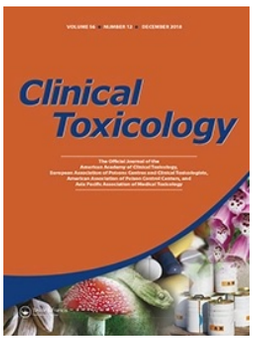

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The unknown known: non-cardiogenic pulmonary edema in amlodipine poisoning, a cohort study

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POISON CENTRE RESEARCH

The unknown known: non-cardiogenic pulmonary edema in amlodipine poisoning, a cohort study

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ABSTRACT

Context: Amlodipine is the most common calcium channel blocker (CCB) on the Swedish market, and poison center (PC) consultations for amlodipine overdoses are increasing. The clinical picture is dominated by vasodilation with relative preservation of cardiac function. CCBs selectively dilate vessels on the afferent side of the capillary network which, in states of preserved or increased blood flow may lead to edema formation, including non-cardiogenic pulmonary edema (NCPE). This complication has been considered rare in CCB poisoning. In this cohort study of nineteen amlodipine poisonings with high amlodipine blood levels, the incidence and clinical significance of NCPE in severe amlodipine poisoning are explored.

Methods: During 2017–2018 the Swedish PC prospectively encouraged the gathering of blood samples in amlodipine poisonings with symptoms requiring treatment with inotropes or vasopressors. Samples were sent by mail to the Forensic Toxicology Division at the Swedish National Board of Forensic Medicine for screening and quantification of relevant toxicants. Patients with blood amlodipine levels >0.25 μg/mL were included in a cohort whose case details were gathered from medical records and PC-case notes with a special focus on signs of NCPE.

Results: Nineteen patients met the blood amlodipine inclusion criteria. Four (21%) died and one patient was treated with VA-ECMO. Nine patients developed NCPE defined as a need for positive pressure ventilation (PPV) while having an echocardiographically normal left ventricular function.

Conclusion: In this prospective cohort study of consecutive and analytically confirmed significant amlodipine poisonings NCPE was a common finding occurring in 47% of the whole cohort and in 64% of patients who did not go on to develop complete hemodynamic collapse.

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Calcium channel blocker overdose; vasoplegia; high dose insulin therapy

Introduction

Amlodipine is, by far, the most commonly used calcium channel blocker (CCB) in Sweden [1]. The number of patients treated with amlodipine has tripled during the last decade and in 2018 5% of the Swedish population was prescribed the drug. Patients on amlodipine now outnumber patients on non-dihydropyridine CCBs (verapamil and diltiazem) by a factor of 50 [1]. Calls to the Swedish Poison Center (PC) concerning amlodipine poisoning have increased in parallel with the increase in prescriptions. The rising number of exposures, coupled with an increased vigilance on the part of the PC in following up all cases of CCB and beta blocker (BB) poisoning during the process of implementing a high-dose insulin treatment (HDI) protocol has made us aware of several cases of pulmonary edema occurring in amlodipine poisoning [2,3].

Pulmonary edema has been documented in many prior cases of CCB-poisoning. In an early account from 1985, a patient with nifedipine overdose developed rapidly progressing dyspnea and radiographic signs of pulmonary edema as the initial hemodynamic shock resolved and blood pressure improved [4]. Humbert reported a similar dynamic in a case of diltiazem overdose with pulmonary edema appearing after 24 h of steady improvement and in the presence of a high cardiac index and a low wedge pressure [5].

Peripheral edema is a common and dose-dependent side effect in patients treated with CCBs, with ankle edema occurring in around 10% [6]. The edema develops because CCBs selectively dilate vessels located on the afferent side of the capillary network and suppress the autoregulatory response that normally protects the capillary beds from excessive hydrostatic pressure [6–8]. CCBs have similar effects on the pulmonary circulation, as demonstrated by their usefulness in select cases of pulmonary hypertension (*via* vasodilatation) and by their ability to prevent the development of high-altitude pulmonary edema (*via* suppression of hypoxic vasoconstriction) [9,10]. Precapillary vasodilation was the mechanism proposed by Humbert to explain the non-cardiogenic pulmonary edema (NCPE) of CCB overdose in his original case report [5]. In non-dihydropyridine CCB overdose a severely depressed cardiac function usually dominates the

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clinical picture, which may explain the seeming rarity of NCPE in these poisonings [5,11,12]. In dihydropyridine overdoses by contrast, the cardiac function is typically relatively preserved while vasodilation is more pronounced, which should lead to a greater risk of NCPE. The large number of case reports describing pulmonary edema in amlodipine poisoning published during the past 15 years supports this notion [13–24]. However, NCPE continues to be described as a rare or unexpected complication of amlodipine poisoning and the existence of the phenomenon is questioned or is mentioned only in passing in recent editions of important textbooks of clinical toxicology [16,19,25,26].

In the present manuscript we attempt to clarify the incidence of NCPE in severe amlodipine poisoning and to describe this complication in the context of therapeutic interventions aimed at maximizing cardiac output.

Methods

Study design and setting

The Swedish PC is a national service that takes calls from the public (population 10 million) and from hospitals. The PC receives over 90,000 calls annually, a third of which are from hospitals. During 2017–2018 the PC followed up all hospital consultations involving overdoses of CCBs and beta blockers (BBs) as a quality control measure upon implementing a HDI-treatment protocol (see under "PC recommendations" below) [2]. The follow-up project was designed as prospective observational study and was approved by the local ethical review board. Patients were selected for inclusion when there was a deliberate ingestion of CCBs and/or BBs and symptoms (bradycardia and/or hypotension) requiring treatment with vasopressors or inotropes occurred. The project was conducted in collaboration with the Forensic Toxicology Division of the Swedish National Board of Forensic Medicine (FToX) to whom clinicians were encouraged to send blood samples from patients meeting the criteria for follow-up.

Selection of patients

For the present manuscript the patients from the follow-up project with a blood amlodipine concentration greater than 0.25 μg/mL were included. This blood concentration is well above therapeutic levels (0.001–0.024 μg/mL) and levels that have previously been associated with pulmonary edema (0.088 μg/mL in serum) [24,27]. The level was chosen to maximize the likelihood that included patients would exhibit significant toxic symptoms associated with amlodipine exposure, while still retaining a majority of confirmed amlodipine cases in the study (19/24). The inclusion process is detailed in Figure 1. The present manuscript is thus a cohort

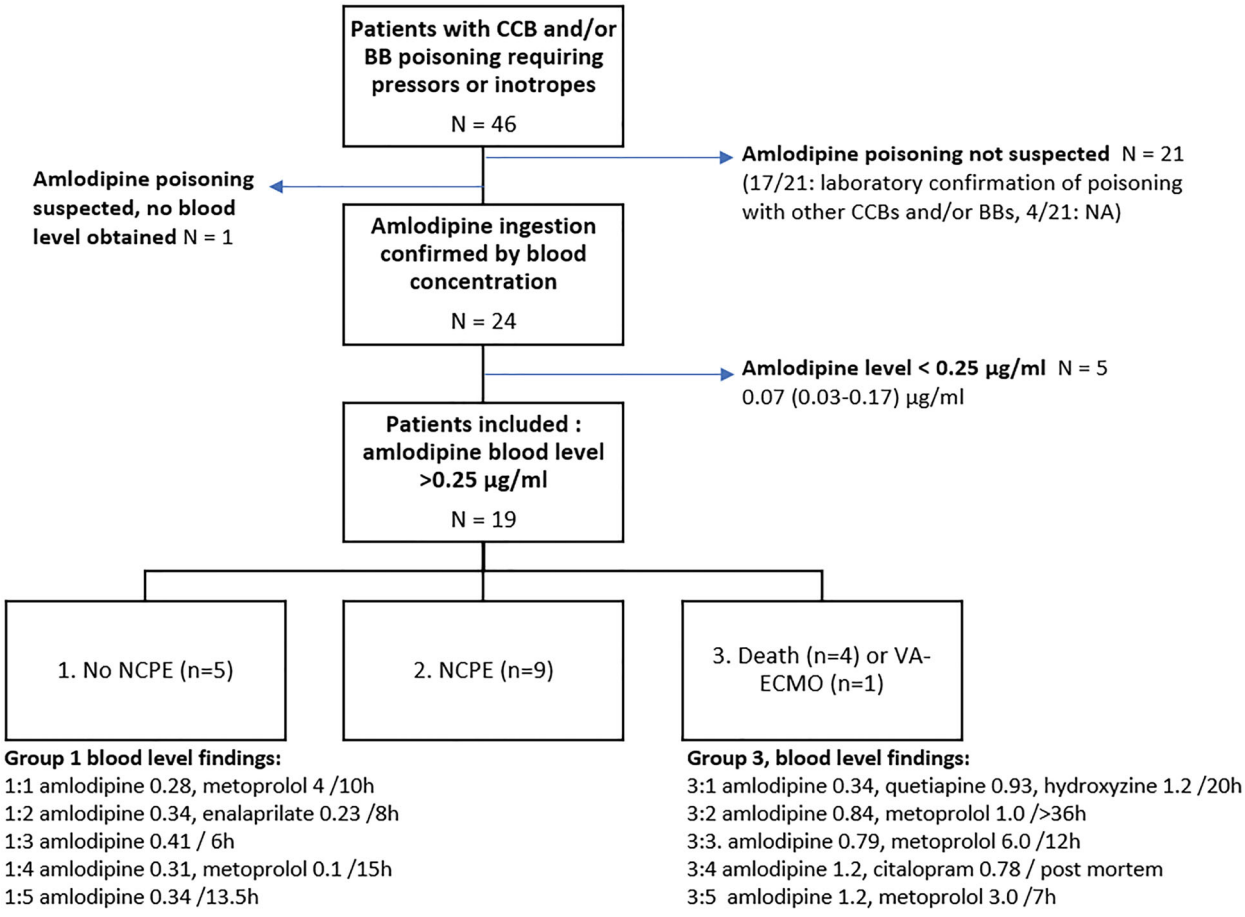

Figure 1. Flow-chart depicting the case selection process. Of the 19 included patients the nine patients in group 2 (NCPE) are described in detail in Table 1. For patients in group 1 and 3 blood concentrations of relevant toxicants are given below the respective group boxes in (μg/mL)/estimated sampling-time in hours after ingestion. All patients in groups 2 and 3 received HDI, in group 1 only patient 1:5 received HDI.

study of consecutive, analytically confirmed and severe amlodipine poisonings, which enables an estimation of the risk of NCPE developing under such conditions [28].

Laboratory methods

Blood samples were collected as soon as clinically possible after presentation and sent for analysis to the FToX. The samples were screened for the presence of pharmaceutical and illicit drug substances using LC-TOF mass spectrometry [29]. Detected toxicants deemed relevant for the clinical course (determined by the PC-physician handling the case) were then quantified using LC- MS/MS methodology. Results were never available to guide clinical decision-making.

Data collection

All cases meeting the inclusion criteria were prospectively assigned to one of two PC-physicians (dr. Grass or dr. Lindeman), who narratively recorded relevant clinical details obtained through multiple telephone consultations as the cases unfolded. After case completion medical records were requested from the treating hospitals.

PC treatment recommendations

Overdoses of CCBs are among the most severe poisonings commonly encountered in Sweden, with high case-fatality rates [2]. The ambition of the PC is to give treatment advice tailored to the clinical situation at hand, encouraging treating physicians to continually determine whether cardiac dysfunction or vasodilation is the dominating pathology. If cardiac dysfunction is present (heart rate (HR) $<$70 bpm or a left ventricular ejection fraction (LVEF) $<$50% in the presence of shock), initiation of HDI is encouraged. A protocol based on recommendations from current guidelines is used [30]. After a loading-dose of 1 U/kg an infusion is started at 1 U/kg/h. The infusion rate is increased to 5 U/kg/h, followed by 10 U/kg/h if evaluations at 15–30 min after the set infusion rate show persistent cardiac dysfunction. Caregivers are instructed to concentrate insulin infusions to avoid unnecessary fluid loading [31,32].

Outcomes

Pulmonary edema was considered present when unintubated patients developed dyspnea that needed treatment with positive pressure ventilation and that was not better explained by another cause (e.g. a clinical diagnosis of lung injury caused by gastric aspiration, trauma or infection). The pulmonary edema was considered non-cardiogenic when cardiac function was judged as normal (LVEF $>$50%) on transthoracic echocardiography (TTE). Positive pressure ventilation modalities included high flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIV) or invasive mechanical ventilation (IMV). Patients who were intubated on arrival were considered to have NCPE on the same basis as unintubated patients, with the addition of the Berlin oxygen requirement criteria for moderate to severe ARDS (PaO_2/FiO_2 $\leq$26.6 kPa or 200 mmHg) [33].

Data analysis

Due to the small group sizes in this study only descriptive statistics were used. Data are expressed as median (range) and percentages.

Results

General findings

During the study period, 19 patients met inclusion criteria (see Figure 1). Nine were females (47%) and the median age was 60 (14–81). All patients, by design, had a blood amlodipine concentration exceeding 0.25 μg/mL and the median concentration was 0.47 (0.28–1.2) μg/mL. In nine cases, amlodipine was the only drug with cardiovascular toxicity detected in the blood and in ten cases there were significant co-ingestions. Blood concentrations of relevant toxicants can be found in Figure 1 and Table 1.

A flow chart dividing the cases into three groups is presented in Figure 1. Figure 2 illustrates the group level increases in median amlodipine blood levels from group 1 (less symptoms) through group 2 (NCPE) to group 3 (death or ECMO).

The patients in group 3 either died ($n = 4$) or were treated with V-A ECMO (case 3:5, see referenced article for details on this case) [34]. For this group, where intractable hemodynamic collapse occurred, NCPE was taken as not present after hypoxia had been excluded as the cause of death or VA-ECMO. The patients in group 1 all made complete recoveries without meeting the NCPE inclusion criteria. Two of these patients (1:2–3) required only modest norepinephrine (NE) infusions and 2–3 L of crystalloid and were discharged to psychiatric care within 36 h. One patient (1:1) received a similar treatment but was discharged from the ICU to psychiatry after ten hours, only to be readmitted to a pulmonary care ward a few hours later for progressive dyspnea and the need for 5–10 L of supplemental oxygen by facemask. The PC was not contacted about this development and the patient was treated for a presumed pneumonia. Two patients were treated with NE + vasopressin and HDI (case 1:4) or milrinone (case 1:5). These latter patients had a positive fluid balance of 4–5 L at 24 h. Case 1:4, like case 1:1, developed dyspnea after discharge to psychiatry and was treated with supplemental oxygen and diuretics. Neither case 1:1 or case 1:4 were treated with PPV or examined with TTE during their bouts of dyspnea and so were not eligible as NCPE cases in the present study.

Non-cardiogenic pulmonary edema

The clinical details for the patients who developed NCPE (group 2) are summarized in Table 1. All patients were treated in an ICU-setting and all received multiple therapies aimed at alleviating hemodynamic symptoms. Four patients

Table 1. Details on patients from group 2, where the diagnosis of NCPE was considered present.

Pat no.	Age + sex	Dose ingested	Admission after ingestion	Blood Amlo/ sampling time after ingestion	Other relevant drugs in blood	Symtoms at presentation	Vasopressors and inotropes	Other therapies	HDI timing after arrival/ max dose	Cumulative fluid-balance / time	Type and timing of PPV (hours post admission)	FiO_2 max	Dynamics of pulmonary symptims	Chest x-ray findings/time	TTE at time of max pulmonary symptoms
2:1 Case vignette	26 F	amlo 1 g	4 h	0.51 μg/mL/ 13 h	None	Tachycardia, hypotension	NE, AVP, GLUC	Calcium	4 h/ 10 U/kg/h	5 L/24 h	HFNC 22 h, NIV 38 h IMV 39 h	1.0 (NIV)	Progression to resp. failure	Perihilar haze + minor pleural effusion/40 h	LVEF > 50%
2:2	62 F	NA	>12 h	0.52 μg/mL/ 18 h	Metoprolol 0.2 μg/mL	Bradycardia, hypotension	EPI, NE, MB	Calcium, t-v PM, CRRT	2 h/ 10 U/kg/h	NA	NIV 12-48 h	0.4	Moderate dyspnea	Minor pleural effusion/24 h	LVEF > 50%
2:3	14 F	amlo 350mg proranolol candesartan	4 h	0.47 μg/mL/ 11 h	Propranolol neg candesartan NA	Bradycardia, hypotension	NE, DOB	Calcium	2 h/ 10 U/kg/h	0.7 L/24 h	HFNC 14-52h	0.3	Moderate dyspnea	Perihilar haze + minor pleural effusion/ 14h	LVEF > 50%
2:4	68 M	amlo 1g	15 h	0.65 μg/mL/ 21 h	None	Bradycardia, hypotension	EPI, NE, AVP, GLUC	Calcium	5 h/5 U/kg/h	7 L/24 h	HFNC 24-104h	0.5	Moderate dyspnea	Retrocardial atelectasis/48 h	LVEF > 50%
2:5	77 F	amlo 250mg	7 h	0.39 μg/mL/ 18 h	None	Bradycardia, hypotension	EPI, NE, AVP, MB	Calcium, ILE	7 h/5 U/kg/h	NA	HFNC 24h NIV 48h IMV 54h	0.5	Progression to resp. failure	Perihilar haze + minor pleural effusion/36 h	LVEF > 50%
2:6	49 M	amlo 900mg +metoprolol	8 h	0.82 μg/mL/ 11 h	Metoprolol 0.06 μg/mL	Bradycardia, hypotension	EPI, NE, AVP, GLUC	Calcium, t-v PM, CRRT, ILE	3 h/ 10 U/kg/h	4 L/10 h	IMV on arrival	0.8–1.0 from 0 to 48 h	Intermittant prone ventilation 10-48 h	Perihilar haze + minor pleural effusion/10 h	LVEF > 50%
2:7	58 F	NA	12 h	0.37 μg/mL/ 20 h	Bisoprolol 0.2 μg/mL, mirtazapine + citalopram	Unconscious Bradycardia Hypotension	EPI, NE, ISO, GLUC	Calcium, CRRT	2 h/ 10 U/kg/h	6 L/24 h	IMV on arrival	0.6–1.0 from 24 to 60h	Obstructive symptoms + air trapping from 24 h	Perihilar haze + minor pleural effusion/48 h	LVEF > 50%
2:8	81 M	amlo 1 g diazepam	4 h	0.68 μg/mL/ 18 h	Diazepam	Unconscious bradycadia hypotension	NE, AVP, MB	Calcium, CRRT, ILE	3 h/ 10 U/kg/h	7 L/24 h	IMV on arrival	0.4	Failed extubation 48h. Edema	Minor pleural effusion/48 h	LVEF > 50%
2:9	60 F	amlo 350mg +metoprolol	8 h	0.40 μg/mL/ 20 h	Metoprolol 3 μg/mL, ethanol 31 mmol/L	Asystolic arrest Hypotension	NE, AVP, ISO, DOB, GLUC, MB	CPR, ILE, calcium, t–v PM, CRRT	8 h / 10 U/kg/h	6.5 L/24 h	IMV on arrival Intermittent HFNC 48-72h	0.7–1.0 from 0 to 24 h	Persistent dyspnea after extubation	Perihilar haze/16h	LVEF > 50%

Abbreviations: M: male; F: female; amlo: amlodipine; NA: not available; NE: norepinephrine; AVP: vasopressin; GLUC: glucagon; EPI: epinephrine; MB: methylene blus; DOB: dobutamine; ISO: isoprenaline; t–v PM: transvenous pace maker; CRRT: continous renal repalcement therapy; ILE: intravenous lipid emulsion; CPR: cardiopulmonary resuscitation; HDI: high dose insulin; PPV: positive pressure ventilation; HFNC: high flow nasal cannlula; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; TTE: trasthoracic echocardiogram; LVEF: left ventricular ejection fraction.

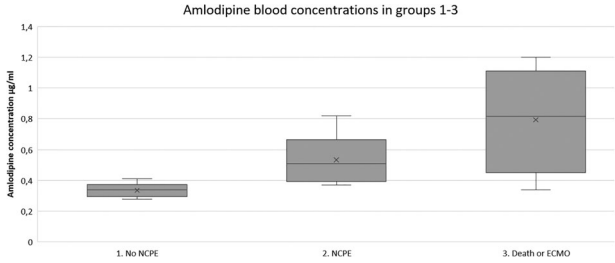

Figure 2. Box and whiskers plot displaying the median (solid central line), mean (x), interquartile range (box) and total range (whiskers) of blood amlodipine concentrations for groups 1–3. The increase in median amlodipine levels from group 1–3 corresponds to the increase in disease severity between groups. There was a similar increase in ingested amlodipine doses between groups (not shown in the diagram) with median values in group 1: 415 (300–500) mg, group 2: 625 (250–1000) mg and group 3: 750 (500–1000) mg. The plot was made with Excel.

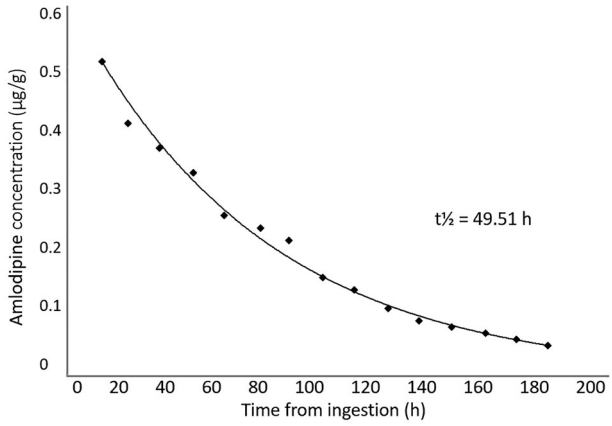

Figure 3. Serial blood concentrations of amlodipine in patient 2:1. Half-life of amlodipine was 49.5 h, calculated with Excel Curve Fit.

were intubated on arrival due to decreased consciousness caused by co-ingestions or pronounced circulatory failure (cases 2:6–2:9). Five patients developed dyspnea during treatment and were started on positive pressure ventilation at 12–24 h (cases 2:1–2:5), two of whom progressed to respiratory failure requiring intubation (2:1 and 2:5). Chest x-ray (CXR) findings consistent with pulmonary edema (perihilar haze and/or pleural effusions) were present in all patients except 2:4, but were generally not pronounced and in three cases (2:6–7 and 2:9) were markedly inconsistent with the degree of respiratory failure present (FiO2 1.0 in all cases, ventilation in the prone position in case 2:6). Patients 2:7 and 2:8 had protracted clinical courses with ICU-care lasting 2–3 weeks, but ultimately all patients made good recoveries.

Crystalloid resuscitation

The median positive fluid balance at 24 h, when pulmonary symptoms had started to appear in all cases, was 6 (0.7–7) L. In two patients this data could not be recovered and in one patient (2:3), the positive fluid balance at 24 h was only 700 mL . The latter patient had an early onset of moderate dyspnea and was treated with an infusion of furosemide from 12 to 24 h, responding with a brisk diuresis. In all cases most of the fluids administered during the first 24 h were crystalloids given in an attempt to improve perfusion.

Glucose disposal rates

Median blood glucose on arrival was 9 (5–13) mmol/L (162 (90–234) mg/dL), with a level above 10 mmol/L (180 mg/dL) in only one case (2:6). Except for the latter case all patients required glucose infusions from the start of HDI to maintain euglycemia. The mean maximal glucose disposal rate needed to maintain euglycemia was 0.44 g/kg/h (range 0.30–0.68 g/kg/h) in cases where this could be determined (1:1, 1:3, 1:7 and 1:8) [3]. This disposal rate translates into volumes of glucose 20% (D20W) of 100–240 mL /h in a 70 kg person. D20W was the most concentrated glucose solution available in Swedish hospitals at the time of the study.

Case vignette

A somatically healthy 26-year-old woman (case 2:1) was admitted to the hospital 4 h after ingesting 0.5–1 g of her mother's amlodipine in a suicidal gesture. Her GCS was 15, BP was 100/50, HR 140–170 and lactate 5 mmol/L. She received 50 g activated charcoal and was taken to the ICU and treated with crystalloids, repeated bolus injections of 20 mL calcium gluconate and an infusion of NE titrated to 0.35 µg/kg/min. After 4 h her hemodynamic status had not improved, she was anuric and lactate had risen to 7 mmol/L. TTE showed a slightly-reduced LVEF of 40–50%. Treatment with HDI was started according to protocol and the infusion rate was raised to 5 U/kg/h after 45 min. During the following 12 h lactate dropped to 2 mmol/L, urine production returned, and the NE infusion was lowered to 0.2 µg/kg/min. A follow up TTE showed LVEF $>$ 50%. About 22 h after admission and 18 h after initiation of HDI, dyspnea set in and worsened over the following hours, accompanied by a rise in blood lactate. Treatment with HFNC was followed by NIV and emergency intubation due to respiratory failure at 39 h after admission. During the progression to respiratory failure, she was treated with 5 mg of glucagon, HDI was increased to 10 U/kg/h and she received 750 mL of albumin in an effort to increase cardiac performance. She also received an infusion of furosemide with a moderate diuretic response. Her cumulative fluid balance at the time of intubation was + 6 L. After intubation the NE infusion was raised to 0.35 µg/kg/min and a vasopressin infusion of 0.03 U/min was added to maintain a mean arterial pressure of 60–65 mmHg. A transthoracic chest ultrasound revealed bilateral pleural effusions and B-lines confirming the diagnosis of pulmonary edema. Bilateral pleural drains were placed with an immediate yield of 1000 mL of clear fluid from each pleural cavity. The patient remained tachycardic and TTE showed LVEF $>$ 55%. After a lung recruitment manoeuvre the FiO_2 could be lowered from 100% to 40%. Thus stabilized, the patient was moved by ambulance to a neighbouring hospital with a thoracic surgery unit and the capability of rapidly implementing extracorporeal life support should the patient's condition deteriorate. During the following days her condition improved, she was extubated 24 h after transfer and was

discharged from the ICU 48 h later after all hemodynamic support had been tapered. Her blood amlodipine concentration was followed every 12 h during the hospital stay and is presented in Figure 3.

Discussion

In this cohort of severe amlodipine poisonings, the case fatality rate was 21% (4/19). In the patients who did not die or require treatment with VA-ECMO, NCPE was a common finding, occurring in 64% of patients in group 1 + 2. Patients in group 1 received less polypharmacy and had less positive median fluid balances at 24 h compared to group 2 (+3 (1–5) L vs +6 (0.7–7) L). While the initial fluid loading in group 2 was not insignificant, it was not large when compared to other published cases were fluid overload has been a more obvious direct cause of pulmonary edema [32,35].

The role of cardiac output in NCPE

The patients in group 2 received more resuscitative fluids than patients in group 1, and were consistently treated with HDI, a treatment given to only one patient in group 1. While it is tempting to view group differences in treatment efforts and in the occurrence of complications such as pulmonary edema as a natural consequence of the more severe poisonings in group 2, the possibility of a direct association between NCPE and HDI should not be discounted. In fact, in light of the current understanding of the physiological mechanisms behind edema formation in CCB exposure, any therapy capable of increasing cardiac output in this context can be predicted to increase the risk of NCPE [7,8]. In CCB poisoning an increased blood flow to the pulmonary circuit is transmitted to a capillary network where the precapillary resistance vessels are dilated while the postcapillary venules are not. This will cause an increase in capillary hydrostatic pressure and increase fluid filtration to the interstitium [7,8]. The process is analogous to the (perhaps more familiar) regulation of primary urine formation in the kidney, where the glomerular filtration rate (GFR) rises when the afferent arteriole is dilated relative to the efferent arteriole.

The role of glucose infusions in NCPE

HDI may also (independently of its effects on cardiac output) increase the risk of NCPE *via* volume loading with dextrose solutions required to maintain euglycemia. While hyperglycemia is considered a hallmark of severe verapamil and diltiazem overdoses and insulin resistance is reported to limit the need for glucose supplementation when HDI is used in these poisonings, this was not the case for the amlodipine poisonings in the present cohort [36,37]. Instead, for 8/9 patients in group 2, glucose supplementation was necessary from the start of HDI and the glucose requirements were similar to the maximal glucose disposal rates of non-diabetics subjected to insulin-clamp testing indicating that no insulin resistance was present [3,38]. The long half-life of amlodipine (49.5 h in case 2:1, see Figure 3) led to protracted symptoms and long durations of HDI-treatment in several cases. The concomitant need for prolonged large-volume infusions of D20W likely contributed to an extended need for ventilatory support in several cases, notably cases 2:7–8. The same dynamic appears to have been responsible for a case of veno-venous ECMO treatment in an amlodipine poisoning who developed severe respiratory failure after the infusion of 23 L D10W in 48 h [39]. Since the completion of this study the PC has included D50W in the list of essential antidotes recommended for all Swedish hospitals and now routinely recommends the use of this highly concentrated glucose solution in HDI to minimize fluid overloading. Other centres recommend using D70W for similar reasons [40].

The role of ventilation-perfusion mismatch in NCPE

All patients in group 2 had some degree of cardiac dysfunction that prompted the consistent use of HDI in this group. In the patients with co-ingestions of BBs (2:6–7 and 2:9) the dysfunction was particularly pronounced. Thus, it is difficult to exclude with certainty that a pulmonary edema of cardiogenic origin may have caused lingering symptoms after the normalization of cardiac function. However, as described in the index cases of NCPE, the respiratory symptoms for all patients in group 2 seemed to worsen as cardiac function improved [4,5]. Additionally, the CXR findings were relatively subtle in all cases, including the cases with profound respiratory failure (see Table 1 case 2:6–7 and 2:9), a finding we speculate can be invoked as supporting the diagnosis of NCPE. The selective precapillary vasodilation of amlodipine poisoning could be expected to lead to an exact matching of regions of maximal perfusion with regions of maximal edema formation, causing a significant shunt not readily visualized on CXR. Inhibition of hypoxic vasoconstriction by amlodipine would then cause this ventilation-perfusion mismatch to persist [9].

NCPE, the lesser evil?

Avoidance of NCPE should not be the guiding principle in the treatment of amlodipine poisoning. Maintaining an adequate cardiac output in circulatory shock is essential for the perfusion of vital organs and the exclusive use of vasopressors in the context of toxic cardiomyopathy may be deleterious [41,42]. However, as the case vignette illustrates, an insufficient grasp of the pathophysiology of NCPE can lead to the provision of treatments (i.e. increased insulin infusion dose, administration of glucagon and albumin) that are more likely to exacerbate rather than alleviate the pulmonary edema that prompted the interventions in the first place. In this context the early application of PPV and the use of diuretics may be better advised.

Limitations

A major limitation of this study is the retrospective review and interpretation of clinical data. Given the complexity of the cases at hand this introduces an inevitable risk of bias

that is difficult to control for. We consider the use of a high blood amlodipine inclusion criterium a significant strength that increases the likelihood that the symptoms described are connected to the amlodipine exposure.

Conclusion

In this cohort study of 19 laboratory confirmed severe amlodipine poisonings the development of non-cardiogenic pulmonary edema was common, occurring in almost half of all patients and in 64% (9/14) of patients who did not progress to complete hemodynamic collapse. Recognition of this complication and an understanding of its physiological underpinnings are important for the optimal management of amlodipine poisoning.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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