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Massive lignocaine overdose while on veno-arterial extracorporeal membrane oxygenation (VA ECMO)

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ABSTRACT

We present the extraordinary circumstance of a female patient in her sixties who suffered a massive lignocaine overdose while undergoing treatment with Veno-Arterial Extracorporeal Membrane Oxygenation (VA ECMO) following an emergency coronary artery bypass graft (CABG). The patient was initially admitted to the Intensive Care Unit (ICU) due to unstable angina and a history of insulin-dependent type two diabetes mellitus, hypertension, hypercholesterolemia, carotid artery stenosis, and an extensive smoking history. Despite initial improvements following surgery, she experienced repeated episodes of nonsustained polymorphic ventricular tachycardia (VT) that were refractory to conventional antiarrhythmic medications. The overdose occurred due to a medication administration error, leading to the infusion of lignocaine at a rate eight times higher than intended, over the course of 36 h (total dose of 9964 mg, or 153 mg/kg). Remarkably, the patient remained haemodynamically stable throughout the overdose period, with normal sinus rhythm, requiring minimal ECMO support and no vasoactive agents. Further investigation into the pharmacokinetics of lignocaine during VA ECMO treatment suggested that the patient's unexpected stability and survival could be attributed to the adsorption of lignocaine onto the components of the ECMO circuit. This phenomenon potentially mitigated the cardiotoxic effects typically associated with such high doses of lignocaine, thus presenting an unusual but critical aspect of pharmacokinetics in the context of ECMO support. This case underscores the importance of investigating the complex interactions between medications and extracorporeal circuits, which can significantly alter drug pharmacokinetics and toxicity profiles.

1. Background

Lignocaine is a local anaesthetic agent and Vaughan-Williams Class Ib antiarrythmic agent indicated for ventricular arrythmias. The unionised form of the drug diffuses through cell membranes, becoming ionised upon exposure to hydrogen ions in the cytoplasm, and then binds reversibly to the intracellular component of inactive sodium channels, inhibiting their opening [1] In cardiomyocytes, inhibited sodium efflux results in a prolonged depolarisation phase and therefore in relative prolongation of the refractory period compared to the action potential duration [2], functionally increasing the threshold potential, and thereby reducing both cardiomyocyte automaticity and excitability of Purkinje fibres without reducing cardiac contractility [3].

The pharmacokinetics of lignocaine are best described by a two-compartment model and dosing by weight is preferred [4]; a typical dosing consists of an initial bolus of 1 mg/kg, followed by an infusion of 10–50 mcg/kg/min, [5]. In circulation, lignocaine is 65 % protein bound, and has a volume of distribution of 0.7–1.5 L/kg [1,6]. It undergoes predominantly hepatic metabolism, and liver failure or congestive cardiac failure therefore both decrease clearance, placing patients with these comorbidities at an increased risk of toxicity [7].

Lignocaine at therapeutic doses has a favourable safety profile [8,9]. Toxicity, when it occurs, manifests primarily with peripheral and central nervous system effects ranging from sensory disturbances and

Abbreviations: VA ECMO, Veno-Arterial Extracorporeal Membrane Oxygenation; ICU, Intensive Care Unit; CABG, Coronary Artery Bypass Graft; VT, Ventricular Tachycardia; VF, Ventricular Fibrillation; ECMO, Extracorporeal Membrane Oxygenation; ECG, Electrocardiogram; EEG, Electroencephalogram; PVC, Polyvinyl Chloride; GC/MS, Gas Chromatography/Mass Spectrometry; HR, Heart Rate; MAP, Mean Arterial Pressure.

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fasciculations to seizures [10], and cardiac ones including bradycardia and other arrythmias [7]. Management of lignocaine toxicity is largely supportive, involving airway and haemodynamic support, including extracorporeal cardiorespiratory suport if necessary [11], and control of seizures with benzodiazepines [7,12]. Infusion of a 20 % lipid emulsion is a therapy the use of which is supported largely by case reports; it is hypothesised to reduce toxicity primarily by acting as a sink for the drug (due to its high lipid solubility), with other possible effects on its distribution or metabolism [13].

2. Case presentation

A female patient in her sixties was admitted to the ICU following an emergency coronary artery bypass graft (CABG) in the context of unstable angina. Her background consisted of insulin-dependent type two diabetes mellitus with multiple systemic complications, hypertension, hypercholesterolaemia, carotid artery stenosis, and an extensive smoking history. Her progress prior to surgery was complicated by recurrent episodes of nonsustained polymorphic VT. Post-operative echosonography revealed that her left ventricular ejection fraction improved to 30–35 % from 19 % at admission. The patient was extubated on the first postoperative day. At this stage, routine bloods indicated a modestly elevated serum creatinine (94 umol/L) and urea (8.1 mmol/L) as well as trivially elevated ALT and AST (41 and 49 IU/L, respectively). Serum albumin was slightly depressed at 34 g/L. Apart from an expected postoperative leukocytosis, other haematological and biochemical investigations were normal, as listed in the first column (Day 0) of Table 1.

The post-operative course was complicated by repeated episodes of nonsustained polymorphic VT refractory to amiodarone and mexiletine. The insertion of an automated implantable defibrillator was expedited on Day 3, when the rhythm became increasingly difficult to control with associated haemodynamic instability despite escalating medical therapy, with periods of profound bradycardia intermittently punctuated by short episodes of VT.Upon induction of anaesthesia, the patient had a cardiac arrest with the dominant rhythms being VT and VF. A return to spontaneous circulation was achieved, but due to global ventricular hypokinesis resulting in cardiogenic shock, central VA ECMO was instituted prior to return to the ICU. Investigations immediately following return from theatre revealed worsening organ function, with evidence of acute renal failure (serum creatinine 156 umol/L, urea 11.2 mmol/L), liver failure (AST 2966 IU/L, ALT1526 IU/L), a severe metabolic acidosis (serum bicarbonate 14 mmol/L) with hyperlactataemia (lactate 13.6 mmol/L) as well as anaemia (Hb 72 g/L). These and other results are listed for comparison in the second column (Day 3) of Table 1.

During the immediate period following the initiation of VA ECMO the rhythm had remained unstable with multiple episodes of nonsustained VT, occurring at least once every 5–10 minutes. Intravenous lignocaine was commenced for rhythm control, consisting of a 200 mg loading dose followed by a continuous infusion of 1 mg/kg/hr, corresponding to a dose of 61 mg/hr or 8.125 mL per hour of a diluted ligonocaine infusion solution with a concentration of 8 mg per mL. Because of a drug administration error, after seven hours of infusion at the correct dose, the infusion rate was increased to 61 mL/hr (equivalent to 8 mg/kg/hr) of lignocaine. A further change in the dose occurred at the 20th hour of the infusion (down to 5.24 mg/kg/hr). During this time the patient remained haemodynamically stable, requiring no vasoactive agents, and only on a modest amount of ECMO support with a blood flow rate flow of 2.5–2.8 L/min, resembling a weaning flow rate; whereas a normal VA ECMO blood flow rate for an adult should be 60–80 mL/kg/min, corresponding to 3.6–4.9 L/min for this patient [14]. During the period of lignocaine infusion renal function remained impaired (serum creatinine 148 and 174 umol/L, urea 10.9 and 10.6 mmol/L) but indices of hepatic injury peaked and started to improve (ALT 1218 IU/L and 620 IU/L, AST 4577 IU/L and 2535 IU/L). The metabolic acidosis due to hyperlactataemia was slow to resolve, suggesting impaired hepatic clearance due to ischaemic hepatic injury, as can be inferred from the lactate level remaining elevated (5.4 mmol/L) for over 24 h following the initiation of VA ECMO and restoration of satisfactory organ perfusion.

Table 1
Biochemical and haematological investigations during the period of lignocaine exposure.

Parameter	Normal value range	Day 0	Day 3	Day 4	Day 5	Day 6
Sodium (mmol/L)	135–145	138	136	145	142	139
Potassium (mmol/L)	3.5–5.0	4	5.1	4.5	4.9	5.5
Chloride (mmol/L)	97–108	101	96	99	100	100
Bicarbonate (mmol/L)	22–29	26	14	32	38	34
Lactate (mmol/L)	0.5–2.2	2.3	13.6	5.5	1.2	1.4
Urea (mmol/L)	2.5–7.5	7.3	11.2	10.9	10.6	11.4
Creatinine (umol/L)	64–104	90	156	148	174	179
Calcium (mmol/L)	2.10–2.60	2.53	2.19	2.62	2.3	2.04
Corrected calcium (mmol/L)	2.10–2.60	2.61	2.55	2.94	2.62	2.32
Magnesium (mmol/L)	0.7–1.1	1.45	1.53	1.80	1.79	1.28
Phosphate (mmol/L)	0.75–1.50	1.69	2.55	1.62	1.54	1.79
Bilirubin (total) (umol/L)	<20	5	14	38	28	29
Albumin (g/L)	31–47	36	22	24	24	26
Alanine transaminase (ALT) (IU/L)	10–35	41	1526	1218	620	502
Aspartate transferase (AST) (IU/L)	10–35	49	2966	4577	2535	1247
Gamma-glutamyl transpeptidase (GGT) (IU/L)	5–35	24	65	26	46	83
Alkaline phosphatase (IU/L)	30–110	71	149	71	94	125
Haemoglobin (g/L)	115–165	89	72	88	80	90
WCC (x10^9/L)	3.9–11.1	20.7	16.5	4.3	7.8	13.6
Platelets (x10^9/L)	150–400	154	127	88	65	63
MCV (fL)	82–98	83	89	86	87	89
Neutrophils (x10^9/L)	2.0–8.0	18.7	14.8	3.8	6.5	12.0 H
INR	0.9–1.1	1.2	>10.0	1	1.3	1.3

*Day 0: day of CABG surgery, post-op bloods
Day 3: day of emergency VA ECMO initiation, post-op bloods
Days 4–5: trend of results during VA ECMO
Lignocaine infusion commenced on Day 3, completed on Day 4.

The lignocaine infusion was ceased immediately as the drug administration error was discovered, blood samples were collected for lignocaine testing, and a bolus of 20% Intralipid (750 mL) was administered. The ECG demonstrated sinus rhythm without any electrophysiological changes that would be consistent with lignocaine toxicity (T-wave elevation, prolonged PR interval, widened QRS complexes). ECMO support was continued and lignocaine level testing was carried out until the level had fallen to within therapeutic range at 3.5 mg/L. An EEG performed to exclude non-convulsive status epilepticus (a possible complication of lignocaine toxicity that could confound neurological prognostication) revealed electrocerebral inactivity consistent with severe diffuse cerebral dysfunction, intermittently interrupted by electromyographic movement artefacts secondary to ongoing rhythmic twitching. These movements, identified to be myoclonic jerks consistent with severe brain injury, continued to increase in frequency and intensity; the patients neurology remained otherwise unchanged to multiple assessments. Her cardiac rhythm at that time was sinus with

increasingly frequent ventricular ectopic beats. Having excluded lignocaine toxicity as a confounder for the neurological examination findings, a diagnosis of severe hypoxic brain injury was made on the basis of a multimodal assessment, and following ongoing discussion with her family, the decision was made to discontinue life support.

3. Toxicology results and pharmacokinetic modelling

Timeline of lignocaine infusion dose rate superimposed with measured lignocaine levels and lipid emulsion antidote doses is presented in Fig. 1. Haemodynamic variables consisting of heart rate (HR), mean arteral blood pressure (MAP) and noradrenaline dose (mcg/kg/min) are presented in Fig. 2. VA ECMO blood flow rates, recorded hourly for the duration of the treatment, are presented in Fig. 3. Lignocaine levels were collected as part of routine blood collection and tested in accordance with standard practice by the laboratories of Royal Brisbane Hospital.

Post mortem samples of ECMO circuit tubing (two 5 cm lengths, 1.0 g) were collected and stored at −20°C. Adsorbed lignocaine was eluted from the samples using 2-propanol and the solution was analysed by Gas Chromatography/Mass Spectrometry (GC/MS) using a Perkin Elmer Clarus 680 Gas Chromatogram coupled to a Perkin Elmer Clarus 600 S Mass Spectrometer with a known reference standard used as comparison for quantitation. The total amount of lignocaine detected in the ECMO tubing (35 mcg) is presented in Fig. 1. Heart rate, blood pressure and vasopressor doses are represented as line graphs on the same timeline.

Measured plasma lignocaine concentration values were compared to expected values to determine whether lignocaine was lost from the circulation, as an explanation for the ongoing stable cardiac rhythm. The expected values were computed using a two-compartment pharmacokinetic model using published values to describe the volume of distribution (Vd=1.1 L/kg) and the rate constants K10 (0.08 h^{-1}), K12 (0.9 h^{-1}) and K21(1.74 h^{-1}) [15,16–18,12]. Clearance variables for the model were selected from ranges reported in patients with heart failure, impaired clearance due to poor hepatic perfusion, or reabsorption due to bladder pathology, as these groups would represent the patient in this case report better than would data from healthy volunteers or animals. The volume of distribution was approximated from data for cardiopulmonary bypass [19]. This modelling suggest that the expected lignocaine concentration should have been approximately 50 mg/L at the time the infusion was ceased, and 33.3 mg/L at the time of the first actual plasma lignocaine measurement.

4. Discussion

This report suggests that the pharmacokinetics of lignocaine are altered during VA ECMO, allowing patients to escape the normal dose-dependent cardiotoxicity associated with high dose local anaesthetic exposure. This is supported by the findings of relative haemodynamic stability and modest ECMO support requirements in the presence of a lethally high lignocaine level even following the administration of intralipid.

There are no precise data to describe the relationship between lignocaine concentration and cardiotoxicity in humans, mostly because such events are known from case reports in which the plasma levels are often not reported. The concentration required to produce serious cardiac arrhythmias appears to be approximately 2–3 times higher than the upper range of therapeutic dosing, which is 1–4 mg/kg, or 1–5 mg/L [20]. Animal data [21] found reliable depression of contractility and

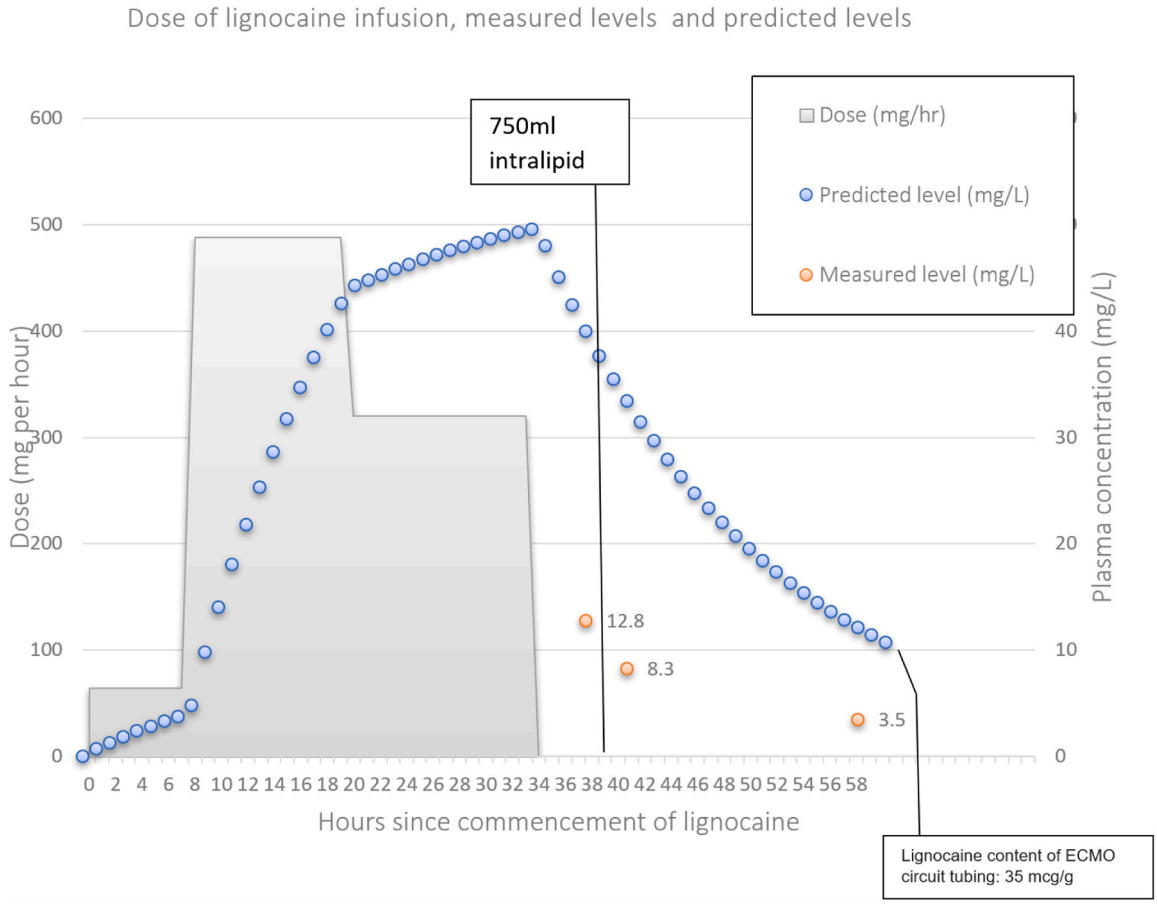

Fig. 1. Dose of lignocaine infusion, measured levels, and predicted levels over 72 h.

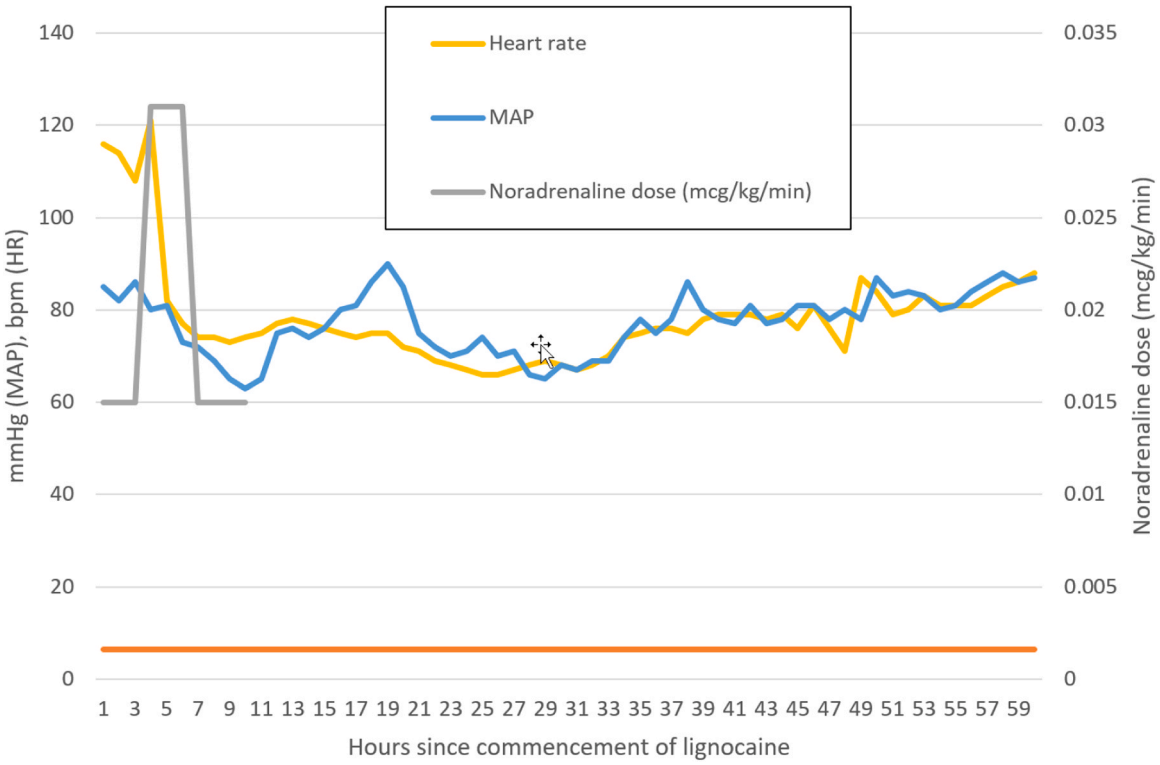

Fig. 2. Haemodynamic variables during lignocaine infusion.

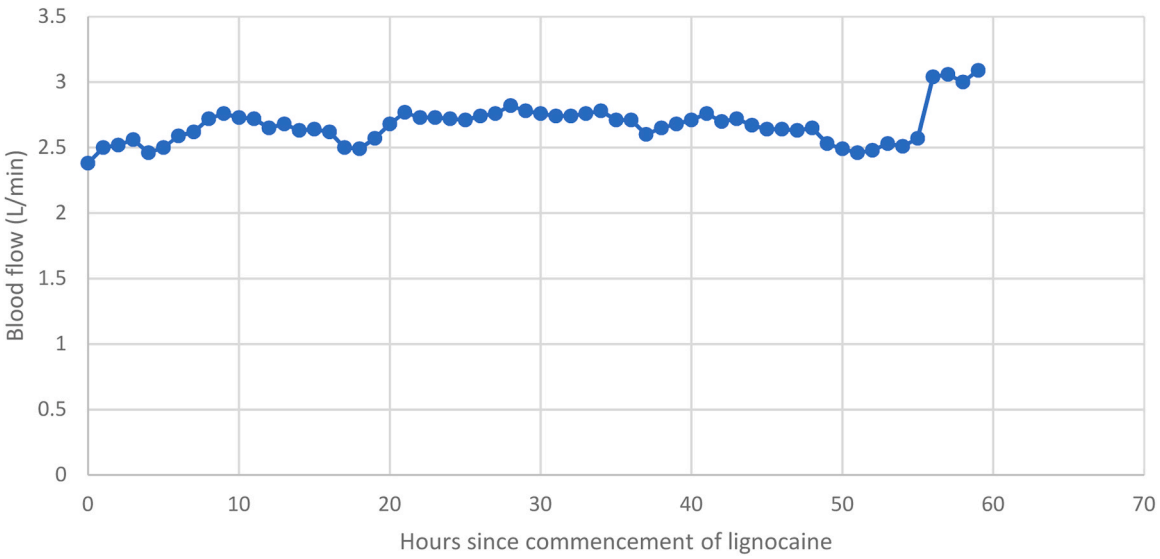

Fig. 3. VA ECMO flow rate during the period of lignocaine infusion.

abnormalities in conduction associated with concentrations of 10 mg/L. Plasma concentration values of lignocaine associated with refractory cardiac arrest were in the range of 7.6 mg/L in vulnerable elderly patients [22] and 12.9 mg/L corresponding to total dose of 1200 mg in young healthy patients [23,24]. The patient presented in this case report remained haemodynamically stable on a modest amount of ECMO support with a plasma lignocaine level of 12.8 mg/L.

A series of thirty cases found that lifethreatening cardiotoxicity had corresponded to doses of approximately 1000 mg, or 10–12 mg/kg [25]. In this case report, the total dose administered over the period of infusion was 9964 mg, or 153 mg/kg. This exceeds the next highest reported survivable dose of lignocaine in published literature (3000 mg, [26]). Case reports of fatal lignocaine overdose [27] present total doses resembling the total dose administered to this patient (10 g) and measured postmortem blood levels which correspond to the model-predicted maximum concentration of the drug (40 mg/L).

The discrepancy between the cardiotoxic measured levels and the clinical effect, or the predicted levels and the measured levels, can be explained by the adsorption of lignocaine on to the components of the ECMO circuit. [28] found that tubing made of polyvinyl chloride (PVC) was capable of acting as a substrate for the deposition of lignocaine. The ECMO tubing used in this case (Raumedic ECC NoDop 3/8 ×3/32) was composed of a proprietary biocompatible PVC material. That ECMO circuit components can adsorb xenobiotics is well known [12,29] and

VA ECMO is a recognised rescue therapy for local anaesthetic induced toxicity [26], but lignocaine adsorption has not been demonstrated in ECMO components. The finding of a small amount of lignocaine in lengths of tubing recovered postmortem (35 mcg/g) suggests that some measurable deposition has occurred in this case.

The discussion has limitations. The measured lignocaine content of the PVC tubing does not make it possible to describe the total absorptive capacity of the circuit, as it consists of many PVC and non-PVC components. The ECMO circuit may have acted as a reservoir of drug and it is possible that lignocaine had eluted from the tubing during the period of time following the cessation of lignocaine infusion, leading to a lower measured lignocaine content in the sample of PVC tubing. The use of the lipid emulsion antidote during this period may have accelerated this process by stripping adsorbed lignocaine molecules from the PVC tubing. The use of pharmacokinetic models to predict lignocaine concentrations depend on data from diverse sources, and may suffer from the poor generalisability of the variables extrapolated from observations collected among patients, animals and healthy volunteers. The clearance values used for the model assume below-normal lignocaine clearance, but may still overestimate the clearance of lignocaine in the presence of an ischaemic liver injury, as was the case in this patient. The effect of this source of error would be to increase the difference between the measured and expected lignocaine concentration.

5. Conclusion

We present the first published case of a massive lignocaine overdose that did not result in cardiotoxicity, which we propose may have been due to lignocaine adsorption onto the components of an ECMO circuit. Measured levels were unexpectedly low, as compared to the levels predicted by pharmacokinetic modelling. This may be attributed to the altered pharmacokinetics of lignocaine distribution in the extracorporeal circuit.

Data statement

Due to concerns regarding patient confidentiality, data regarding this case remain confidential and would not be shared. Data not available / The data that has been used is confidential

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CRediT authorship contribution statement

Amelia Scott: Writing – original draft, Software, Resources, Investigation. **Alex Yartsev:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data that has been used is confidential.

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