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Demographic Characteristics of Zipeprol-associated Deaths in Korea

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The abuse of zipeprol, an antitussive agent, was found to be most prevalent among young people in Korea. Because abusers take large doses of this drug for its hallucinogenic effects, fatalities from zipeprol overdose abuse have been on the rise since 1991. Since 1991, a total of 69 zipeprol-related deaths have occurred throughout the nation. A demographic study shows that in ninety six percent of cases involving zipeprol alone, the victims were in their teens and twenties. The male/female ratio in zipeprol related death was 3.5:1. Most of these zipeprol-associated deaths occurred in the larger cities of Seoul and Inchon. The blood concentration of zipeprol ranged from 0.8 to 38.3 μg/mL in single drug involved deaths, while zipeprol varied from 0.1 to 35.3 μg/mL in zipeprol and dextromethorphan victims.

Key words : Zipeprol, Dextromethorphan, Zipeprol-associated deaths, Demographic study, Postmortem blood concentration

INTRODUCTION

In Korea, the drug found to be abused at the highest rate is Methamphetamine, which is followed by cannabis and the opiate group (Supreme Prosecutor's Office, 1994). The abuse of methamphetamine has been prevalent since 1985. In 1996, 2666 specimens were submitted for methamphetamine testing, while 1182 specimens were tested for cannabis at this Institute. Among these, 1220 samples were positive for methamphetamine, whereas 654 were positive for cannabis. In the case of specimens tested for opiates, the positive rate was quite low, in that only 37 out of 193 were reported as a positive (Chung, 1997).

There has been a growing tendency for the abuse of the common medicines (i.e. over-the-counter medications) among young people in Korea. This is due to the easy availability of these products. Even though the portion of these non-controlled drugs, when compared against controlled drug abuse, represented only ~10% of the total abuse picture, the seriousness of this abuse is related to how easily these medicines can be obtained. In 1995, 267 urines tested positive for various common medicines. Zipeprol, dextromethorphan, nalbuphine and carisoprodol are among those non-controlled medicines most commonly abused (Yoo *et al.*, 1996a)

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The abuse of zipeprol, an antitussive agent, was found to be most prevalent among young people in Korea (Yoo *et al.*, 1992, 1994). Because abusers take large doses of this drug for its hallucinogenic effects, fatalities from zipeprol overdose abuse have been on the rise since 1991. Yoo *et al.* (1994) reported the postmortem distribution of zipeprol in 4 fatal cases and additional postmortem zipeprol blood concentrations in 23 cases during 1991 to 1993. However, since 1991 a total of 69 zipeprol-related deaths have occurred throughout the nation. In addition, to obtain a stronger hallucinogenic effect, young people are abusing both zipeprol and dextromethorphan in combination. Because large amounts of these drugs are taken for recreational purposes, an additional 12 fatal poisonings due to this combination have been reported since 1991. Yoo *et al.* (1996b) have reported nine cases of combined zipeprol and dextromethorphan poisoning in Korea. In the current study, the demographic aspect of zipeprol related deaths have been studied in 69 cases.

MATERIALS AND METHODS

Demographic data

The demographic data of gender, age, address in each case were obtained from police files.

Reagents

Zipeprol and dextromethorphan were obtained from

Sigma Co. (St.Louis, MO). All other chemicals and solvents were of analytical reagent grade. The standard stock solutions of zipeprol and dextromethorphan were prepared at a concentration of 1 mg/ml in ethanol. Working standards were prepared by dilution with ethanol. Cinnarizine was used as an internal standard for the quantification of zipeprol and dextromethorphan.

Equipment

A Varian model 4600 gas chromatograph (GC) equipped with TSD and Star data system was used for determination of drug concentrations. A DB-5 Megabore column (15 m×0.53 mm) was used in this system. The GC conditions were as follows: The temperature was programmed from 150°C to 250°C at 10°C/min: the injection port temperature was 270°C; and the detector temperature was 280°C. The flow rate of carrier gas, helium was 7 mL/min.

A Finnigan MAT GCQ was used to qualitatively identify the drugs and metabolites. A fused-silica capillary SE-54 column (15 m×0.32 mm) was utilized in this instrument. The instrumental conditions were as follows: The column temperature was programmed from 150°C to 250°C at 10°C/min; the ionization energy was 70 eV; the transferline temperature was 270°C; and the EM voltage was 1600 V.

Biological specimens

Blood samples were obtained at autopsy from 69 zipeprol involved deaths. The police department provided the histories surrounding these deaths.

Calibration curve

Calibration curves for zipeprol and dextromethorphan over the range of 1~20 μg/mL were determined.

Extraction procedures

The analyses were performed on 1ml of blood. Samples were adjusted to pH 11~12 with 6N NaOH, and extracted x 3 with 5 mL ethyl acetate. The pooled ethyl acetate was then evaporated under vacuum. The residues prepared were then dissolved in 100 μl of internal standard containing ethyl acetate. One microliter of this solution was then injected into the GC. The integrated peak area ratio of the drug analytes to that of the internal standard was used to calculate the concentration of each analyte.

RESULTS AND DISCUSSION

In March of 1995, there was a police crackdown on illegal drug use among gang members in the western port city of Inchon. As result of this police effort, 242 urines were submitted for drug testing. The testing revealed that zipeprol, which was not a controlled drug at that time, was at the top of the drug incidence list followed in order by methamphetamine, cannabis and dextromethorphan. A total of 74 urines

Table I. Postmortem zipeprol blood levels in 69 zipeprol-detected cases

case	age	sex	level (ug/ml)	case	age	sex	level (ug/ml)	case	age	sex	level (ug/ml)
1	-	-	2.9	24	25	f	5.7	47	23	m	3.7
2	-	f	4.3	25	17	f	13.9	48	18	m	2.6
3	16	m	8.2	26	18	m	5.3	49	16	m	10.9
4	17	m	10.2	27	16	m	6.1	50	21	f	13.1
5	21	m	20.2	28	31	m	10.5	51	26	m	6.8
6	21	m	14.6	29	15	m	0.8	52	23	m	3.7
7	19	f	8.8	30	23	m	5	53	19	m	-
8	20	m	6.2	31	25	m	8.2	54	18	f	5.8
9	16	f	12.2	32	29	m	13.3	55	27	m	7.5
10	21	m	15.8	33	25	m	15.6	56	21	m	4.3
11	18	m	3.4	34	20	m	5.8	57	20	m	31.4
12	27	m	38.3	35	18	m	7.3	58	19	f	24.7
13	17	m	8.3	36	24	m	22.1	59	22	f	1.3
14	-	f	6.6	37	19	m	4.8	60	21	m	13.9
15	18	f	31.1	38	21	m	7.3	61	21	m	10.5
16	14	m	2.3	39	29	m	4.2	62	20	m	15.8
17	19	f	3.1	40	23	f	8.2	63	25	m	0.1
18	22	m	20.5	41	29	m	10.2	64	21	f	28.6
19	22	f	11.8	42	15	f	8.7	65	19	f	14.3
20	19	m	7.6	43	19	m	11	66	22	m	5.1
21	20	m	16.3	44	17	m	5.6	67	29	f	11.1
22	20	f	11.7	45	19	m	11.7	68	19	f	35.3
23	15	m	7.6	46	32	m	24.8	69	22	f	27.7

were positive for zipeprol, 29 for methamphetamine, 24 cannabis, and 14 for dextromethorphan. Additionally, 11 samples were positive for both dextromethorphan and zipeprol. These findings demonstrated in a clear fashion the abuse potential of these commonly available medicines.

Zipeprol is a non-opiate, antitussive agent. In an abuse context, people take it at a dosage rate 10~15 times higher than that recommended (75 mg single dose) to obtain a hallucinogenic effect (Moroni *et al.*, 1984; Perraro and Berporchia, 1984). During 1991 to 1995, a total of 69 zipeprol related overdose cases occurred throughout the nation. Deaths in these cases due to zipeprol alone totaled 82.6%. The remaining deaths (17.4%) in this group were associated with the combination of zipeprol and dextromethorphan.

Fatalities from the overdose of zipeprol

These fatalities are shown in Table I. In 1991, there were 10 zipeprol related deaths, in 1992, 15 cases, in 1993, 14 cases, 1994, 23 cases, in 1995, 6 cases and in 1996, 1 case. The drop off in case frequency in 1995-96 is in all probability related to government intervention by in-acting controls for the trade and possession of zipeprol. These controls were put into place in September 1995. Table I shows the age, gender and blood level of deceased in total 69 zipeprol overdose cases.

Fig. 1 shows the distribution of deaths involving zipeprol by age and gender. A total of 42 men and 12 women were included with a mean age of 21 years old (range 15~31 years). The male: female ratio was 3.5:1. Nearly 70% of them were male and only 20% were female. The majority, 50% of zipeprol victims were in their twenties with an additional 46% in their teens. This demonstrated the great popularity of zipeprol among a younger age group. It was also possible to break out geographic demographics from the date obtained on these cases. As demonstrated in Fig. 2, among 69 of these deaths the larger Korean cities

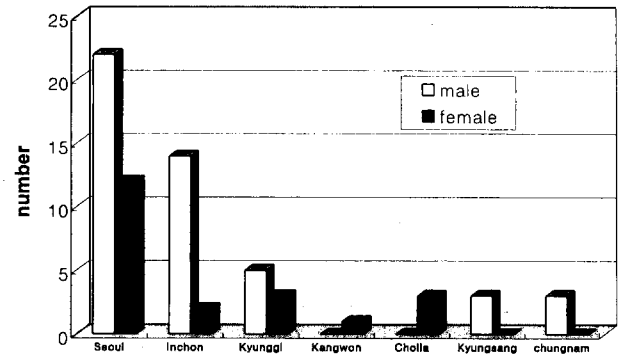

Fig. 2. Distribution of death involving ziperprol (gender by region).

had a higher percent of zipeprol-associated deaths.

Most of these zipeprol-associated deaths were from Seoul and Inchon (34 from Seoul and 16 from Inchon respectively). Seoul and Inchon together demonstrated an 80% cases of zipeprol- associated death in comparison with a 20% for the smaller cities noted. It is important to note that Seoul alone accounted for 50% of the total.

In Seoul and Inchon, male deaths were noted to be higher than the female deaths with 76.6% of the total male deaths due to zipeprol being accounted for in this population. In Fig. 3, the range of zipeprol blood concentrations and the distribution of these concentrations are reported. Overall, the concentration of zipeprol in blood samples ranged from 0.8 to 38.3 μg/mL. This can be compared with the 2.3~38.3 μg/mL concentration range observed from case population reported on 23 fatalities by Yoo *et al.* (1994). In the current case group, 32% of the cases demonstrated a blood zipeprol range of from 5 to 10 μg/mL, 25% of the cases demonstrated a range from 10 to 15 μg/mL, and in 5 cases a range of concentration from 20~40 μg/mL of zipeprol was noted.

Fatalities from the overdose of both zipeprol and dextromethorphan: As discussed above, in order to obtain a stronger hallucinogenic effect, an additional

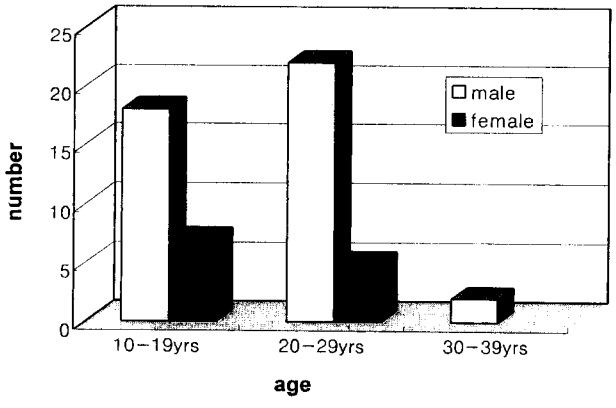

Fig. 1. Disribution of deaths involving zipeprol (gender by age).

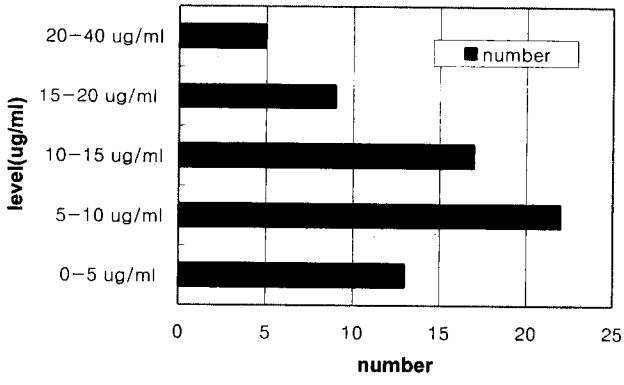

Fig. 3. Range of zipeprol blood levels in drug involved deaths.

Table II. Postmortem blood concentrations of zipeprol and dextromethorphan

case no	age	sex	blood level (ug/ml)	
			ziperol	dextromethorphan
1	19	f	24.7	4.09
2	22	f	1.3	18.3
3	21	m	13.9	2.9
4	21	m	10.5	2.6
5	20	m	15.8	1.2
6	25	m	0.1	1.6
7	21	f	28.6	1.8
8	19	f	14.3	1.4
9	22	m	5.1	1.1
10	29	f	11.1	1.8
11	19	f	35.3	2.9
12	22	f	27.7	11.5

custom of abuse that has presented itself in recent years, is the abuse of both zipeprol and dextromethorphan together. Dextromethorphan, which is an antitussive agent, produces little or no central nervous system (CNS) depression, but manifestations of an acute overdose include hallucination and toxic psychosis (Bem and Peck, 1992). Because a drug abuse custom has emerged to take large amounts of these two agents together for the purpose of recreational drug abuse, 12 fatal poisonings due to the zipeprol and dextromethophan combination have been reported since 1991. Table II shows the age, gender and blood level concentrations of decedents in these 12 zipeprol and dextromethorphan overdose cases.

Zipeprol and dextromethorphan related deaths could also be broken down according to the age, gender and geographic place of origin for each of these 12 decedents. Fig. 4 demonstrates this information in graphic format. The age range of 5 men and 7 women in this population was from 19 to 29 years with an average age of 21.6 years. More females than males died from this overdose combination, with a female/male ratio of 1.4: 1 being observed. The majority of these overdose victims (75%) were in the 20-30 year

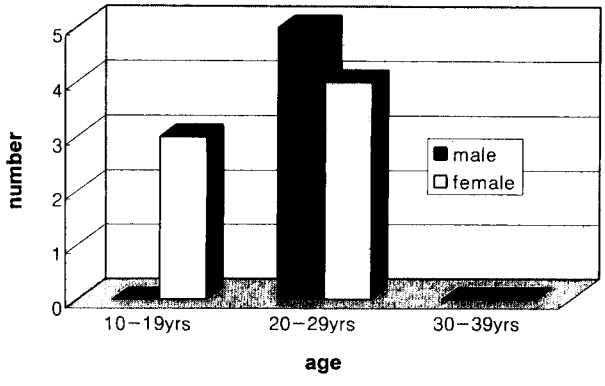

Fig. 4. Distribution of deaths involving zipeprol and dextromethorphan (age by gender)

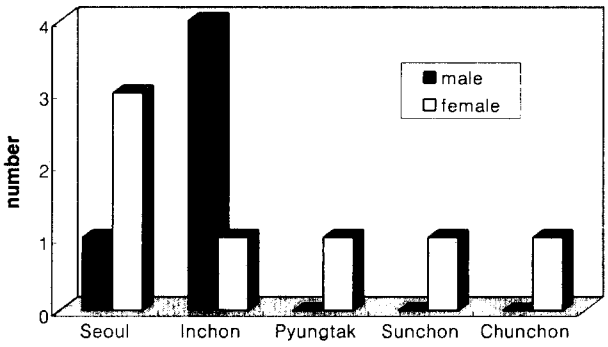

Fig. 5. Distribution of deaths involving zipeprol and dextromethorphan (gender by region)

age group, with remaining 25% of the population being in their teenage years.

In Fig. 5, the distribution of the deaths involving the zipeprol and dextromethorphan combination is shown by gender and region. As with zipeprol alone data presented above, the larger cities had a higher percentage of zipeprol-associated deaths, in this case however, it was the city of Inchon, which had the larger number of cases. Interestingly Seoul, however, demonstrated the greater number of deaths in the female population. The reverse was the case in the city of Inchon. Of the total combined drug death cases, 41.7% occurred in Inchon, while 33.3% of deaths in Seoul. In smaller cities such as Pyungtak, Sunchon and Chunchon, of the cases reported, all deaths were female.

In Fig. 6, the range of plasma concentration of zipeprol and dextromethorphan are compared graphically.

The blood concentration of dextromethorphan in these cases ranged from 1.1 to 18.3 μg/mL which were consistent with levels previously reported by Yoo *et al.* (1988, 1996). Zipeprol in this population, varied from 0.1 to 35.3 μg/mL. In the case of zipeprol, the variation in concentration is as follows: 16.6% of the case group were within 0~5 ug/ml, 8.3% in 5~10 μg/mL, 41.6% in 10~15 μg/mL and 33.3% in a range over 20 μg/mL. In 83.3% of these same cases, the blood concentration of dextromethorphan was in 0~5 μg/mL range, 8.3% in a 10~15 μg/mL range and 8.3%

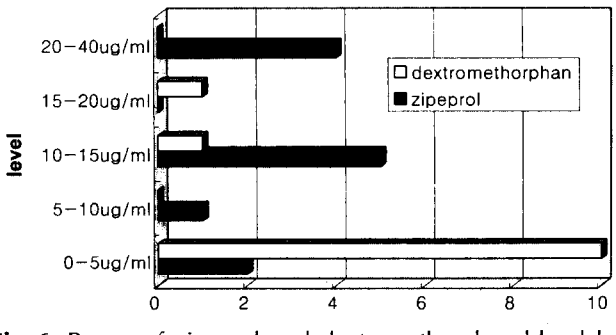

Fig. 6. Range of zipeprol and dextromethorphan blood levels in drug-related deaths.

in 15~20 μg/mL.

CONCLUSION

The present study demonstrates age, gender and intra-city differences in the demographic aspects of deaths associated with zipeprol. For ninety six percent of cases involving zipeprol alone, the victims were in their teens and twenties. This contrasts with the zipeprol and dextromethorphan combination drug deaths, where 100% of these victims were in this age range. The male/female ratio in zipeprol related death was 3. 5:1 whereas in the combined drug death combination this ratio was 0.71: 1. Most of these zipeprol and/or dextromethorphan-associated deaths occured the larger cities of Seoul and Inchon.

The blood concentration of zipeprol ranged from 0. 8 to 38.3 μg/mL in single drug involved deaths, while zipeprol varied from 0.1 to 35.3 μg/mL in zipeprol and dextromethorphan victims. The blood concentration of dextromethorphan in the late group ranged from 1.1 to 18.3 μg/mL. Finally, it is very important to note that with the recognition of the drug abuse potential of zipeprol, its placement on the list in Korea as a controlled substance was an important and timely action in improving community health. This is demonstrated by the significant drop-off in zipeprol related drug deaths following this action.

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