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Lidocaine Intoxication: Two Fatal Cases

Sang-Ki Lee, Soo-Yeun Lee, Sang-Whan In[1], Hwa-Kyung Choi, Mi-Ae Lim, Kyu-Hyuck Chung[2], and Hee-Sun Chung[1]

National Institute of Scientific Investigation, Seoul 158-707, Korea, [1]Southern District Office, National Institute of Scientific Investigation, Busan 606-081, Korea, and [2]College of Pharmacy, Sungkyunkwan University, Suwon 440-746, Korea

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We present two fatal cases, a 41-year-old male (case 1) and his 8-year-old daughter (case 2), resulting from acute lidocaine poisoning. Lidocaine was quantified by gas chromatography (GC) analysis using nitrogen-phosphorus detection. The lidocaine concentrations of cases 1 and 2 were: liver, 27.7 μg/g and 24.9 μg/g; spleen, 70.1 μg/g and 29.9 μg/g; and gastric contents, 23.6 μg/g and 42.8 μg/g, respectively.

Key words: Lidocaine, Intoxication, Distribution, GC-NPD

INTRODUCTION

Lidocaine (Lignocaine, 2-Diethylamino-2',6'-acetoxylidide), first synthesized in 1948, has been used as a local anesthetic. It is also available as a therapeutic agent in the treatment of cardiac disorders (Baselt, 2000a). Lidocaine self-poisoning is rare as no formulations for oral use are available except mouth and throat gels (Dawling *et al.*, 1989). However, several accidental fatalities and suicides following intravenous injection and oral ingestion of lidocaine, as well as some cases of sudden death due to high spinal anesthesia with local anesthetic drugs including lidocaine, have been reported (Dawling *et al.*, 1989; Shimizu *et al.*, 2000; Polkis *et al.*, 1984; Sawaguchi *et al.*, 1997; Engelhart *et al.*, 1998; Hino *et al.*, 2001; Sakata *et al.*, 1988). It was also found that the mechanism of death after fatal intravenous injection of lidocaine was respiratory depression with bradycardia and hypotension without arrhythmias in lidocaine-treated animals (Nancarrow *et al.*, 1989). The presence of lidocaine has frequently been determined by gas chromatography (GC) with flame ionization, nitrogen and phosphorous detector (NPD), or mass spectrometry (MS) after extraction from aqueous alkaline solution of various biological samples (Baselt, 2000b; Engelhart *et al.*, 1998; Hino *et al.*, 2001; Sakata *et al.*, 1988; Shimizu *et al.*, 2000). This paper describes the separation and analysis of lidocaine after fatal overdose in postmortem specimens using GC-NPD and GC-MS.

Correspondence to: Sang-Ki Lee, National Institute of Scientific Investigation, 331-1, Shinwol-7-dong, Yangcheon-gu, Seoul 158-707, Korea
Tel: 82-2-2600-4925, Fax: 82-2-2600-4919
E-mail: skleedoc@nisi.go.kr

CASE REPORT

A 41-year-old male (case 1) and his 8-year-old daughter (case 2) were found dead at home with several vials, syringes, and a suicide note near the bodies. The vials contained small amounts of clear liquid. He had already attempted suicide twice since losing his employment. His wife was a nurse at a hospital. Autopsies were conducted and no trace of injections was found due to severe postmortem decomposition.

MATERIALS AND METHODS

Specimens

Postmortem livers, spleens, and gastric contents were obtained during autopsies and stored at 4°C. Lidocaine-free postmortem biological samples were collected from the cadaver of a separate fatality from a fall.

Extraction

Lidocaine, using dextromethorphan as the internal standard, was extracted as previously described (Chung *et al.*, 1996). Briefly, 1 g of sample was homogenized in 3 mL of distilled water and 3 drops of 6 N NaOH (pH 12-13) were added. The drug was extracted with 5 mL of ethyl

acetate twice and then back extracted from ethyl acetate with 2 mL of 0.25 N H_2SO_4. Again, 1 N NaOH (pH 11-12) was added to the acid and lidocaine was extracted with 5 mL of ethyl acetate twice. The organic layer was evaporated to dryness, reconstituted in an adequate amount of ethanol, and injected into the GC. A standard curve of drug concentration versus the peak-area ratio of a drug and an internal standard was used for quantification. A recovery test was performed in triplicate on two different days comparing with the drug-free liver, spiked at 20 μg/g lidocaine.

Instrumentation

Lidocaine was quantified by GC analysis using a Varian 3400 Cx equipped with a nitrogen-phosphorus detector. The column was a fused silica capillary DB-1 (30 m×0.25 mm, 0.25 μm film thickness) with nitrogen as the carrier gas. The inlet and detector temperatures were 270°C and 280°C, respectively. The oven temperature was programmed to hold at 120°C for 1 min, rise to 260°C at 10/min, and then hold for 5 min.

The results were confirmed by GC-MS analysis using Agilent 6890 N and 5973 N. The column was a fused silica capillary HP-5MS (30 m×0.25 mm, 0.25 μm film thickness). The mass spectrometer was set to monitor the molecular ions using electron impact at 69.9 eV. The temperatures of the ion-source and transfer line were 230°C and 280°C, respectively. The EM voltage was set at 1294 V.

RESULTS AND DISCUSSION

The minimum detectable/detection level/limit (MDL= considered as the analyte concentration above zero that can practically be determined in a sample) and linearity for lidocaine in liver were determined. The MDL was 0.5 ng, and the calibration curve was linear within the concentration range from 0.5 μg/mL to 25 μg/mL with the correlation coefficient of 0.999. The intra- and inter-day recoveries were 89.1±2.06% and 83.0±7.38%, respectively (Table I). This methodology was used successfully in postmortem specimens to quantify lidocaine concentrations.

Quantitative lidocaine results are given in Table II. We tested the livers, spleens, and gastric contents because we could not obtain blood from the heart of the decomposed bodies. Lidocaine concentrations of cases 1 and 2 were as follows: liver, 27.7 μg/g and 24.9 μg/g; spleen, 70.1 μg/g and 29.9 μg/g; and gastric contents, 23.6 μg/g and 42.8 μg/g, respectively. Shimizu *et al.* reported a liver concentration of 14 μg/g and a spleen concentration of 126 μg/g in a 78 year-old-woman who committed suicide with a bolus injection of 870 mg of lidocaine (Shimizu *et al.*, 2000). Liver concentrations of 23 μg/g and 96 μg/g were measured after the intravenous injection of 1000 mg and the subcutaneous injection of 2500 mg of lidocaine, respectively

Table I. Intra- and inter-day recoveries of lidocaine from human liver

	Intra-day (n=3)	Inter-day (n=6)
Recovery (%)*	89.1 ± 2.06	83.0 ± 7.38

*Values are mean ± SD.

Table II. Concentrations of lidocaine (μg/g) in the liver, spleen and gastric contents as determined by GC-NPD

	Case 1			Case 2		
	Liver	Spleen	Gastric contents	Liver	Spleen	Gastric contents
Lidocaine	27.7	70.1	23.6	24.9	29.9	42.8

(Baselt, 2000b). A spleen concentration of 115 μg/g was reported after the accidental, intravenous injection of 2000 mg of lidocaine (Polkis *et al.*, 1984). A 2-year old boy who died after receiving chloral hydrate, nitrous oxide and lidocaine had a liver concentration of 19.0 μg/mL and a gastric contents concentration of 15.3 μg/mL (Engelhart *et al.*, 1998). Death resulted within 10 hours after the administration of spinal anesthesia comprising 2.8 mL of hyperbaric solution with 3% lidocaine to an 11-year-old girl, with postmortem liver and spleen concentrations of 0.11 μg/mL and 0.22 μg/mL, respectively, as determined by GC-MS (Sakata *et al.*, 1988).

Fig. 1 illustrates typical results from the GC-MS procedure. Characteristic ions at *m/z* 86, 58, 72, and 120 were detected for lidocaine. Fig. 2 shows typical gas chromatograms obtained from the GC-NPD procedure. Analysis of the blank liver sample showed that there was no interference of endogenous substances with lidocaine and dextromethorphan. Ethanol levels in the liver of cases 1 and 2 were 0.09% and below 0.05%, respectively. It is inferred that ethanol was given to case 1, as Winek reported that the blood alcohol produced by postmortem decomposition rarely exceeds 0.05 g/dL in concentration (Winek, 1975), although ethanol is both formed and destroyed in biological specimens *in vitro*.

Toxic reactions to lidocaine administration include confusion, dizziness, apprehension, delirium, paresthesia, hypotension, central nervous system depression, and convulsion, and these reactions may lead to unconsciousness, followed by respiratory and cardiac arrest. These signs may appear at plasma concentrations exceeding 8 mg/L. Lidocaine toxicity is generally does-related and may result either from the high plasma levels caused by excessive dosage, rapid absorption, or unintentional intravascular injection, or from the individuals hypersensitivity, idiosyncrasy or diminished tolerance (Baselt, 2000b, PDR, 2002).

In summary, these data clearly demonstrate that the two fatal cases presented were caused by lidocaine poisoning

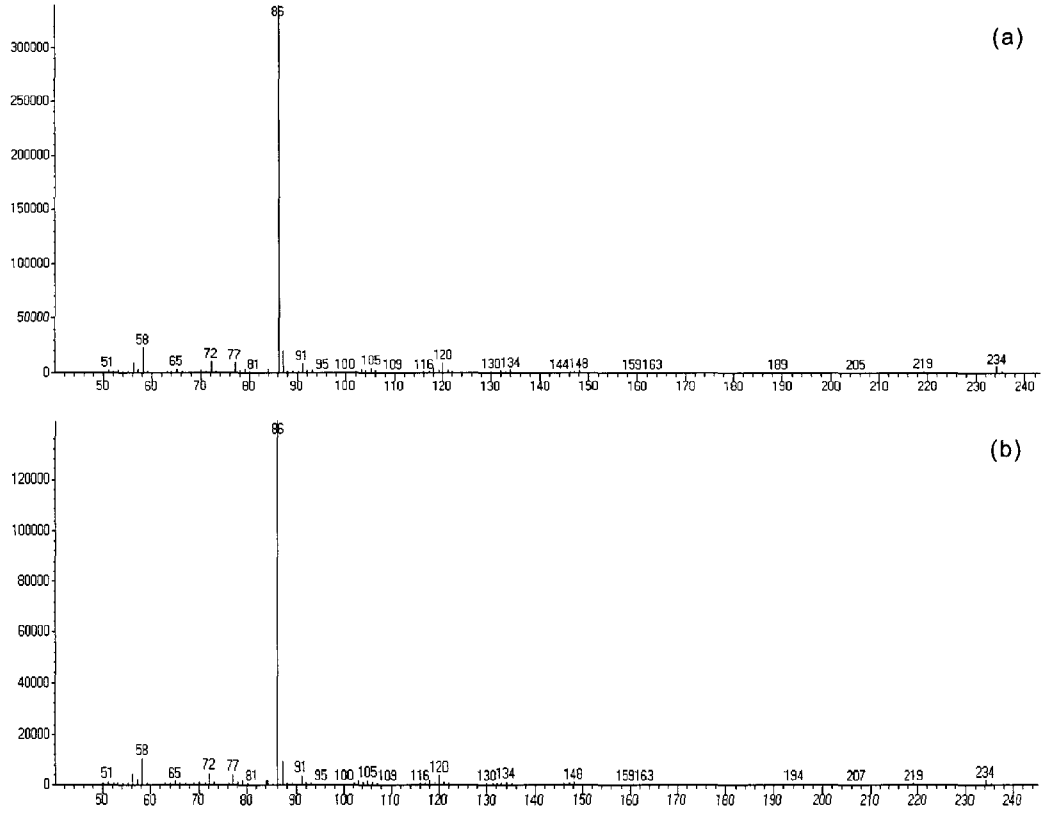

Fig. 1. EI mass spectra of standard lidocaine (a) and of the lidocaine extracted from the sample liver of case 1 (b)

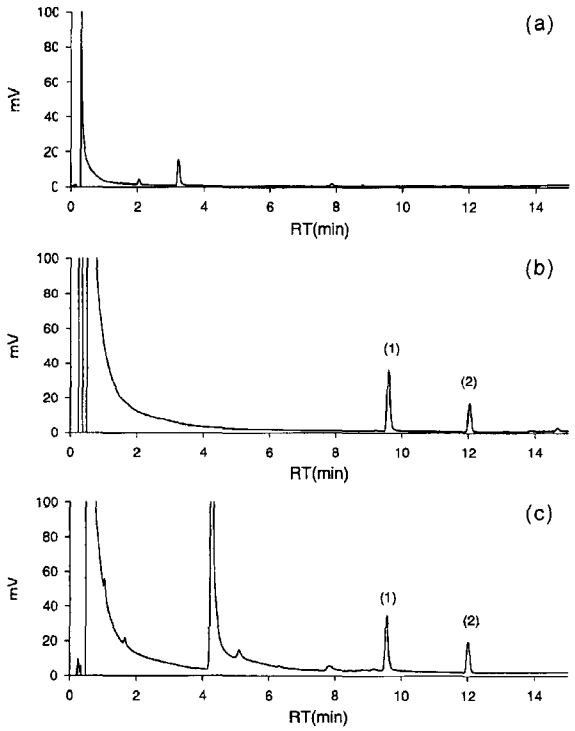

Fig. 2 Chromatograms of blank liver (a), standard lidocaine (b, 20 ppm) and lidocaine extracted from the sample liver of case 1 (c). The retention times of lidocaine (1) and dextromethorphan (I.S.) (2) were 9.5 min and 12.0 min, respectively.

as determined in biological tissues and gastric contents.

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