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The General Toxicology Unknown II. A Case Report: Doxylamine and Pyrilamine Intoxication

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ABSTRACT: A general toxicology unknown case is presented to demonstrate our systematic approach. A 20-year-old male was found dead with multiple suicide notes. Overdose was suspected but substances were not known. Blood alcohol was negative. Urine was analyzed by enzyme-multiplied immunoassay technique and was negative for all drugs assayed. Urine was then extracted with ethyl acetate:hexane (1:1) at pH 10 and back-extracted into 1.0*N* sulfuric acid. The acidic layer was adjusted to pH 10, and re-extracted with ethyl acetate:hexane (1:1). The residue was analyzed by gas chromatography (GC) on a 3% OV-101 column. It was found to be negative for all commonly screened substances. However, several unknown peaks were observed. Electron impact mass spectra of these unknown peaks were obtained and searched for in our computer library of more than 25 000 mass spectra. These unknown peaks were identified as doxylamine and pyrilamine by gas chromatography/mass spectrometry. The base peak and molecular ion for pyrilamine were at m/z 121 and 285, respectively. The base peak for doxylamine was at m/z 58. No molecular ion was observed for doxylamine. Both doxylamine and pyrilamine are antihistamines, but are promoted and used in the management of insomnia. Quantitation was performed on a GC using dexbrompheniramine as an internal standard. Blood concentrations for doxylamine and pyrilamine were 0.7 and 7.0 mg/L, respectively. Concentrations in other tissues were determined. Death was caused by combined doxylamine and pyrilamine intoxication; the manner of death was suicide.

KEY WORDS: toxicology, doxylamine, pyrilamine, systematic approach, general toxicology unknown, chromatographic analysis, mass spectrometric analysis

A general toxicology unknown case is presented here, to demonstrate the systematic approach to the identification of toxicology unknowns discussed in Part I of this manuscript [*1*].

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Equipment and Methods

Equipment and methods used were the same as those discussed previously in Part I of this manuscript [*1*], except as otherwise noted.

GC/MS Search and Confirmation

The gas chromatography/mass spectrometry (GC/MS) conditions were the same as described previously [*1*], except the OV-1 column temperature was at 170°C isothermal for 15 min. Qualitative doxylamine and pyrilamine standards were also analyzed accordingly by GC/MS during the confirmation procedure.

Doxylamine and Pyrilamine Quantitation

The extraction procedure was the same as described for basic drug screening [*1*], except 50 μL of 100 mg/L dexbrompheniramine was used as the internal standard for quantitation. The gas chromatographic (GC) column and conditions were the same as described for basic drug screening [*1*], except the OV-101 column temperature was 200°C isothermal for 5 min. Quantitation was based on the peak area ratios of doxylamine and pyrilamine to the internal standard, dexbrompheniramine. The peak area ratios and doxylamine and pyrilamine concentrations were studied, and found to be linear between 0.5 and 10 mg/L. All specimens were properly diluted to fall within this range. With each set of biological specimens analyzed daily, a doxylamine standard (2.5 mg/L) and a pyrilamine standard (2.5 mg/L) were processed accordingly, and its GC responses were used for the automatic quantitation for that day. The average of two determinations was reported.

Case History

The decedent, a 20-year-old white male, was found unresponsive at his home with three suicide notes and a bottle of green solution with a powdery like residue. Overdose was suspected but substances were not known.

Autopsy Finding

The body was that of a young white male weighing 57.2 kg (126 lb)[2] and measuring 1.75 m (5 ft 9 in.) in length. The external and internal examinations at autopsy revealed no gross abnormalities other than pulmonary congestion and inflammation of the tracheal and bronchial mucosa. Blood, urine, bile, gastric contents, and the bottle of green solution from the scene were sent to the toxicology laboratory for analysis.

Toxicology Finding

A systematic search [*1*] was performed on the postmortem specimens. A steam distillate of blood was found to be negative for alcohols and was negative for ethchlorvynol. Enzyme-multiplied immunoassay technique (EMIT) analysis for urine resulted in negative findings for all drugs screened (barbiturates, opiates, amphetamines, phencyclidine, cocaine metabolites, benzodiazepine metabolites, methadone, and propoxyphene). A hydrolyzed and extracted bile specimen was analyzed for opiates by EMIT in addition to urine and was found to be negative for opiates. A neutral extract of blood was found to be negative for those commonly screened neutral and weakly acidic drugs. A basic extract of urine was analyzed by

[2]Original data were given in inch-pound units.

GC on an OV-101 column and was found to be negative for many of the most common basic drugs. However, this chromatogram revealed four unknown peaks. A basic extract of another aliquot of urine was prepared in the same manner but without the addition of internal standard and was subsequently analyzed by GC/MS on an OV-1 column. Again four unknown peaks (Scan 14, Scan 86, Scan 105, and Scan 287) were observed on the reconstructed ion chromatogram (RIC) (Fig. 1). Enhanced mass spectra (background subtracted mass spectra) were obtained for each of the four unknown peaks. An enhanced mass spectrum of Scan 14 showed a base peak at m/z 58 (Fig. 2). The computer recognized it as doxylamine after a search. The base peak for the doxylamine standard was at m/z 58 and no molecular ion was observed. The retention time and mass spectrum of the doxylamine standard were consistent with those of Scan 14. The enhanced mass spectrum of Scan 86 had a significant peak at m/z 58, a base peak at m/z 121, and a good size peak at m/z 285 on the high mass end (Fig. 3). The computer recognized this spectrum as pyrilamine. The base peak and molecular ion for the pyrilamine standard were at m/z 121 and 285, respectively. An intense peak at m/z 58 was also observed in the mass spectrum of the pyrilamine standard. The retention time and mass spectrum of the pyrilamine standard were consistent with those of Scan 86. The computer did not recognize the enhanced mass spectra of Scan 105 (Fig. 4) and of Scan 287 (Fig. 5). We propose that they are the *O*-demethylated pyrilamine metabolite (Scan 105) and the hydroxylated pyrilamine metabolite (Scan 287) from their enhanced mass spectra.

Quantitation of doxylamine and pyrilamine in blood, urine, bile, and gastric contents was performed with dexbrompheniramine as an internal standard by GC. Tissue distribution of doxylamine and pyrilamine is shown in Table 1. Blood concentrations for doxylamine and pyrilamine were 0.7 and 7.0 mg/L, respectively. Aside from the gastric contents, the concentration of doxylamine was highest in urine (17.0 mg/L), while the pyrilamine concentrations in urine (80.0 mg/L) and in bile (82.8 mg/L) were comparable. The appearance of the green gastric contents and of the bottle from the scene (green solution with powdery like

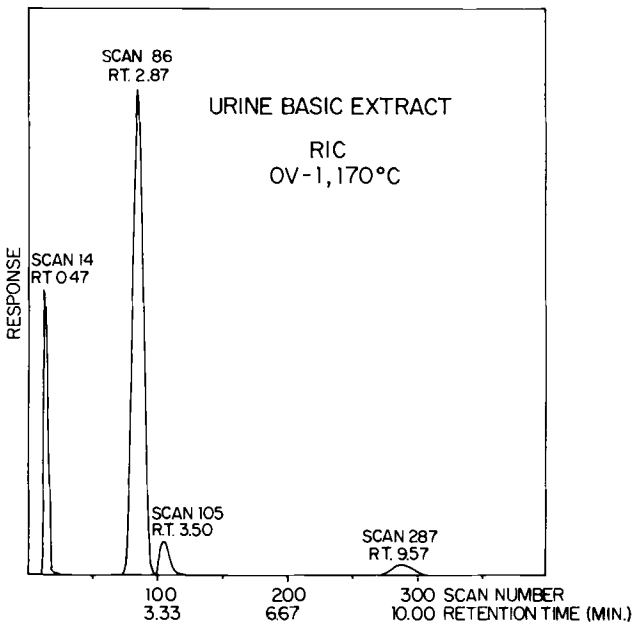

FIG. 1—*Reconstructed ion chromatogram of the basic extract of urine.*

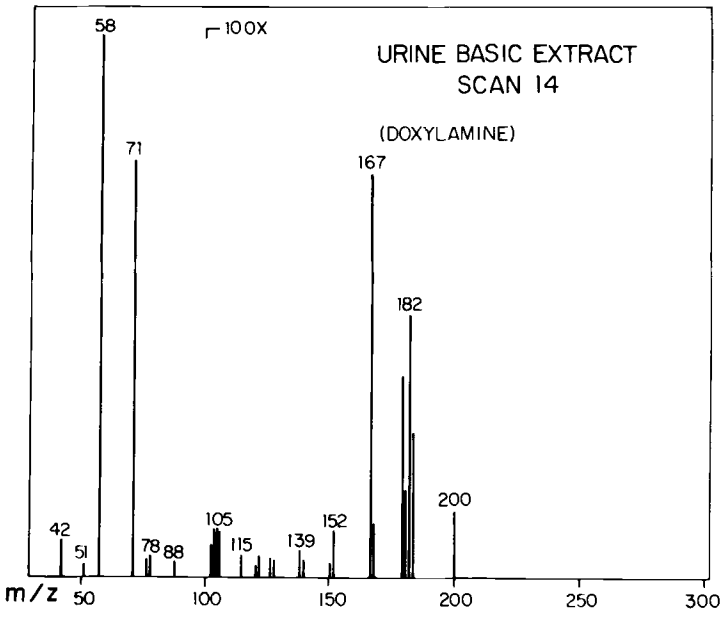

FIG. 2—*Electron impact mass spectrum of Scan 14 of the basic extract of urine.*

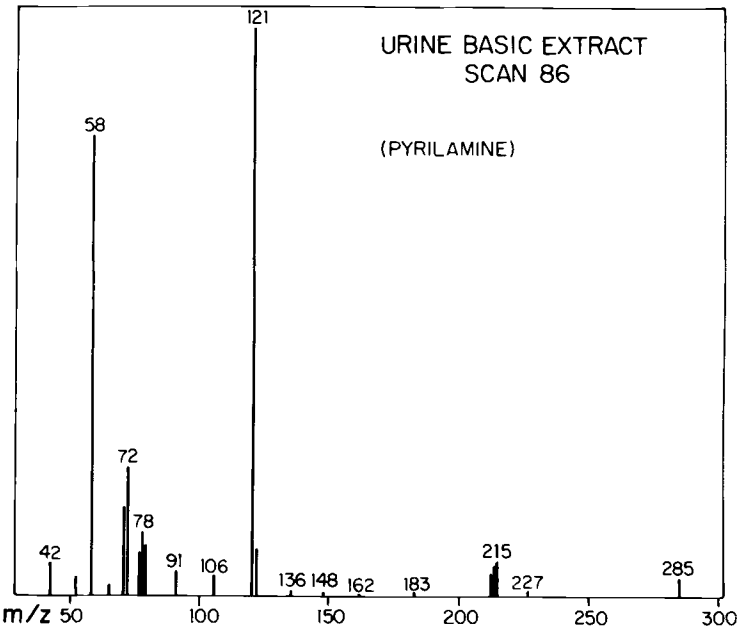

FIG. 3—*Electron impact mass spectrum of Scan 86 of the basic extract of urine.*

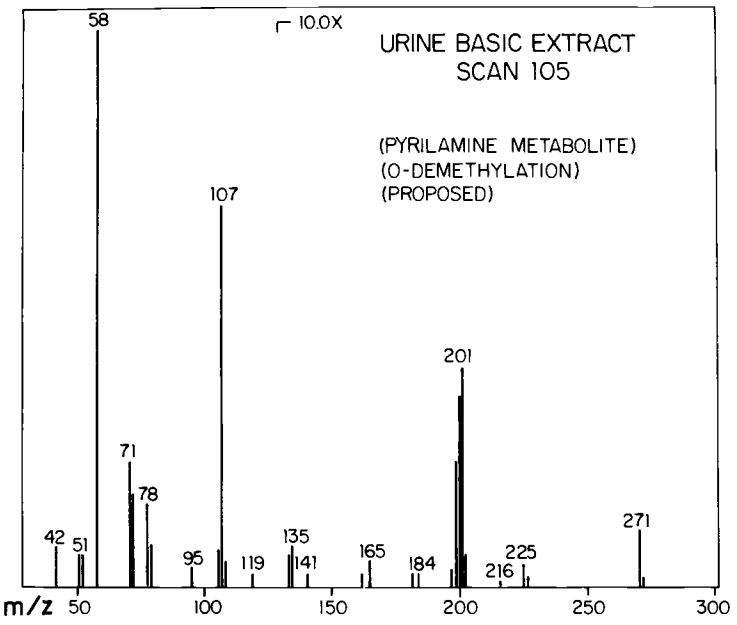

FIG. 4—*Electron impact mass spectrum of Scan 105 of the basic extract of urine.*

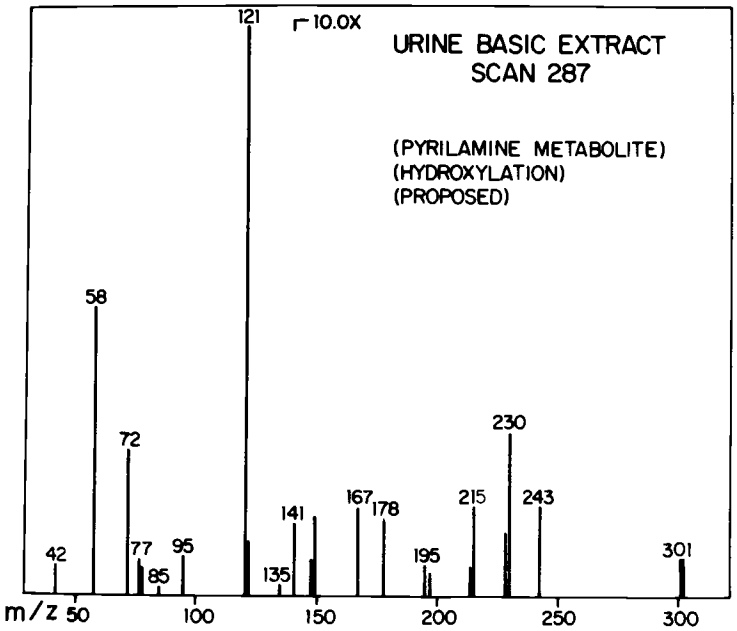

FIG. 5—*Electron impact mass spectrum of Scan 287 of the basic extract of urine.*

TABLE 1—*Tissue distribution of doxylamine and pyrilamine.*

	Doxylamine, mg/L	Pyrilamine, mg/L
Blood	0.7	7.0
Urine	17.0	80.0
Bile	3.2	82.8
Gastric contents, total mg	5	147

substance) were very similar. Analysis of the bottle also demonstrated the presence of doxylamine and pyrilamine.

Conclusion

Pyrilamine and doxylamine are both antihistamines, but are promoted and used in the management of insomnia [*2*]. Doxylamine is the active component of the over-the-counter medication Unisom®. Some medications that contain pyrilamine are Sominex®, Nytol®, and Sleep-Eze®. The decedent in this case probably tried to dissolve some over-the-counter sleeping aids and ingested the mixture. The pyrilamine and doxylamine concentrations (Table 1) are comparable with the concentrations reported in the literatures for antihistamine fatalities [*3*], including two recent pyrilamine fatalities [*4,5*]. With the above toxicology data, the death was attributed to pyrilamine and doxylamine intoxication and manner of death was taken to be suicide.

Acknowledgments

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