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Original Article

Antipsychotic Exposures in an Emergency Department

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Abstract

Purpose: We analyzed the antipsychotic medication exposures' distribution in typical and atypical antipsychotic exposures and severity of the clinical signs and symptoms admitted to the Department of Emergency Medicine at Dokuz Eylul University (EMDEU) between 1993 and 2015.

Methods: Demographics of patients, type of exposure, distribution according to the reason, the amount of the exposed antipsychotics, clinical findings, the length of hospital stay, and the outcome of the patients in typical and atypical antipsychotic exposures were analyzed.

Results: Among all of the adult poisonings in EMDEU, 2.6% of them were due to exposure to antipsychotic medication. Most of the antipsychotic exposures were intentional (95.5%). Most antipsychotics exposed were atypical antipsychotics (77.3%). Frequently exposed atypical and typical antipsychotics were quetiapine (52.9%) and chlorpromazine (26.7%), respectively. 46.7% of typical antipsychotics and 35.3% of atypical antipsychotics were in toxic doses. Tachycardia (39.4%) was the most common symptom in typical (40.0%) and atypical (39.2%) antipsychotic exposures. Atypical antipsychotic exposure did not cause fewer clinical findings than that of typical antipsychotics. Gastric decontamination was applied to 56.1% of the patients. All of the patients exposed to antipsychotics recovered.

Conclusion: Because of the widespread use of atypical antipsychotics, we observed atypical antipsychotic exposures more than typical antipsychotic exposures. Although mild and moderate clinical findings are common in both typical and atypical antipsychotic exposures, serious clinical findings can be observed in all intoxications. Therefore, all patients poisoned with typical or atypical antipsychotic toxic doses should be closely monitored in the emergency department.

Keywords: Antipsychotic, atypical, typical, poisoning, clinical finding

INTRODUCTION

Antipsychotic medications have been used in psychotic disorders such as schizophrenia, paranoia, and psychotic depression for many years (1). Nearly seven decades ago, phenothiazines and butyrophenones were used to manage the positive symptoms of schizophrenia and they called typical antipsychotics (2). Because of the excess adverse effects of typical antipsychotics, atypical antipsychotics such as olanzapine, risperidone, and clozapine, which have fewer extrapyramidal adverse effects, were developed (3, 4). The adverse effects of antipsychotics are related to their typical or atypical structure. Although all antipsychotics more or less block the transmission of dopamine in the brain, atypical antipsychotics have a different pharmacological profile with blockade of serotonin $5HT_2$ receptors (5).

Antipsychotic medication overdose results, important life-threatening toxic effects mainly on cardiovascular and central nervous system (CNS). Tachycardia, mild hypotension, and QT prolongation in electrocardiogram are the most common cardiovascular findings and sedation, agitation, coma are the most common CNS findings of antipsychotic exposures. Extrapyramidal symptoms are dose-independent and mostly develop at the beginning of the antipsychotic treatment or observed in toxic doses. Anticholinergic effects observed in therapeutic doses and also more prominent in overdose (6).

In recent years, atypical antipsychotics have largely replaced typical antipsychotics because they have fewer potential adverse effects. However, in a limited number of studies, atypical antipsychotics were not found to be safer than typical antipsychotics (7, 8). Although there are many reports that have studied the frequency of antipsychotic exposures among all of the poisonings, there are no studies related to subgroups distribution of antipsychotic exposures. We analyzed the antipsychotic medication exposure distribution and severity of the clinical findings in typical and atypical antipsychotics exposures on the admission to Department of Emergency Medicine at Dokuz Eylul University Hospital (EMDEU) between 1993 and 2015.

METHODS

This retrospective descriptive study was approved by the institutional ethics committee of the Dokuz Eylul University School of Medicine (20.10.2016 no: 27-32/2016). Because of the retrospective nature of this study, informed consent from the patients was not required. We scanned the data of patients with antipsychotic medication exposure who were admitted to the Department of Emergency Medicine at Dokuz Eylul University (EMDEU) and reported to the Dokuz Eylul University Drug and Poison Information Center (DPIC) between 1993 and 2015. Patient information was obtained by scanning DPIC records. Patient files were removed from the archive. Demographics of the patients, type of exposure (acute, acute on chronic), distribution according to the reason (unintentional, intentional), amount (toxic, non-toxic, unknown) of the exposed antipsychotics, clinical findings, the length of hospital stay, and the outcome of the patients in typical and atypical antipsychotic exposures were recorded in a Data collection form. The toxic dose was determined by the dose the patient declared taking. The severity of clinical manifestations was graded into mild, moderate, or severe according to the European Association of Poison Centers and Clinical Toxicologists/International Programme on Chemical Safety Poisoning Severity Score (9).

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) 15.0 for Windows. The chi-square test and Fisher's exact test were used to compare the groups. Results were considered statistically significant when $p<0.05$.

RESULTS

Over a 20-year period, 88,569 poisoning exposures were reported to the DPIC. The number of antipsychotic exposure cases admitted to EMDEU and consulted by the DPIC was 116, but only 66 (56.9%) could be retrospectively evaluated from the patients' charts. Among all of the adult (4,440) poisonings between 1993 and 2015 in EMDEU, 2.6% of were antipsychotic medication exposures.

Demographics of the Acute Antipsychotic Exposures

Most of the patients exposed to antipsychotics were female (68.1%, n=45), and the female/male ratio was 2/1. The mean age of the patients was 31.7±1.5 years (30.8±2.2 years for females and 34.1±13.3 years for males). The ages ranged from 18 to 69 years (Table 1).

Table 1. Demographics, toxicities, causes, ingested amount, and the poisoning severity score of the typical and atypical antipsychotic exposures

	Typical		Atypical		Total	
	n	%	n	%	n	%
Gender						
Female	9	20.0	36	80.0	45	100.0
Male	6	28.6	15	71.4	21	100.0
Age (Mean±SD)	33.0±3.7		31.3±1.6		31.7±1.5	
Toxicity						
Acute	14	22.9	47	77.1	61	100.0
Acute on chronic	1	20.0	4	80.0	5	100.0
Causes						
Intentional	12	19.0	51	81.0	63	100.0
Unintentional	3	100.0	0	0.0	3	100.0
Ingested amount						
Toxic	7	28.0	18	72.0	25	100.0
Nontoxic	4	22.2	14	77.8	18	100.0
Unknown	4	17.4	19	82.6	23	100.0
Poisoning severity score						
Asymptomatic	3	18.8	13	72.2	16	100.0
Mild	4	18.2	18	81.8	22	100.0
Moderate	6	30.0	14	70.0	20	100.0
Severe	2	25.0	6	75.0	8	100.0

Table 2. The distribution of typical and atypical antipsychotic exposures

Antipsychotics		n	%
Typical antipsychotics	Thioridazine	4	6.1
	Chlorpromazine	5	7.6
	Mesoridazine	1	1.5
	Trifluoperazine	3	4.5
	Zuclopenthixol	1	1.5
	Haloperidol	1	1.5
	Total	**15**	**22.7**
Atypical antipsychotics	Quetiapine	27	40.9
	Risperidone	15	22.8
	Olanzapine	8	12.1
	Clozapine	1	1.5
	Total	**51**	**77.3**
Total		66	100.0

Most of the antipsychotic exposures were suicidal (95.5%, n=63) (Table 1). Most exposed antipsychotics were atypical antipsychotics (77.3%, n=51). Toxic amount of ingestions were common both in typical (46.7%, n=7) and atypical (35.3%, n=22) antipsychotic exposures. Concomitant medication ingestion was present in 50.0% (n=33) of the patients, and concomitant alcohol ingestion was present in 9.1% (n=6) of the patients. Most of the typical and atypical antipsychotic

Table 3. Clinical findings observed in typical and atypical antipsychotic exposures

	Typical		Atypical		Total				
Symptoms	**n**	**%**	**n**	**%**	**n**	**%**	***p**	**OR**	**95% CI**
Tachycardia	6	40.0	20	39.2	26	39.4	1.0	1.033	0.3187-3.351
Unconsciousness	5	33.3	17	25.8	22	33.3	1.0	1.0	0.2948-3.392
Nausea	4	26.7	8	15.7	12	18.2	0.4	1.955	0.4961-7.701
Hypotension	1	6.7	8	15.7	9	13.6	0.7	0.3839	0.04405-3.346
Sleep propensity	2	13.3	8	15.7	10	15.2	1.0	0.8269	0.1557-4.390
Vomiting	1	6.7	2	3.9	3	4.5	0.5	1.750	0.1475-20.761
Acute dystonic reaction	1	6.7	2	3.9	3	4.5	0.5	1.750	0.1471-20.761
QRS prolongation	1	6.7			1	1.5	0.4	3.571	0.2097-60.832
Neuroleptic malignant syndrome	6	40.0	20	39.2	26	39.3	1.0	1.033	0.3187-3.351

*p-value was calculated with Fisher's exact test

Table 4. Clinical findings in atypical antipsychotic exposures

	Quetiapine		Risperidone		Olanzapine		Clozapine		Total	
Symptoms	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**%**	**%**
Tachycardia	10	37.0	6	40.0	3	37.5	1	100.0	20	39.2
Unconsciousness	4	14.8	3	20.0	3	37.5			10	19.6
Sleep propensity	4	14.8	1	6.7	3	37.5			9	17.6
Nausea	4	14.8	3	20.0	1	12.5			8	15.7
Hypotension	1	3.7	2	13.3	1	12.5			4	7.8
Vomiting	1	3.7			1	12.5			2	3.9
Acute dystonic reaction			1	6.7	1	12.5			2	3.9

Table 5. Applied treatment, follow-up, and duration of hospital stay in typical and atypical antipsychotic exposures

	Typical		Atypical		Total				
	n	**%**	**n**	**%**	**n**	**%**	***p**	**OR**	**95% CI**
Applied treatment									
Observation alone	4	21.0	15	79.0	19	100.0	1.0	0.8727	0.294-3.182
Gastric lavage + Activated charcoal	3	16.7	15	83.3	18	100.0	0.7424	0.6000	0.1477-2.437
Activated charcoal	4	21.0	15	79.0	19	100.0	1.0	0.8727	0.2394-3.182
Supportive treatment	1	50.0	1	50.0	2		0.4056	3.571	0.2097-60.832
Follow-up									
Observation in emergency service	13	24.1	41	75.9	54	100.0	0.7118	1.585	0.3070-8.187
Service treatment			3	100.0	3	100.0	1.0	0.4470	0.02184-9.147
Intensive care treatment	1	14.385.7	6		7	100.0	1.0	0.5387	0.05931-4.839
Dispatch to another hospital	1	50.0	1	50.0	2	100.0	0.4056	3.571	0.2097-60.832
Duration of hospital stay (Mean ± SD)	15.1±5.9		20.6±4.9		19.3±3.9				

*p-value was calculated with Fisher's exact test

exposures were acute (93.3% [n=14] and 92.2% [n=47], respectively). Most of the admissions (53.0%, n=35) to EMDEU were between 19.00 and 23.59 hours, and most of the patients (53.1%, n=26) presented to the emergency room within two hours. Seasonal distribution of antipsychotic exposures was as follows: summer (36.4%, n=24), spring (30.3%, n=20), winter (21.2%, n=14), and autumn (12.1%, n=8).

The Rate and Clinical Findings of Typical and Atypical Antipsychotic Exposures

Frequently exposed atypical and typical antipsychotics were quetiapine (52.9%, n=22) and chlorpromazine (26.7%, n=5), respectively (Table 2). On presentation, 75.8% (n=50) of the patients were symptomatic in the emergency department. The

rate of mild clinical findings was 35.2% (n=18) in atypical antipsychotics and 26.7% (n=4) in typical antipsychotics. Tachycardia (39.4%, n=26) was the most common symptom in typical (40.0%, n=6) and atypical (39.2%, n=20) antipsychotic exposures. Unconsciousness (33.3%, n=2), nausea (18.2%, n=12), and hypotension (13.6%, n=9) are the other clinical findings (Table 3). Atypical antipsychotics; risperidone, olanzapine, and a typical antipsychotic, thioridazine, led to acute dystonic reactions (ADRs) in our patients. A neuroleptic malignant syndrome was reported due to the exposure of a typical antipsychotic, zuclopenthixol (Table 4).

Gastric lavage and gastric lavage with activated charcoal were applied to 56.1% of the patients. The vast majority of the patients (81.8%, n=54) were observed in the emergency department, and 18.2% of them were referred to either to outpatient clinics or to intensive care units (ICUs) for further evaluation. The durations of hospital stay were 20.6±4.9 hours (range: 2–192 hours) and 15.1±5.9 hours (range: 3–96 hours) in atypical and typical antipsychotic exposures, respectively. All of the antipsychotic-exposed patients admitted to EMDEU recovered (Table 5).

In our study, severe clinical findings were observed in a patient poisoned by quetiapine and risperidone, the most exposed atypical antipsychotics. Supportive treatment and intravenous lipid treatment were applied to this patient. A 45-year-old male presented to EMDEU with hypotension (84/53 mmHg), tachycardia (132 bpm), and a lack of consciousness (GCS: $E_1M_5V_2$) five hours after ingesting quetiapine (8000 mg) and risperidone (80 mg). The patient's clinical findings were scored as severe, and he was intubated. He was unresponsive to norepinephrine and dopamine treatment. Vital findings of the patient were reversed after 1.5 mL/w intravenous bolus lipid treatment (20% Clineloic®, Baxter Healthcare Ltd., United Kingdom) followed by 0.25 mL/kg/h intravenous lipid. He was treated by supportive treatment in the ICU and recovered.

DISCUSSION

In the present study, we analyzed the antipsychotic exposure distribution and severity of the clinical findings in typical and atypical antipsychotic-exposed patients admitted to Department of Emergency Medicine at Dokuz Eylul University Hospital (EMDEU). The ratio of antipsychotic medication exposures admitted to EMDEU was 2.6%. The ratio of reported antipsychotic exposures among all poisonings was in a wide range between 1.1 and 12.0% in different studies (10-15). Although our rate was in the lower bound, it is comparable to the rates reported by studies. In this study, antipsychotic exposures were more frequent in females. Women tend to commit suicide with pharmacological drugs, and our results are compatible with the previous studies (16). In addition, most of the patients were between 18 and 29 years old. In some international studies and studies from Turkey, poisonings were also more frequent in young adults (10, 12, 17-19).

In reported previous studies, which were related to the evaluation of different medication exposures, the rate of intentional exposures was high (17, 20, 21). The California Poison Information Center reported that the two-thirds of atypical antipsychotic exposures were intentional (22). In our study, the vast majority of EMDEU admissions were intentional in female and male patients in all age groups. Intentional exposure dominance may be explained by being the suicide is the most common cause in psychosis in both gender (23).

We noted that antipsychotic exposures were more frequent in the summer and spring. Poisonings were common in summer according to a study by Tufekci et al. (11) In the studies that evaluated the seasonal distribution of various poisonings, poisonings were observed generally in the spring and summer months in accordance with our study (20, 24).

In our study, most of the atypical or typical antipsychotic exposures were in toxic doses. This is consistent with the situation that they were taken intentionally. Alcohol or other medication ingestion was present in 48.9% of exposures. In intentional toxic dose exposures, concomitant medications or alcohol ingestion are common. Definitely, concomitant alcohol or medication ingestion may increase the central nervous system findings in antipsychotic exposures. However, in our study, simultaneously received medications did not increase the severity of clinical signs. The dose of the additional medication is important in multiple medication exposures. Lack of severe clinical findings in multiple medication exposures may be explained in this study by the nontoxic doses of other medications ingested.

Atypical antipsychotic exposures were found in our study to be more frequent than typical antipsychotic exposures. Typical antipsychotics, which were developed in the 1950s, had many adverse effects, even in therapeutic doses. Therefore, antipsychotics such as olanzapine and risperidone which had lower adverse effects related to their mechanism of action named atypical antipsychotics were developed. With the widespread use of atypical antipsychotics, typical antipsychotic prescription by the physicians decreased and typical antipsychotics were replaced by atypical antipsychotics (25-27). Bateman et al. (24) reported that, a typical antipsychotic, thioridazine prescription decreased in England and Scotland at the beginning of the 2000s.

In this study, the most frequently exposed antipsychotics were quetiapine, an atypical antipsychotic, and chlorpromazine, a typical antipsychotic. Most of the patients were symptomatic, and moderate clinical findings were common in both typical and atypical antipsychotic exposures. It is known that the antipsychotic exposure may cause serious life-threatening toxic effects, especially in high doses. However, antipsychotics may cause serious adverse effects, even in therapeutic doses, due to the drug-drug interactions. Sedation, convulsion, coma, hypotension, QRS and QT prolongation in the electrocardiogram, respiratory depression, extrapyramidal effects, anticholinergic effects and death are among these effects. In our patients, the most prominent clinical symptom was tachycardia. Unconsciousness and hypotension were the other most frequent clinical symptoms in typical and atypical antipsychotic exposures. The distribution of clinical findings was not different from each other in the typical and atypical antipsychotic exposures. In a study by Ciranni et al. (7), atypical antipsychotics were not found, similar to our findings, to be safe compared with typical antipsychotics in toxic doses. Severe clinical findings were observed in a patient poisoned by the most exposed atypical antipsychotic, quetiapine,

in our study. This patient was intubated and treated in an ICU. Similar clinical symptoms such as coma and respiratory depression requiring intubation and hypotension were also reported in an acute quetiapine exposure by Ngo et al. (28). Magdalan et al. (25) also reported serious clinical symptoms in toxic dose antipsychotic exposures by clozapine and olanzapine.

Acute dystonic reactions was noted by the exposure of atypical antipsychotics risperidone, olanzapine, and the typical antipsychotic thioridazine in our study. ADR may occur slightly with the use of atypical antipsychotics and requires treatment. ADR is a side effect that is caused by dopaminergic receptor blockade and is characterized by clinical signs such as torticollis, opisthotonus, muscle spasms in various parts of the body, and eye spotting. ADR may due to atypical antipsychotics as well as typical antipsychotics with dopaminergic receptor blocking properties (3, 4, 29). Therefore, patients with ADR may be observed in high doses of atypical antipsychotics. Neuroleptic malignant syndrome (NMS) was observed in a patient with depot injection of a typical antipsychotic, zuclopenthixol. Erermis et al. (30) also reported NMS by single depot injection of zuclopenthixol.

Most of our patients presented to EMDEU within two hours of antipsychotic ingestion, and gastric decontamination was performed in most of them. Gastric decontamination is recommended in toxic dose exposures, especially within one hour of toxic ingestions (31). In our patients, the amount of ingested antipsychotics was mostly unknown, and nearly one-third of them were in toxic doses. Therefore, all unknown amounts of ingestions were accepted as toxic and gastric decontamination was performed in most of them. The presence of moderate clinical findings may be explained by performing of gastric decontamination within two hours in most of the patients.

Although not significantly important, the duration of hospital stay was longer in atypical antipsychotic exposures than in typical antipsychotic exposures. This can be explained by the fact that higher doses of atypical antipsychotics are not as safe as typical antipsychotics (7) and that both typical and atypical antipsychotics can cause serious clinical findings at high doses.

The treatment of clinical findings in antipsychotic overdose includes symptomatic supportive treatment. Most of our patients took supportive treatment, and additionally, intravenous lipid emulsion (ILE) treatment was applied in a patient overdosed by quetiapine and risperidone. ILE treatment is being mentioned a new antidote in drug toxicities. It is one of the treatment alternatives in a state of cardiovascular collapse in antipsychotic overdose (32). After treatment with ILE in our patient who has unconsciousness and hypotension unresponsive to the inotropic therapy, he recovered. ILE can be considered a treatment option in life-threatening antipsychotic intoxications that do not respond to other treatments.

Gastric decontamination was applied to the majority of the patients who were admitted to EMDEU due to antipsychotic exposure. Gastric decontamination is a method that prevents the absorption of the drugs and toxic effects in oral drug overdoses (33). In our study, all patients who were exposed to antipsychotics recovered. Deaths were reported in toxic doses of antipsychotics or even in therapeutic doses of antipsychotics due to the drug-drug interactions (8). Only one male patient with severe clinical findings due to quetiapine exposure required ICU observation and recovered finally. Therefore, after appropriate decontamination methods and supportive treatment, antipsychotic poisoning cases should be closely monitored in emergency departments.

Study Limitations

Because of the retrospective nature of this study, we could not reach all of the antipsychotic exposure cases from the archive. We excluded the patients who had insufficient information in their charts. Therefore, the basic limitation of our work is that we have reached a limited number of patients and a limited number of knowledge.

For the use of atypical antipsychotics instead of typical antipsychotic, we frequently observe exposures to atypical antipsychotics. The most exposed antipsychotic was quetiapine, an atypical antipsychotic. Both atypical and typical antipsychotic exposures should be observed and monitored cautiously in overdoses.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University Non-interventional Ethics Commitee (20.10.2016 no: 27-32/2016).

Informed Consent: Because of the retrospective nature of this study, informed consent from the patients was not obtained.

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