Chemical and Toxicological Diagnosis of Acute Poisoning with Clozapine, Olanzapine, Quetiapine and Risperidone

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RELEVANCE The large number of atypical antipsychotic drugs on the market, the breadth of their medical and non-medical use, and their relative affordability make atypical antipsychotics common causes of overdose, suicidal actions or non-medical use of drugs. At the same time, they remain insufficiently studied from the chemical and toxicological point of veiw.

AIM OD STUDY: creation of available express method of detection of clozapine, olanzapine, quetiapine and risperidone in the urine of patients with acute poisoning.

MATERIAL AND METHODS Thin layer chromatography (TLC), gas chromatography with mass selective detection (GC-MS), and high performance liquid chromatography with mass selective detection (HPLC-MS/MS) were used. The preparation of intact urine samples with addition of standard solutions of clozapine, olanzapine, quetiapine, risperidone and urine samples of patients with symptoms of acute poisoning with given drugs was carried out by methods of liquid-liquid extraction at alkaline pH values for TLC chloroform, a mixture of ethyl acetate-diethyl ether (1:1) for GC-MS and acetonitrile for HPLC-MS/MS.

RESULTS A TLC method has been developed to detect clozapine, olanzapine, quetiapine and risperidone, which allows its the presence to be quickly revealed in the patient's urine at the preliminary examination stage and also distinguish them from each other in case of the same type of symptoms of poisoning. For confirmatory analysis, it is advisable to use the methods of HPLC-MS/MS and GC-MS. Compared to confirmatory methods, the developed TLC-screening technique is expressive, does not require the use of expensive high-tech equipment and allows clozapine, olanzapine, quetiapine and risperidone to be differentiated from other toxicologically significant psychoactive substances found in general screening.

Keywords: clozapine, olanzapine, quetiapine, risperidone, atypical antipsychotics, acute poisoning, TLC, HPLC-MS/MS, GC-MS

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EIA - enzyme immunoassay
GC-MS - gas chromatography with mass selective detection
HPLC-MS/MS - high performance liquid chromatography coupled with mass selective detection
ICM - immunochromatographic methods
MC - mobility coefficient
TLC - thin layer chromatography
UV spectroscopy - ultraviolet spectroscopy

INTRODUCTION

In recent years, there has been an increase in the number of cases of poisoning with antipsychotic drugs, both in the treatment of mental illness and non-medical use due to the large number of relatively affordable cheap generic drugs on the pharmaceutical market [1–5].

Poisonings with antipsychotics in patients with mental and behavioral disorders are often deliberate [2], although occasional poisonings occur due to misuse or dosing error. Despite the relatively low toxicity of these drugs, acute poisonings occurred even when taking therapeutic doses [3, 4]. Often, poisonings occur against the background of alcoholic or drug intoxication, when antipsychotics are taken for the purpose of self-medication (elimination of psychosis, withdrawal symptoms) or potentiation of the intoxicating effect [5–7].

Despite the exhaustive amount of information on the pharmacological properties and toxicity of atypical antipsychotics, which are most often found in the diagnosis of patients with acute poisoning [7–9], they continue to attract the attention of researchers. In

scientific publications for the majority of modern atypical antipsychotic people there is no information about the available specific methods of isolating and identifying them. The available experimental data are ambiguous and insufficient to obtain a universal method for the detection of these drugs. Difficulties arise when trying to distinguish antipsychotics both from each other and from other psychoactive substances. In addition, the clinical symptoms and pathological picture of olanzapine, quetiapine, and risperidone poisoning are nonspecific [10]. In this regard, their determination in biological objects is decisive in the diagnosis of acute poisoning [10–11].

Clozapine, olanzapine, quetiapine, and risperidone can be detected by thin layer chromatography (TLC) [12-14]. However, the suggested mobile phases and developers are not selective for the detection of the presented substances. Immunochemical methods , for example, immunochromatographic one(ICA), are ineffective for these drugs and are not used. Cases of false positive results of enzyme immunoassay (EIA) tests for methadone and tricyclic antidepressants in the study of biological media of patients taking quetiapine have been reported [15].

The method of ultraviolet (UV) spectroscopy for the identification of atypical antipsychotics in biological samples is of limited use, as for quetiapine there are no characteristic clear maxima on the absorption curve [16] , and the absorption maxima for clozapine and olanzapine are too close for substances to be confidently differentiated [11].

Methods of gas chromatography with mass selective detection (GC-MS) [12, 13, 16] and high-performance liquid chromatography (HPLC) with various and detecting systems [17] have been suggested for confirmatory chemical-toxicological analysis of poisoning with clozapine, olanzapine, quetiapine and risperidone. [17-19].

Aim of study: to develop a method for the analysis of atypical antipsychotic drugs - clozapine, olanzapine, quetiapine and risperidone, suitable for the differential diagnosis of acute poisonings with them.

MATERIAL AND METHODS

The study used: a substance-powder of clozapine (AO "Organika", Russia), olanzapine (OOO "Tekhnologiya lekarstv", Russia), quetiapine fumarate (OOO "Tekhnologiya lekarstv", Russia) and risperidone (OOO "Tekhnologiya lekarstv", Russia).

Stock standard solutions of clozapine, olanzapine, quetiapine fumarate (in terms of free quetiapine) with a concentration of 10 mg / ml and risperidone with a concentration of 2 mg / ml were prepared by dissolving accurately weighed portions of the substances in ethanol. The resulting solutions were used later for the preparation of working solutions and model samples with different concentrations: 20, 10, 8, 4, 2, 0.08, 0.04 and 0.01 μg / ml.

Thin layer chromatography (TLC) was performed on *Riedel-de-Haën silica gel F* 254 plates on an aluminum substrate with a 0.20 mm *silica gel UV* 254 sorbent layer. The following mobile phases were used: toluene-aceton -ethanol-25% ammonia (45: 45: 7.5: 2.5), toluene-acetone-25% ammonia solution (50: 50: 1), chloroform-ethanol (7 : 3), ethyl acetate – methanol – 25% ammonia solution (85: 10: 5). For detection, UV radiation with a wavelength of 254 nm, Dragendorff's reagent and concentrated nitric acid were used.

GC-MS and HPLC with mass-selective detection — MS / MS — were used as confirmatory methods for the developed TLC method.

Analysis conditions of GC-MS method: *Thermo Trace GC Ultra* gas chromatograph with a *DSQ* II mass spectrometric detector. Column *TR*-5 *MS*, length 30 m, inner diameter 0.25 mm, film thickness of the stationary liquid phase - 0.25 μm. The carrier gas is helium. Column temperature program: 50 ° C - 3 minutes, heating 100 ° C / min to 100 ° C, 100 ° C - 1 minute, heating from 15 ° C / min to 280 ° C, 280 ° C - 20 minutes. Injector temperature - 220 ° C. Detection by total ion current in the range of *m/z* 45–650, ionization by electron impact with an energy of 70 eV. The duration of the analysis is 18 minutes.

Analysis conditions of HPLC-MS/MS: HPLC system *Nexera* with mass spectrometric detector *LCMS*- 8040 (triple quadrupole mass analyzer) *Shimadzu* (Japan). For chromatographic separation *Luna C* 18 column was used, 50h4,6 mm, 5 micron (*Phenomenex* , USA) at 40 °C, eluent *A* - 0.1% (vol.) formic acid / deionized water, eluent *B* - 0.1% (vol.) formic acid / acetonitrile. Elution was carried out in a gradient mode; the gradient of the composition of the mobile phase is presented in Table 1.

Table 1

Gradient composition of the mobile phase for analysis with HPLC-MS / MS method

Analysis time, min	Volume fraction of eluent B, %
0.00 → 0.50	5
0.50 → 3.50	5 → 55
3.50 → 4.00	55 → 100
4.00 → 5.50	100
5.50 → 6.50	100 → 5
6.50 → 8.00	5

The volume of the injected sample is 1 μl. The retention time of olanzapine was about 1.77 minutes, clozapine was about 2.63 minutes, and quetiapine was about 2.77 minutes.

Ionization was carried out by electrospray in the positive mode; detection was carried out by multiple reactions monitoring (*MRM* $^{+}$). The values of *m/z* ion precursors, daughter ions, and the collision energy were chosen experimentally and are summarized in Table 2.

Table 2

Detection parameters of olanzapine, clozapine and quetiapine in MRM $^{+}$ mode

Ion predecessor, *m/z*	Fragment ion, *m/z*	Energy of collisions, B
Olanzapine		
312.95	255.95	-24.0
312.95	84.10	-24.0
Quetiapine		
383.95	279.00	-27.0
383.95	253.00	-25.0
Clozapine		
326.90	270.05	-24.0
326.90	191.95	-46.0

SAMPLE PREPARATION FOR ANALYSIS BY TLC

The test urine sample with a volume of 5 ml or a model sample was alkalinized with 10% ammonia solution to pH 9-11 and was extracted with two portions of chloroform, 10 ml. The combined chloroform extracts were evaporated. The dry residue was redissolved in 0.2 ml of chloroform and applied to the start line of the plate, 10 μL of the analyzed and standard solutions. To assess the sensitivity and objectify the semi-quantitative determination according to the presented TLC method, we used extracts from model samples obtained by adding working standard solutions of clozapine, olanzapine, quetiapine and risperidone to intact urine until different concentrations were obtained: 20, 10, 8, 4, 2, 0.08, 0.04, 0.01 μg / ml. To control false-positive results, a blank experiment was performed on intact urine. The extraction procedure and chromatography of the urine sample was carried out as described above. Spots in the chromatographic zones with a mobility coefficient (R_f) similar to the standards of clozapine, olanzapine, quetiapine, and risperidone were absent.

SAMPLE PREPARATION OF GC-MS ANALYSIS

One g of sodium chloride, 50 μl of 25% ammonia solution, 50 μl of diphenylamine solution (internal standard at a concentration of 100 μg / ml), and 2.5 ml of a mixture of ethyl acetate – diethyl ether (1:1) were added to 3 ml of urine. The extraction was carried out for 10 minutes with stirring in a shaker, then the layers were separated by centrifugation for 10 minutes at a speed of 3500 rpm. The organic layer was transferred into glass vials, evaporated to dryness in vacuo, and the residue was dissolved in 100 μl of ethyl acetate. The chromatograph received 2 ul of the resulting solution.

SAMPLE PREPARATION OF HPLC-MS / MS ANALYSIS

In centrifuge tubes with a capacity of 2 ml, 0.4 g of sodium chloride, 300 μL of intact or test urine, and 900 μL of acetonitrile were placed, stirred with a *Vortex*-type shaker for 10 seconds, and then centrifuged for 15 minutes at a speed of 14,500 rpm. Then, 500 μL of the upper (organic) layer of the liquid was transferred into chromatographic vials and placed in an autosampler of a chromatograph.

RESULTS AND DISCUSSION

DEVELOPMENT OF A TLC METHOD FOR THE DETECTION OF CLOZAPINE, OLANZAPINE, QUETIAPINE, AND RISPERIDONE

Selection of the mobile phase was carried out taking into account the effect of composition and polarity on the mobility of substances and the resolving power of the chromatographic system. Results for clozapine, olanzapine, quetiapine and risperidone TLC in comparable systems, the values of R_f and times of chromatography established during the experiment are presented in Table 3.

Table 3

The values of R_f for clozapine, olanzapine, quetiapine, risperidone in various solvent systems

Substance	The value of R_f in the solvent system			
	Toluene-acetone - ethanol - 25% ammonia solution (45: 45: 7.5: 2.5)	Toluene-acetone - 25% ammonia solution (50:50: 1)	Chloroform-Ethanol (7: 3)	Ethyl acetate-methanol - 25% ammonia solution (85:10: 5)
Clozapine	0.47	0.37	0.67	0.56
Olanzapine	0.40	0.26	0.56	0.43
Quetiapine	0.50	0.37	0.84	0.66
Risperidone	0.28	0.44	0.73	0.30
Chromatography time , min	12	14	8	16

As seen from the Table 3, the ethyl acetate – methanol – 25% ammonia solution (85: 10: 5) fully meets the requirements of the chemical and toxicological diagnostics of acute poisoning most: it provides sufficient separation of all four substances; chromatographic zones have clear contours and high density. This mobile phase is a common solvent system for basic substances. Its use in a non-directional chemical-toxicological studies can detect clozapine, olanzapine, quetiapine and risperidone outfit have with other medicinal substance - you do not change the general course of study. The chromatography time is 16 minutes, which meets the speed requirement.

For the detection of analytes chromatographic plates were viewed in UV light at a wavelength of 254 nm. Quenching of the fluorescence of the zones of all four preparations was observed in a relatively wide range of their concentrations in the sample. The possibility of detecting clozapine and olanzapine in relatively small amounts (0.02 μg and 1 μg per spot, respectively) has been experimentally proven. The results are shown in Table 4.

Table 4

The detection limits at the spot of clozapine, olanzapine, quetiapine, risperidone for several detectors in the method of thin layer chromatography

Substance	Detection method		
	UV, 254 nm	Dragendorff's reagent	Nitric acid, mcg
Clozapine	0. 02 mcg	0 . 01 mcg	0. 02
Olanzapine	1 mcg	1 mcg	one
Quetiapine	5 mcg	2 mcg	-
Risperidone	5 mcg	1 mcg	-

After the plates were treated with Dragendorff's reagent, the chromatographic zones of all four substances were colored orange. The use of the Dragendorff reagent in this technique is due to the versatility and high sensitivity of the detecting reagent.

Concentrated nitric acid caused brown coloration for clozapine upon drop application, burgundy for olanzapine and made it possible to confirm their presence a concentration of 1 μg / ml and higher in model mixtures.

The obtained limits (Table 4) were stably repeated with repeated measurements, including those carried out by different specialists on different days, which confirms the reliability and reproducibility of the proposed TLC technique.

The technique developed by us was used in the study of urine samples from patients with suspected antipsychotic poisoning. In all experiments, the spots corresponding to the studied substances on the chromatograms of extracts from the urine of patients with acute poisoning and from model samples had the same color and R_f values. The results are shown in Table 5.

Table 5

The results of the study of biological samples of patients with suspected poisoning with clozapine, olanzapine, and quetiapine

Number of sample	Detection of other substances						
	TLC	GC-MS	HPLS-MS/MS	Ethanol in blood, g/L	Ethanol in urine, g/L	Other substances	Notes
1	clozapine	clozapine	clozapine	n/d	n/d	doxylamine, amitriptyline	
2	clozapine	clozapine	clozapine	n/d	n/d		
3	clozapine	clozapine	clozapine	n/d	n/d		
4	n/d	clozapine	clozapine	n/d	n/d	trihexyphenidyl	Low concentration of clozapine in a sample
5	clozapine	clozapine	clozapine	n/d	n/d	doxylamine, benzodiazepines	
6	clozapine	clozapine	clozapine	1.18	2.23		
7	quetiapine	quetiapine	quetiapine	n/d	n/d	benzodiazepines, carbamazepine	
8	quetiapine	quetiapine	quetiapine, clozapine	0.32	1.56		Low concentration of clozapine in a sample
9	n/d	quetiapine	quetiapine	n/d	n/d	phenothiazines, other antidepressants	Low concentration of quetiapine in a sample
10	quetiapine	quetiapine	quetiapine	n/d	n/d	phenothiazines, tricyclic antidepressants	
11	н/о	quetiapine	quetiapine	n/d	n/d	tricyclic antidepressants	Low concentration of quetiapine in a sample
12	quetiapine	quetiapine, olanzapine	quetiapine, olanzapine	n/d	n/d	carbamazepine, amitriptyline	Low concentration of olanzapine in a sample
13	olanzapine	olanzapine	olanzapine	n/d	n/d	tricyclic antidepressants	

Notes: HPLC-MS / MS - high-performance liquid chromatography with tandem mass spectrometry; GC-MS - gas chromatography with mass selective detection; n / d - not detected; TLC - thin layer chromatography

Moreover, the detection of quetiapine and risperidone was not complicated by the presence of other toxicants in the sample. Detection of clozapine and olanzapine somewhat hampered by the presence in the sample of substances such as amitriptyline, carbamazepine and benzodiazepine derivatives which exhibit fluorescence and near values R_f(0.60-0.70), give staining with Dragendorff reagent and can therefore mask spots to clozapine and olanzapine. The problem was solved by using concentrated nitric acid as a detecting reagent with a corresponding color reaction, while other components do not give a similar result, and a mixture of concentrated sulfuric acid and alcohol (1: 1), with which clozapine and olanzapine, in contrast to interfering toxicants do not interact [20]. The presence of phenothiazines, doxylamine, tricyclic antidepressants in the sample did not interfere with the analysis.

GC-MS and HPLC-MS/MS were used to monitor the TLC results and confirm the detection of clozapine, olanzapine and quetiapine.

For GC-MS methods and HPLC-MS / MS selectivity has been previously installed by comparing chromatograms of urine samples with intact chromatogram model and test samples (samples from patients). In the chromatograms of intact urine, there were no peaks corresponding to the retention time of the studied substances, which excluded false positive results. Each test sample was analyzed in three replicates. In this case, the retention times and peak areas were consistently reproduced.

Among the samples analyzed, seven confirmed the presence of antipsychotics detected by TLC. In four of the studied samples, the suggested TLC method gave negative results for the desired substances, while they were found in confirmatory studies. The reason for the false negative results was the low concentration of antipsychotics in the samples, in which they were no longer the main cause of poisoning. This is indicated by the detection of other psychoactive substances and ethanol in these samples.

The GC-MS used as a confirmatory method is distinguished by a relatively simple sample preparation, the ability to detect both native substances and non-polar metabolites due to the presence of extensive electronic libraries of mass spectra and a relatively short analysis time (18 minutes). HPLC-MS / MS has greater selectivity and sensitivity than GC-MS as a confirmatory analysis method through the use of detection by monitoring multiple reactions. So, for example, in sample no. 8 (Table 5) this method, in addition to quetiapine, was found to contain clozapine, the presence of which was not established by other methods. In other cases, the results of the confirmatory analysis by GC-MS and HPLC-MS / MS were the same. However, the HPLC-MS / MS method is of little use for nondirectional analysis - in contrast to the presented TLC and GC-MS methods, which have the advantages of a screening method.

In comparison with confirming methods, the developed TLC technique is simple, does not require the use of expensive high-tech equipment and allows for reliable detection of concentrations in the urine of clozapine (over 0.04 μg / ml), olanzapine, quetiapine and risperidone (over 4-8 μg / ml), which is observed in acute poisoning.

CONCLUSION

The suggested method of detection of clozapine, olanzapine, quetiapine and risperidone TLC in ethyl acetate-system methanol 25% ammonia solution (85: 10: 5) and using a UV light with a wavelength of 254 nm as detector, followed by treatment of the plate with Dragendorff reagent and concentrated nitric acid, is quick, convenient and well suited for chemical and toxicological analysis of these substances in urine in acute poisoning.

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