Predictors of Mortality in Verapamil Overdose: Usefulness of Serum Verapamil Concentrations

Bruno Mégarbane1,2, Souheil Karyo1, Khalid Abidi3, Brigitte Dellhotal-Landes4, Mounir Aour5, Philippe Sauder3 and Frédéric J. Baud1,2

1Medical and Toxicological Critical Care Department, Lariboisière Hospital, Paris-Diderot University, Paris, France, 2INSERM U 705; CNRS, UMR 7157; Paris-Descartes University, Paris, France, 3Critical Care Department, Calmette Hospital, Louis Pasteur University, Strasbourg, France, 4Laboratory of Toxicology, Lariboisière Hospital, Paris-Diderot University, Paris, France, and 5Department of Biostatistics, Lariboisière Hospital, Paris-Diderot University, Paris, France

(Received 23 September 2010; Accepted 29 November 2010)

Abstract: Verapamil poisoning may result in life-threatening cardiovascular morbidities and fatalities. To date, prognosticators of mortality have been poorly investigated and the use of serum verapamil concentration for prognosis remains unclear. We aimed to evaluate the ability of usual clinical and laboratory parameters including serum verapamil concentrations measured on admission to predict outcome (survival versus death) in verapamil poisoning. We reviewed the medical records of all intentional and symptomatic verapamil poisonings admitted over 8 years to two medical intensive care units. Clinical and laboratory parameters were measured in 65 patients, and final outcomes of survival or death recorded. A multivariable analysis was conducted to evaluate the prognostic values of recorded parameters. Life-threatening complications of verapamil poisonings included shock (62%), atrioventricular blocks (24%), sinoatrial blocks (20%), acute respiratory distress syndrome (19%) and cardiac arrest (11%) resulting in death (8%). Verapamil concentration measured on intensive care unit admission was the only independent factor associated with mortality ($p = 0.01$). The optimal verapamil cut-off point was 5.0 µM (100% sensitivity, 91% specificity), which conferred a 2.76-times increase in odds of fatality. In conclusion, cardiovascular monitoring and assessment of organ failure are vital in symptomatic verapamil poisonings. The serum verapamil concentration has excellent prognostic ability for predicting fatality in verapamil overdose.

Calcium-channel blockers represent a growing cause of toxic exposures, accounting for one-third of fatalities attributed to cardiotoxicants in the USA in 2008 [1]. Poisonings may result in severe bradycardia, dysrhythmias, cardiovascular failure and death [2]. Among calcium-channel blockers, verapamil (a phenylalkylamine) is likely the most toxic; verapamil can suppress sinoatrial and atrioventricular nodal conduction, decrease myocardial contractility and lower peripheral vascular resistance [1–4]. Timely recognition of severity is critical to poisoning management. To our knowledge, prognosticators of mortality and the role of verapamil concentration as such a prognosticator have been inadequately investigated in calcium-channel blocker toxicity. Our objectives were (i) to report the prognostic value of usual clinical and laboratory parameters measured on admission in symptomatic verapamil-poisoned patients and (ii) to evaluate the serum verapamil concentration as a predictor of final outcome of survival or death.

Methods

Study design We reviewed the medical records of all symptomatic verapamil-poisoned patients admitted consecutively between 2002 and 2009 to two medical intensive care units. In both hospitals, patients were either directly transported from the scene to the intensive care unit by the pre-hospital medical services or rapidly transferred from the emergency department. Diagnosis of verapamil poisoning was made based on history, clinical findings and laboratory confirmation, if available. Cardiovascular symptoms were defined by the presence of at least one of the following: heart rate $<50$/min., systolic blood pressure $<100$ mmHg or any abnormality on the electrocardiogram. Patients were treated in the intensive care unit according to the French Critical Care Society’s national guidelines [5]. Serum and urine toxicology analyses were performed at the clinician’s discretion. This study was conducted according to the Helsinki principles and approved by our institutional review board.

Study measurements Clinical and laboratory parameters measured on admission, intensive care unit treatments, as well as complications and final outcomes were recorded. Electrocardiograms were interpreted by a cardiologist. QT intervals were corrected for heart rate (QTc) using the Bazett’s correction equation (QTc = QT/RR$^{1/2}$) and prolonged QTc, defined using standard criteria as QTc $\geq 0.470$ sec. in women and $\geq 0.450$ sec. in men. Serum verapamil and norverapamil concentrations were determined using high-performance liquid chromatography coupled with fluorometric detection (therapeutic ranges: 0.20–0.75 µM for verapamil concentration; 0.23–1.30 µM for verapamil + norverapamil concentration; limit-of-quantification <0.05 µM). In patients with at least four concentration measurements during the course of poisoning, terminal half-lives were calculated based on a mono-compartmental model using Siphar/Win software (Simed, Créteil, France).

Statistical analysis Results are expressed as medians (25–75% percentiles) or percentages when appropriate. Mann–Whitney and Wilcoxon tests were used for between-group comparisons. A logistic regression model was performed to evaluate the contribution of each parameter obtained on admission to predicting verapamil-related fatality. Statistically significant variables at a 10% threshold in the
univariate analysis were introduced into a stepwise multivariate model to select independent predictive factors of this end-point. The obtained model was evaluated for its predictive performance using the area under the receiver operating characteristic (AUROC) curve that was reported with its corresponding 95% confidence intervals. To test the robustness of the model, we performed an internal validation using bootstrap procedure (100 bootstrap samples) to estimate over-optimism associated with AUROC and Brier score [model scores range from 0 (perfect) to 0.25 (worthless)]. The diagnostic test characteristics were calculated with their 95% confidence intervals. Significance level was set at $p \leq 0.05$. Analysis was carried out using the SAS-9.2 software (SAS Inc, Cary, NC, USA).

**Results**

Sixty-five patients [31F/34M; age: 42 years (25–53); previous cardiac disease: 49%] were admitted for symptomatic verapamil poisoning. Sustained-release formulations were involved in 55% of ingestions [dose: 3000 mg (1770–5430); time to intensive care unit admission: 5.0 hr (3.0–11.2)]. Significant cardotoxicant co-ingestions included digoxin (N = 3), beta-blocker (N = 2), angiotensin II-receptor antagonist (N = 2), angiotensin-converting enzyme inhibitor (N = 1), amlodipine (N = 1), hydroxyquinidine (N = 1), tricyclic antidepressant (N = 1) and venlafaxine (N = 1). Severity of cardiovascular failure [systolic blood pressure: 90 mmHg (72–110) and heart rate: 71/min. (55–85)] ranged widely on admission. Electrocardiograms showed sinoatrial (20%), atrioventricular (6%) and QTc prolongation (18%). Forty blocks (low-grade: 18%; high-grade: 6%), QRS widening (43%), mechanical ventilation (43%, duration: 4 days [2–9]), cardiac arrest; six others suffered cardiac arrest while in-hospital. One patient was admitted with sustained pre-hospital cardiac arrest; six others suffered cardiac arrest while in-hospital. Management included multiple dose-activated charcoal (36%), mechanical ventilation (43%, duration: 4 days [2–9]), calcium salts (36%), epinephrine (30%), norepinephrine (30%), dobutamine (28%), sodium bicarbonate (26%), dopamine (15%), isoprenaline (15%), glucagon (15%), high-dose insulin (15%), terlipressin (3%) and haemodialysis (3%).

Sixteen patients (25%) developed mechanical ventilation-acquired pneumonia and twelve (19%) acute respiratory distress syndrome. Additionally, two patients (3%) were treated with transvenous ventricular pacing and five (8%) with extracorporeal life support. Despite optimal supportive and antidotal therapies, five patients (8%) died.

Characteristics on admission of verapamil-poisoned patients according to their final outcomes are shown in table 1. The lowest reported ingested dose resulting in fatality was 4800 mg, while the highest dose in a survivor was 14,400 mg. Admission serum verapamil concentration [median value in all the 48 patients with available measurements: 1.81 µM (1.24–3.73)] was the parameter which differed most significantly between survivors and fatalities ($p = 0.002$). Serum norverapamil [1.45 µM (1.15–1.93)] did not differ between survivors and fatalities according to outcome (fig. 1). Six of eight patients with verapamil concentrations >5 µM suffered cardiac arrest. Of these six, five required extracorporeal life support for refractory cardiac failure, but only one survived.

Using multivariable analysis, verapamil concentration on admission was the only independent factor associated with mortality (N = 48, $p = 0.01$) (table 2). The AUROC for the model was 96% (89; 100). Optimism associated with the AUROC using the bootstrap procedures was 0.6%, and the bias-corrected Brier score was 0.1. The verapamil cut-off point maximizing the sum of sensitivity and specificity was 5.0 µM, with 100% (40; 100) sensitivity, 91% (78; 98) specificity, 50% (16; 84) positive predictive value, 100% (91; 100) negative predictive value, and 92% (80; 98) accuracy. This cut-off level conferred a 2.76-times increased odds of mortality [Odds Ratio: 2.76 (1.22; 6.23)]. The AUROC curve of serum verapamil for predicting mortality was 0.96 (0.89; 1.00).

![Fig. 1. Comparison of serum verapamil (1A), norverapamil (1B) and verapamil + norverapamil (1C) concentrations measured on admission according to the patient’s final outcome in the intensive care unit (N = 48). The solid horizontal lines denote the mean concentration in each group. The dotted horizontal lines show the upper limit of the therapeutic range according to our laboratory. Comparisons were performed using Mann–Whitney. Significance level was set at $p \leq 0.05$.](image)
While in the intensive care unit, verapamil [peak values: 1.85 µM (1.28–3.87), \( p = 0.03 \)] and norverapamil concentrations [peak values: 1.51 µM (1.16–2.33), \( p = 0.01 \)] significantly increased when compared to admission. The elimination half-lives of verapamil and norverapamil were calculated as 11.8 hr (7.7–18.6) and 15.4 hr (11.2–20.0) (N = 26), respectively.

Discussion

We are unaware of any previous study specifically addressing predictive factors of mortality in verapamil poisoning. Our data support the assumption that verapamil concentrations >5.0 µM on admission are predictive of life-threatening outcomes.
toxicity which may result in cardiac arrest or require extracorporeal life support.

This is the largest reported series of verapamil poisonings. Onset of cardiovascular symptoms was rapid after ingestion. However, in massive intoxications involving sustained-release formulations, there was a delay in worsening of cardiovascular function, as demonstrated by the six (of seven total) cardiac arrests which occurred in the intensive care unit despite optimal treatment. Sinusoidal and atrioventricular blocks were the most frequently observed ECG abnormalities. Verapamil-induced hypotension was mainly related to vasodilatation (50% of the cases), while fatalities resulted from cardiac dysfunction. A high incidence of respiratory complications including infections and acute respiratory distress syndrome was noted despite preserved consciousness on admission (Glasgow Coma Score >12 in 60/65 patients), questioning verapamil’s role in precipitating non-cardiogenic pulmonary oedema as previously suggested [6]. Although only one of the five patients treated with extracorporeal life support survived, the benefit of this heroic technique in refractory verapamil poisonings cannot be evaluated based on our series. Lipid emulsion therapy, levosimendan, enoximone, 4-aminopyridine and 3,4-diaminopyridine were not available in either intensive care unit at the time of these patients’ hospitalization.

Verapamil poisoning results in impaired insulin secretion, hypoinsulinaemia, insulin resistance and hyperglycaemia [2,7]. As in our series, serum glucose concentrations have previously been shown to correlate with the severity of calcium-channel blocker intoxication [7]. However, the percentage increase in peak glucose concentrations, previously determined to be a better predictor of illness severity than haemodynamic derangements, was not significantly different according to final outcome in our study [13% (0–62) in survivors versus 34% (17–92) in fatalities, p = 0.3]. Different endpoints for each study (i.e. death plus need for temporary pacemaker plus need for vasoactive agents in Levine’s study [7] versus final outcome in our study) may explain these discrepancies. Moreover, as several factors may influence blood glucose like catecholamines or early use of hyperinsulinaemic euglycaemia therapy, it seems difficult to correlate any increase or decrease in blood glucose with the variation of serum verapamil concentrations.

Outcome in verapamil poisoning could be determined on admission and was related to serum verapamil concentration assessed as the unique independent predictive factor in our multivariate analysis. We evaluated only those cases in which admission verapamil concentrations had been obtained, as we were interested in determining how well the verapamil concentration obtained on admission could predict fatality. As shown in table 2, arterial pH was the most significant variable associated with the outcome in the univariate analysis; however, when the analysis was restricted to the 48 patients with available verapamil concentrations on admission, the verapamil concentration was the most significant variable and remained the only independent one in the multivariate analysis. Previous studies suggested that verapamil levels cannot uniformly predict outcome [3,8], but this is based on an analysis using post-mortem determination of verapamil concentrations and reported cases where verapamil’s contribution to death was not always clear. Interestingly, reports of survival in verapamil poisonings with concentrations >5.0 µM have been rarely reported [9–11].

Verapamil is extensively metabolized in the liver with up to thirteen identified metabolites including norverapamil. In poisonings, factors including rate-limiting absorption, increased volume of distribution in relation to saturable protein binding, impaired liver verapamil clearance because of hypoperfusion, and decreased renal norverapamil elimination may alter verapamil kinetics, resulting in prolonged half-lives as observed in our cases [11–13]. The usefulness of norverapamil concentrations for predicting outcome appears limited because norverapamil’s cardiovascular activity represents 20% that of verapamil. Effective hepatic metabolism of verapamil into norverapamil, however, is a critical step in reducing cardiotoxicity, thus highlighting the potential value of obtaining alanine aminotransferase for evaluating clinical prognosis.

As verapamil determination is not widely available, clinicians have to rely on the severity of haemodynamic disorders to treat the poisoned patient. However, if rapidly available, assessing an elevated verapamil concentration may encourage the treating physicians to more closely monitor the patient and be aware of possible extracorporeal life support requirement. In contrast, based on verapamil pharmacokinetic parameters (large volume of distribution, extensive protein binding and presence of active liver metabolites), any removal by extracorporeal techniques including haemofiltration, haemofiltration and charcoal haemoperfusion should be minimal with no expected effect on poisoning severity [2,5]. Thus, we believe that early assessment of elevated verapamil concentrations will not result in the use of an elimination enhancing technique, although the definitive interest of the more recently developed albumin dialysis using the molecular adsorbent recalculating system remains unknown.

Our study has limitations which should be considered. The small number of fatalities may have underpowered our analysis or altered the predictive values of verapamil concentrations. As this was retrospective, admission verapamil concentrations were only available in 48/65 patients: this may have introduced a bias in the calculation of the predictive value of the 5.0 µM cut-off. Patients with no available concentrations ingested significantly lower doses (p = 0.0001), presented less severe signs on admission regarding their blood pressure (p = 0.009), prothrombin index (p = 0.002), and SAPS2 (p = 0.01) and had shorter length of intensive care unit stay (p = 0.006). However, verapamil concentrations were measured in all 48 poisonings when life-threatening features were presented, limiting the likelihood of false-negative observations. This study was conducted in two intensive care units which routinely measure verapamil concentrations and have emergent extracorporeal life support availability. Measurement of verapamil concentrations may
not be obtainable in a clinically relevant fashion in all institutions. Finally, we cannot rule out if implementing extracorporeal life support earlier implementation in the patients who ultimately died would have been life-saving.

Consequently, in verapamil-poisoned patients with significant hypotension, bradycardia or conduction disturbances, we recommend assessing clinical severity using renal, liver and coagulation tests. If available, serum verapamil concentrations may be helpful for prognostic purposes, with a >5.0 μM cut-off value to predict life-threatening toxicity. In patients with shock, cardiac output should be attentively monitored to identify early those refractory heart failure cases which might benefit from extracorporeal life support.

Acknowledgement
The authors acknowledge Jenny Lu, MD, from Toxikon Consortium, Chicago, USA, for her review of this manuscript.

Conflict of interest statement
All authors have no conflicts of interest to disclose.

References