benzodiazepines was associated with a decreased frequency of seizures.

In most cases, there was a good outcome following propranolol overdose with supportive care alone. Epinephrine and high-dose insulin were the most commonly used inotropes in this series. Epinephrine is recommended as first-line management for beta-adrenoceptor blocking drug toxicity in the Australian Therapeutic Guidelines [13] due to its action on beta-adrenoceptors and resultant inotropic and chronotropic effects, which likely explains its preferential use in this series. There is surprisingly little evidence for catecholamine inotrope administration in beta-adrenoceptor blocking drug poisoning, although their use is commonly reported in case reports to increase vasomotor tone rather than for chronotropy [14]. High-dose insulin euglycaemic therapy is used in beta-adrenoceptor blocking drug poisoning for its inotropic action, which is thought to occur in part through improved glucose transport in a stressed myocardium [15]. There are multiple animal studies which support the use of high-dose insulin euglycaemic therapy in propranolol poisoning [16–19]. Glucagon is not recommended in Australia for the management of beta-adrenoceptor blocker poisoning due to insufficient stocks of the large doses required, emetogenic effects and tachyphylaxis, which likely reflects its low use in this series [20, 21].

While ECG evidence of sodium channel blockade was present in larger ingestions, most had only modest QRS complex widening. The cases with very wide QRS complex were all associated with acidaemia. It is difficult to interpret the effect of sodium bicarbonate in these cases as paired ECG and pH data were not available in a serial manner in many cases. Widening of the QRS complex appeared to resolve in a relatively short time frame, irrespective of whether sodium bicarbonate was used. Indeed, in many cases of sodium bicarbonate use, there was no QRS complex widening. The overzealous use of sodium bicarbonate in sodium channel blocker overdose, in general, has been described previously [22]. The role of sodium bicarbonate in the management of propranolol poisoning is unclear. A previous animal study suggested sodium bicarbonate was ineffective as a single therapy to treat propranolol overdose [23]. It is possible there is a role for correction of pH towards the normal range with sodium bicarbonate, but this series does not support an alkalaemic pH target as is sought with sodium bicarbonate therapy in other sodium channel blocking overdoses like tricyclic antidepressant overdose [24]. A prospective series with serial paired ECG and pH values may be helpful to further define this.

Limitations

This study has a number of limitations. Dose information relied on patient history, which may have been inaccurate, although there was a moderately strong association between the dose ingested and propranolol concentration in patients in whom drug concentrations were measured. Some data points, like QRS complex widening, relied on serial ECGs, which may not have been performed frequently enough to identify changes. It is possible the maximal duration of QRS complex widening was unreliable. In addition, propranolol ingestion was not confirmed by analytical testing in all cases, but the unique propranolol toxicity profile in overdose of beta-adrenoreceptor blockade and neurotoxicity makes it less likely that patients did not ingest propranolol when they stated they had. For patients in whom analytical confirmation was performed, sampling time was not standardized, and it is possible the actual peak concentration was missed. Similarly, there was no analytical confirmation of reported co-ingestions, and this information may have been unreliable.

Conclusion

Bradycardia, severe hypotension, coma and seizure were common following propranolol overdose in this series. Severe toxicity appeared more common in ingestions larger than 2,000 mg, with

approximately 50% of those patients ingesting only propranolol having severe toxicity above this threshold; there were no cases of severe toxicity below this threshold (95% CI: 0–8%). Even in patients ingesting large propranolol overdoses, the outcome was usually favourable with good supportive care.

Authors' contributions

KI, AC and GI conceived the study. KI, AC, MH and GI recruited patients. All authors contributed to data collection. KI and GI analyzed data. KI drafted the manuscript. All authors contributed to its revision. KI takes responsibility for the paper as a whole.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

AC is funded by a National Health and Medical Research Council Investigator Grant, Emerging Leadership 1 (ID 2016380). The Frazer Institute is located within the Translational Research Institute, Brisbane.

Trial registration

Australian Toxicology Monitoring (ATOM) Study – Australian Paracetamol Project: ACTRN12612001240831 (ANZCTR) Date of registration: 23/11/2012.

ORCID

Katherine Z. Isoardi http://orcid.org/0000-0002-1176-7923
Angela L. Chiew http://orcid.org/0000-0002-0079-5056
Michael Humphreys http://orcid.org/0000-0003-1834-0030
Michael S. Roberts http://orcid.org/0000-0003-3894-5301
Geoffrey K. Isbister http://orcid.org/0000-0003-1519-7419

Data availability statement

The de-identified data we analyzed are not publicly available, but requests to the corresponding author will be considered on a case-by-case basis.

References

[1] Reith DM, Dawson AH, Epid D, et al. Relative toxicity of beta blockers in overdose. J Toxicol Clin Toxicol. 1996;34(3):273–278. doi:10.3109/15563659609013789.
[2] Love JN, Howell JM, Litovitz TL, et al. Acute beta blocker overdose: factors associated with the development of cardiovascular morbidity. J Toxicol Clin Toxicol. 2000;38(3):275–281. doi:10.1081/clt-100100932.
[3] Jovic-Stosic J, Gligic B, Putic V, et al. Severe propranolol and ethanol overdose with wide complex tachycardia treated with intravenous lipid emulsion: a case report. Clin Toxicol (Phila). 2011;49(5):426–430. doi:10.3109/15563650.2011.583251.
[4] Love JN, Litovitz TL, Howell JM, et al. Characterization of fatal beta blocker ingestion: a review of the American Association of Poison Control Centers data from 1985 to 1995. J Toxicol Clin Toxicol. 1997;35(4):353–359. doi:10.3109/15563659709043366.
[5] Szeleszczuk Ł, Frączkowski D. Propranolol versus other selected drugs in the treatment of various types of anxiety or stress, with particular reference to stage fright and post-traumatic stress disorder. Int J Mol Sci. 2022;23(17):10099. doi:10.3390/ijms231710099.
[6] Investigation report. Potential under-recognised risk of harm from the use of propranolol. Health Services Safety Investigations Body.
[7] Dyer C. Doctors and paramedics must be better prepared to deal with propranolol overdoses. BMJ: British Medical Journal (Online). 2020;358:m566.
[8] Williams H, Jagpal P, Sandilands E, et al. 1456 Fatal propranolol overdoses reported to the UK National Poisons Information Service (NPIS) over 5 years 01/01/2017–31/12/2021. Emerg Med J. 2022;39(12):A979.1–A979. doi:10.1136/emermed-2022-RCEM2.30.
[9] Lauterbach M. Clinical toxicology of beta-blocker overdose in adults. Basic Clin Pharmacol Toxicol. 2019;125(2):178–186. doi:10.1111/bcpt.13231.
[10] Porapakkham P, Porapakkham P, Krum H. Is target dose of beta-blocker more important than achieved heart rate or heart rate change in patients with systolic chronic heart failure? Cardiovasc Ther. 2010;28(2):93–100. doi:10.1111/j.1755-5922.2010.00136.x.
[11] KDIGO clinical practie guideline for acute kidney injury. Kidney Int. 2012;2(Suppl):1–138.
[12] Huang J, Buckley NA, Isoardi KZ, et al. Angiotensin axis antagonists increase the incidence of haemodynamic instability in dihydropyridine calcium channel blocker poisoning. Clin Toxicol (Phila). 2021;59(6):464–471. doi:10.1080/15563650.2020.1826504.
[13] Therapeutic guidelines: toxicology and toxinology. Melbourne: Therapeutic Guidelines Limited; 2020. (Opioid Poisoning).
[14] Rotella JA, Greene SL, Koutsogiannis Z, et al. Treatment for beta-blocker poisoning: a systematic review. Clin Toxicol (Phila). 2020;58(10):943–983. doi:10.1080/15563650.2020.1752918.
[15] Alho H, Dematteis M, Lembo D, et al. Opioid-related deaths in Europe: strategies for a comprehensive approach to address a major public health concern. Int J Drug Policy. 2020;76:102616. doi:10.1016/j.drugpo.2019.102616.
[16] Holger JS, Engebretsen KM, Fritzlar SJ, et al. Insulin versus vasopressin and epinephrine to treat beta-blocker toxicity. Clin Toxicol (Phila). 2007;45(4):396–401. doi:10.1080/15563650701285412.
[17] Katzung KG, Leroy JM, Boley SP, et al. A randomized controlled study comparing high-dose insulin to vasopressors or combination therapy in a porcine model of refractory propranolol-induced cardiogenic shock. Clin Toxicol (Phila). 2019;57(11):1073–1079. doi:10.1080/15563650.2019.1580372.
[18] Cole JB, Stellpflug SJ, Ellsworth H, et al. A blinded, randomized, controlled trial of three doses of high-dose insulin in poison-induced cardiogenic shock. Clin Toxicol (Phila). 2013;51(4):201–207. doi:10.3109/15563650.2013.770152.
[19] Engebretsen KM, Kaczmarek KM, Morgan J, et al. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clin Toxicol (Phila). 2011;49(4):277–283. doi:10.3109/15563650.2011.582471.
[20] Nissen LM, Wong KH, Jones A, et al. Availability of antidotes for the treatment of acute poisoning in Queensland public hospitals. Aust J Rural Health. 2010;18(2):78–84. doi:10.1111/j.1440-1584.2010.01129.x.
[21] Nickson C. Glucagon as an antidote, 2020. [cited 2024 16/10/24]. Available from: https://litfl.com/glucagon-as-an-antidote/.
[22] Isoardi KZ, Chiew AL. Too much of a good thing: bicarbonate toxicity following treatment of sodium channel blocker overdose. Emerg Med Australas. 2022;34(4):639–641. doi:10.1111/1742-6723.13995.
[23] Love JN, Howell JM, Newsome JT, et al. The effect of sodium bicarbonate on propranolol-induced cardiovascular toxicity in a canine model. J Toxicol Clin Toxicol. 2000;38(4):421–428. doi:10.1081/clt-100100952.
[24] Bruccoleri RE, Burns MM. A literature review of the use of sodium bicarbonate for the treatment of QRS widening. J Med Toxicol. 2016;12(1):121–129. doi:10.1007/s13181-015-0483-y.