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RESEARCH OF THE CLINICAL MANIFESTATIONS OF ACUTE ATYPICAL ANTIPSYCHOTICS POISONINGS IN ADULTS

ISPITIVANJE KLINIČKIH MANIFESTACIJA AKUTNIH TROVANJA NETIPIČNIM ANTIPSIHOTICIMA KOD ODRASLIH

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Ključne reči
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Abstract

Introduction: Atypical antipsychotics are nowadays widely used in psychiatric practice. They gradually replace the old conventional antipsychotics and become first-line therapy in the treatment of schizophrenia and other psychiatric disorders. This is related to increased frequency of poisonings with these agents and requires good knowledge of the clinical manifestations in cases of overdose.
Methods: We conducted a research of the clinical manifestations of atypical antipsychotics poisonings in adults (18 year and older), admitted to the Clinic of Toxicology, UMHATEM „N. I. Pirogov", Sofia, Bulgaria.
Results: The study includes 73 cases of monointoxications with these agents and demonstrates the primary toxic effects that may be expected.
Discussion and Conclusion: Our report demonstrates three main syndromes, following atypical antipsychotics overdose – cerebrotoxic, cardiotoxic and antimuscarinic, as well as three main clinical forms of the course of these poisonings – cerebrodepressive, biphasic (cerebrodepressive-antimuscarinic) and antimuscarinic.

INTRODUCTION

In the recent years atypical antipsychotics (AAP) become first-line therapy in the treatment of schizophrenia and other psychiatric disorders and the frequency of poisonings with these agents increases. As the theme becomes actual in the last years, a research of the clinical manifestations of acute atypical antipsychotics poisonings in adults admitted in the Clinic of Toxicology UMHATEM „N. I. Pirogov", Sofia, Bulgaria was conducted. According to literature date the most serious toxicity in overdose with AAP involves effects of the central nervous system and cardiovascular effects, as well as antimuscarinic effects [1, 2, 3, 4, 5].

Study objective

The aim of the study is to investigate the clinical manifestations and the outcome of acute atypical antipsychotics poisonings in adults.

Materials and methods

Object of the study, inclusion criteria and exclusion criteria

Object of the study are adult patients (18 years of age or older), who overdosed atypical antipsychotics and were admitted to Clinic of Toxicology, UMHATEM „N. I. Pirogov", Sofia, Bulgaria in the period 2007-2014. Patients who overdosed other drugs in addition to atypical antipsychotics were excluded, as were the cases in which more than one type of atypical antipsychotic was ingested. The research is on the base of 73 cases of monointoxications with atypical antipsychotics. In all of the cases the overdose is per os.

Main indicators to be observed

1. Age and sex of the patients.
2. Type of atypical antipsychotic.
3. Clinical manifestations of atypical antipsychotics overdose.
4. Clinical course of intoxication.
5. Severity of poisoning.
6. Complications.
7. Outcome of poisoning.

Methods

1. Sociological methods: analysis of medical documentation.

2. Clinical methods in the course of the acute poisonings with atypical antipsychotics: case history and physical examination.

3. Laboratory tests: blood tests (total blood count, serum glucose, blood gases), chemical-toxicological analysis of urine by thin-layer chromatography.

4. Roentgenography of chest.

5. Funtional diagnostic tests – elecrocardiography.

6. Statistical tests.

Results

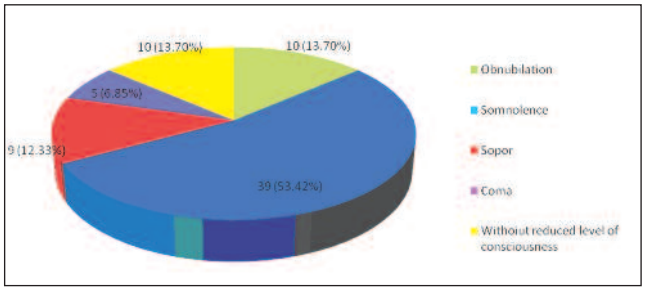
We found 73 cases meeting criteria for analysis. Patient ages ranged from 19 to 82 years, as patients under 50 presented 72.60% (95% CI 62.37%-82.83%). Females prevailed – 64.38% (95% CI 53.39%-75.37%) compared to males, who amounted to 32.62% (95% CI 21.87% - 43.37%). The toxic effects, observed in the cases of acute atypical antipsychotics overdoses, and their frequency are presented in Table 1.

Table 1 *– Toxic effects in atypical antipsychotics overdose*

		Cases	
		Number	%
CNS effects	CNS depression	63	86.30
	Delirium as a part of antimuscarinic syndrome	22	30.14%
	Psychomotor agitation as a part of antimuscarinic syndrome	9	12.33%
	Seizures	4	5.48%
	Extrapyramidal effects	3	4.11%
Antimuscarinic effects	Antimuscarinic toxic delirium	22	30.14%
	Psychomotor agitation without delirium	9	12.33%
	Tachycardia	31	42.47%
	Mydriasis	20	27.40%
	Dry skin and mucosis	19	26.03%
	Transitory hyperthermia	6	8.22%
	Slow bowel sounds	3	4.11%
	Urine retention	1	1.37%
	Total (Antimuscarinic syndrome)	31	42.47%
Cardiovascular effects	Tachycardia (cases with and without antimuscarinic syndrome)	51	69.86%
	Arterial hypotension	2	2.78%
	Prolonged QTc interval	3	4.11%
Other effects	Miosis	12	16.44%
	Hypersalivation	7	9.59%
	Pulmonary oedema	1	1.37%
	Hyperglycemia	19	26.03%

CNS depression was observed in 63 cases (86.30%; 95% CI 80.52%-92.08%) and varied from obnubilation to coma. It was registered on admission. There were only 10 patients (13.70%) who didn`t present with reduced level of consciousness, but were psychomotor agitated or developed delirium. The grades of CNS depression in the studied cases is demonstrated on Figure 1.

Figure 1 *– CNS depression in cases of atypical antipsychotics poisoning*

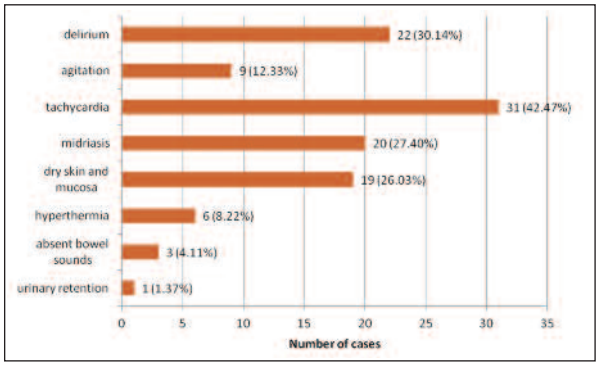


A statistically significant dependence between the grade of CNS depression and the type of the antipsychotic was demonstrated by Fisher test (P=0.04). In most of the cases of Olanzapine, Clozapine and Quetiapine overdoses the level of consciousness varied from somnolence to coma and in cases of Risperidone, Paliperidone, Amisulpride and Ziprazidone poisonings it varied from obnubilation to somnolence. The average duration of CNS depression in the cases of acute atypical antipsychotics overdose was 10 hours (95% CI 7-11).

Extrapyramidal symptoms such as dystonic reactions (spastic torticollis, oculogyric crisis, trismus) occurred only in two cases (poisoning with Amisulpride and poisoning with Risperidone). They disappeared within 1 to 5 hours. Seizures were observed in 2 cases of Quetiapine and in 2 cases of Clozapine overdose.

Antimuscarinic syndrome was registered in 31 cases (42.47%; 95% CI 31.13%-53.81%) – in 7 of the patients on admission and in 24 patients - later, following a state of CNS depression. The frequency of the antimuscarinic effects is illustrated in Figure 2.

Figure 2 *– Antimuscarinic effects, observed in the cases of atypical antipsychotics overdose*

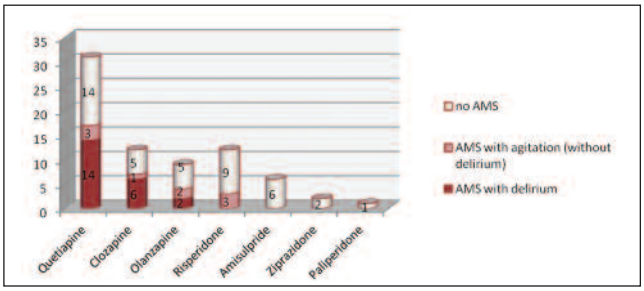


The statistical analysis demonstrated a dependence between the severity of AMS and the prior grade of CNS depression (Fisher test, P=0.003). In the cases of severe CNS depression (sopor and coma) the following AMS was severe. The average duration of antimuscarinic effects was 26.88 hours (95% CI 19.87-33.88).

The research demonstrated that 28 (90.32%; 95% CI 79.91-100%) patients, who developed antimuscarinic toxic effects, were in cases of multiacting-receptor targeted

antipsychotics overdose (MARTA) - Clozapine, Olanzapine and Quetiapine. Only in 9.68% (95% CI 0%-20.09%) of the cases AMS occurred in overdose with some of the rest atypical antipsychotics (Risperidone). The analysis showed that all cases of severe antimuscarinic syndrome (cases with toxic antimuscarinic delirium) in AAP overdose were cases of overdose with MARTA (Figure 3).

Figure 3 *- Cases of severe antimuscarinic syndrome (cases with toxic antimuscarinic delirium) in AAP overdose*



The main toxic cardiovascular effects that occurred in the poisonings with the different atypical antipsychotic medications include tachycardia, arterial hypotension and prolonged QTc interval (Table 2).

Table 2 *– Cardiovascular effects in AAP poisonings*

Type AAP	Cardiovascular effects – number of cases (%)				
	Tachycardia	Hypotension	Prolonged QTc intervalcases	Prolonged QT interval	Total number of with the relevant AAP
Quetiapine	22 (70.97%)	-	1 (3.23%)	-	31
Clozapine	10 (83.33%)	-	1 (8.33%)	-	12
Olanzapine	7 (77.78%)	-	-	-	9
Risperidone	8 (66.67%)	1 (8.33%)	1 (8.33%)	-	12
Amisulpride	3 (50.00%)	1 (16.67%)	-	-	6
Ziprazidone	1 (50%)	-	-	-	2
Paliperidone	-	-	-	-	1
Total	51 (69.86%)	2 (2.74%)	3 (4.11%)	-	73

The most often observed cardiovascular toxic effect was sinus tachycardia (122.12±12.67/min.). It was registered in 69.86% (n=51) of the cases, with calculated CI 95% 59.33%-80.39%. There were only 2 cases of AAP poisonings (2400 mg Amisulpride and 180 mg Risperidone), in which hypotension was registered and catecholamines were administered. Prolonged QTc interval (>460 ms for males and >470mf for females) was registered in 3 (4.11%) cases – in a poisoning with 500 mg Quetiapine (QTc=570ms), unknown dose of Clozapine (QTc=470 ms) and 180 mg Risperidone (QTc=480ms). In all of the cases it was accompanied by sinus tachycardia.

Other manifestations of AAP poisoning included miosis in 12 (16.44%) patients with Olanzapine, Clozapine or Risperidone overdose, hypersalivation in 7 (9.57%) patients with Clozapine poisoning and pulmonary oedema in 1 (1.67%) case of Clozapine intoxication. Hyperglycemia occurred in19 (26.03%) patients, without a history for prior Diabetes mellitus. The level of serum glucose varied from 8.0 to 14.5 mmol/l. A significant correlation between the cases of high serum glucose and the type of AAP wasn`t found (P=0.282).

The alignment of the cases according to presence/absence of CNS depression and AMS in the course of the clinical presentation outlined 3 main forms of intoxication with these medications – cerebrodepressive, biphasic (cerebrodepressive-antimuscarinic) and antimuscarinic.

Cerebrodepressive form was observed in 39 (61.90%; 95% CI 50.76%-73.04%) cases. The patients admitted with reduced level of consciousness, which gradually resolved to clear consciousness without development of AMS in the course of intoxication. The average duration of CNS depression was 11 (95% CI 10-12) hours. In 18 (46.15%) of these cases sinus tachycardia was registered. AMS didn`t occur in the course of poisoning. The intoxication resolved average within 13 (95%CI 12-16) hours.

Biphasic (cerebrodepressive-antimuscarinic) form was observed in 39 (61.90%; 95% CI 50.76%-73.04%) cases. The patients admitted with reduced level of consciousness, which gradually converted into qualitative impairment of consciousness (delirium) or agitation as a part of AMS. The average duration of CNS depression was 6 (95% CI 6-8) hours. The resolution time of the quantitative disturbance of consciousness and the beginning of AMC coincided in all 24 cases, which outlined biphasic course of the clinical picture.

Antimuscarinic toxic delirium was observed in 20 (83.33%) cases, and AMC with agitation without delirium in only four (16.67%) cases. The average duration of AMS was 24 (95% CI 12-30) hours. The analysis demonstrated that in 87.50% (n = 22) of the cases the duration of AMC was greater than the duration of CNS depression. The test of Mann-Whitney showed a statistically significant difference (P <0.001). Sinus tachycardia was observed in all cases (n = 24). The symptoms of intoxication resolved for an average of 37 (95% CI 24-48) hours.

Antimuscarinic form of poisoning was observed in 7 (9.59%; 95% CI of 2.84% to 16.34%) patients. The patients admitted with agitation (n = 5) or delirium (n = 2) as a part of developed AMS. CNS depression didn`t occurred in the course of intoxication.

The average duration of AMS was 12 (95% CI 7-20) hours. Tachycardia was registered in all cases. Manifestations of intoxication disappeared average within 12 (95% CI 7-20) hours.

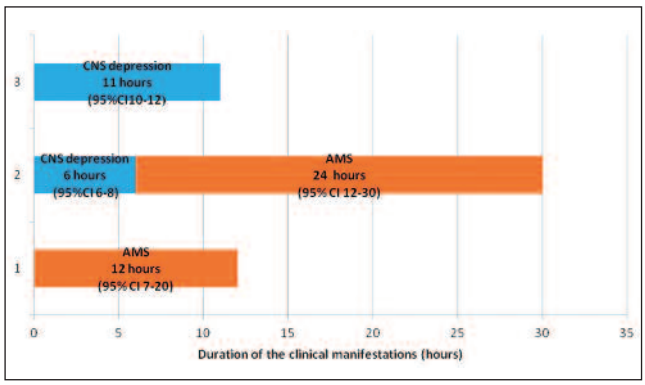


Figure 4 *– Duration of the CNS depression and the AMS in the three main forms of clinical presentation of AAP poisonings*

The alignment of the studied cases according to the form of the clinical course and the type of AAP demonstrated that the form of the clinical course depends on the type of AAP. This dependence is expressed in the fact that the biphasic form occurred only in the poisonings with AAP from the group of MARTA (Quetiapine, Clozapine and Olanzapine).

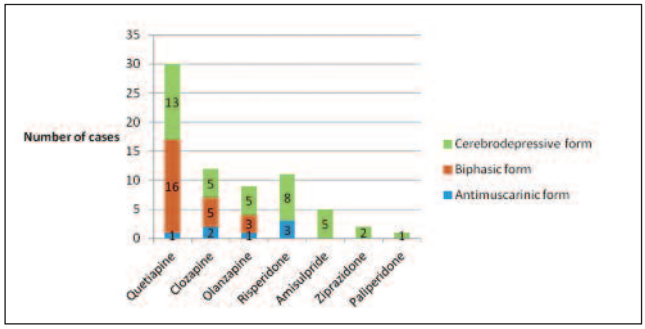


Figure 5 *- Alignment of the studied cases according to the form of the clinical course and the type of AAP*

Poisoning Severity Score of EAPCCT was used to determine the severity of intoxications in the studied cases. The research illustrated that in most cases acute monointoxications with AAP were with moderate severity grade – 47.95% (n=35). The proportion of severe poisonings with AAP in the studied patients was 37.00% (n=27), and the proportion of poisonings with minor severity grade was 15.07% (n=11). There were no patients without manifestations of poisoning, as well as patients with fatal outcome.

Complications were observed only in 4(5.48%; 95% CI 0.13% - 10.83%) patients with acute AAP monointoxications. All of them were with severe intoxications. Complications affected the respiratory system and necessitated treatment in ICU and administration of mechanical ventilation.

DISCUSSION

The purpose of this study was to investigate the toxic effects of atypical antipsychotics, taken in overdose and the outcome of these intoxications. The main findings of the research were that the primary toxicities associated with AAP overdose involve the central nervous and cardiovascular systems, as well as antimuscarinic effects.

In the recent years numerous atypical antipsychotics are introduced to the market and these new agents little by little displace the old conventional neuroleptics in the treatment of psychiatric disorders because of their effectiveness and safer profile [1,6]. The main criteria for atypicality of antipsychotics are production of no or fewer extrapyramidal symptoms; efficacy in treating both negative and affective symptoms, as well as different sites of cognition; absence or induction in a lower extent of prolactinemia; efficacy in treatment-resistant schizophrenia [7, 8, 9]. There are 4 main groups of atypical antipsychotics in accordance to their receptor-binding profiles. AAP with a high selectivity for serotonin 5-HT2A receptors and dopamine D2 receptors (and alfa-adrenoreceptors) are called serotonin-dopamine antagonists, SDA (Risperidone, Paliperidone). AAP showing an affinity for D2 receptors, 5-HT2A receptors and receptors of other systems (cholinergic, histaminergic, 5-HT1A receptors and other receptors) are called multi-acting receptor-targeted antipsychotics, MARTA (Clozapine, Quetiapine, Olanzapine). AAP with a high affinity to D2 and D3 subtypes of D2-like receptors are called combined D2/D2 receptor antagonists (Amisulpride, Sulpiride). Another class AAP are called partial dopamine agonists. Aripirazole is the only antipsychotic that is partial dopamine agonists [6]. Following overdose of an atypical antipsychotic, the clinical effects observed are largely predictable based on the receptor binding profiles of the agents [1].

The CNS effects in AAP poisonings most often present with CNS depression (from sedation to coma) and agitation or delirium as a part of antimuscarinic syndrome. Profound CNS depression may lead to respiratory depression and loss of airway reflexes. The sedation effect of these agents is as a result of blockage of histamine receptors. Some authors explain it also with the blockage of central muscarinic receptors [1, 2]. The highest sedative potential is of Clozapine, followed by Quetiapine and Olanzapine [10. 11].

In AAP overdose occurance of seizures is possible. All atypical antipsychotics lower seizure threshold but the more sedating the antipsychotic, the more it lowers the seizure threshold [1,10,11]. The highest seizure potency is of Clozapine [1, 10]. It may lower seizure thresholds via neuronal reuptake of norepinephrine and GABA-A receptor antagonism [12].

AAP are associated with lower risk to cause extrapyramidal symptoms, when administered in therapeutic doses. Extrapyramidal symptoms are related to dose-dependent blockage of striatal D2 receptors [13]. In acute intoxications with AAP may occur reversible extrapyramidal effects such as acute dystonia [1]. Some studies demonstrates extrapyramidal symptoms are one of the main manifestations in Risperidone poisonings [2,14,15]. The non-reversible extrapyramidal symptoms such as tardive dyskinesia are not likely to develop in acute AAP poisoning. Parkinsonism is also unlikely to occur [14,1].

Antimuscarinic effects in AAP overdose are a result of antagonism to central and peripheral muscarinic receptors. Agents from the group of MARTA (Clozapine, Olanzapine, Quetiapine) have high affinity to these receptors, which is a reason for a classical antimuscarinic toxicity in overdose, including delirium or agitation, tachycardia, mydriasis, dry

skin, absent bowel sounds, urinary retention [1, 2]. Other AAP such as Risperidone and Ziprazione don`t have high affinity for muscarinic receptors [2, 6, 11, 16]. It is interesting that the affinity of antipsychotics for muscarinic receptors is inversely correlated with their propensity for causing extrapyramidal symptoms [6, 17].

Cardiovascular manifestations, following overdose of AAP include tachycardia, hypotension and prolongation of QTc interval. Hypotension is caused by alfa1-adrenergic blockage in blood vessels and thus peripheral vasodilatation [1; 18] Tachycardia occurs reflectory, following the peripheral vasodilatation and as a result of muscarinic receptor antagonism [1, 2]. Some authors discuss that another mechanism also contributes to induction of tachycardia – blockage of presynaptic alfa2-adrenoreceptors, increased sympathetic activity and indirect activation of beta1-adrenoreceptors in heart [18]. Antipsychotics overdose can lead to prolongation of ventricular repolarization (QT interval on an ECG), which increases the risk of torsades de pointes and sudden cardiac death. Prolongation of QT interval is thought to be linked to antagonism of the delayed rectifier potassium channel (Kir) [1, 2]. QT interval varies in accordance to the heart rate and for more accurate assessment the rate-corrected QT interval (QTc) should be evaluate: $QTc = QT/\sqrt{RR}$ [2, 19, 20]. QTc values > 460 ms in men and > 470 ms in women are considered prolonged [21].

Other more rare clinical manifestations following AAP overdose include miosis, hypersalivation, pulmonary oedema. Miosis due to greater affinity of some agents for alfa-adrenergic receptors in the eye and it may occur despite of presence of antimuscarinic symptoms [1, 22]. Miosis is often reported in Olanzapine poisonings [22, 23]. Hypersalivation is described in cases of overdose as well as in cass of therapeutic ingestion of Clozapine. It due to antagonism to muscarinic M4 receptors [1, 7]. Because of the high sedating potency of Clozapine this adverse reaction, especially in overdose, is linked to increased risk of aspiration and pulmonary complications [24, 25]. In the literature there are some reports of noncardiogenic pulmonary oedema in acute Clozapine poisonings [26, 27]. For the mechanism of this toxic manifestation, the authors comment the high concentrations Clozapine found in the lung tissue, the toxic injury of the permeability of the lungs capillaries and the impaired production of surfactant [28].

AAP interact with a wide variety of receptors, which is in the basis of the clinical manifestations, observed in overdose. The knowing of their mechanism of action could allow early recognition of acute poisoning and adequate medical behavior.

CONCLUSION

The conducted study is focused on the clinical manifestations of AAP poisonings in patients, who are 18 years or older. The research demonstrates three main toxic syndromes of the clinical manifestation of AAP poisonings – cerebrotoxic, cardiotoxic and antimuscarinic. Three main possible clinical forms of intoxications with these agents are outlined – cerebrodepressive, biphasic (cerebrodepressive-antimuscarinic) and antimuscarinic. Most often the severity of AAP poisonings is moderate and the complications, which occur are mainly from the respiratory system, but their frequency is low. These poisonings are with favourable outcome, when adequate treatment is administered.

Conflict of Interest: *The authors declare that they have no conflict of interest.*

Sažetak

Uvod: Netipični antipsihotici su danas u širokoj upotrebi u psihijatrijskoj praksi. Oni postepeno zamenjuju konvencionalne antipsihotike i postaju prva linija u lečenju šizofrenije i drugih psihijatrijskih oboljenja. Ovo je povezano sa povećanjem broja trovanja ovim lekovima i zahteva dobro poznavanje kliničkih simptoma u slučajevima predoziranja.
Metode: Sprovedeno je ispitivanje kliničkih manifestacija u trovanjima netipičnim antipsihoticima kod odraslih (preko 18 godina), primljenih na Kliniku za toksikologiju, UMHATEM „N. I. Pirogov", Sofia, Bulgaria.
Rezultati: U ispitivanje je uključeno 73 slučaja trovanja jednim od ovih agenasa koja ukazuju na primarne toksične efekte koji se mogu očekivati.
Diskusija i zaključak: Naše istraživanje pokazuje tri glavna sindroma koji se mogu pojaviti nakon predoziranja netipičnim antipsihoticima. To su cerebrotoksični, kardiotoksični i antimuskarisnki sindrom, kao i tri glavna klinička oblika u ovim trovanjima – cerebrodepresivni, bifazni (cerebrodepresivni-antimuskarinski) i antimuskarinski.

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