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Codeine concentrations in human samples in a case of fatal ingestion

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Summary. Capillary gas chromatography coupled to mass spectrometry was employed to quantify codeine in biological fluids and tissues in a death attributed to oral codeine ingestion. The blood concentration of codeine was 22.1 mg/l. Results are discussed in the light of the existing literature.

Key words: Codeine – Opiates – Poisoning – Analysis

Zusammenfassung. Nach Einnahme einer tödlichen Menge von Codein wurde die Substanz in postmortalen Geweben bzw. Flüssigkeiten durch eine GC-MS Methode bestimmt. Die Blutkonzentration von Codein war 22,1 mg/l. Die Ergebnisse sind beschrieben im Vergleich mit der bezüglichen Literatur.

Schlüsselwörter: Codein – Opiate – Vergiftung – Bestimmung

Introduction

Codeine, an alkaloid obtained from opium, has been an ingredient in a great variety of analgesic or antitussive preparations for about 100 years. As it can be easily obtained without a medical prescription in France, it is also widely used by drug addicts as a substitute for illicit opiates. For example, the combination of codeine and glutethimide is believed to be an inexpensive, readily available, oral substitute for heroin.

The estimated minimum lethal dose is 800 mg [1], but codeine is much less toxic than morphine and death directly attributable to codeine is rare. In most fatalities involving codeine, other drugs and/or alcohol are also present [2–6, 9].

The following report describes an acute death after oral codeine overdose and the disposition of the drug in the body.

Case report

A white 19-year-old (1,68 m tall), unemployed woman was found dead lying on the floor in a squatter flat. There was no evidence of violence and no needle marks were found. At autopsy, no particular morphological changes were noted except for pulmonary and visceral congestion. Specimens of body fluids and tissues were collected for toxicological analysis.

Toxicological analysis. Blood and urine samples were screened qualitatively using fluorescence polarization detection (Abbott ADx). Ethanol was analyzed by head space gas chromatography using a standard method after separation on a Chromosorb 102 column using isopropanol as an internal standard. Body fluids and tissue samples were analyzed for codeine using a capillary gas chromatography procedure coupled to mass spectrometry [7, 8].

Body fluids (urine and bile were previously hydrolyzed) and tissue homogenates (approximately 2 g homogenized in 2 ml phosphate buffer using an ultra Turax) were pippeted into a 15 ml pyrex centrifuge tube, followed by 2 ml phosphate buffer (40%, pH 9,2), 20 µl levallorphan (10 µg/ml) used as internal standard and 10 ml chloroform-isopropanol-*n*-heptane (50:17:33, v/v).

After agitation and centrifugation, the organic phase was purified by acidic extraction (5 ml 0,2 *N* HCl). The aqueous layer was re-extracted in 5 ml chloroform, after addition of 2 ml phosphate buffer and 0,5 ml concentrated ammonia solution.

After agitation the organic phase was removed and evaporated to dryness at 45°C in a Speed Vac Concentrator. 50 µl TFA was added to the dried extract, which was then stoppered and incubated at 60°C for 45 min. Excess reagent was completely evaporated to dryness. The residue was dissolved in 20 µl ethyl acetate and 1 µl was injected into a BP 5 capillary column (SGE; 25 mm × 0,22 mm i.d.).

The flow of carrier gas (helium, purity grade N55) through the column was 1,8 ml/min. The column oven temperature was programmed to rise from an initial temperature of 60°C to 280°C at 30°C/min and kept at 280°C for the final 10 min. Splitless injection with a split valve off-time of 1 min was employed.

The GC system consisted of a Perkin-Elmer (8500) chromatograph with an Ion Trap Detector (ITD), operated at 70 eV with an ion source temperature of 200°C. The electron multiplier voltage was set at 1350 V.

Selected ion monitoring was used to quantify codeine (m/z 282 for codeine and m/z 379 for levallorphan).

Table 1. Levels of codeine (mg/l or mg/kg) in post mortem biological samples

Sample	Concentrations
Whole blood	22.1
Urine	6.2
Bile	9.2
Stomach contents (150 ml)	280.6
Liver	41.7
Heart	17.9
Kidney	32.9
Brain	11.4

Results and discussion

No barbiturates, (response: 0.04 mg/l) benzodiazepines, (response: 17 µg/l) antidepressants (response: 6 µg/l), amphetamines (response: 0.00 mg/l) or cocaine (response: 0.00 mg/l) were detected by enzyme-immuno-assay, as all responses were under the detection limits. The ADx (Abbott Laboratories) response was high for opiates. Blood ethanol was found in a concentration of 1.25 g/l, which certainly influenced the lethal outcome.

Codeine was detected in all the autopsy samples. Concentrations are presented in Table 1.

Morphine, a codeine metabolite, was also found in the autopsy specimens [10], at concentrations of 0.18, 2.37 and 1.60 mg/l in whole blood, bile and urine, respectively. Norcodeine was not investigated.

As in the case of morphine, codeine concentration in liver tissue is greater than the blood value. This observation was also made by Havier and Lin [4].

In 8 cases of pure codeine overdosage, concentrations of codeine in the blood were 1.4–5.6 mg/l (mean 3,6) [9].

In other fatal cases in which codeine was implicated, the post mortem blood concentrations for codeine ranged from 0.02 to 0.85 mg/l (association with glutethimide, [4], 15 and 48 mg/l (association with acetaminophen or propoxyphene, [5]), 0.05 and 1.2 mg/l (association with various barbiturates, [11]).

Codeine post-mortem concentrations are generally about 1 mg/l. These observations are also reported by Baselt with levels from 1.0 to 1.8 mg/l [12].

The blood codeine concentration in the present case was nevertheless within the range of fatal concentrations previously reported. The medical examiner ruled the cause of death to be acute oral codeine intoxication.

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