FATAL INTOXICATION BY CIBENZOLINE (CIPRALAN®)

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ABSTRACT: We report here a fatal case of intoxication by an antiarrythmic drug, cibenzoline, concerning a woman who was found dead 3 hours after ingesting an unknown amount of Cipralan® tablets. Toxicological screening is performed on blood, gastric content and bile after extraction using Toxi-Tube®A. Cibenzoline is identified by gas chromatography with mass spectrometry detection (GC/MS) and high performance liquid chromatography with diode array detection (HPLC-DAD). Quantitation of cibenzoline is performed by HPLC at 220 nm after liquid extraction at pH 9 by chloroform/isopropanol (9:1, v/v) using di-p-methylcibenzoline as internal standard. Column used is a C_{18} Nova Pack Waters, mobile phase is acetonitrile, methanol and ammonium acetate at 7,5 g/l (30:30:40, v/v/v). Flow rate is 0.7 ml/min. Blood alcohol concentration is 2.9 g/l. Mesured concentrations of cibenzoline are 22.8 mg/l in blood, 31.4 mg/l in gastric content and 76.1 mg/l in bile.

KEY WORDS: Cibenzoline; Antiarrythmic drug; Post-mortem material.

Problems of Forensic Sciences, vol. XLIII, 2000, 243–249
Received 9 September 1999; accepted 16 May 2000

INTRODUCTION

Cibenzoline (cifenline, 2-(2,2-Diphenylcyclopropyl)-4,5-dihydro -1H-imidazole; Cipralan® 30 mg, UPSA Lab.) (Figure 1), antiarrythmic drug available since 1984, has a powerfull Vaughan-Williams class Ic action and it also has some class III and IV effects as well [6, 9]. It is prescribed to prevent the ventricular and supra-ventricular tachycardia.

Its pharmacokinetic properties are represented by fast digestive absorption with maximum plasma concentration at 1 to 3 hours; bioavailability of 85% after oral administration; urinary elimination unchanged of 60% and half life from 5 to 7 hours increasing with age. The daily dosage varies between 260 and 380 mg, inducing blood concentrations ranging from 0.3 to 1 mg/l [1].

The intoxication by cibenzoline, whether voluntary or not, has seldom been described in literature. We are presenting a case of voluntary fatal intoxication.

An electron-capture gas-liquid chromatography [3] and HPLC [5] procedures for the determination of cibenzoline have already been reported. The present work describes a GC/MS screening and quantitation by HPLC-DAD.

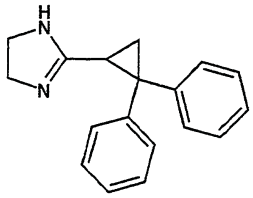

Fig. 1.Cibenzoline.

CASE HISTORY

A 35-year-old female with alcohol habits, treated by cibenzoline without any further details than "because of her heart troubles", was found dead in her bedroom 3 hours after a family lunch. She was suspected to take cibenzoline but the amount of tablets ingested remains unknown.

EXPERIMENTAL

Chemicals and reagents

Cibenzoline and di-p-methylcibenzoline was obtained courtesy of UPSA France.

Chloroform, isopropanol, methanol, acetonitrile were of HPLC grade and obtained from Carlo Erba. Potassium hydrogenophosphate and ammonium acetate of analytical grade were purchased from Merck.

Buffer preparation: 17.4 g of potassium hydrogenophosphate were dissolved in 100 ml ultrapur water and the pH adjusted to 8.5 with acetic acid at 5%.

A stock standard reference solution of cibenzoline (100 mg/l) and solution of di-p-methylcibenzoline (100 mg/l) were prepared in methanol.

INSTRUMENTATION

A Carlo-Erba GC 8000 chromatograph with BPX5 (SGE France) column (25 m x 0.22 mm id., 0.25 µm film thickness) was used for initial screening.

The initial oven temperature was 40°C held for 1 min, followed by an increase in the temperature at a rate of 25°C/min to 180°C then to 280°C at 10°C/min and held for 10 min. The injection port and interface temperatures were 250°C and 280°C, respectively, helium was used as a carrier gas at a flow rate of 1 ml/min.

The presence of cibenzoline was confirmed using a mass selective detector (MSD) Fisons MD 800. The MSD was operated in the electron impact ionization mode with an electron energy of 70 eV and a full scan mass-to-charge (m/z) ratio range 35–650 amu.

High Performance Liquid Chromatography was performed on pump MERCK L6200A equiped with C_{18} Nova Pack Column (300 mm x 4,6 mm DI, 4 µm particle size, Waters).

Mixture of acetonitrile, methanol and ammonium acetate 7.5 g/l (30/30/40, v/v/v) was used as the mobile phase at a flow rate of 0.7 ml/min. Diode array detector was a LDC SM 5000 scanned between 200 and 360 nm.

ANALYTICAL PROCEDURE

General screening include ethanol blood level, performed by headspace gas chromatography. Extraction of post-mortem samples (1 to 3 ml) were realised with Toxi-Tube®A (Ansys® Diagnostics, Inc.). After shaking during 5 min, the Toxi-tube® A were centrifuged before removing organic layer and evaporating to dryness. Extracts were reconstituted with 100 µl of methanol then analysed by GC/MS and HPLC-DAD.

Quantitation of cibenzoline was performed by HPLC-DAD after special extraction procedure: 1 ml of blood, gastric content and 0.5 ml of bile were spiked with 200 µl of a 100 mg/l solution of internal standard (di-p-methylcibenzoline). pH was brought to 9 by addition of 1 ml phosphate buffer (pH 8.5) and 1 N NaOH. 10 ml of chloroform/isopropanol (9/1, v/v) mixture were added. After agitation for 10 minutes and centrifugation, the organic layer was removed and 2 ml 0.2 N HCl were added. The samples were mixed before collection of the aqueous layer. Then, the pH was brought to 9 by addition of 1 ml phosphate buffer (pH 8.5) and 1 N NaOH. After addition of 7 ml chloroforme/isopropanol (9:1, v /v), agitation for 10 minutes and centrifugation, the organic layer was removed and evaporated to dryness.

Calibration procedure: blood samples were spiked with cibenzoline to concentrations of 0, 2, 5, 10, 20, 30, 40 mg/l. At each sample were added, 200 µl of a 100 mg/l solution of internal standard (di-p-methylcibenzoline). Extractions were the same than for post-mortem samples. The quantitations by HPLC-DAD using the same conditions as above, were performed at 220 nm.

RESULTS

Blood alcohol concentration is 2.9 g/l. Cibenzoline was detected in all post-mortem samples. Retention time for cibenzoline in GC was 16.64 min. Figure 2 presents mass spectrum of cibenzoline.

Cibenzoline is quantitated by HPLC. Figure 3 shows HPLC chromatogram of blood extract containing cibenzoline (Tr 6.816) and di-p-methylcibenzoline (Tr 12.857), Figure 4 – the UV spectrum of cibenzoline and Figure 5 the calibration curve for cibenzoline.

The concentrations of cibenzoline found are the following: whole blood – 22.8 mg/l, bile – 76.1 mg/l, gastric content – 31.4 mg/l.

No other drug or toxic substance was found out.

DISCUSSION AND CONCLUSIONS

In our knowledge, only 5 cases of voluntary massive overdoses have been described in literature [4, 7, 8, 10]. The symptoms resembled a sudden cardiovascular collapse: the first electrocardiographic and haemodynamic troubles occured 2 or 3 hours after ingestion. This fact was validated with the cibenzoline's pharmacokinetic properties. The prognosis is particulary redoutable in the short term since 3 out 4 patients died in spite of an early hospitalization. In these 5 cases of voluntary intoxications, the concentrations found varied from 3.4 to 12 mg/l.

5 cases of accidental intoxications have also been published, in 2 cases they led to death [2, 11]. In this 2 cases of fatal accidental overdoses, cibenzoline concentration was 2.5 mg/l [11] or not detected.

The concentrations found in this case report are, at our knowledge, the highest ever registred in literature. Nevertheless, it's the only case on blood collected at autopsy.

We can not exclude postmortem redistribution.

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Fig. 2. Mass spectrum of cibenzoline.

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Fig. 3. HPLC-chromatogram of blood extract containing cibenzoline.

Fig. 4. UV spectrum of cibenzoline.

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Fig. 5. Calibration curve for cibenzoline (HPLC).

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