Letter to the Editors

Overdose of meprobamate: plasma concentration and Glasgow Coma Scale

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Meprobamate is a carbamate, main active metabolite of carisoprodol [1], used as an anxiolytic agent and prescribed in Europe and the USA. Carisoprodol is a prescribed centrally active muscle relaxant analgesic. Carisoprodol is extensively converted to meprobamate. Meprobamate plasmatic levels exceed those of carisoprodol 2.5 h after oral administration of 700 mg of carisoprodol to healthy volunteers [2].

Meprobamate is involved in 7% of psychotropic poisonings [3]. Meprobamate has a barbiturate-like mode of action at the GABA_A receptor and at high concentrations is able to cause chloride ion infuse. Well-known toxic effects of a meprobamate overdose include central nervous system (CNS) depression, weakness, clonus and hyperactive reflexes, tachycardia, hypotension and respiratory depression. Meprobamate produces CNS-depressing symptoms [4]. Meprobamate intoxications are often serious and sometimes fatal (5%), resulting from haemodynamic disturbance and circulatory collapse, secondary to severe acute cardiac failure [3]. The mechanism of cardiac toxicity is unknown. An overdose of meprobamate results in coma, generally estimated by the Glasgow Coma Scale (GCS). Only one study, including few patients ($n = 21$), has evaluated the relationship between meprobamate plasmatic concentrations and GCS [5]. Classically, a non-severe coma appears with meprobamate concentration between 60 and 120 mg l⁻¹ and deep coma >120 mg l⁻¹.

We have studied the relationship between GCS and meprobamate plasma concentration in meprobamate intoxication and evaluated the pertinence of determining the meprobamate plasma level. We have reviewed all toxicological analyses made from January 2002 to September 2007. All patients with a plasma concentration of meprobamate higher than normal (>20 mg l⁻¹) have been included. Blood samples were collected when the patient was admitted to the Emergency Department of the University Hospital. Meprobamate plasma concentrations and GCS were analysed. Meprobamate plasma concentrations were determined by a simplified, rapid and accurate gas

chromatographic method [6], using a Delsi Instrument Series 30 gas chromatograph equipped with a flame ionization detector and split-splitless injection. GCS was classified into three groups: as severe group A (GCS 3–8); moderate group B (GCS 9–12); and mild group C (GCS 13–15). Statistical analysis was conducted using an analysis of variance (ANOVA) and the Kruskal–Wallis test, with a level of significance $P = 0.05$. The research was conducted in compliance with the requirements of our Institutional Review Board.

A total of 59 cases were collected. Mean age was 43 years (range 16–69) with a male : female ratio of 0.6. The mean plasma meprobamate concentration was 99.9 ± 13 mg l⁻¹ (therapeutic range 10–25 mg l⁻¹) with a maximal concentration of 271 mg l⁻¹. Mean GCS was 7.1 ± 0.95 (range 3–15). The GCS partition was group A, $n = 42$; group B, $n = 9$; and group C, $n = 8$. In 87% of cases ($n = 51$), meprobamate had been ingested with concomitant drugs, mainly benzodiazepines ($n = 35$) or alcohol ($n = 17$). In 25 cases, the drug involved was the associated meprobamate/aceprometazine, brand name Mepronizine® in France. Meprobamate was the only drug detected in eight cases. Combination with tricyclic antidepressants was found in three cases. Concomitant ingestion of benzodiazepine was equally distributed among the three groups.

Fifty-eight patients recovered. One fatal outcome was observed in a 57-year-old woman with a plasma level of meprobamate of 147 mg l⁻¹, associated with a lethal concentration of propranolol of 1260 µg l⁻¹, (therapeutic range 50–150 µg l⁻¹). A high concentration of meprobamate was associated with low GCS ($P = 0.0194$) (Table 1).

For patients with GCS = 3, meprobamate was detected in three cases, with a plasma concentration from 37 to 177 mg l⁻¹. At a high level of consciousness (GCS = 15) a patient presented a meprobamate plasma concentration of 95 mg l⁻¹.

In the fatal case, the cause of death could not be attributed to meprobamate alone. According to the American Association of Poison Control Centers, propranolol is

Table 1

Analysis by groups

Glasgow Coma Scale	n	Mean meprobamate plasma concentration, mg l ⁻¹	Tests
Group A: 3–8	42	111.05 ± 52.68	Kruskal–Wallis test: P = 0.0155 ANOVA test: P = 0.0194
Group B: 9–12	9	80.77 ± 36.94	
Group C: 13–15	8	62.6 ± 27.11	

responsible for 71% of fatal β -blocker ingestion [7]. In our study, some interindividual variations were observed. Genetics differences have been studied only with carisoprodol. The study about CYP2C19 genotype and the pharmacokinetics of carisoprodol [8] concluded that there are no significant differences with respect to normal and nonfunctional CYP2C19 alleles in acute impairing effects of a single dose of carisoprodol.

Conscious patients, with high meprobamate concentrations, are probably addicted to this drug. GCS, as a surrogate marker of meprobamate toxicity, is inferior to direct objective serum measurement and meprobamate levels, despite a high correlation based upon patient sample. Meprobamate concentration determination remains essential for the diagnosis of poisoning and ensures appropriate care of patients (electrocardiogram, intensive care).

In our hospital, when meprobamate intoxication is suspected, we systematically determine the dosage of plasma meprobamate. This attitude may explain the absence of fatal outcomes.

Competing interests

None declared.

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