Fatal Zipeprol and Dextromethorphan Poisonings in Korea*

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Abstract

Zipeprol and dextromethorphan are abused together by young people in Korea to obtain a stronger hallucinogenic effect. Because large amounts of these drugs are taken for this reason, nine fatal poisonings due to zipeprol and dextromethorphan have been reported since 1993. In this paper, the concentration of drugs in the postmortem blood and gastric contents of these victims is examined. The determination and identification of the drugs in biological fluids were conducted by gas chromatography (GC)-thermionic specific detection and GC-mass spectrometry. Linear calibration curves and high recoveries were obtained. The blood concentrations of zipeprol varied from 1.3 to 28.6 µg/mL, and the concentrations of dextromethorphan ranged from 1.1 to 18.3 µg/mL. The concentration of zipeprol in the gastric contents ranged from 26.8 to 1384.8 µg/g, and dextromethorphan concentrations varied from 2.1 to 243.7 µg/g.

Introduction

Because zipeprol has been known to produce an opioid-like euphoria if taken in large amounts (1-4), its abuse has been prevalent among young people in Korea. We previously reported 23 fatal cases due to zipeprol abuse between 1991 and 1993 (5). There is a growing tendency to abuse this drug with dextromethorphan, which is also an antitussive agent, to obtain a stronger hallucinogenic effect. As the abuse of these drugs has continued, many intoxicated abusers have been involved in crimes.

Dextromethorphan is not addictive; it produces little or no central nervous system depression, but manifestations of acute overdose include hallucination, insomnia, and toxic psychosis. Because both drugs are taken in overdose for this reason, the number of fatalities has increased. Fatalities from the overdose of dextromethorphan alone have been reported (6). Although these drugs are not regulated by the government, the concentration in fatalities needed to be investigated.

Since 1993, nine fatal zipeprol and dextromethorphan poisonings have occurred. The concentrations of zipeprol and dextromethorphan in the blood and gastric contents of the victims were determined by gas chromatography–thermionic specific detection (GC-TSD) and identified by GC–mass spectrometry (MS). These results, along with case histories, were used to determine the cause of death for each individual.

Materials and Methods

Reagents

Zipeprol dihydrochloride was supplied by the Dongsung Pharmaceutical Co. (Seoul, Korea). Dextromethorphan hydrobromide was purchased from Sigma Co. Cinnarizine hydrochloride was obtained from the Bukwang Pharmaceutical Co. (Seoul, Korea). All other chemicals and solvents were of analytical grade. The standard stock solutions of zipeprol and dextromethorphan were 1 mg/mL in ethanol. Working standards (1, 5, 10, and 20 µg/mL) were prepared by dilution with ethanol. The standard stock solution of cinnarizine was 0.1 mg/mL in methanol. This was diluted to 10 µg/mL with methanol and served as the chromatographic standard.

Equipment

A Varian model 4600 gas chromatograph equipped with a TSD and a DS 654 data system was used for the screening and quantitation of zipeprol and dextromethorphan. The GC conditions were as follows: A DB-5 Megabore column (15 m x 0.53 mm) was used. The temperature was programmed from 150°C (1 min) to 250°C (10 min) at 10°C/min; the injection port temperature was 270°C; and the detector temperature was 280°C. The carrier gas, helium, had a flow rate of 7 mL/min.

A Finnigan MAT 800 ITD was used to identify the drugs. The MS conditions were as follows: A fused-silica capillary SE-54 column (15 m x 0.25 mm) was used. The column temperature was programmed from 150 to 250°C at 10°C/min; the ionization energy was 70 eV; the transfer line temperature was 270°C; and the EM voltage was 1600 V.

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Biological specimens

Blood and gastric content samples were obtained at autopsy from nine decedents who had a history of drug abuse. These samples were stored at -40°C until analysis.

Calibration curve

Calibration curves for zipeprol and dextromethorphan over the range of 1, 5, 10, and 20 µg/mL were determined; cinnarizine was used as the chromatographic standard. The recoveries of drugs from 1 mL of drug-free whole blood spiked with drugs were calculated from these curves. These specimens were extracted according to the method described below.

Extraction procedures

The analyses were performed on 0.5 or 1 mL of blood and 1 g of gastric contents. Both samples were adjusted to pH 11-12 with 6N NaOH and extracted three times with 5 mL ethyl acetate. The combined organic extracts were re-extracted with 2 mL 0.25N H₂SO₄. After discarding the organic layer, the pH was adjusted to 11-12 by adding 6N NaOH to the aqueous phase, and this solution was extracted twice with 5 mL ethyl acetate. The pooled ethyl acetate was evaporated in vacuo, and the residue was dissolved in 100 µL of the 10 µg/mL cinnarizine. One microliter of this solution was then injected into the GC. The ratio of the peak area of zipeprol and dextromethorphan to that of the chromatographic standard was used to calculate the concentration of each analyte. Appropriate dilution factors were applied to the gastric content samples for calculating their concentrations because of their varied drug concentrations. GC–MS was used for the identification of the drugs.

Results and Discussion

Analysis of zipeprol and dextromethorphan

Zipeprol and dextromethorphan were analyzed by GC–TSD with high precision and good recoveries. The calibration curves in blood were linear over the concentration ranges studied, and correlation coefficients (r) of 0.999 and 0.998 for zipeprol and dextromethorphan, respectively, were found. The percentage of recovery from spiked human blood for zipeprol was 97.2, 92.5, and 86.9% at 5, 10, and 20 µg/mL. The corresponding values were 95.4, 92.1, and 89.4% for dextromethorphan. Coefficients of variation (CV) for recoveries were between 4.01 and 5.29% and between 4.87 and 5.14% for zipeprol and dextromethorphan, respectively.

Zipeprol, dextromethorphan, and cinnarizine were well-separated using the cited conditions. Figure 1 shows the chromatogram of zipeprol, its metabolites, and dextromethorphan extracted from postmortem blood. Those peaks were identified by GC–MS (Figure 2). The mass spectrum of zipeprol was characterized by a peak at m/z 384, which represents the molecular ion, and by peaks at m/z 263 and 121, which represent an N-dealkylated fragment ion (M-121) and C₈H₉O, respectively. Two metabolites of zipeprol were determined in the postmortem blood. The peaks, eluting at 7.5 min (metabolite I) and 9.8 min (metabolite II), were identified as 2-methoxy-2-phenylethylpiperazine (MW, 220) and 2-hydroxy-3-methoxy-3-phenylpropylpiperazine (MW, 250), respectively. Dextromethorphan was identified by its molecular ion at m/z 271 and fragment ions at m/z 59 and 150.

Concentration of zipeprol in the blood

Table I shows the postmortem concentrations of zipeprol and dextromethorphan in the blood and gastric contents and the related personal histories in nine fatal cases. The five female and four male victims were aged 19 through 29.

The zipeprol concentrations in the blood ranged from 1.3 to 28.6 µg/mL in these nine cases, which were comparable with the 2.3-38.3-µg/mL concentrations in the 23 fatal cases reported by Yoo et al. (5). In the paper by Yoo et al. (5), the decedents allegedly ingested 1500-3000 mg zipeprol in four of the cases, and their blood concentrations ranged from 2.0 to 15.8 µg/mL. However, in cases 3 and 6 of the current study, the victims allegedly ingested 1125 and 1500 mg, respectively, of zipeprol, but their blood zipeprol concentrations were 24.7 and 11.0 µg/mL. These concentrations were not consistent with the alleged dose. Because the blood collection time after drug ingestion was not measured in most cases, unavailable data regarding the duration of drug in the body after ingestion and inaccurate allegation might cause this inconsistency. Two metabolites of zipeprol were detected in all blood examined; however, the concentration was not measured because of the lack of authentic standards. The identification of two metabolites is consistent with the observation of Yoo et al. (7), who found three metabolites in zipeprol abusers’ urine. Among the reported metabolites, demethylated zipeprol was not detected in blood, which was probably due to the small concentration of metabolites in blood relative to urine.

The blood dextromethorphan concentration ranged from
1.1 to 18.3 μg/mL. Yoo et al. (6) reported dextromethorphan blood concentrations of 7.4–54.0 μg/mL in five fatal cases. Dextromethorphan concentrations in the current study were lower than those reported by Yoo et al. (6), but this can be explained by the dose involved. No metabolite of dextromethorphan was detected in the blood specimens.

Large amounts of residual unabsorbed drug in gastric contents were also observed. The concentration of zipeprol in the gastric contents was 26.8–1384.8 μg/g. The concentration of dextromethorphan in the gastric contents was between 2.1 and 243.7 μg/g. Crippa et al. (8) reported two fatal cases in which 10.6 and 5.8 μg/g zipeprol were detected in gastric contents. It is difficult to correlate the amount ingested with the concentration in gastric contents. However, most cases showed a high concentration in gastric contents, which indicated oral ingestion. In case 2, the concentration of drugs in the gastric con-

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### Table 1. Postmortem Dextromethorphan (DEX) and Zipeprol (ZPL) Blood and Gastric Contents Concentrations and Personal Histories in Nine Fatal Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Blood (pg/mL)</th>
<th>Gastric contents (pg/g)</th>
<th>History</th>
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<td></td>
<td></td>
<td></td>
<td>DEX</td>
<td>ZPL</td>
<td>DEX</td>
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<tr>
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<td>21</td>
<td>M</td>
<td>2.6</td>
<td>10.5</td>
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<tr>
<td>2</td>
<td>20</td>
<td>M</td>
<td>1.2</td>
<td>15.8</td>
<td>243.7</td>
</tr>
<tr>
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<td>19</td>
<td>F</td>
<td>4.1</td>
<td>24.7</td>
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<tr>
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<td>F</td>
<td>1.8</td>
<td>28.6</td>
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<tr>
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<td>5.1</td>
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</table>

*NA = Not available.
tents was much higher than in the other cases. One could presume that a large amount of drug was involved in this fatality. This study noted tremor and convulsions as the major symptoms before the decedents’ deaths, confirming the findings of Yoo et al. (5).

Because many fatal cases of zipeprol and dextromethorphan overdose were reported, public concern has grown over the problem of drug abuse. These drugs are involved in fatalities as well as in crimes, and, therefore, the availability of these drugs, especially to the young, should be controlled by the government.

Conclusion

The recoveries of zipeprol and dextromethorphan in blood ranged from 86.9 to 97.2%; the corresponding CVs ranged from 4.01 to 5.29. Linear calibration curves for both drugs were obtained between 1 and 20 μg.

In the nine cases where zipeprol and dextromethorphan were determined, the concentration of zipeprol in the blood ranged from 1.3 to 28.6 μg/mL, and the concentration of dextromethorphan in the blood ranged from 1.1 to 18.3 μg/mL. The gastric contents contained zipeprol and dextromethorphan concentrations of 26.8–1384.8 and 2.1–243.7 μg/g, respectively. This report documented the lethal potential of the misuse of zipeprol, which is enhanced by concomitant misuse of dextromethorphan. Methods to control their availability, particularly to young adults, should be considered by all those concerned with improving community health.

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References


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