Coupling thin layer chromatography with mass spectrometry for detection and identification of sertraline and its metabolite in the urine

S. V. Baiurka [1,A,B,C,D], S. A. Karpushyna [*2,A,C,D], N. M. Kosmina [3,A,E], L. V. Krychkovska [A,E], I. Ye. Bylov [1,A,F], O. O. Altukhov [3,B,F]

[1]National University of Pharmacy of the Ministry of Health of Ukraine, Kharkiv, [2]Uman National University of Horticulture, Ukraine, [3]Kharkiv Scientific Research Forensic Center of the Ministry of Internal Affairs of Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article;
E – critical revision of the article; F – final approval of the article

The aim of the study was to detect sertraline and its metabolites in urine under standardized thin layer chromatography (TLC) screening conditions and identify the metabolites using the mass spectrometry method.

Materials and methods. Urine samples, collected within 30 hours in portions of 20–50 mL, commenced from the seventh hour after the administration of a single therapeutic dose of the drug. The sample preparation process involved dilute acid hydrolysis, followed by the extraction of the native compound and metabolites with chloroform at a pH of 8–9. Thin layer chromatography studies of the extracts were conducted using four unified TLC systems recommended by The International Association of Forensic Toxicologists for general drug screening. Chromatograms were subjected to color reactions with a variety of chromogenic reagents. For the analysis of eluates from chromatograms, a Varian 1200 L mass spectrometer (Netherlands) equipped with a dual quadrupole mass analyzer was employed. Identification was performed through direct sample introduction into the ion chamber, electron-impact ionization (70 eV), and full ion scanning mode.

Results. The spot of the native drug on the chromatogram was identified by the R_f value. Metabolite of sertraline was identified as N-desmethyltrihydroxysertraline by the molecular ion peak in the mass spectrum.

Conclusions. The study demonstrated the ability of TLC to detect sertraline and its metabolite, N-desmethyltrihydroxysertraline, in urine after the administration of a single therapeutic dose of the drug. The chromatographic mobility of the native compound and N-desmethyltrihydroxysertraline in the unified TLC screening systems, along with the results of their visualization using chromogenic reagents for toxicological drug screening, was determined. Furthermore, the potential of coupling TLC with mass spectrometry for the separation, detection, and confirmatory identification of sertraline and its metabolic products in urine was established.

Keywords: sertraline, hydroxysertraline, N-desmethyltrihydroxysertraline, urine, thin layer chromatography, mass spectrometry.

Current issues in pharmacy and medicine: science and practice. 2024;17(1):21-25

Поєднання тонкошарової хроматографії з мас-спектрометрією для виявлення й ідентифікації сертраліну та його метаболіту в сечі

С. В. Баюрка, С. А. Карпушина, Н. М. Косміна, Л. В. Кричковська, І. Є. Билов, О. О. Алтухов

Мета роботи – виявлення сертраліну та його метаболітів у сечі за уніфікованих умов скринінгу за допомогою тонкошарової хроматографії (ТШХ) та ідентифікація метаболітів методом мас-спектрометрії.

Матеріали і методи. Сечу збирали протягом 30 годин порціями по 20–50 мл, починаючи із сьомої години після прийому одноразової терапевтичної дози препарату. Пробопідготовка включала кислотний гідроліз із наступною екстракцією нативної сполуки та метаболітів при рН 8–9. Дослідження екстрактів методом тонкошарової хроматографії здійснили в 4 уніфікованих ТШХ-системах, запропонованих Міжнародною асоціацією судових токсикологів для загального скринінгу лікарських засобів. Кольорові реакції проводили з використанням ряду хромогенних реактивів. Для аналізу елюатів із хроматограм використовували мас-спектрометр Varian 1200 L (Нідерланди) з подвійним квадрупольним мас-аналізатором. Ідентифікацію здійснили при прямому введенні зразка в іонну камеру, іонізації електронним ударом (70 еВ) в режимі повного сканування іонів.

Результати. Пляму сполуки речовини на хроматограмі ідентифікували за величиною R_f. Метаболіт сертраліну ідентифікований як N-дезметилтригідроксисертралін за молекулярним іоном у мас-спектрі.

Висновки. Показана здатність ТШХ виявляти сертралін і його метаболіт *N*-дезметилтригідроксисертралін у сечі після приймання одноразової терапевтичної дози препарату. Визначено хроматографічну рухливість нативної сполуки та *N*-дезметилтригідрокси-сертраліну в уніфікованих скринінгових ТШХ-системах, а також результати їх візуалізації за допомогою хромогенних реагентів, що застосовують для токсикологічного скринінгу лікарських засобів. Показано здатність поєднання ТШХ із мас-спектрометрією для розділення, виявлення та підтверджувальної ідентифікації сертраліну та продуктів його метаболізму в сечі.

Ключові слова: сертралін, гідроксисертралін, N-дезметилтригідроксисертралін, сеча, тонкошарова хроматографія, мас-спектро-метрія.

Sertraline ((1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahy-dro-N-methyl-1-naphthalenamine) is a widely prescribed antidepressant [1,2], belonging to the class of selective serotonin reuptake inhibitors. It is commonly used to manage mental health symptoms associated with depression, including major depressive disorder [2,3,4,5,6,7,8], anxiety disorders, and obsessive-compulsive disorder [9,10]. The therapeutic dose typically ranges from 50 mg/day to 200 mg/day [6,11]. While considered relatively safe, sertraline, like many medications, is associated with side effects and complications. These include potentially severe conditions such as life-threatening serotonin syndrome [12,13,14,15], neurological disorders like Neuroleptic malignant syndrome [16] and hemichorea-hemiballism [17], as well as hepatotoxicity [9] leading to acute liver injury [18].

Episodes of acute and lethal sertraline poisoning also were registered [11,13,19,20,21,22,23]. The toxic *per os* dose was 8000 mg in acute sertraline poisoning with the toxic concentration being in the blood serum 2930 µg/L for sertraline and 1679 µg/L for N-desmethylsertraline [11]; registered doses were in the range of 250–5000 mg in other cases of sertraline overdoses [20]. Thus, developing the analytical aspects of sertraline toxicology is a topical issue.

The current trend in the development of bioanalytical methods for the determination of antidepressants is the prevalence of gas chromatography and liquid chromato-graphy with mass spectrometric detection [24]. Most of the methods cited in the literature for the determination of sertraline in biological fluids and biological materials are based on the use of high-performance liquid chroma-tography with tandem mass spectrometric detection [25]. However, it's worth noting that these analytical methods often necessitate high-cost equipment, which may not always be readily available.

One of the most accessible types of screening procedures in forensic toxicology is thin layer chromatography (TLC screening), owing to its low cost, simplicity, quick deve-lopment time, high sensitivity, and good reproducibility. The International Association of Forensic Toxicologists (TIAFT) has recommended unified TLC systems with an R_f database for over 16,000 toxicologically important drugs [11]. However, the parameters of chromatographic mobility for sertraline in these unified TLC systems remain incompletely studied, and R_f values for sertraline metabolites have yet to be determined.

Despite several advantages, the TLC method does not offer direct identification and structural characterization of analytes on the TLC plate. To overcome this limitation, various tech-niques involving the indirect and direct coupling of TLC to mass spectrometry have been developed in recent years [26].

Aim

The aim of the study was to detect sertraline and its meta-bolites in urine under unified TLC screening conditions and identify the metabolites using the mass spectrometry method.

Materials and methods

The pure substance of sertraline was isolated from the medi-cation Stimuloton® (28 tablets, each containing 100 mg, Egis, Budapest, Hungary) using the following method: 14 tablets were placed into a glass beaker, and 10 mL of methanol was added. The tablets were left until the shells dissolved. Subse-quently, the tablets, now freed from shells, were transferred to a porcelain mortar and ground to form a homogeneous mass. A mixture of 50 mL of methanol and chloroform (1:1) was added and mixed. The contents of the mortar were then filtered through a paper filter into a porcelain cup and eva-porated in a water bath at a temperature not exceeding 40 °C until the organic solvent was removed. The residue in the cup was dried. The purity of the substance was assessed through TLC, UV spectrophotometry, and HPLC.

The volunteer's urine samples after taking a single thera-peutic dose of sertraline (2 tablets of 100 mg each Stimulo-ton®) were studied. Urine was collected within 30 hours in portions of 20–50 mL, starting from the seventh hour after taking the drug.

All chemicals were of analytical grade or better.

Sample preparation. The concentrated hydrochloric acid in the volume of 1 mL (it was based on the ratio of 0.10 mL of the acid for every 2.0 mL of the biological fluid) was added to 20 mL of the urine and the mixture was heated in a boiling water bath for 30 min. The obtained hydrolyzate was cooled, placed in a separatory funnel, and shaken with 10 mL of diethyl ether three times for 5 min each time. The organic layer was separated and discarded. The aqueous layer was placed in a separatory funnel again, alkalified with the sodium hydroxide 20 % solution to pH of 8–9 and sertraline-base was extracted with 10 mL of chloroform three times each time. The extracts obtained were combined, filtered through a pleated blue band paper filter containing 0.2 g of anhydrous sodium sulfate, and evaporated in a water bath at 40 °C to remove chloroform. The dry residue was dissolved in 5 mL of chloroform, mixed thoroughly, and transferred to a volumetric flask with a capacity of 25.00 mL adjusting to the specified volume with the same solvent.
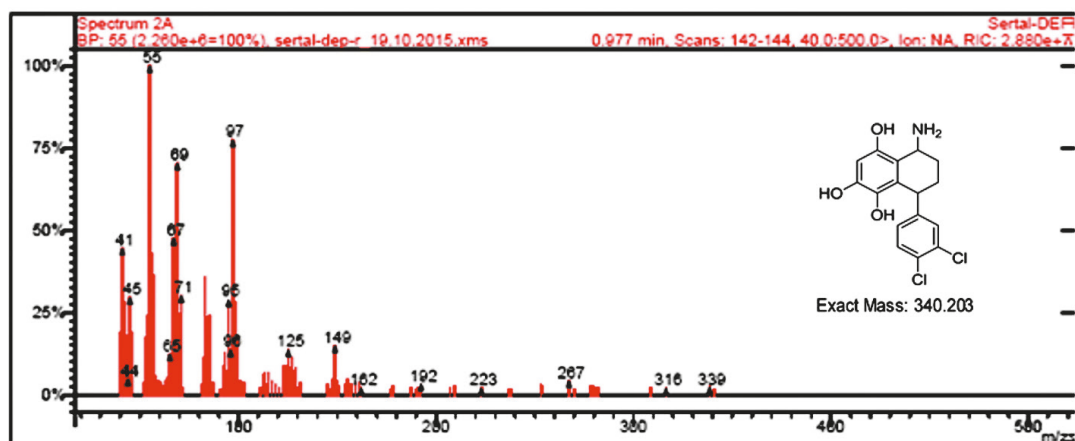
Fig. 1. Mass-spectrum of *N*-desmethyltrihydroxysertraline extracted from the urine samples.

The standard solution of sertraline in methanol (1.0 mg/mL) was previously subjected to acid hydrolysis under the described conditions. The potential appearance of acid destruction products of the drug was monitored by TLC using Merk chromatographic plates and the mobile phases listed below. Notably, no additional spots were detected in the chromatograms.

Thin layer chromatography studies of the extracts. The Merk chromatographic plates were applied. Aliquot of the 1/10 part of the biological extract, aliquot of the 1/10 part of the blank biological extract were concentrated to the minimum volume of ~0.05 mL and spotted on four TLC plates. Then 10 μL of the methanol standard solution of sertraline (1.0 mg/mL) was spotted next with the help of a microsyringe. The rest of the biological extract evaporated to the volume of ~0.05 mL was applied as a band only on the chromatography plate, which then was developed in the mobile phase of ethyl acetate – methanol – 25 % ammonia solution (85:10:5). Importantly, the zone in the chromatogram corresponding to this band was not treated with the location reagent.

Chromatograms were initially developed in the chloroform mobile phase and subsequently in one of the mobile phases listed in *Table 1*. Rectangular glass chambers (25 × 25 × 12 cm) were used for this process. Visualization was performed using ninhydrin solution in acetone and acidified potassium iodoplatinate reagent. Subsequently, sertraline was eluted from the chromatogram band untreated by the location reagents with 4 mL of methanol, resulting in an elution yield of 99.5 %. The eluate was then filtered through a blue band paper filter.

The color reactions were performed with 0.5 mL of the obtained eluates using pieces of chromatographic plates and a range of the chromogenic reagents listed in *Table 2*.

Mass Spectrometry analysis of the eluates. A Varian 1200 L mass spectrometer (Netherlands) equipped with a dual quadrupole mass analyzer was used. Detection was undertaken at the direct introduction of the sample into the ion chamber, electron-impact ionization (70 eV), and full ion scanning mode.

Results

On the chromatograms of the biological extracts obtained after the sample preparation of the volunteer's urine following a single therapeutic dose of sertraline, two spots were detected. In contrast, blank biological extracts did not exhibit corresponding spots. The spot of the native compound was identified by the R_f value, which coincided with the specified retention parameter for sertraline in the standard solution.

Fig. 1 shows mass spectrum of the eluate from chromatograms corresponding to other spots that did not match the native drug. The suspected product of sertraline biotransformation was identified as *N*-desmethyltrihydroxysertraline by the molecular ion peak in the mass spectrum.

N-desmethyltrihydroxysertraline mass spectrum (EI, 70 eV), *m/z* (I_{rel},%): 339 [M]$^+$(2.5), 316 (2.5), 267 (5), 223 (2.5), 192 (2.5), 162 (5), 149 (32.5), 125 (30), 97 (77.5), 96 (30), 95 (30), 71 (30), 69 (70), 67 (47.5), 65 (12.5), 55 (100), 45 (30), 41 (45) (*Fig. 1*). Found, m/z: 339 [M]$^+$. $C_{16}H_{15}Cl_2NO_3$. Calculated, m/z: 340.203.

R_f values of sertraline and *N*-desmethyltrihydroxysertraline extracted from the urine are shown in *Table 1*. Color reactions for sertraline and *N*-desmethyltrihydroxysertraline are presented in *Table 2*.

Discussion

The urine samples were collected based on literature data regarding sertraline pharmacokinetics. Approximately 40–45 % of the drug is excreted in the urine, with a half-life ranging from 22–36 hours [11] and 28 hours following overdose [20]. Sertraline and its main metabolite, N-desmethylsertraline, found in the blood, undergo hydroxylation followed by conjugation with glucuronic acid [11,27]. This necessitates a pretreatment step involving dilute acid hydrolysis. Consequently, the hydroxylated product of N-desmethylsertraline, namely N-desmethyltrihydroxysertraline, was detected in the urine after acid hydrolysis of the biological fluid.

Table 1. R_f values of sertraline and *N*-desmethyltrihydroxysertraline extracted from the urine

Mobile phase	R_f	
	Sertraline	*N*-desmethyltrihydroxysertraline
Ethyl acetate – methanol – 25 % ammonia solution (85:10:5)	0.54	0.31
Methanol – 25 % ammonia solution (100:1.5)	0.67	0.48
Cyclohexane – toluene – diethyl amine (15:3:2)	0.64	0.47
Toluene – acetone – ethanol – 25 % ammonia solution (45.0:45.0:7.5:2.5)	0.75	0.28

Table 2. Color reactions for sertraline and *N*-desmethyltrihydroxysertraline

Reagent	Sertraline (sensitivity, µg in spot)*	*N*-desmethyltrihydroxysertraline
Dragendorff–Munier	orange (1.0)	orange
Acidified potassium iodoplatinate	blue-violet (1.0)	blue-violet
Ninhydrin solution	no color	no color
Potassium permanganate	blue-violet (5.0)	blue-violet
Van Urk reagent	yellow (5.0)	yellow
Froehde	brownish green (5.0)	yellowish brown
Liebermann	violet → brown → discolouration (2.0)	brown
Marquis	brownish yellow (2.0)	brown
Sulphuric acid concentrated	brown (2.0)	no color
Froehde	blue (5.0)	blue → brown
Mandelin	no color	no color
Erdmann	no color	no color
Nitric acid concentrated	no color	no color

*: it was determined using standard solutions of sertraline in methanol.

The conditions for sample preparation were optimized using previously obtained data on the extraction yield of sertraline from aqueous solutions with organic solvents, dependent on pH. The maximum extraction yield, reaching 79 %, was observed at pH 8 for chloroform. The chosen organic solvent needed to exhibit an efficiency of at least 50 %, preferably higher, while minimizing the extraction of endogenous substances. To meet this requirement, a back-extraction step was incorporated into the extraction scheme to minimize the extraction of matrix components. Diethyl ether was selected for this purpose due to its low extraction yield of 28 % at pH 1.

The chromatographic mobility of sertraline and its isolated metabolite, N-desmethyltrihydroxysertraline, was investigated in four mobile phases, including those recommended by TIAFT for general drug screening [11]. Following TIAFT guidelines, the use of multiple chromatographic systems, a minimum of three, significantly enhances the reliability of substance identification by TLC [11]. *Table 1* demonstrates that all applied mobile phases offer satisfactory separation of sertraline and N-desmethyltrihydroxysertraline. For the current study, mobile phase No. 1 was utilized for TLC purification.

The color selection for the biogenic matrix components was obtained with potassium permanganate, Van Urk, Liebermann reagents *(Table 2)*.

N-desmethyltrihydroxysertraline contains a primary amino group in its structure, but like the native compound, it does not react with ninhydrin, probably because of the steric effect arising from the cyclohexane ring. The sensitivity of the color reactions for the sertraline determined using the standard methanol solution of the drug was in the range of 1.0–5.0 µg in the spot.

This work is a contribution to the toxicological screening of sertraline using TLC. Obtained data can be used in the practice of forensic and clinical toxicology.

Conclusions

1. The study demonstrated the ability of TLC to detect sertraline and its metabolite, N-desmethyltrihydroxysertraline, in urine after a single therapeutic dose of the drug.

2. The chromatographic mobility of the native compound and N-desmethyltrihydroxysertraline in unified TLC screening systems, along with the results of their visualization using chromogenic reagents for toxicological drug screening in systematic toxicological analysis, has been determined.

3. The study showcased the potential of coupling TLC with mass spectrometry for the separation, detection, and confirmatory identification of sertraline and its metabolic products in urine.

Prospects for further research. The developed conditions for detection of sertraline in the urine in the presence of its metabolite products under conditions the unified TLC screening systems will be used for further creation of toxicological examination algorithm of biological samples for the presence of sertraline in the cases of lethal intoxications by antidepressants.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Information about authors:
Baiurka S. V., PhD, DSc, Professor of the Department of Medicinal Chemistry, National University of Pharmacy, Kharkiv, Ukraine.
ORCID ID: 0000-0001-7505-6322
Karpushyna S. A., PhD, Associate Professor of the Department of Biology, Uman National University of Horticulture, Ukraine.
ORCID ID: 0000-0001-8834-4286
Kosmina N. M., PhD, Senior Research Fellow, Head of the Department of Materials, Substances and Products, Kharkiv Scientific Research Forensic Center of the Ministry of Internal Affairs of Ukraine.
ORCID ID: 0000-0002-9334-1036
Krychkovska L. V., PhD, DSc, Professor of the Department of Biotechnology, National University of Pharmacy, Kharkiv, Ukraine.
ORCID ID: 0000-0003-3136-3149
Bylov I. Ye., PhD, Associate Professor of the Department of General Chemistry, National University of Pharmacy, Kharkiv, Ukraine.
ORCID ID: 0000-0001-7685-465X
Altukhov O. O., PhD, Associate Professor, Forensic Expert of the Department of Materials, Substances and Products, Kharkiv Scientific Research Forensic Center of the Ministry of Internal Affairs of Ukraine.
ORCID ID: 0000-0001-6930-8917

Відомості про авторів:
Баюрка С. В., д-р фарм. наук, професор каф. медичної хімії, Національний фармацевтичний університет, м. Харків, Україна.
Карпушина С. А., канд. хім. наук, доцент каф. біології, Уманський національний університет садівництва, Україна.
Косміна Н. М., канд. юрид. наук, старший науковий співробітник, зав. відділу матеріалів, речовин та виробів, Харківський науково-дослідний експертно-криміналістичний центр МВС України.
Кричковська Л. В., д-р біол. наук, професор каф. біотехнології, Національний фармацевтичний університет, м. Харків, Україна.
Билов І. Є., канд. фарм. наук, доцент каф. загальної хімії, Національний фармацевтичний університет, м. Харків, Україна.
Алтухов О. О., канд. фарм. наук, доцент, судовий експерт відділу матеріалів, речовин та виробів, Харківський науково-дослідний експертно-криміналістичний центр МВС України.

References
1. Stoiljkovic M, Nikolic VN, Ilic N, Vujovic M, Popovic D, Milovanovic J, et al. Population Pharmacokinetic Modeling to Inform Sertraline Dosing Optimization in Patients with Depression. Pharmacology. 2023;108(4):409-15. doi: 10.1159/000530084
2. Hsu LM, Lane TJ, Wu CW, Lin CY, Yeh CB, Kao HW, et al. Spontaneous thought-related network connectivity predicts sertraline effect on major depressive disorder. Brain Imaging Behav. 2021;15(4):1705-17. doi: 10.1007/s11682-020-00364-w
3. Gregg LP, Carmody T, Le D, Bharadwaj N, Trivedi MH, Hedayati SS. Depression and the Effect of Sertraline on Inflammatory Biomarkers in Patients with Nondialysis CKD. Kidney360. 2020;1(6):436-46. doi: 10.34067/KID.0000062020
4. Strumia M, Guerrero F, Maurel-Ribes A, Garcia C, Payrastre B, Bagheri H. Platelet function defects and sertraline-induced bleeding: a case report. Fundam Clin Pharmacol. 2020;34(5):632-6. doi: 10.1111/fcp.12552
5. Schafer SM, Wager TD, Mercado RA Jr, Thayer JF, Allen JJ, Lane RD. Partial Amelioration of Medial Visceromotor Network Dysfunction in Major Depression by Sertraline. Psychosom Med. 2015;77(7):752-61. doi: 10.1097/PSY.0000000000000200
6. Mowla A, Dastgheib SA, Razeghian Jahromi L. Comparing the Effects of Sertraline with Duloxetine for Depression Severity and Symptoms: A Double-Blind, Randomized Controlled Trial. Clin Drug Investig. 2016;36(7):539-43. doi: 10.1007/s40261-016-0399-6
7. Greenberg T, Fournier JC, Stiffler R, Chase HW, Almeida JR, Aslam H, et al. Reward related ventral striatal activity and differential response to sertraline versus placebo in depressed individuals. Mol Psychiatry. 2020;25(7):1526-36. doi: 10.1038/s41380-019-0490-5
8. Gilliam FG, Black KJ, Carter J, Freedland KE, Sheline YI, Tsai WY, Lustman PJ. A Trial of Sertraline or Cognitive Behavior Therapy for Depression in Epilepsy. Ann Neurol. 2019;86(4):552-60. doi: 10.1002/ana.25561
9. Chen S, Wu Q, Li X, Li D, Fan M, Ren Z, et al. The role of hepatic cytochrome P450s in the cytotoxicity of sertraline. Arch Toxicol. 2020;94(7):2401-11. doi: 10.1007/s00204-020-02753-y
10. Jha MK, Minhajuddin A, Chin Fatt C, Trivedi MH. Improvements in irritability with sertraline versus placebo: Findings from the EMBARC study. J Affect Disord. 2020;275:44-7. doi: 10.1016/j.jad.2020.06.021
11. Moffat AC, Osselton MD, Widdop B. Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids and postmortem material. 4th ed. London, Chicago: Pharmaceutical Press; 2011.
12. Speerforck S, Janowitz D, Schomerus G, Grabe HJ. [Psychosis, Intoxication or Serotonin Syndrome? – A 20-Year Old Male with Ziprasidone und Sertraline]. Psychiatrische Praxis. 2017;44(8):473-5. German. doi: 10.1055/s-0043-114869
13. Pitzianti MB, Marciano S, Minnei M, Baratta A, Pasini A. Asynchronicity of Organic and Psychiatric Symptoms in a Case of Sertraline Intoxication. Clin Neuropharmacol. 2016;39(5):269-71. doi: 10.1097/WNF.0000000000000169
14. Srisuma S, Hoyte CO, Wongvisavakorn S, Wanaukul W. Serotonin syndrome precipitated by sertraline and discontinuation of clozapine. Clin Toxicol (Phila). 2015;53(8):840-1. doi: 10.3109/15563650.2015.1064940
15. Fitzgerald KT, Bronstein AC. Selective serotonin reuptake inhibitor exposure. Top Companion Anim Med. 2013;28(1):13-7. doi: 10.1053/j.tcam.2013.03.003
16. Uvais NA, Gangadhar P, Sreeraj VS, Rafeeque PA. Neuroleptic malignant syndrome (NMS) associated with amisulpride and sertraline use: A case report and discussion. Asian J Psychiatr. 2019;41:82-3. doi: 10.1016/j.ajp.2017.10.021
17. Gatto EM, Aldinio V, Parisi V, Persi G, Da Prat G, Bullrich MB, et al. Sertraline-induced Hemichorea. Tremor Other Hyperkinet Mov (N Y). 2017;7:518. doi: 10.7916/D8XK999F
18. Suen CF, Boyapati R, Simpson I, Dev A. Acute liver injury secondary to sertraline. BMJ Case Rep. 2013;2013:bcr2013201022. doi: 10.1136/bcr-2013-201022
19. Nedahl M, Johansen SS, Linnet K. Reference Brain/Blood Concentrations of Citalopram, Duloxetine, Mirtazapine and Sertraline. J Anal Toxicol. 2018;42(3):149-56. doi: 10.1093/jat/bkx098
20. Cooper JM, Duffull SB, Saiao AS, Isbister GK. The pharmacokinetics of sertraline in overdose and the effect of activated charcoal. Br J Clin Pharmacol. 2015;79(2):307-15. doi: 10.1111/bcp.12500
21. Gurbanov A, Kandemir F, Gurbanova L, Gün E, Botan E, Balaban B, et al. Antidepressant Poisoning Trends in Pediatric Intensive Care: A Comparative Study of New- and Old-Generation Antidepressants. J Clin Psychopharmacol. 2023;43(2):139-44. doi: 10.1097/JCP.0000000000001668
22. Overberg A, Morton S, Wagner E, Froberg B. Toxicity of Bupropion Overdose Compared With Selective Serotonin Reuptake Inhibitors. Pediatrics. 2019;144(2):e20183295. doi: 10.1542/peds.2018-3295
23. Sasaki C, Shinozuka T, Murakami C, Irie W, Maeda K, Watanabe T, et al. Simultaneous determination of 5 psychotropic drugs of various types in an autopsy case of acute multiple drug poisoning. Forensic Sci Int. 2013;227(1-3):90-4. doi: 10.1016/j.forsciint.2012.11.015
24. Gegedish LR, Bidnichenko YI, Feduschak NK. [Using gas chromatography-mass spectrometry for the determination of amitriptyline in biological material]. Current issues in pharmacy and medicine: science and practice. 2013;(2):93-4. Ukrainian. Available from: http://nbuv.gov.ua/UJRN/apfimntp_2013_2_29
25. Dziurkowska E, Wesolowski M. Sertraline – isolation methods and quantitation in biological material. Psychiatr Pol. 2018;52(6):997-1012. English, Polish. doi: 10.12740/PP/85788
26. Zou X, Liu X, Zhang J. [Advances in thin layer chromatography coupled with mass spectrometry technology]. Se Pu. 2023;41(1):24-36. Chinese. doi: 10.3724/SP.J.1123.2022.03038
27. Baselt CR. Disposition of Toxic Drugs and Chemicals in Man. 12th ed. Seal Beach, CA: Biomedical Publications; 2020.