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Sedative-Hypnotic Medication Exposures and Poisonings in Izmir, Turkey*

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Abstract: The aim of this study was to analyse intoxications concerning sedative-hypnotic medication patients admitted to the Department of Emergency Medicine in Dokuz Eylul University Hospital (EMDEU) between 1993 and 2005. Demographics of the patients, characteristics of sedative-hypnotic exposures, performed treatment attempts and outcome of the poisoned patients were recorded on standard data forms that were later entered into a computerized database programme. Related to the sedative-hypnotic exposures, 686 poisoning cases were admitted to the EMDEU. Mean age was 10.8 ± 6.5 years among the paediatric age group (<17 years old, 169, 24.6%) and 30.3 ± 12.8 years among the adult group (>17 years old, 509, 74.2%). The most common sedative-hypnotic agents were benzodiazepines (286, 35.8%), alprazolam accounted for 41.6% of them (119). Most of the patients admitted to EMDEU were asymptomatic (61.7%). Observation alone was recommended in 53.9% of EMDEU cases. Although prescription of benzodiazepines is restricted, benzodiazepine was the most common cause of sedative-hypnotic medication exposures. As only a minority of patients (3%) had clinically serious signs and symptoms, most of the overdoses might be under toxic levels or the decontamination methods might be efficient. In this study, the clinical outcome of the patients is relatively better than previous results described in literature.

Sedative-hypnotic medications have sedative (tranquilizing) effects when ingested in small amounts; however, if used in larger doses, they act as hypnotics. Despite the fact that a great majority of these medications are prescribed by the physicians, they have recently been much abused and incidents of sedative-hypnotic-related poisoning exposures have increased dramatically. Sedative-hypnotic ingestion at high doses may result in death without appropriate and adequate treatment [1]. With regard to the data gathered from all poison control centres all over the world, it has been stated that 56.6–69.1% of poisoning incidents have occurred as a result of ingestion of medications [2,3]. Among all medication-related poisonings, almost 5.3% of them are caused by sedative-hypnotic antipsychotics. Sedative-hypnotic antipsychotics are considered as causative agents for adult poisonings and all poisoning-induced deaths, ranking the second place (11.7%) [2].

Benzodiazepines are generally used in the treatment of anxiety, insomnia, seizures, medication-related agitation and alcohol withdrawal syndrome. Overdose of pure benzodiazepines very rarely results in death. However, concomitant ingestion of sedative-hypnotics with alcohol or other sedative-hypnotic medications may result in severe poisoning and death [4]. In addition, in therapeutic doses, benzodiazepines have many side effects on the cardiovascular, central nervous, endocrine, respiratory, metabolic, gastrointestinal, haematological, genitourinary systems [5].

No sufficient epidemiologic research is available concerning the frequency and severity of sedative-hypnotic medication-related poisoning exposures in our country. The objective of our study is to present demographic features, clinical findings and treatment attempts with regard to sedative-hypnotic exposures admitted to the Department of Emergency Medicine in Dokuz Eylul University Hospital (EMDEU) between 1993 and 2005.

Materials and Methods

A cross-sectional, descriptive review with regard to all cases of sedative-hypnotic exposures between 1993 and 2005 admitted to the EMDEU was conducted with the approval of Institutional Ethics Committee of the Dokuz Eylul University, School of Medicine. The study population are patients with sedative-hypnotic exposure from the Dokuz Eylul University Drug and Poison Information Center (DDPIC) archives and some with admission to EMDEU are included in the study. In our emergency department, all poisoning patients admitted to EMDEU are consulted to DDPIC after completion of physical examination, and they are managed according to the protocol of poisoned patients. DDPIC is one of three poison information centres throughout Turkey and it mainly serves physicians and the public of the Aegean region of Turkey.

Data regarding demographics, sedative-hypnotic medication type, distribution according to month and year, route and reason for the exposure, time and circumstances of poisoning (unintentional, intentional and unknown), clinical effects, Glasgow Coma Scale (GCS) score, methods of management, length of hospital stay and outcome (complete recovery or death) were recorded on standard data forms. Ages of patients were categorized as 0 to 17 for children, 18 and more for adults. The sedative-hypnotics were categorized

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Table 1.

The gender and age distribution of sedative-hypnotic exposures.

	Children		Adults		Undetermined		Total	
	No.	%	No.	%	No.	%	No.	%
Gender								
Male	47	21.3	171	77.4	3	1.3	221	100.0
Female	121	26.2	337	72.9	4	0.9	462	100.0
Undetermined	1	33.3	1	33.3	1	33.3	3	100.0
Age								
Mean ± S.D.	10.8 ± 6.5 years		30.3 ± 12.8 years				25.5 ± 14.3 years	
Range	1 month–17 years		18–88 years				1 month–88 years	

into eight groups: benzodiazepines, barbiturates, antihistamines, chloral hydrates, antipsychotics, anticonvulsants, muscle relaxants and anti-emetics. The severity of clinical manifestations were graded into asymptomatic, mild, moderate or severe and assessed according to the European Association of Poison Centers and Clinical Toxicologists, International Program on Chemical Safety Poisoning Severity Score [6]. Statistical analysis was performed by using the chi-square test (SPSS 11.0 Standard Version, SPSS Inc., Chicago, IL, USA). Results were considered statistically significant when $P < 0.05$. Data in this article are provided as tables and charts by means of Microsoft Excel (Redmond, WA, USA).

Results

Among sedative-hypnotic poisoning exposures, 686 cases (9.4%) were admitted to the EMDEU. Most of the sedative-hypnotic exposures were in adults (74.2%). Women dominated in all age groups. Women-to-men ratio was 2.1:1 (table 1).

The seasonal distribution in sedative-hypnotic exposures peaked in August (10.3%). Median time elapsed between sedative-hypnotic exposures and admission time was 2 hr in 50.7% of cases (mean 5.1 ± 11.9, range: 0–168 hr). Approximately, in one third of cases (207, 30.2%), sedative-hypnotic exposures occurred at nighttime (8 p.m. to 12 p.m.).

Acute exposure was the main type of sedative-hypnotic exposures in 96.2% (660) of the cases, followed by chronic (22, 3.2%) and unknown (4, 0.6%).

Regarding intentional sedative-hypnotic exposures (suicidal attempt, misuse or abuse), predominance was measured for all age groups (82.9%, 561 cases), except for the children who were poisoned accidentally. When the causes of poisonings were compared, intentional sedative-hypnotic exposures were higher in adults than in children ($\chi^2 = 129.380$, $P < 0.0001$). When the relation between the cause of poisoning and gender was analysed, it was determined that intentional exposure to sedative-hypnotics was more common in women than men (69.7% versus 30.3%). Intentional sedative-hypnotic exposures were found to be significantly higher for women than for men for all age groups ($\chi^2 = 6.713$, $P < 0.01$). While intentional sedative-hypnotic exposures were at a significantly higher rate in girls than boys ($\chi^2 = 13.736$, $P < 0.001$), in adults, the rate of intentional exposures in women did not reach a statistically significant value ($\chi^2 = 0.832$, $P > 0.05$; table 2).

Benzodiazepines were the most frequent cause of sedative-hypnotic exposures (35.8%) followed by antipsychotics (16.2%) and antihistamines (14.0%). The most common benzodiazepines were alprazolam (41.6%) and diazepam (32.9%). Total number of sedative-hypnotic agents of 686 patients in the study was measured as 1436 and the number of agents concurrent to sedative-hypnotics was 798 (table 3). The most common medications ingested together with sedative-hypnotics were paracetamol (64, 34.0%), opipramol (36, 19.1%), fluoxetine (34, 18.1%) and sertraline (19, 10.1%). The rate of taking alcohol together with sedative-hypnotic medications was 18.6%.

While 15.7% (108) of patients were regularly using the medication ingested, 28% (192) were not taking sedative-hypnotics. In approximately half of the patients (57.3%, 386), no information about their taking sedative-hypnotic medications earlier or not was available. With regard to intentional sedative-hypnotic exposures, 87.0% (94) of the patients were exposed to sedative-hypnotic medications that had been taken regularly in their past medical history.

Table 2.

Distribution of causes for sedative-hypnotic exposures by age and gender.

	Children				Adults				Total			
	Male		Female		Male		Female		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Intentional	16	34.0	79	65.3	154	90.1	312	92.6	170	77.9	391	85.4
Unintentional	28	59.6	30	24.8	5	2.9	4	1.2	33	15.1	34	7.4
Adverse reaction	2	4.3	7	5.8	6	3.5	10	2.9	8	3.7	17	3.7
Unknown	1	2.1	5	4.1	6	3.5	11	3.3	7	3.3	16	3.5
Total	47	100.0	121	100.0	171	100.0	337	100.0	218	100.0	458	100.0

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Table 3.

Distribution of exposures according to the classification of sedative-hypnotics.

Classification of sedative-hypnotics	Subgroups	No.	%
Benzodiazepines	Alprazolam	119	41.6
(286, 35.8%)	Diazepam	94	32.9
	Chlordiazepoxide	16	5.6
Antipsychotics	Thioridazine	33	25.6
(129, 16.2%)	Haloperidol	21	16.3
	Zopiclon	16	12.4
Antihistamines	Doxylamine	23	20.5
(112, 14.0%)	Hydroxizin	20	17.9
	Pheniramin maleat	12	10.7
	Cetirizine	12	10.7
Muscle relaxants	Phenprobamat	64	64.0
(100, 12.5%)	Tizanidine	12	12.0
	Thiocolchicoside	7	7.0
Anticonvulsants	Carbamazepine	38	49.4
(except benzodiazepines,	Valproic acid	19	24.7
barbiturates) (77, 9.6%)	Phenytoin	14	18.2
Other sedative-hypnotics	Biperiden	25	35.2
(71, 8.9%)	Lithium	17	23.9
Barbiturates (23, 2.9%)	Phenobarbital	23	100.0
Total		798	100.0

In our study, 69 (10.1%) of patients with intentional ingestion of sedative-hypnotics had medical histories of suicidal attempts earlier. For 167, it was their first suicidal attempt (24.3%).

Ingestion was the main route of exposure in 99.1% of sedative-hypnotic exposures. Amounts of sedative-hypnotics ingested were graded as toxic (43.9%), non-toxic (33.1%) and unknown (23.0%). Toxic and non-toxic amounts of sedative-hypnotic exposures were not found to be significantly different in children and adults ($\chi^2 = 0.549$, $P > 0.05$). Clinical signs and symptoms of sedative-hypnotic poisonings were graded as mild (27.4%), moderate (6.7%) or severe (4.2%). When grades of clinical manifestations of poisoning were compared, no difference was found on the presence of clinical signs and symptoms between children and adults ($\chi^2 = 0.696$, $P > 0.05$; table 4).

The most common symptoms of sedative-hypnotic exposures were drowsiness, nausea and slurred speech (table 5). Most of the patients with sedative-hypnotic exposure (95.5%, 278) had GCS scores of 10 and higher. When the low (<10) and high (≥10) GCS scores were compared, no difference was found between in toxic and non-toxic sedative-hypnotic exposures ($\chi^2 = 0.481$, $P > 0.05$).

Table 4.

Distribution of medical outcome of sedative-hypnotic exposures by age.

Scoring of clinical signs and symptoms	Children		Adults		Total	
	No.	%	No.	%	No.	%
Asymptomatic	110	65.1	311	61.1	423	61.7
Mild	44	26.0	138	27.1	188	27.4
Moderate	9	5.3	37	7.3	46	6.7
Severe	6	3.6	23	4.5	29	4.2
Total	169	100.0	509	100.0	686	100.0

Table 5.

Distribution of symptoms by age.

Symptoms	Children		Adults		Total	
	No.	%	No.	%	No.	%
Drowsiness	15	25.0	77	27.9	92	27.4
Nausea	3	5.0	35	12.7	38	11.3
Slurred speech	6	10.0	29	10.5	35	10.4
Confusion	2	3.3	32	11.6	34	10.1
Vertigo	7	11.7	21	7.6	28	8.3
Dizziness	5	8.3	20	7.2	25	7.4
Agitation	4	6.7	10	3.6	14	4.2
Hallucination	5	8.3	3	1.1	8	2.4
Nistagmus	0	0.0	6	2.2	6	1.8
Dystony	5	8.3	0	0.0	5	1.5
Delirium	3	5.0	1	0.4	4	1.2
Ataxia	1	1.7	3	1.1	4	1.2
Others	4	6.7	39	14.1	43	12.8
Total	60	100.0	276	100.0	336	100.0

Gastrointestinal decontamination methods were already applied for 19.4% of poisoned patients when they were admitted to EMDEU. After admission to EMDEU, 43.0% of patients were decontaminated according to the recommendations of DDPIC. Specific antidotes (flumazenil for three patients, sodium bicarbonate for one patient, and kayexalate for one patient) were already given to 0.7% of all before admission to EMDEU. After admission, flumazenil and sodium bicarbonate were given to three and two patients, respectively. In EMDEU, 53.9% of the patients were only observed (table 6). Gastrointestinal decontamination methods were performed more frequently in patients with toxic amounts of sedative-hypnotic exposure than in patients with non-toxic amounts of exposure ($\chi^2 = 45.525$, $P < 0.0001$). When the absence and presence of performed gastrointestinal decontamination methods in the EMDEU were compared, no significant difference was found in between asymptomatic and symptomatic cases ($\chi^2 = 1.383$, $P > 0.05$).

Table 6.

Distribution of applied and recommended treatment attempts.

Treatment methods	Applied before admitting to EMDEU		Performed by EMDEU	
	No.	%	No.	%
Observation alone	531	77.4	370	53.9
Mechanical emesis	4	0.6	0	0.0
Gastric lavage alone	22	3.2	9	1.3
Activated charcoal alone	37	5.4	173	25.2
Gastric lavage and activated charcoal	70	10.2	113	16.5
Specific antidote treatment	5	0.7	5	0.7
Other	17	2.5	16	2.3
Total	686	100.0	686	100.0

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While most of the admitted patients with sedative-hypnotic exposure (94.8%) were observed in the emergency room, 4.1% of them were hospitalized. The follow-up period of hospitalization for the patients was as follows: 78.2% (537) for 1–6 hr, 10.2% (71) for 7–12 hr, 5.8% (39) for 13–24 hr and 5.8% (39) for more than 24 hr. The mean duration of hospitalization was 9.8 ± 1.7, 8.3 ± 3.3 and 11.9 ± 7.7 hr in patients with toxic, non-toxic and unknown amounts of exposure, respectively. Severe sedative-hypnotic poisoning cases in hospitalized patients (9, 1.3%) were transferred to the intensive care units for further treatment. After stabilization, 1.2% (8) of cases were transferred to other hospitals due to their health insurance problems. Two of the patients, who were 47- and 52-year-old men, died from chronic lithium ingestion and concomitant ingestions of dextromethorphan, pseudoephedrine and triprolidine, respectively.

Discussion

This study analysed sedative-hypnotic exposures, admitted to the EMDEU over a period of 12 years.

In the studies, where components of medications ingested in overdoses by patients were analysed, it is quite striking to find out that the medication components vary between countries. In the 2004 report of the American Association of Poison Control Centers (AAPCC), the most frequently accounted medication group following analgesics was sedative-hypnotic antipsychotics (11.7%) [2]. Sedative-hypnotics were the first cause of drug-related overdoses, which were consistent with the data from Iran [3,7]. Among all sedative-hypnotic poisonings, benzodiazepines were again the most frequently ingested medication, while some studies reported that these agents were listed in the second rank [8–11].

In a study conducted in our country, the most frequently ingested agents following analgesics were psychoactive medications (20.8%; antidepressants, psychosomatic regulators, benzodiazepines and antipsychotics) and antihistamines (3.5%) [12]. Similarly, the majority of poisoning incidents reported to the DDPIC in Izmir, Turkey, between 1993 and 1995 were benzodiazepines, antipsychotics, central muscle-relaxing agents, antidepressants, anticholinergics and other sedative-hypnotics [13]. In our study, sedative-hypnotic poisonings made up 13.8% of all medication-related poisonings. Benzodiazepines (35.8%) were the most commonly used agents of all other sedative-hypnotic medication groups. Alprazolam (41.6%) and diazepam (32.9%) made up the most commonly used agents among benzodiazepines. Although benzodiazepine-containing medication sales are regulated by the Ministry of Health through direct control of prescribing in Turkey, exposures to these drugs are relatively higher. Other sedative-hypnotic drugs can be purchased without regulations. The second most frequently used agents were antipsyhotics (16.2%). The most frequently used antipsychotics were thioridazine, haloperidol and chlorpromazine. It was reported that 3.6% of medications affecting central nervous system were antipsychotics and phenothiazines, which were the most frequently used in Iran [14].

In the 2004 report of AAPCC, antihistamines represented 5.2% of all other sedative-hypnotics and 38.6% of them were diphenhydramines [2]. The third most frequently used agents were antihistamines (14.0%) in our study. Among antihistamines, while doxylamine (20.5%) was listed in the first place, hydroxyzine (19.6%) and cetirizine (10.7%) were reckoned just after doxylamine. The use of antihistamines as sleeping pills in our country is increasing the ingestion of these medications at a higher frequency.

We found that central muscle relaxant agents ranked the fourth place among the most frequently ingested sedative-hypnotics with the rate of 12.5% and among them, phenprobamate and tizanidine were listed with regard to their frequency scale of being ingested.

In our study, the rate of taking alcohol together with sedative-hypnotic medications was 18.6%. Concomitant alcohol ingestion with medications were found to be 11%, 26%, 36% and 38%, respectively, in different studies [12,15–17]. Additionally, we found that the most common medications ingested together with sedative-hypnotics were paracetamol (34.0%), opipramol (19.1%), fluoxetine (18.1%) and sertraline (10.1%).

It is noted that poisonings occur more frequently during summer time, particularly in June and July [13,18]. We determined that the highest number of patients was found in August (10.3%).

It is crucial for patients attempting suicide to receive treatment as soon as possible in order for treatment to work. In the studies carried out in Turkey, the patients admitted to the emergency departments within the first 2 hr after ingestion are 50% and 52% of all poisoning cases [15,19]. The mean time between ingestion of sedative-hypnotics and admission the EMDEU was 5.1 ± 11.9 hr and the most visits to the emergency department happened within 2 hr of ingestion (50.7%). The most frequent admission hours to the EMDEU were between 8 and 24 p.m. Other studies have found that hardly any admission to emergency departments took place after midnight [13–15].

When the cause of poisoning is examined in various studies, it is seen that while adults ingest medication intentionally (suicidal attempt, abuse), the majority of children, still depending on the age group, ingest the medication accidentally [2,11,12,14,18]. In the 2004 report of AAPCC, it was reported that while there were more unintentional poisonings under 12 years, the intentional poisonings were constant for patients over 12 years [2]. It was determined in our study that of all cases of sedative-hypnotic ingestion, 82.9% were intentional and 13.6% were unintentional. When the causes for ingesting sedative-hypnotic medications by both children and adults were studied, it was found that intentional ingestion of sedative-hypnotics was higher in a statistically significant manner for adults; a finding that complies with the literature. Comparing female patients to male, intentional ingestion of sedative-hypnotics by women was significantly higher for the childhood period, while it

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was not significantly higher for the adult age group. In evaluation of all age groups, intentional ingestion of sedative-hypnotics for women was significantly higher than for men. Evaluating incidents of poisoning in terms of gender, it is striking to find out that the number of women is higher than that of men (51% versus 75%), although the rates may vary [2,12,14,15,18]. We found that the majority of patients were women (64.4% among children and 72.1% among adults).

It is well known that some patients admitted to hospital with an intentional poisoning have been involved in suicidal attempts before. In our study, 10.1% of patients with the complaint of intentional sedative-hypnotic ingestions had a history of suicidal attempts. It was noted that the rates for patients to reiterate suicidal attempts were high and 18% of the in-patients had a history of reiterating suicidal attempts [20].

The majority of our patients (61.7%) had no clinical symptoms or findings according to the scoring of clinical situation [6], and major findings (such as altere mental status and coma, respiratory distress, severe acid-base disorders) were recognized for only 4.2% of them. This shows either that the ingestion of sedative-hypnotic medication was not at toxic doses or that decontamination methods were efficient.

Although the percentage of gastrointestinal decontaminations performed before admission to EMDEU was 19.4%, more than 43.0% of patients were decontaminated after admission to EMDEU. With regard to studies carried out in our country, the rate of practicing decontamination methods is higher than in other countries [12,19]. The rate of practicing decontamination methods in our study was higher compared to studies from abroad, yet less compared to the ones in our country. The reason for attaining higher rates of decontamination practices compared to the ones abroad is thought to be originating from decontamination practices carried out in other health centres before patients have actually been admitted to the EMDEU or called the DDPIC. Moreover, as the practicing guide books of gastric lavage and activated charcoal in cases of poisonings were published after 1997 by the American and European associations of poison control centres, it is likely that the decontamination rates might be measured less in the studies carried out later than 1997 [2,21,22].

Current evidence shows that flumazenil, a benzodiazepine antagonist, may be effective in the reversal of coma in patients presented to the emergency department. Conversely, a couple of studies failed to show the effectiveness of flumazenil for decreasing needed procedures, such as endotracheal intubation, computerized tomography and lumber puncture or shortening of hospitalization [23,24]. Additionally, flumazenil administration is harmful to the patients with a history of seizures, head injury, chronic benzodiazepine use, coingestion of benzodiazepine and tricyclic antidepressant or other proconvulsants. The risk ratio of administering flumazenil should be determined in each overdose patient [25]. In our study, flumazenil has been used in only six cases, as the medical history reported by the poisoned patients was found mostly truthful; in unclear cases, urine analysis was performed.

In this study, the mean observation time for sedative-hypnotic exposures was almost 10 hr. It varied from 12 to 24 hr in other studies reporting all medication poisoning [12,18]. Several factors might have shortened the hospitalization period in our study, for example, a low rate of severe poisoning cases or extensive consulting of poisonings to DDPIC in EMDEU.

AAPCC reported that 0.1% of all poisonings resulted in death. Sedative-hypnotics were the second cause of fatal poisonings (0.28%); 0.26% of all fatalities resulted from muscle relaxants, 0.2% from anticonvulsants and 0.07% from antihistamines [2]. In a study from Australia, 3452 deaths were diagnosed as sedative-hypnotic poisoning as the primary cause, and these fatalities occurred in 1% of all sedative-hypnotic exposures in 1983–1999 [26]. In our study, two (0.3%) of sedative-hypnotic exposures were fatal. One patient, a 47-year-old man, died from chronic lithium ingestion and the other patient, a 52-year-old man, died from concomitant ingestions of dextromethorphan, pseudoephedrine and triprolidine.

In conclusion, the rate of sedative-hypnotic exposures admitted to EMDEU was similar to other countries. However, although non-toxic amounts of sedative-hypnotic exposures accounted for most of the cases, the high rate of performed gastrointestinal decontamination procedures is surprising. Poison control centres should play an important role in changing the habit of performing gastrointestinal decontamination for every patient suspected of poisoning.

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