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BRIEF REPORT

Bruno Mégarbane
Pascal Leprince
Nicolas Deye
Gilles Guerrier
Dabor Résière
Vanessa Bloch
Frédéric J. Baud

Extracorporeal life support in a case of acute carbamazepine poisoning with life-threatening refractory myocardial failure

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B. Mégarbane · N. Deye · G. Guerrier · D. Résière · V. Bloch · F. Baud (✉)
Université Paris VII, AP-HP, Hôpital Lariboisière, Réanimation Médicale et Toxicologique, INSERM U705, CNRS, UMR 7157,
2 Rue Ambroise Paré, 75010 Paris, France
e-mail: baud.frederic@wanadoo.fr
Tel.: +33-1-49956491
Fax: +33-1-49956578

P. Leprince
AP-HP, Hôpital Pitié Salpétrière, Chirurgie Cardiovasculaire et Thoracique,
47-83 Boulevard de l'Hôpital, 75013 Paris, France

Abstract *Objective:* To report the efficacy of extracorporeal life support (ECLS) in acute carbamazepine poisoning with sustained refractory myocardial failure and a high degree of conductance disturbances. *Design and setting:* Case report from the toxicological and medical intensive care unit in a university hospital. *Patient:* A 26-year-old man with severe myocardial failure unresponsive to 1.7 $\mu g\ kg^{-1}\ min^{-1}$ epinephrine and 1.9 $\mu g\ kg^{-1}\ min^{-1}$ norepinephrine (SvO_2, 17.8% and cardiac index, 0.8 $l\ min^{-1}\ m^{-2}$) following a suicidal ingestion of 32 g slow-release carbamazepine. *Interventions:* ECLS (Jostra-Maquet centrifugal pump (Rotaflow) connected to a hollow-fiber membrane oxygenator). *Measurements and results:* ECLS device allowed inotropic drug weaning while maintaining end-organ function and supported the patient until myocardial recovery. The plasma carbamazepine level was 224 μmol/l on admission and peaked at 338 μmol/l 101 h after admission with a prolonged gastrointestinal absorption phase despite multiple doses of activated charcoal. The patient survived and was successfully explanted on day 6. An extensive and regressive thrombosis of the inferior vena cava was noted. Cardiac function totally recovered and at 2-year follow-up. There were no significant sequelae. *Conclusions:* We report a case of life-threatening myocardial failure with conductance disturbances secondary to an acute carbamazepine poisoning, demonstrating the efficacy of ECLS to assist recovery.

Keywords Acute poisoning · Carbamazepine · Extracorporeal life support · Myocardial dysfunction · Toxicokinetics

Introduction

The indications for carbamazepine therapy are growing, including partial and general tonic-clonic seizures, trigeminal neuralgia, bipolar disorders, neuropathic pain, and attention-deficit/hyperactivity disorders. Carbamazepine poisoning is relatively rare, with the report of 5,144 exposures and 9 deaths in 2003 by the American Association of Poison Control Centers [1]. Intoxication may be responsible for life-threatening coma, seizures, and respiratory depression. However, although carbamazepine is structurally and, in some aspects, pharmacologically similar to tricyclic antidepressants with membrane-stabilizing properties, poisonings rarely result in serious cardiotoxicity in adults. Conduction delays, severe arrhythmia, and cardiac failure have been observed. Survival from severe carbamazepine poisonings has been reported following ventricular fibrillation with conduction defects [2], dobutamine-responsive left ventricular dysfunction with complete atrioventricular block [3], and prolonged cardiac arrest with broad complex junctional tachycardia [4]. In contrast, the reported fatalities have been due to unresponsive shock with ventricular premature contraction [5] or refractory cardiac arrest [6]. Management is mainly

supportive [7]. Multiple doses of activated charcoal are recommended [8]. Isolated case reports suggest the interest of extracorporeal removal of carbamazepine [4, 9]. We report here a case of massive carbamazepine poisoning resulting in a cardiogenic shock refractory to conventional therapies and successfully treated with extracorporeal life support (ECLS).

Case report

A 26-year-old man with a past history of juvenile diabetes, epilepsy, and depression was referred to our intensive care unit (ICU) after ingestion of 32 g slow-release carbamazepine and a subcutaneous injection of 600 IU insulin in a suicide attempt approx. 7 h previously. He was found comatose (Glasgow Coma Score 3) at home, did not improve while receiving intravenous glucose (blood glucose level, 1.4 mmol/l corrected to 4.4 mmol), and was promptly intubated. On ICU admission he presented in cardiovascular shock (arterial blood pressure 82/54 mmHg, heart rate 88/min). Examination revealed mild hypothermia (34.7 °C), generalized hypotonia, no discernible focal neurological defect, depressed deep tendon reflexes, and flexor plantars. Electrocardiography showed a right bundle-branch block with 200 ms QRS duration and an unusual ST segment elevation in the right precordial leads (V_1–V_3), mimicking a Brugada electrocardiographic pattern (Fig. 1). Laboratory tests revealed serum potassium concentration at 1.8 mmol/l, serum creatinine concentration at 110 μmol/l, PaO_2/FIO_2 112 mmHg, plasma lactate concentration at 4.4 mmol/l, and prothrombin time (expressed as percentage of normal) at 80%. Usual toxicological screenings were negative and serum carbamazepine level was 224 μmol/l (therapeutic range 20–40; homogeneous Enzyme Multiplied Immunoassay test, EMIT, aca star, Dade Behring). Administration of multiple doses of charcoal (50 g/day over 8 days) was started. Electroencephalography showed slow activity (5–6 cycles/s), with bilateral delta, triphasic, or pseudoperiodic waves. Within hours his hemodynamic status worsened (blood pressure 67/40 mmHg, heart rate 111/min) despite volume expansion (500 ml gelatin), 500 ml 84‰ sodium bicarbonate, and inotropic support (1.7 $\mu g\,kg^{-1}\,min^{-1}$ epinephrine, 1.9 $\mu g\,kg^{-1}\,min^{-1}$ norepinephrine; Table 1). He was oliguric with acute renal failure. Refractory cardiogenic shock was demonstrated by a persistent hypotension despite increasing epinephrine requirements, pulmonary edema on chest radiograph, and severe hypoxemia. Transthoracic echocardiography revealed marked global hypokinesia (fractional shortening 10%, left ventricular ejection fraction 20%) without dilatation and signs of hypovolemia. Right heart catheterization confirmed severe myocardial dysfunction (SvO_2 17.8%, pulmonary artery occlusion pressure 15 mmHg, cardiac index 0.8 $l\,min^{-1}\,m^{-2}$, stroke volume 17 ml, systemic vascular resistance 1,850 dyne $s^{-1}\,cm^{-5}$, arteriovenous oxygen difference 11.1 ml/%).

Seven hours after his admission the refractory cardiogenic shock required mechanical circulatory support. We used the Jostra-Maquet centrifugal pump (Rotaflow) connected to a hollow-fiber membrane oxygenator with a modified circuit (BEHQV-50600) suitable for use in ICU. Peripheral femorofemoral cannulation with distal limb perfusion was immediately performed as previously described [10, 11]. Anticoagulation was achieved with intravenous heparin. Heparin was started 14 h after implantation aiming at a time of activated kephalin at 1.5 times

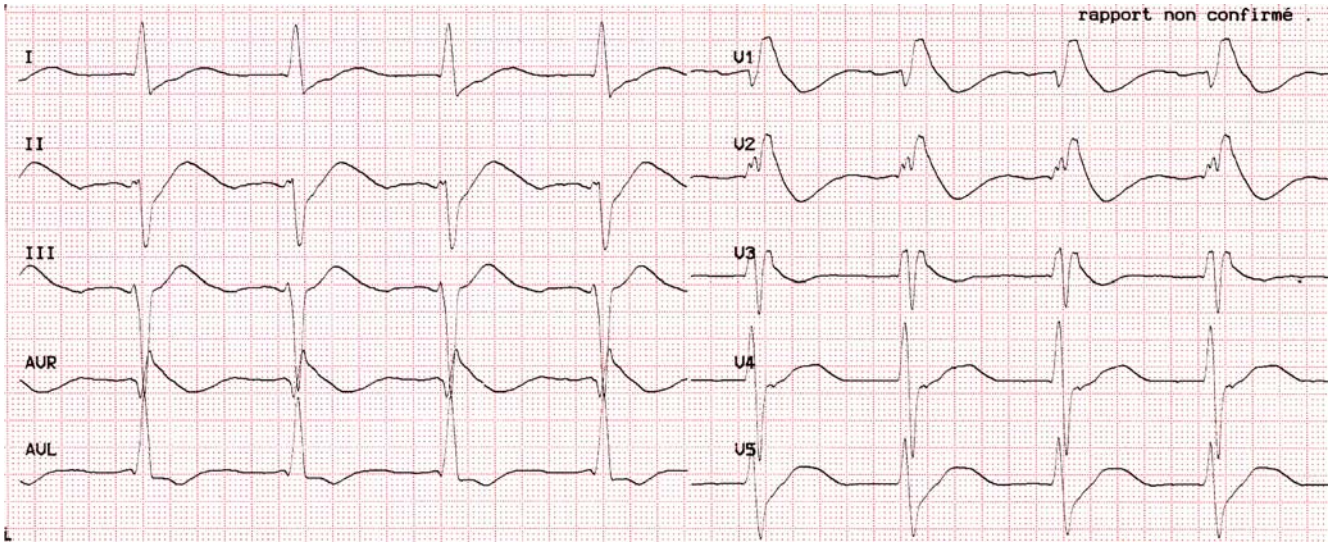

Fig. 1 Brugada electrocardiographic pattern with a right bundle-branch block, a 200 ms QRS duration, and an unusual ST segment elevation in the right precordial leads (V_1–V_3)

Table 1 Hemodynamic parameters of the acutely carbamazepine poisoned patient treated with extracorporeal life support (*ASAT* aspartate aminotransferase, *ALAT* alanine aminotransferase, *ECLS* extracorporeal life support, *ND* not determined)

	1 h before ECLS	12 h after ECLS	Day 3 on ECLS	Day 6 on ECLS	12 h after ECLS explantation
Hemodynamic variables					
Spontaneous cardiac index ($l\,min^{-1}\,m^{-2}$)[a]	0.8	0	1.5	2.6	3.0
Left ventricular ejection fraction (%)[a]	< 10	0	25	40	55
ECLS assistance (l/min)	–	4	3.4	2.2	–
QRS duration (ms)	180	160	110	100	80
Organ perfusion variable					
PaO_2/FIO_2 (mmHg)	56	269	150	342	219
SvO_2 (%)	17.8	ND	72.0	76.0	65.0
Plasma lactate concentration (mmol/l)	5.43	13.80	1.97	1.28	1.11
Serum creatinine concentration (mmol/l)	150	230	132	146	151
Prothrombine time (%)[b]	26	46	56	70	69
Liver enzymes AST/ALT (IU/l)[c]	24/20	72/17	369/142	110/49	56/19
Doses of vasoactive drugs					
Epinephrine ($\mu g\,kg^{-1}\,min^{-1}$)	1.7	0.8	0.1	–	–
Norepinephrine ($\mu g\,kg^{-1}\,min^{-1}$)	1.9	0.3	0.5	–	–
Dobutamine ($\mu g\,kg^{-1}\,min^{-1}$)	–	–	10	10	7

[a] Evaluation using transthoracic echocardiography was performed by the same operator
[b] Expressed as percentage of normal values
[c] Normal range: ASAT < 50 IU/l, ALAT < 50 IU/l

of normal values. During cardiac assistance complete electromechanical dissociation was noted. Epinephrine and norepinephrine were rapidly tapered and withdrawn on days 4 and 5. Dobutamine ($10\,\mu g\,kg^{-1}\,min^{-1}$) was administered until device explantation on day 6 with almost complete recovery of myocardial function assessed by subsequent echocardiography.

During the entire period of assistance transfusions of 12 red cell, 16 platelet, and 5 fresh plasma packs were necessary to compensate losses and disseminated intravascular consumption. On day 11 the patient developed a hospital-acquired *Pseudomonas aeruginosa* pneumonia and was successfully treated with antibiotics (imipenem plus ciprofloxacine). Extubation was possible on day 14. Due to the persistence of a right inferior limb edema a 12-cm-long thrombus extending from the common illiac vein to the insertion of the renal veins in the inferior vena cava was diagnosed using Doppler and echography. The patient was discharged from hospital on day 40. Electrocardiographic and cardiac function were normalized while the inferior vena cava thrombosis regressed with heparin. Coumadin treatment was continued for the following 3 months. At 2-year follow-up the patient showed complete and stable cardiac recovery without neurological sequelae.

Discussion

Carbamazepine poisoning rarely causes myocardial dysfunction, severe conduction defects, and fatalities [1, 2, 3, 4, 5, 6]. To our knowledge, this is the first reported case of carbamazepine poisoning induced sustained refractory shock treated with ECLS. Only one previously published report described a deeply hypothermic carbamazepine-poisoned patient successfully rewarmed using extracorporeal circulation [12].

Several mechanisms have been proposed to explain carbamazepine cardiotoxicity at elevated concentrations, including anticholinergic action facilitating the formation of reentry circuits, increased ectopic pacemaker automaticity, sodium channel blocking effects, and depression of myocardial cell phase 2 depolarization [2, 3, 13]. In our patient the cardiac inotropism inhibition associated with conduction abnormalities including a right bundle-branch block and a Brugada electrocardiographic pattern supported the hypothesis of a severe membrane stabilizing activity.

Predictive factors of death have not yet been determined in carbamazepine poisoning. However, serious complications have been reported to be significantly correlated with serum carbamazepine level of 170 μmol/l or higher [2, 13, 14]. Here we measured one of the highest reported serum carbamazepine concentrations on admission (224 μmol/l), peaking at 338 μmol/l at 101 h, with a prolonged absorption phase despite multiple doses of charcoal for 8 days (Fig. 2). As previously reported [4, 15], delayed absorption of extended-release carbamazepine was observed in spite of gastrointestinal decontamination. Moreover, as in tricyclic antidepressant poisonings [16, 17, 18], severity was clearly demonstrated in our patient with the occurrence of refractory shock and

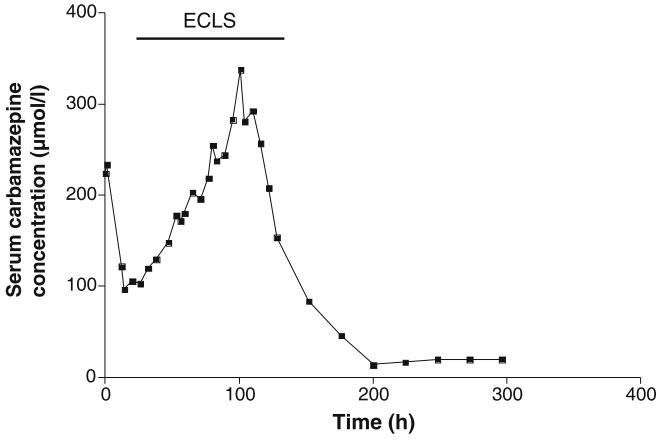

Fig. 2 Time-course of serum carbamazepine concentrations following the ingestion of 32 g slow-release carbamazepine in a patient with sustained refractory cardiac failure treated with extracorporeal life support (*ECLS*)

QRS interval widening of 160 ms or more. Hypotension and electrocardiographic abnormalities usually resolve quickly after sodium bicarbonate administration [18]. Refractoriness to this treatment may have reflected here a massive sodium channel blockage.

ECLS for reversible cardiac toxicity has a sound basis but clinical experience is still limited in toxicology with insufficient evidence to conclude for its recommendation (grade C) as well as potential severe risks (bleedings, cannulated limb ischemia, and mechanical problems) [19, 20]. However, based on the review of seven case reports from the literature, a recent article concluded that cardiopulmonary bypass may have potential benefits for hemodynamic instability not responding to conventional measures provided that the patient has not sustained hypoxic cerebral damage due to resistant hypotension prior to its use [20]. Adequate supportive care remains essential before considering cardiac assistance. The purpose of ECLS is to take over heart function during refractory cardiac shock until recovery can occur, thus minimizing myocardial work, improving organ perfusion, and maintaining the renal and biliary elimination of the toxicant. In this case all supportive treatments failed to improve cardiac function while ECLS resulted in a rapid improvement in tissue parameters, a complete reversibility of cardiac failure, and survival despite a documented 12-h electromechanical dissociation. It is also noteworthy that insulin, which has been proposed as an efficient therapy in acute calcium channel antagonist and β-blocker poisonings [21], failed to prevent carbamazepine-induced cardiac failure in this case despite self-injection of massive doses. Otherwise, initial mild hypothermia was rapidly corrected and was not thought to be contributive to the cardiac disturbances.

Carbamazepine and its main liver metabolite carbamazepine-10,11-epoxide are measured by EMIT serum assays [22]. Both are active, making the clinical consequences of this cross-reactivity debatable [15]. We thus calculated a carbamazepine elimination half-life of 22.6 h (WinNonlin program, Scientific Consulting, N.C., USA), which was close to the range (12–20 h) observed in chronically treated epileptic patients with enzyme induction of hepatic cytochrome P450 3A4. This clearly showed that ECLS-induced clinical improvement allowed for maintenance of carbamazepine liver metabolism and elimination. In addition, ECLS avoided potential delayed serious consequences, as previously reported, despite a decline in serum levels to its putatively nontoxic range [5, 15]. Unfortunately, we were unable to measure carbamazepine-10,11-epoxide concentrations and thus monitor its ratio to the parent compound, which increase has been shown to be indicative of the rate of carbamazepine gastrointestinal absorption and to be significantly correlated with clinical deterioration [15].

In conclusion, this is the first report to our knowledge demonstrating the efficiency of ECLS in a massive carbamazepine poisoning with sustained refractory heart failure and conductance disturbances, followed by an electromechanical dissociation. We think that ECLS should be considered in cases with severe myocardial failure following carbamazepine intoxication. However, criteria for refractoriness to conventional medical therapies indicating the need for early implantation before the occurrence of multiple organ failure and cardiac arrest remain to be determined. Moreover, the broad implementation of ECLS technique will require a cost-effectiveness evaluation.

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