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BRIEF REPORT

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Incidence, causes and prognosis of hypotension related to meprobamate poisoning

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Abstract *Objective:* Meprobamate self-poisoning has been reported as potentially inducing hypotension. We examined the incidence and causes of hypotension induced by this poisoning and its prognosis. *Design and setting:* Retrospective observational study conducted in a medical ICU between June 1997 and October 2003. Seventy-four patients admitted for meprobamate poisoning and needing mechanical ventilation were included. Demographic, clinical, and laboratory data were compared between patients with and without hypotension. All echocardiograms recorded in patients with hypotension were reviewed, and left ventricular (LV) and right ventricular (RV) functions were assessed. *Results:* Twenty-nine (40%) patients exhibited hypotension without any significant difference in age, gender, cardiac history, or meprobamate concentration in blood when compared to patients without hypotension. Base excess was significantly lower in patients with hypotension. Echocardiography demonstrated a hypokinetic state, associating decreased LV ejection fraction (45±15%) and cardiac index (2±0.7 l min^{-1} m^{-2}), and increased inferior vena cava diameter. Most patients with hypotension received inotropic drugs by infusion, and were ventilated for significantly longer. *Conclusions:* Meprobamate self-poisoning induces hypotension, notably related to cardiac failure, in about 40% of cases. This has important therapeutic consequences, as frequent inotropic drug infusion. The mechanisms of cardiac toxicity remain largely unknown, and no predictive factor could be isolated.

Keywords Meprobamate · Self-poisoning · Hypotension · Echocardiography · Cardiogenic shock · Cardiac failure

Introduction

Acute self-poisoning accounts for a large proportion of admissions to intensive care units [1]. Although mortality is usually less than 1% [2], it is related to aspiration pneumonia [3] and cardiac and circulatory disorders and thus leads as much as 15–20% mortality for poisoning with cardiotropic drugs [4]. Meprobamate, a psychotropic drug given to anxious and depressed patients, is well known to have cardiovascular effects. It continues to be prescribed widely in Europe, especially in France (Groupement pour l'Elaboration et la Réalisation de statistiques, 2004; available at: http://www.gie-gers.fr/$$). The first case of poisoning with meprobamate was reported in 1956 [5], and although relatively frequent is of uncertain prognosis. Allen et al. [6] reported 20 years ago that meprobamate was implicated in 7% of self-poisoning cases.

In an initial description in 141 patients mortality related to meprobamate poisoning was 5%, the principal cause being severe acute circulatory failure [7]. However, the features of such failure have been described only in a few cases and in retrospective studies [6, 7, 8, 9]. It is commonly agreed that hypotension consists especially of

peripheral arterial vasodilatation and hypovolemia [7, 9]. This leads to the widespread use of volume expansion and vasoconstrictive drugs. However, hypotension was initially described using pulmonary artery catheterization. Concerns about the data obtained by this technique and their interpretation in a mechanically ventilated patient are well known [10]. In addition, meprobamate may depress ventricular contractility, although the underlying mechanisms are poorly understood [2]. In a case report Lhoste et al. [11] suggested predominant cardiogenic mechanisms as being responsible for such hemodynamic failure. A general review has since reemphasized this point [12].

Since 1990 we have used exclusively echocardiography to diagnose and monitor shock, regardless of origin. This procedure permits systematic evaluation of left (LV) and right ventricular (RV) function [13, 14]. The objective of this study was to determine the incidence, causes, and prognosis of hypotension related to meprobamate poisoning.

Materials and methods

Patients

Between June 1997 and October 2003 we retrospectively reviewed the reasons for admission of all patients to our ICU. Of the 3,373 patients admitted during this period 74 (2.2%) required respiratory assistance because of a deliberate meprobamate poisoning and were included in the study.

Clinical and biological data

Patients were classified according to the presence of hypotension at admission, defined as systolic blood pressure lower than 90 mmHg during the 24 h following admission. Epidemiological data (age, gender, weight) and medical history were recorded. The Logistic Organ Dysfunction (LOD) score was calculated in the first 24 h following admission to the ICU [15]. The lowest values of the systolic, mean, and diastolic blood pressures during the first 24 h were noted, together with the highest value of the heart rate and the lowest value of the PaO_2/FIO_2 ratio. The estimated ingested dose of meprobamate and its concentration in the blood, measured by gas chromatography, were also recorded when available, and the presence of associated drugs was noted. Base excess (BE) was calculated using arterial blood gas analysis and the presence of metabolic acidosis was defined as a negative BE. We measured the duration of the QRS complex from the electrocardiogram. Finally, pneumonia related to aspiration was noted.

Echocardiographic data

Echocardiography was systematically performed in cases of hypotension. All examinations are recorded on videotape in our unit, thus enabling us to review the echocardiograms of the patients who exhibited hypotension, so as to evaluate LV and RV systolic function. Measurements were performed by an experienced investigator unaware of the clinical features of the patients. Echocardiography was performed by a transthoracic approach using a Toshiba Corevision (model SSA-350A). From an apical four-chamber view we measured the LV end-diastolic (LVED) and end-systolic (LVES) volumes (V) using the area-length method [16] and then calculated the LV ejection fraction (LVEF). Pulsed-Doppler at the LV outflow tract was also performed from this view. Velocity-time integral of aortic flow (VTI_A), averaged over the entire respiratory cycle, and aortic annulus diameter (D) were measured. LV stroke volume (LVSV) was then calculated as $VTI_A \times \Pi D^2/4$, and related to body area to obtain LV stroke index (LVSI). Cardiac index was calculated by multiplying LVSI by heart rate. Finally, we searched for RV dilatation, defined as an RVEDV/LVEDV ratio above 0.6 [17]. We also measured the diameter of the inferior vena cava at end-expiration by a subcostal approach, which reflects cardiac filling pressure [18].

Statistical analysis

Statistical analysis was performed using SPSS version 11.5 statistical software (SPSS, Chicago, Ill., USA). Data were compared between patients with and without hypotension. Continuous variables were expressed as mean ±standard deviation (SD) and were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were compared using the unpaired two-tailed *t* test (for parametric variables) or Mann-Whitney test (for nonparametric variables). Categorical variables, expressed as percentages, were analyzed by the χ^2 test or Fisher's exact test. Differences with a *p* value less than 0.05 were considered statistically significant.

Results

Demographic data and characteristics of meprobamate poisoning (Table 1)

Among the 74 patients 29 (39.2%) exhibited hypotension at admission. No significant difference was found between patients with or without hypotension in terms of age, gender, weight, cardiovascular history, or number of patients whose usual treatment was meprobamate. In 54 patients meprobamate was combined with benzodiazepines (*n*=43), tricyclics (*n*=4), barbiturates (*n*=4), alcohol (*n*=2), or opiates or their derivatives (*n*=3). There was no between-group difference in estimated ingested dose or the level of meprobamate in the blood.

Clinical and laboratory parameters

Systolic blood pressure differed between the two groups by definition. Diastolic and mean blood pressures as well as base excess were also significantly lower in patients with hypotension (Table 2).

Echocardiographic description

Echocardiography was performed in eight patients after drug infusion (dobutamine in three, and dopamine in five). Among the 29 patients with hypotension echocardiography demonstrated a marked decreased LVSI

Table 1 Demographic data and characteristics

	Total (*n*=74)	No hypotension (*n*=45)	Hypotension (*n*=29)	*p*
Male gender	25 (34%)	15 (33%)	10 (34%)	1.0
Age (years)	42±14	41±14	44±14	0.48
Weight (kg)	63±5	64±5	63±5	0.79
Cardiac history	3 (4.1%)	2 (4.4%)	1 (3.4%)	1.0
Chronic meprobamate use	42 (57%)	27 (60.0%)	15 (52%)	0.77
Estimated dose ingested (g)	13±9	14±10	12±6	0.62
Concomitant ingestion of other agent(s)	64 (86%)	40 (89%)	24 (83%)	0.50
Plasma meprobamate concentration (mg/l)	101±48	98±48	106±48	0.57

Table 2 Clinical and laboratory findings

	Overall (*n*=74)	No hypotension (*n*=45)	Hypotension (*n*=29)	*p*
LOD score	6±2	6±1	7±3	0.07
Arterial pressure (mmHg)				
Systolic	95±21	105±16	80±18	<0.0001
Diastolic	58±16	66±14	47±14	<0.0001
Mean	70±17	79±13	58±14	<0.0001
Heart rate (bpm)	88±20	89±19	87±22	0.59
Temperature (°C)	36.5±1.1	36.6±1.1	36.3±1.1	0.16
QRS duration (ms)	91±15	90±15	93±16	0.58
PaO_2/FiO_2 ratio (mmHg)	284±114	286±108	282±124	0.78
Base excess (mmol/l)	−1.9±3.6	−0.9±2.92	−3.1±4.1	0.03

Table 3 Management and outcome

	Overall (*n*=74)	No hypotension (*n*=45)	Hypotension (*n*=29)	*p*
Activated charcoal	36 (48.6%)	21 (51.2%)	15 (53.6%)	1.0
Gastric emptying	33 (44.6%)	17 (42.5%)	16 (57.1%)	0.33
Fluid loading during the first 24 h (l)	1.9±0.8	1.7±0.6	2.2±0.8	<0.01
Mechanical ventilation (h)	39±74	26±29	59±111	0.02
Length in ICU (days)	3±5	3±2	4±7	0.56

(25±6 ml m^{-2}) and CI (2±0.7 l min^{-1} m^{-2}), associated with a decreased LVEF (45±15%). In 61% of the patients LVEF was below 50% (mean 35±11%, range 14–49%). LV dimensions were in the normal range, without any dilatation. The mean diameter of the inferior vena cava was increased (19±4 mm), and the RV appeared dilated in five patients.

Treatment and outcome (Table 3)

Among patients with hypotension 28 needed drug infusion: dobutamine in 14 patients (mean dose 7.5± 2.3 μg kg^{-1} min^{-1}), dopamine in 7 (mean dose 9.1± 3.1 μg kg^{-1} min^{-1}), epinephrine in one patient, and norepinephrine in one; in five patients, drugs were used in combination. The mean duration of drug infusion was 26.6±44.5 h. None of the other patients required drug infusion. Mechanical ventilation lasted significantly longer in patients with hypotension. Most patients (65%) developed pneumonia related to aspiration, with no significant difference between the two groups. No patient died.

Discussion

Our findings concerning the causes of hypotension are not in accordance with traditional descriptions. The mechanisms usually reported are hypovolemia and vasoplegia [6]. However, the most recent study was only performed in six patients using pulmonary artery catheterization [8]. Echocardiography directly visualizes RV and LV function at the bedside [13, 14], and in the present study this showed that hypotension was related to a hypokinetic state in most cases, defined by a decreased LVEF associated with a low cardiac index and an increased cardiac filling pressure, as demonstrated by dilatation of the inferior vena cava. This led us to infuse an inotropic drug in most of our patients. Our results were prefigured in only a few previous case reports [11, 19, 20, 21].

Such results are of great importance when managing shock related to meprobamate poisoning. Vasoconstrictor perfusion, recommended in one study [8], can worsen cardiac function, especially in the case of cardiac failure [22]. Volume expansion can also be deleterious, inducing fluid overload and pulmonary edema [11]. None of the patients died, suggesting either an optimal hemodynamic management using echocardiography or a good prognosis of meprobamate poisoning. In an earlier study Gaultier et al. [7] reported a mortality rate of meprobamate poisoning of 5%.

We did not find any factor predictive of hypotension. The fact that the patient's usual treatment was meprobamate did not appear as a protective factor. Poisoning due to concomitant ingestion of agents in addition to meprobamate did not appear more frequent in patients with hypotension, as has been suggested [3]. In particular, combination with tricyclics, which are well known to induce cardiac depression, was found only in four cases. In two studies temperature was considered responsible for cardiac failure [8, 11], whereas in our patients it was in the normal range. The level of meprobamate in the blood was not significantly higher, whereas cardiogenic shock is usually suspected when it is higher than 150 mg/l [6]. In our study it was only around 106 mg/l. This could indicate a highly individual susceptibility to cardiac failure related to meprobamate poisoning. This was previously suggested by Gaultier et al. [7] who reported shock in patients with ingested doses as low as 10 g or less or higher than 40 g. However, we did not perform pharmacokinetic analysis, which is probably the appropriate way to compare the level of meprobamate between our patients. A single determination of plasma meprobamate concentration is not enough to indicate drug pharmacokinetics and especially peak concentration.

The mechanisms of meprobamate's cardiac toxicity are unknown [2]. Accumulation of meprobamate in the myocardium has been suggested by Kintz et al. [23], who reported in autopsies that meprobamate concentration in cardiomyocytes was three times higher than in blood. However, the effect of this accumulation is unknown. A direct lesion of cardiomyocytes is unlikely, and most cases of cardiac failure in our study were quickly reversible in approx. 24 h. On the other hand, we found that troponin Ic, measured in blood 24 h after the admission of eight patients with meprobamate poisoning and cardiac failure, was in the normal range. Finally, we did not observe QRS prolongation, thereby precluding a membrane stabilizing effect of meprobamate.

A few limitations of our study should be noted. First, the main criterion used to select our patients was hypotension, which does not automatically mean shock. However, hypotension was associated with increased metabolic acidosis, suggesting a certain degree of tissue hypoperfusion. Second, echocardiography was not performed in patients without hypotension and, in eight cases, was performed when inotropic drug infusion had already started. Therefore one could argue that the incidence of cardiac dysfunction related to meprobamate poisoning was underestimated. Finally, in most patients blood volume expansion was performed before admission to our intensive care unit, precluding elimination of any hypovolemia at baseline.

In conclusion, hypotension at admission occurs in about 40% of cases of meprobamate self-poisoning and is especially related to cardiac failure. The therapeutic consequences are important since these results suggest frequent inotropic drug infusion. The mechanisms of cardiac toxicity remain largely unknown and no predictive factor could be isolated.

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