

A problem of multiple drug overdose by patient with schizophrenia - case report

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ABSTRACT

Introduction

Suicidal risk caused by drug overdose is a considerable factor influencing earlier mortality among people with schizophrenia. An adjustment of effective pharmacological treatment is essential to sustain the stability of the patient. Commonly, the treatment divides to two groups: first generation antipsychotics (FGA) and second-generation antipsychotics (SGA). Yet, due to significant risk of depression and possible side effects of the drugs, other medicaments should also be introduced.

Case report

A 38 years old woman that was repeatedly hospitalized at the local ward, brought by ambulance and admitted to the Clinical Toxicology Department. She was admitted to the department for 20th time in period between April 2013 and May 2019 due to deliberate drug overdoses. During last hospitalization laboratory tests indicated presence of valproic acid (121,41 µg/ml). Moreover, psychiatric consultation revealed that although she was balanced state, she was not critical about her behavior. Patient was diagnosed with schizophrenia and mild intellectual disability. Each time, the intoxication was followed by medications from group of antipsychotics and tranquilizers used in treatment of the illness. Additionally, she confirmed that some of intoxications had suicidal attempt. 60% of hospitalizations of the patient were followed by stay in Neuropsychiatric hospital for further observation and treatment.

Conclusion

The administration of proper dosage of antipsychotics should be precisely controlled by the psychiatrist that takes care of the patient. For patients with greater suicidal risk, SGA are more recommended than FGA. Moreover, drugs from other groups such as antidepressants should also be introduced. Undoubtedly, efficient pharmacological treatment should be supported by psychotherapy of the patient.

Key words: drug overdose, schizophrenia, antipsychotics, suicide

Introduction

Earlier mortality among people with schizophrenia may be influenced by the course of illness and numerous factors. One of them is the difficulty in adjustment of proper medication to sustain the stability of the patient. The need of effective pharmacological treatment is crucial due increased suicidal risk among people with schizophrenia frequently caused by deliberate drug overdose [1]. Introduction of medications depends mainly on patient symptoms that are distinguished to positive symptoms such as hallucinations, delusions, disorganization in speaking, thinking, abnormal motor behavior [3] and negative symptoms including affective flattening, alogia and avolition [4]. According to Polish Psychiatric Association (PPA), the basis of pharmacological treatment of the illness divides to two groups: first generation antipsychotics (FGA) and second-generation antipsychotics (SGA) [2]. The origin of schizophrenia derives from the dysregulation of dopamine. In mesolimbic pathway, excessive dopaminergic activity is responsible for positive symptoms whereas reduced excretion of dopamine in prefrontal cortex stimulates appearance of negative symptoms [6].

First-line recommended medications belong to the SGA and involve olanzapine and risperidone. In general, atypical antipsychotics are preferably chosen over neuroleptics due to minimized side effects and concrete mechanism of action. This group inhibits differentiated receptors mainly focusing on serotonin receptors (anti-HT_{2A} action) and in lower range on dopamine receptors (D₂) [2]. What is more, unlike neuroleptics, atypical antipsychotics show effective results in therapy of both positive and negative symptoms. On the other hand, FGA that inhibit only dopamine receptors (D₂) are still effectively used especially in treatment of positive symptoms and possess sedative activity. Nevertheless, these classical medications have severe side-effects from which the most challenging are extrapyramidal symptoms. They include dystonia, parkinsonism, bradykinesia, tremor and tardive dyskinesia [5]. Dangerous side-effect caused by neuroleptics is also neuroleptic malignant syndrome (NMS) that is fatal in 10% of cases.

In course of pharmacological therapy of the patient with schizophrenia, constant intake of medications is essential. Due to the studies, intermittent dosing regimen leads to decrease in overall effectiveness of the treatment. Among medications, haloperidol was considered as the one that caused the highest rate of resignations from the therapy [7].

Case report

We present a case report of a 38 years old woman that was repeatedly hospitalized at the local ward, brought by ambulance and admitted to the Clinical Toxicology Department. According to information cards of medical treatment, it was hospitalized 20 times in period between April 2013 and May 2019, due to multiple deliberate drug overdoses. Patient was diagnosed with schizophrenia and mild intellectual disability. Each time, the intoxication was followed by medications from group of antipsychotics and tranquilizers used in treatment of the illness. Maximum time of patient hospitalization equaled to 3 days whereas the minimum time was 1 day (Tab.1). During several hospitalizations she mixed drugs with alcohol and painkillers. Additionally, she confirmed that some of intoxications had suicidal attempt (Tab.1). Moreover, 60% of hospitalizations were followed by the transport to Neuropsychiatric Hospital (12 times per 20 hospitalization) for further consultation and hospitalization at specialistic department. Besides, in case of 60% of hospitalizations she was consulted by the psychiatrist at the Clinical Toxicology Department (12 times per 20 hospitalizations). From medical report, we know that patient is emotionally unstable and has problems with her work and family.

INTOXICATIONS OF THE PATIENT

Dates of hosp.	SUBSTANCES	Duration of hosp.	PC	NH	S
03.04-05.04.13	chlorprothixene, haloperidol, carbamazepine, diazepam	3 days	No	Yes	No
30.04-02.05.13	haloperidol, perazine, ethyl alcohol	3 days	*	*	No
12.05-13.05.13	diazepam, perazine, haloperidol	2 days	Yes	Yes	No
01.10-02.10.13	chlorprothixene, ibuprofen, acetaminophen	2 days	No	Yes	Yes
12.03-13.03.14	diazepam	2 days	No	Yes	Yes
19.03-20.03.14	patient left the department on her demand before laboratory tests were carried	2 days	No	Yes	Yes
26.12-27.12.15	carbamazepine, indapamide	2 days	No	Yes	No

INTOXICATIONS OF THE PATIENT

10.01-12.01.15	haloperidol, benzodiazepines	3 days	No	Yes	Yes
14.02-15.02.17	zuclopenthixol	2 days	Yes	No	No
08.08-09.08.17	zuclopenthixol, diazepam, quetiapine	2 days	Yes	No	No
15.08-16.08.17	ketoprofen, bisoprolol, perindopril, diazepam, diclofenac	2 days	Yes	Yes	No
21.09-21.09.17	quetiapine, ibuprofen, acetylsalicylic acid	1 day	No	Yes	-
24.11-25.11.17	quetiapine, diazepam	2 days	Yes	Yes	No
02.03-03.03.18	quetiapine, diazepam	2 days	Yes	No	No
23.04-23.04.18	quetiapine, levomepromazine	1 day	Yes	Yes	Yes
16.07-18.07.18	haloperidol, levomepromazine	3 days	Yes	Yes	No
16.01-18.01.19	quetiapine	3 days	Yes	No	No
06.02-06.02.19	valproic acid	1 day	Yes	Yes	No
07.03-08.03.19	haloperidol	2 days	Yes	No	No
28.05-29.05.19	haloperidol, valproic acid	2 days	Yes	No	No
Abbreviations: NH- Transport to Neuropsychiatric Hospital, PC- psychiatric consultation, S.-suicidal attempt					
*Patient left before mentioned activity					

Tab 1. Intoxications of the patients during hospitalizations (2013-2019)

During last hospitalization, patient was urgently admitted to the Toxicology Department carried by ambulance due to drug overdose- haloperidol (6 tablets) and valproic acid (Absenor, 6 tablets per 500 mg). She did not claim the reason why she had abused the medications. At a time of admission, patient was cardiovascularly and respiratorily stable yet she was difficult in contact.

TOXYCOLOGY

PARAMETER	RESULT
Valproic acid [$\mu\text{g}/\text{mL}$] (therapeutic range of 50–100 $\mu\text{g}/\text{mL}$)	121,41
Tricyclic antidepressants (TCA) [ng/mL]	<75,00
Ethyl alcohol [g/mL]	0.01
Carbamazepine [$\mu\text{g}/\text{mL}$]	<0.50

Table 2. Deviations from laboratory tests

Laboratory tests indicated presence of valproic acid (121,41 µg/ml). The concentrations of tricyclic antidepressants (TCA), ethyl alcohol and carbamazepine remained negative (Tab. 2). No significant changes in morphology nor in blood biochemistry were detected and no deviations in electrocardiograph (EKG) were observed.

According to psychiatric examination the patient was fully oriented and remained in clear consciousness. She presented a balanced, serene mood and was not critical about her behavior. The patient was currently negating the "S" attempt or suicidal thoughts. She claimed she had taken the drugs after quarrel with her husband in order to calm down. The doctor indicated that patient did not need further hospitalization at Neuropsychiatric Hospital yet she should be under constant observation of psychiatrist.

Medical intervention involved administration of Midanium (derivative of benzodiazepine) and electrolytes. The decision of benzodiazepines administration was based on the fact that during previous hospitalizations patient had been anxious and aggressive. In order to bring relief to the patient and sustain the stable state midazolam was chosen.

Discussion

Our case emphasizes the need of holistic approach in treatment of schizophrenia. What is more, patients with schizophrenia have four times higher risk of earlier mortality than healthy people. Also this risk is more significant than in other psychiatric disorders [7]. Both pharmacological treatment and sufficient psychological therapy are essential to sustain the stable state of the patient. Undoubtedly, constant intake of medications prevents relapses and is still considered as the golden standard in terms of therapy of people with schizophrenia. Intermittent dosing regimen creates the higher risk of recurrence of the illness [8]. In case of our patient we may presume that the treatment was not effective. She was probably stopping the therapy for several times and used the medications in contrary to recommendations. That resulted in proved frequent drug abuse, suicidal attempts and multiple hospitalizations at Department of Toxicology. Besides, patient mixed medications with alcohol that led to intoxication of the organism. In both groups - FGA and SGA - interactions between antipsychotics and alcohol may be dangerous, even fatal. Combination of drugs and alcohol may enhance excessive side effects of both groups. [9].

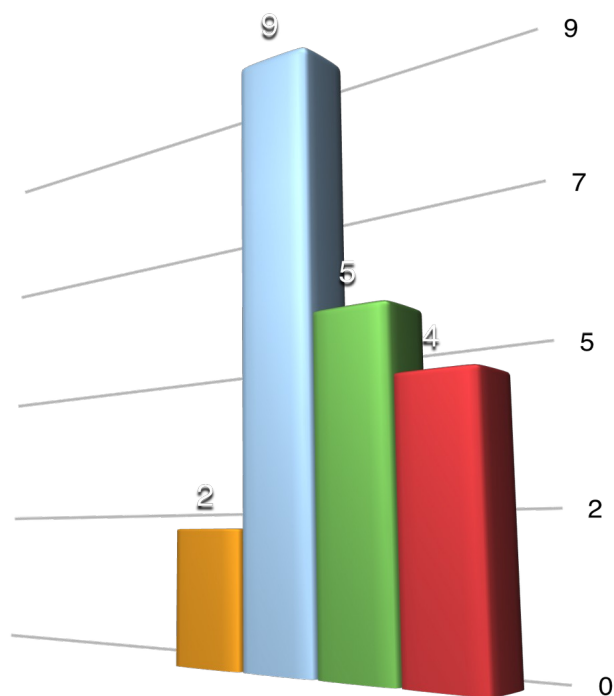
The rate of suicidal attempts in group of people with schizophrenia is estimated to 50% and 10% die because of suicide [10]. In order to prevent it, the most effective drug should be implemented especially when patient has suicidal tendencies or multiple intoxications. According to recommendations, SGA are preferred than FGA due to lower risk of side effects. Furthermore, representative of SGA, clozapine is considered as the most efficient agent in preventing suicides [10]. For our patient clozapine may be even more recommended than first-line drugs: olanzapine and risperidone. The choice of olanzapine in case of patients with risk of suicide is supported by US FDA [11]. From medical history of our patient, we know that such drug was not administered. Also, she was taking first generation neuroleptics and their effect on suicidal effect is still inconsistent. This drug group generates emotional side effects as dysphoria and agitation that may increase the risk of suicide [11].

Last hospitalization of the patient presented in the case report was caused by overdosing the haloperidol and drug with valproic acid as acting agent. Probably it was implemented to prevent her manic episodes. Overdosing of valproic acid is dangerous due to the fact that it is quickly and almost completely absorbed from digestive system after oral intake. Because of that, following complications develop urgently. The most commonly affected is depression of central nervous system due to indirect increase in regional brain g-aminobutyric acid. This may lead to coma, respiratory depression and brain edema. Additionally, frequent complications regard hepatotoxicity, pancreatitis and hematologic derangements [12]. Possibly addition of haloperidol may also elevate the activity of valproic acid. Throughout stays in hospital, patient was treated from intoxication of different substances. Among them, the most frequent were haloperidol, quetiapine and diazepam (Tab.1).

These medications derive from different group of drugs. Haloperidol is a representative of classical neuroleptics (FGA) aimed in treatment of schizophrenic symptoms and its relapses. It majorly acts through dopamine D2 receptor antagonism and also affects α_1 and 5-HT2 receptors at smaller range. The mechanism of efficient interaction with D2 receptor is commonly used in treatment of positive symptoms of schizophrenia. On the other hand, haloperidol alternate histamine H1 receptors and muscarinic M1 acetylcholine receptors that increases the risk of possible extrapyramidal symptoms as well as weigh gain or orthostatic hypotension [13]. Second type of administered medicines were SGA with quetiapine as most frequently used. This drug is used in therapy of both positive and negative symptoms of schizophrenia due to its antagonism to dopamine and serotonin receptors (5-HT2A). What is more possess fewer side-effects than other antipsychotic drugs. The application of quetiapine does not limit to schizophrenia itself. Its spectrum includes also bipolar disorders and depression. That is why the application of quetiapine in case of patients with mania or decreased mood may lead to success in pharmacological therapy [14]. Six out of twenty intoxications involved overdose of diazepam that belongs to benzodiazepines. This drug is commonly introduced in psychiatric disorders due to its anxiolytic and sedative properties. Moreover diazepam is considered as relatively safe due rare side-effects [15]. Unfortunately, despite diversified pharmacology, patient remained emotionally unstable. In case of thirteen hospitalizations, she needed transportation to Neuropsychiatric Hospital for further observation, consultation or treatment. Additionally, during several hospitalizations patient demanded immobilization in safety bed due to exaggerated anxiety. That only underlines serious state of a woman.

Among causes of suicidal attempts the most considerable are depressive symptoms and depressive syndrome [16]. These symptoms may result from low self-esteem, recent stress, stigma and treatment non-compliance. Besides, suicidal tendency and enhanced depressive mood may result from seasonality through the year. According to the references, the most considerable peak in number of suicides is denoted in spring [17,18] and in autumn. In our case, the highest frequency of hospitalization was shown in winter period- especially on the first years of patients history (Graph 1). Suprisingly, two of winter hospitalizations happened during Christmas time (26.12-27.12.15) and Valentine's Day (14.02-15.02.17). We may presume that the aim of suicidal attempts in this period was to bring more attention. During multiple hospitalization patient indicated problems with family, especially with husband. The cooperation of many factors such as family problems and seasonality may affect emotionally unstable patient in significant way. Moreover, during majority of hospitalizations, she was permanently in depressive mood.

RELATIONSHIP BETWEEN SEASON OF THE YEAR AND HOSPITALIZATION



Graph 1. Relationship between seasons of the year and hospitalization.

Apart from proper antipsychotics, in case of such patients, antidepressants should be implemented as during therapy. Results of co-administration of these two types of medications present beneficial potential in reduction of suicides. The evidence base suggests that treatment of depressive symptoms in context of patients with schizophrenia should involve serotonin selective reuptake inhibitors (SSRI). On the contrary, using antipsychotics along with SSRI may lead to interactions. Both groups are metabolized by cytochrome P450, mainly by CYP1A2, CYP2C19, CYP2D6, CYP3A4 isoenzymes [19]. That creates multiple interactions. For example haloperidol, chlorpromazine and perphenazine may elevate the concentration of SSRI. On the other hand antidepressants increases the level of chlorpromazine. Moreover specific medications act through concrete subdivisions of cytochrome P450: „for CYP1A2 (*fluvoxamine and fluoxetine*), CYP2C19 (*fluoxetine, fluvoxamine and sertraline*), CYP2D6 (*paroxetine, fluoxetine and sertraline*), and CYP3A4 (*fluvoxamine, fluoxetine and sertraline*)” [19]. We have to adjust pharmacology precisely to prevent side effects caused by enlarged concentration of the substance due to interaction.

After admitting our patient to the department in hospital, medical intervention involved administration of imidazobenzodiazepine, midazolam (Midanium). This substance was introduced due to its rapid onset and constant effectiveness. Midazolam has sedative, anesthetic and anticonvulsant properties, decreases the anxiety, causes anterograde amnesia and muscle relaxation [20]. Such activity may be explained due mechanism of the drug. As majority of benzodiazepines derivatives, it does not act directly upon GABA_A receptors but it increases the effect of GABA neurotransmitter by enhanced frequency of chloride channels opening [21]. The advantage of midazolam is the possibility of administration in multiple ways; orally, intravenously and subcutaneously. Regarding patients intoxicated with antipsychotics, introduction of midazolam should be followed by observation of circulatory system as the main side-effects of midazolam are

hypotension and respiratory depression. Yet, in case of our patient, application of midazolam brought successful effects.

Conclusion

Intoxication with antipsychotics may lead to permanent complications and eventually cause death. The administration of proper dosage of antipsychotics should be precisely controlled by the psychiatrist that takes care of the patient. Additionally medications should be adjusted to the course of schizophrenia. For patients with increased risk of suicide, clozapine from SGA group should be recommend. Moreover, FGA's action on decreasing the suicidal rate remains unclear. In case of patients intoxicated with antipsychotics, medical intervention involves conservative treatment. Generally, used drugs include sedatives, painkillers and electrolytes. In order to sustain psychological stability, patients with schizophrenia that have suicidal attempts should have antidepressants implemented. The most recommended are SSRI due to minimized side effects. On the other hand, while introduction of antidepressants along with antipsychotics, the possible interactions of these both groups of medications should be evaluated. Undoubtedly patients with schizophrenia need constant care of both- doctor and psychologist to prevent possible life threatening behavior.

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