TITLE PAGE

1. Title of the paper

   Characteristics and trends of emergency patients with drug overdose in Osaka

2. A short running title

   Patients with drug overdose 1

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ABSTRUCT

Background

Drug overdose is an important issue in emergency medicine. However the study which covers all the patients transported by ambulances has not been carried out sufficiently.

Aim

We attempted to clarify problems of suspected drug overdose patients transported by ambulances.

Methods

This is a prospective population-based cohort study. Data were collected by the emergency medical service (EMS) crews in Osaka City between January 1998 and December 2010.

Results

Drug overdose cases increased annually from 1136 in 1998 to 1822 in 2010 ($P<0.0001$ for trend). In these cases, age between 16 and 40 were dominant in number and the age distribution did not change over time. The age of non-overdose cases increased ($p<0.0001$ in trend) with patients aged ≧66 years old becoming most common in recent years reflecting the aging of society. Males comprised most

non-overdose patients, but the percentage of females increased annually ($p<0.0001$ in trend). Females comprised approximately 70 % in overdose cases annually throughout the study period.

The duration from the emergency call to the arrival at the hospital for overdose patients has increased markedly in recent years. It takes more time to take acceptance from hospital to care the patients of suspected overdose than before.

Conclusion

The characteristics of drug overdose patients are clearly different from those of non-overdose patients. Recent trends of drug overdose patients demonstrate the accelerated burden on emergency services.

KEY WORDS

Ambulance diversion, Drug overdose, Emergency Medical Services, Hospital arrival time, Transportation of patients

INTRODUCTION

Background

Drug overdoses are among the most important issues in emergency medicine and comprise of a diversity of problems. These includes epidemiological poisoning deaths (1, 2), poisoning by a specific drug (3-6) , issues concerning suicide (7), and preventive strategies for drug overdoses (8-10). However thereat to emergency system by drug overdose has not been examined in detail. Studies have been performed for all cases treated in emergency departments or hospitals (11, 12). However to our knowledge, a study of emergency cases focused on drug overdose patients transported by ambulances has not been carried out sufficiently. This background led us to analyze emergency patients transported by ambulances in order to describe comprehensive information by covering all emergency patients in certain area.

Recent studies based on emergency medical service (EMS) records have delivered considerable products for resuscitation care of out-of-hospital arrest patients and traumatized patients (13, 14).These products make our investigation consequential as the first step of analyses of overdoes patients in emergency services as a population-based study.

Aim of this study were to determine the characteristic features of the overdose

patients compared to non-overdose patients based on the descriptive epidemiological data such as age and sex. Based on these data, we also performed longitudinal analysis of the increased burden on the emergency system due to overdose patients.

MATERIALS AND METHODS

Setting

This is a population-based observational study in Osaka City which is a metropolis in the western part of Japan. The population of Osaka City was 2 665 314 as of October 1, 2010. The male and female population were 1 293 798 and 1 371 516 (51.5%), respectively. The age distribution of this city's inhabitants was 12.7%, 34.1%, 32.2 %, 20.9% for 0 - 15 years old, 16 - 40 years old, 40 - 65 years old, ≧66 years old, respectively.

Participants

Participants of our study were all the emergency patients who called the ambulance in Osaka City from January 1, 1998 and December 31,2010. The EMS system in Osaka City is operated by the Municipal Fire Department and is activated by dialing 119. All calls were received and recorded by a single dispatch center and ambulances were transferred from 25 fire stations distributed throughout the city. The EMS system is operated by a single-tiered system. When the ambulance reaches the patients, the crew evaluate the patient's condition and determine the most suitable hospital for the patient and take contact the hospital by telephone to confirm availability for receiving the patients.

Outcome Measures

Annual trends in demographic data such as age and sex were evaluated for emergency patients with a focus on drug overdose cases. The time for transportation was measured as the time from the emergency call to arrival at the hospital. Consciousness level was used as an indicator of the patient's condition, since this could influence the time factor. The number of hospitals telephoned by EMS personnel to confirm the availability to receive each patient was also evaluated.

We found in 1312 cases age or sex information were missing in 13 years. We treat them as missing data.

Data Collection and Processing

Data from all emergency patients transported by ambulances were collected prospectively by EMS crews in Osaka City. These were typed and made electronically available by the EMS crews themselves. The research protocol was approved by the institutional review board of Kinki University, with the assent of the EMS Osaka.

Cases of drug overdose are usually **called** as "suspected" overdose and most were caused by miscellaneous drugs. In the International Classification of Diseases Tenth Revision (ICD-10) , the codes from T36 to T50 used to categorize drug overdose cases based on the complexity of drug poisoning. We classified the drugs types

according to these codes based on information from ambulance crews collected in interviews with bystanders or objective evidence such as the label on a drug container. Data collected between January 1, 2010 and December 31, 2010 were used in this analysis.

Analysis

Temporal trends were tested using Cochrane-Armitage and Jonckheere-Terpstra tests based on the data distribution, after dividing the patients into overdose and non-overdose cases. The independent association between calendar year and proportion of overdose patients compared to non-overdose patients, was evaluated with adjustment for age and sex. All statistical analyses were performed with SAS statistical software (version 9.3, SAS Institute, Cary, North Carolina). All tests were two-tailed, and p values less than 0.05 were regarded as statistically significant.

RESULTS

Increase in drug overdose patients

In 1998, 1136 overdose and 134 098 non-overdose patients were transported to hospitals by ambulances in Osaka City. The respective numbers increased to 1822 and 163 367 ($P<0.0001$ for trend). The age- and sex-adjusted odds ratio for the incidence of drug overdose compared to non-overdose cases was 1.39 (95% confidence interval [CI], 1.29 to 1.50) in 2010 as compared with 1998 (Fig 1).

Characteristics of drug overdose patients

The age distribution of the drug overdose cases differed from those of non-overdose patients. Patients aged 41-65 years old accounted for the highest number of non-overdose cases (37%) in 1998. While in 2010, ≧66 years old comprised 43% of these cases($p<0.0001$ for trend). This result reflects the general aging in society. Most overdose cases involved patients aged 16-40 years old in each year (Table 1).

Females accounted for approximately 70% of overdose cases with no annual change in this value. In contrast, most non-overdose patients were males throughout the study period, although the percentage of females increased annually ($P<0.0001$ for trend). (Table 1).

Time factors

For drug overdose patients, the time from the emergency call to arrival at hospital has increased markedly in recent years (Fig 2a). The percentage of these patients with impaired consciousness did not change during study period suggesting this increased time period would not be attributable to increase in number of critically ill patients (Fig 2c). The number of contact calls for each overdose patients increased in recent years (Fig 2a).

For non-overdose patients, the time from the emergency call to arrival at hospital has increased consistently from 20 min in 1998 to 27 min in 2010 (Fig 2b). The median number of contact calls for each emergency non-overdose patient remained at one during the study period. However, it has recently become common for EMS crews to contact two or three hospitals by telephone before transporting a patient.

Categories of causative drugs

Of the 1822 overdose cases in 2010, **over half** were coded in the T42 group of sedative, hypnotic, antiepileptic, and antiparkinsonism as causative agents. (Table 2). **Cases of** the T43 group of psychotropic drugs **and the T42 group were approximately two thirds of all the cases**. Only 8 cases involved narcotics and psychodysleptics. The numbers of other cases were limited and EMS crews paid particular attention cases in which somatic function might have been affected. In 30 such cases, we could not

exclude the possibility that **the dosage was in normal range. It is possible that the event was caused by an allergic reaction or adverse event** of drugs rather than an overdose. **Number of multiple code cases was 101 in which the patients took variety of kinds of drugs**. EMS crews did not record the exact name of the causative drugs in **558** cases.

DISCUSSION

Our results clearly show that cases of suspected drug overdose have increased. The number of all emergency cases has also increased due to particular increase in number of older emergency patients. However the increase in overdose patients was demonstrated after age and sex adjusted. Furthermore we show that the age and sex distribution patterns and trends in overdose cases differed from those in non-overdose cases. Although time for emergency transport of non-overdose patients has increased, this tendency has particularly accelerated in overdose patients in recent years.

The greater availability and use of drugs have placed more emphasis on the importance of emergency care for patients with drug overdose. It is one of contemporary problems in emergency care. Population-based analysis of prehospital data provide important information for understanding the features of specific kinds of emergency patients would have an impact on strategies for patient care or disease preventions in areas such as out-of-hospital cardiac arrest or in trauma (13, 14). Data from this approach may give us a different view by the analysis of the data from the cases in specific hospitals or for specific drugs.

Our results show that drug overdose patients represented approximately 1% of all emergency patients. This result is consistent with other studies (15, 16). However,

the number of opioid overdoses in our study was small compared to reports from other cities (17, 18). Merchant et al. found that 18.6 % of ambulance runs for drug overdose were for cases with suspected opiate overdose (18). The small number of such cases in Osaka reflects the strict prohibition of illicit drugs are the extremely limited use of these drugs in Japan compared with other countries. Osaka police statistics (including the city area and surrounding suburbs of Osaka prefecture) for 2010 showed only 20 arrests involving opiates including heroin and cocaine (19). The CDC in the US emphasizes not only and opioid analgesics also any drug of the codes T36-T50 other than T40 are noted as a cause of drug poisoning by overdose (1). Our results suggest that drug overdose with drugs other than opioid analgesics is a common and shared problems worldwide (3, 20). **In opioid abuse in other countries, it has been reported that male is dominant as patients of overdose (17,18, 21). In contrast in our report in which sedative drugs other than opioid analgesics are main causes of drug overdose, female was dominant as overdose patients. This has been also reported in other survey from hospital-based studies (22).**

Emergency needs in Japanese society recently changed from a severe trauma model by traffic accidents or work injuries to a disease model for elderly patients. As aging in society proceeds, the number and proportion of older women has increased

among emergency patients. In contrast to this trend for non-overdose patients, the age and sex distribution of overdose patients has remained unchanged. This suggests that the increase overdose patients has not arisen from aging of society, although it has been suggested that aging society influences this problem due to an increased number of cases of self-poisoning in older adults and adverse drug events in older patients (23, 24).

Our findings clearly demonstrate an increased burden on the emergency medical system. A trend for an increased time from the emergency call to arrival at hospital was found for all emergency patients, and this increase was particularly marked for drug overdose cases. This problem may come from the increase in the total number of cases and the difficulty to **get permission from hospital to transport** these patients to hospitals. **It is essential to overcome this problem to discuss about sedative abuse in this country, although this problem related with various kind of issues including the improvement of EMS system (25).** Characteristics of suspected overdose cases are unique among emergency cases and involve problems that are beyond technical issue of medical care and are a potential threat to the whole emergency system (26, 27).

Limitations

Limitations of this study include that data were collected in the process of

prehospital care. Our information on the event is limited in terms of causative drugs compared with a hospital study. EMS crews could consult with ER physicians about the overdose drugs upon hospital arrival. However their information was limited in the initial phase of an event and ambulance crews did not necessarily follow the cases. In addition, we could not exclude the possibility to slip into other substances such as agricultural chemicals as report errors of EMS crews.

CONCLUSION

In conclusion, this study shows that characteristics and the trends of drug overdose patients are clearly different from those of non-overdose patients. The features of drug overdose cases suggest that unique emergency needs in drug overdose. It takes more time to take acceptance from hospital to care the patients with drug overdose in recent years. Recent trends of drug overdose patients demonstrate the accelerated burden on emergency services.

FUNDING SOURCE

This study was supported by Grants-in-Aid for Scientific Research (KAKENHI) of the Ministry of Education, Culture, Sports, Science and Technology, Japan (No.25670771) .

CONFLICT OF INTEREST

None.

ACKNOWLEDGMENTS

We thank all the emergency medical service personnel and concerned

physicians in Osaka City, and the staffs of Osaka City Municipal Fire Department, particularly Sumito Hayashida and Takeo Oka.

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FIGURE LEGENDS

Figure 1. The adjusted odds ratio of number of overdose patients by year.

The model was adjusted for patients' age and sex.

The reference year was 1998. I bars represent 95% confidence intervals.

Figure 2. Annual trend for time factors concerning emergency patients.

In overdose cases, time periods from emergency call to hospital arrival were increased markedly ($p<0.0001$ for trend).

The number of hospital to which the EMS crew took contact for each patient was labeled as median (quartiles) (panel a).

Although in non-overdose cases time periods from emergency call to hospital arrival were increased ($p<0.0001$), the increase was not accelerated compared in overdose cases.

The number of hospital to which the EMS crew took contact was staining one as median. (panel b).

Number and percentage of patient whose consciousness impaired were shown in overdose cases (panel c), and in non-overdose cases (panel d).

Fig.1

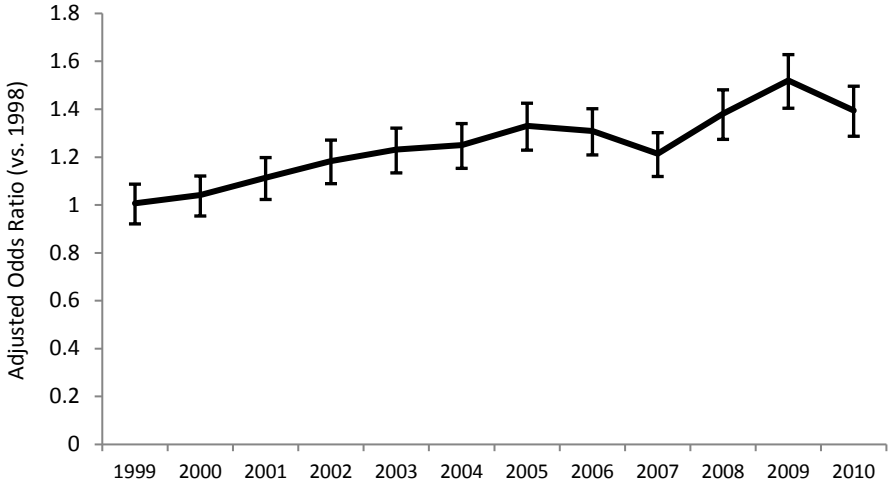
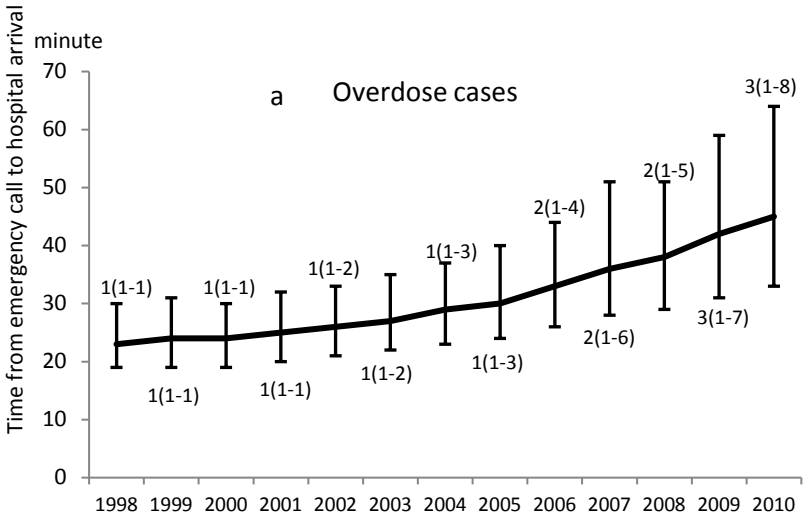
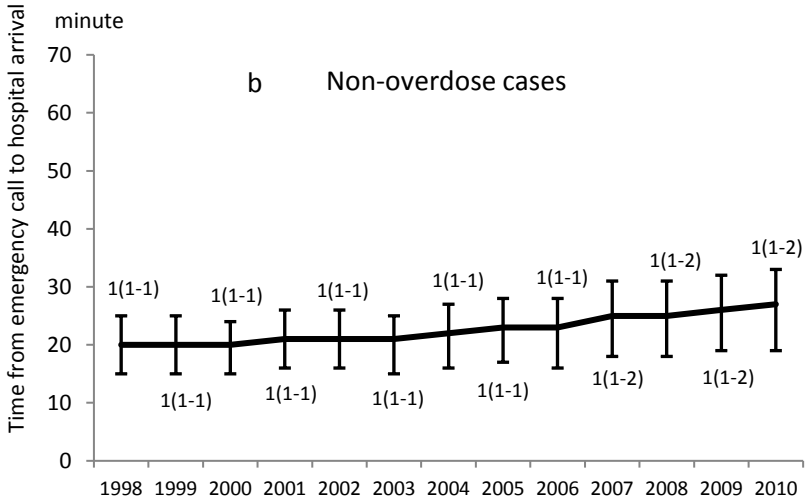
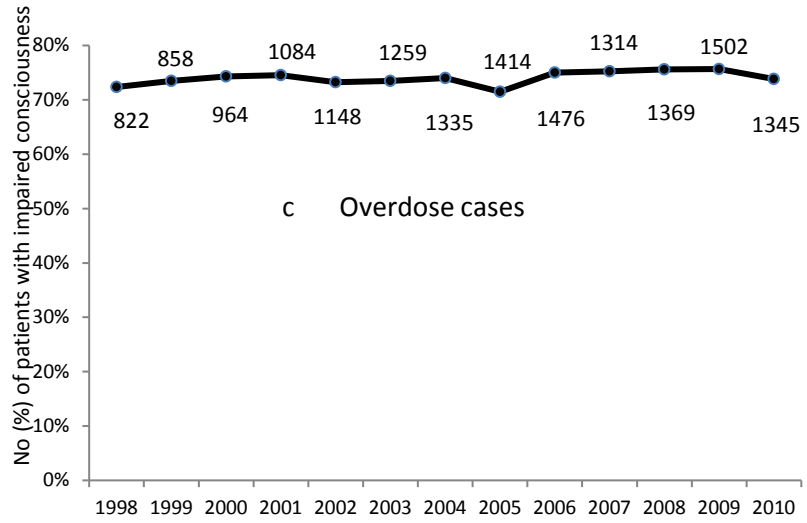

Adjusted Odds Ratio (vs. 1998)
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010

Table 1. Annual trends in age and sex

		1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Significant for Trend
Non-overdose cases	*N.*	134098	136807	146778	154100	156476	164046	170767	176669	177707	172177	159440	159266	163367	P<0.0001 for number
	Age, y,														
	mean (SD)	48.3 ±23.6	48.9 ±24.1	49.1 ±24.0	49.5 ±24.2	50.1 ±24.4	50.4 ±24.7	51.2 ±24.8	51.9 ±24.9	52.1 ±25.0	52.8 ±25.1	53.7 ±25.0	53.9 ±25.4	55.3 ±25.2	
	Median (IQR)	51 (28-66)	52 (29-68)	52 (29-68)	53 (29-69)	54 (30-70)	54 (30-70)	55 (31-71)	56 (31-72)	57 (32-73)	58 (32-74)	59 (34-74)	59 (34-75)	61 (36-76)	
	Age distribution														
	0 -15	12132	12574	12973	13600	14098	14943	15049	15319	15105	14577	12944	13997	12918	
	(%)	(9.0)	(9.2)	(8.8)	(8.8)	(9.0)	(9.1)	(8.8)	(8.7)	(8.5)	(8.5)	(8.1)	(8.8)	(7.9)	P<0.0001
	16-40	36264	36711	40247	41680	41388	43456	44136	44882	45501	42690	37953	36461	35565	for age
	(%)	(27.0)	(26.8)	(27.4)	(27.0)	(26.5)	(26.5)	(25.8)	(25.4)	(25.6)	(24.8)	(23.8)	(22.9)	(21.8)	
	41-65	50523	48856	51444	52643	51671	51695	52574	52700	52229	48955	44579	43317	43741	
	(%)	(37.7)	(35.7)	(35.0)	(34.2)	(33.0)	(31.5)	(30.8)	(29.8)	(29.4)	(28.4)	(28.0)	(27.2)	(26.8)	
	66-	35173	38666	42114	46177	49318	53952	59007	63768	64872	65955	63964	65491	71143	
	(%)	(26.2)	(28.3)	(28.7)	(30.0)	(31.5)	(32.9)	(34.6)	(36.1)	(36.5)	(38.3)	(40.1)	(41.1)	(43.5)	
	Male, N	82664	83150	88522	92153	92380	95774	97940	100006	99167	95723	88174	88111	89110	
	(%)	(61.7)	(60.8)	(60.4)	(59.9)	(59.1)	(58.4)	(57.4)	(56.7)	(55.8)	(55.6)	(55.3)	(55.3)	(54.6)	P<0.0001
	Female, N	51264	53522	58134	61805	63949	68162	72701	76559	78409	76337	71266	71155	74257	for sex
	(%)	(38.3)	(39.2)	(39.6)	(40.1)	(40.9)	(41.6)	(42.6)	(43.4)	(44.2)	(44.4)	(44.7)	(44.7)	(45.6)	
Overdose cases	*N.*	1136	1168	1297	1454	1568	1714	1804	1978	1968	1746	1811	1985	1822	P<0.0001 for number
	Age, y,														
	Mean (SD)	37.9 ±16.5	38.5 ±17.1	37.4 ±16.4	37.0 ±15.9	36.6 ±16.0	36.1 ±16.0	36.4 ±15.8	35.5 ±15.4	35.4 ±15.6	36.1 ±16.0	36.8 ±16.4	37.5 ±16.4	38.6 ±17.1	
	Median (IQR)	34 (26-49)	34 (26-50)	33 (26-48)	34 (26-47)	33 (25-45)	33 (25-45)	34 (25-45)	32 (25-43)	33 (24-42)	33 (24-43)	34 (24-45)	34 (25-46)	35 (26-47)	
	Age distribution														
	0 -15	40	29	35	35	40	52	53	57	55	44	41	44	47	
	(%)	(3.5)	(2.5)	(2.7)	(2.4)	(2.6)	(3.0)	(2.9)	(2.9)	(2.8)	(2.5)	(2.3)	(2.2)	(2.6)	P=0.52
	16-40	667	709	814	939	1012	1119	1187	1345	1345	1165	1170	1255	1084	for age
	(%)	(58.7)	(60.7)	(62.8)	(64.6)	(64.5)	(65.3)	(65.8)	(68.0)	(68.3)	(66.7)	(64.6)	(63.2)	(59.5)	
	41-65	340	326	356	384	405	437	456	475	446	421	466	536	514	
	(%)	(29.9)	(27.9)	(27.4)	(26.4)	(25.8)	(25.5)	(25.3)	(24.0)	(22.7)	(24.1)	(25.7)	(27.0)	(28.2)	
	66-	89	104	92	96	111	106	108	101	122	116	134	150	177	
	(%)	(7.8)	(8.9)	(7.1)	(6.6)	(7.1)	(6.2)	(6.0)	(5.1)	(6.2)	(6.6)	(7.4)	(7.6)	(9.7)	
	Male, N	369	392	448	479	487	541	516	557	501	465	489	611	541	
	(%)	(32.5)	(33.6)	(34.5)	(32.9)	(31.1)	(31.6)	(28.6)	(28.2)	(25.5)	(26.6)	(27.0)	(30.8)	(29.7)	P<0.0001
	Female, N	767	776	849	975	1081	1173	1288	1421	1467	1281	1322	1374	1281	for sex
	(%)	(67.5)	(66.4)	(65.5)	(67.1)	(68.9)	(68.4)	(71.4)	(71.8)	(74.5)	(73.4)	(73.0)	(69.2)	(70.3)	


minute
Time from emergency call to hospital arrival
a Overdose cases
0
10
20
30
40
50
60
70
1(1-1)
1(1-1)
1(1-1)
1(1-1)
1(1-2)
1(1-2)
1(1-3)
1(1-3)
2(1-4)
2(1-6)
2(1-5)
3(1-7)
3(1-8)
1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010


minute
Time from emergency call to hospital arrival
b Non-overdose cases
0
10
20
30
40
50
60
70
1(1-1)
1(1-1)
1(1-1)
1(1-1)
1(1-1)
1(1-1)
1(1-1)
1(1-2)
1(1-2)
1(1-2)
1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010


No (%) of patients with impaired consciousness
c Overdose cases
0%
10%
20%
30%
40%
50%
60%
70%
80%
822
858
964
1084
1148
1259
1335
1414
1476
1314
1369
1502
1345
1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010

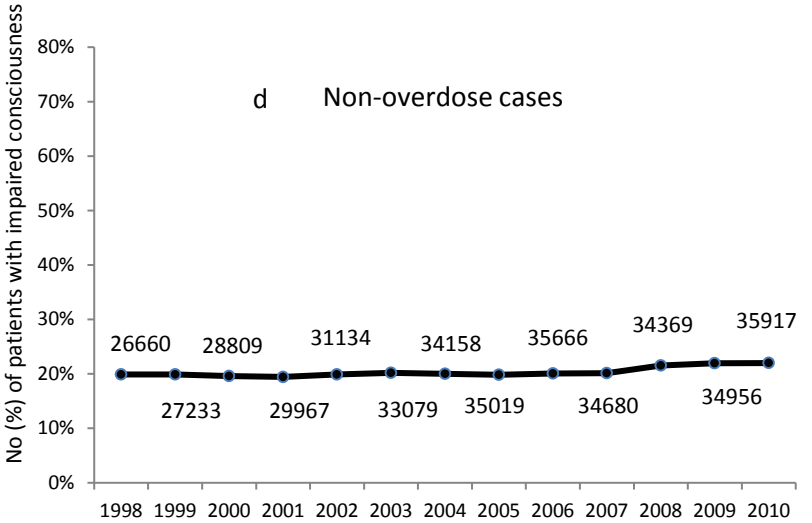

No (%) of patients with impaired consciousness
d Non-overdose cases
0%
10%
20%
30%
40%
50%
60%
70%
80%
26660
27233
28809
29967
31134
33079
34158
35019
35666
34680
34369
34956
35917
1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010

Table 2. Drug category based on the ICD-10 Code

T36-50 Poisoning by drugs, medicaments and biological substances	
T36 Poisoning by systemic antibiotics	8
T37 Poisoning by other systemic anti-infectives and antiparasitics	2
T38 Poisoning by hormones and their synthetic substitutes and antagonists, not classified elsewhere	23
T39 Poisoning by nonopioid analgesics, antipyretics and antirheumatics	60
T40 Poisoning by narcotics and psychodysleptics [hallucinogens]	6
T41 Poisoning by anaesthetics and therapeutic gases	4
T42 Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs	1038
T43 Poisoning by psychotropic drugs, not classified elsewhere	108
T44 Poisoning by drugs primarily affecting the autonomic nervous system	0
T45 Poisoning by primarily systemic and haematological agents, not classified elsewhere	0
T46 Poisoning by agents primarily affecting the cardiovascular system	13
T47 Poisoning by agents primarily affecting the gastrointestinal system	17
T48 Poisoning by agents primarily acting on smooth and skeletal muscles and the respiratory system	49
T49 Poisoning by topical agents primarily affecting the skin and mucous membranes and by ophthalmological, otorhinolaryngological and dental drugs	3
T50 Poisoning by diuretics and other and unspecified drugs, medicaments and biological substances	35
unkown	**558**