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The isolation of Venlafaxine from the biological material by hydrophilic solvents

Aim. To determine the Venlafaxine recovery from biological tissues using generally accepted methods of drug isolation by the extraction with acidified water and acidified ethanol.

Materials and methods. The studies were performed on model samples of the animal liver spiked with Venlafaxine. The drug was isolated by the extraction with water acidified with oxalic acid according to the A. O. Vasylieva method, ethanol acidified with oxalic acid by the Stas-Otto method, water acidified with sulfuric acid according to the V. P. Kramarenko method. The extracts obtained were subjected to the additional cleanup procedure by the back-extraction and TLC. Detection and the quantitative determination of Venlafaxine in the extracts obtained were performed by TLC and UV spectrophotometry.

Results and discussion. While extracting Venlafaxine from the biological material with water acidified with oxalic acid, ethanol acidified with oxalic acid and water acidified with sulfuric acid, the recovery values were 44 ± 2 %, 36 ± 3 % and 28 ± 3 %, respectively. The quantitative determination of the drug in extracts was performed by the UV-spectrophotometric method at λ_{max} 277 nm according to the equation of the calibration curve $y=(0.00368 \pm 2\times10^{-5})\times x$, which showed linearity in the range of the analyte concentrations of 25.00-300 μg/mL.

Conclusions. 1. The recovery values of Venlafaxine from the biological material using generally accepted methods have been determined. The highest recovery was obtained while extracting with water acidified with oxalic acid, which was 44 ± 2 %, which provided its suitability for the sample preparation during the non-directed toxicological examination. 2. The inclusion of the additional cleanup procedure by the back-extraction and TLC into the pretreatment process made possible to apply the UV spectrophotometric method, which was linear within the range of the expected lethal concentrations of Venlafaxine in the biological material. 3. The method of the Venlafaxine isolation from the liver tissue by extracting with acidified water with oxalic acid followed by the additional optimized cleanup procedure can be recommended for the forensic toxicological examination of the biological material for the presence of Venlafaxine.

Keywords: *Venlafaxine; biological material; isolation; TLC; UV spectrophotometry*

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Ізолювання венлафаксину з біологічного матеріалу гідрофільними розчинниками

Метою дослідження було визначити ступінь ізолювання венлафаксину з біологічних тканин за допомогою загальноприйнятих методів виділення лікарських речовин екстракцією підкисленою водою та підкисленим етанолом.

Матеріали та методи. Дослідження виконували на модельних зразках печінки тварини, до яких було додано венлафаксин. Препарат виділяли екстракцією водою, підкисленою кислотою оксалатною, за методом А. О. Васильєвої, етанолом, підкисленим кислотою оксалатною, за методом Стаса-Отто, водою, підкисленою кислотою сульфатною, за методом В. П. Крамаренка. Отримані екстракти додатково очищували за допомогою екстракції та ТШХ. Виявлення та кількісне визначення венлафаксину в отриманих екстрактах здійснювали методами ТШХ та УФ-спектрофотометрії.

Результати та їх обговорення. Ступінь ізолювання венлафаксину з біологічного матеріалу екстракцією водою, підкисленою кислотою оксалатною, становив 44 ± 2 %; етанолом, підкисленим кислотою оксалатною – 36 ± 3 %; водою, підкисленою кислотою сульфатною – 28 ± 3 %. Кількісне визначення препарату в екстрактах здійснювали УФ-спектрофотометричним методом за λ_{max} 277 нм за рівнянням калібрувального графіка $y = (0{,}00368 \pm 2\times10^{-5})\times x$, який був лінійний у межах концентрацій аналіту 25-300 мкг/мл.

Висновки. 1. Визначено ступінь ізолювання венлафаксину з біологічного матеріалу за допомогою загальноприйнятих методів. Найвищий ступінь ізолювання, який становив 44 ± 2 %, отримано за екстракції водою, підкисленою кислотою оксалатною, що забезпечило його придатність для пробопідготовки в межах ненаправленого токсикологічного дослідження. 2. Внесення до схеми пробопідготовки додаткового очищення за допомогою екстракції та ТШХ забезпечило можливість застосувати методику УФ-спектрофотометричного визначення, яка була лінійною в діапазоні очікуваних летальних концентрацій венлафаксину в біологічному матеріалі. 3. Метод ізолювання венлафаксину з тканини печінки екстракцією водою, підкисленою кислотою оксалатною, з подальшою оптимізованою методикою додаткового очищення можна рекомендувати для судово-токсикологічного дослідження біологічного матеріалу на присутність венлафаксину.

Ключові слова*: венлафаксин; біологічний матеріал; ізолювання; ТШХ; УФ-спектрофотометрія*

Introduction. Venlafaxine (1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride), a second-generation antidepressant, is a mixed serotonin-norepinephrine reuptake inhibitor (SNRIs). Venlafaxine is among the most prescribed antidepressant drugs over the world [1, 2] and considered as a first-line option for pharmacological management of the major depressive disorder (MDD) [3-6]. It is also used for the treatment of panic disorder, generalized anxiety and neuropathic pain [5, 7, 8]. The usual prescribed daily dose is 75-150 mg [3, 7].

The discontinuation syndrome [9], dose-dependent blood pressure elevation, cardiovascular disorders up to potentially fatal type of ventricular tachycardia, increased risk of fatal overdoses [10], urinary retention [11] were adverse events reported with Venlafaxine. Moreover, a few literature case reports indicated the ability of Venlafaxine in high doses to have MDMA/amphetamine-like stimulant and psychedelic effects, which led to its non-medical use [12].

Several Venlafaxine lethal intoxications have been reported [10, 13-16]. In lethal cases, drug concentrations were in the range of 41-89 mg/L for the blood and in the range of 21-430 mg/kg for the liver, the value for the brain was 543 mg/L, the average value for the kidneys was 420 mg/kg, while in the urine, the average value was 125 mg/kg, and it was 11 mg/L in the gastro-intestinal tract [13, 15].

Bioanalytical methods for determining the content of Venlafaxine in plasma samples by the liquid chromatography-tandem mass spectrometry (LC-MS/MS) have been developed [8, 17]. We proposed the method of the Venlafaxine isolation from the liver tissue by the extraction with a lipophilic solvent chloroform followed by a cleaning step with hexane and the quantitative determination by the HPLC-UV detection [18].

Isolation methods have been developed for determining Venlafaxine in the brain tissue by the solid-phase extraction, in the liver tissue by the liquid-phase microextraction with a 1-octanol-acetic acid mixture (recovery was 47 %) and the extraction by butyl chloride from the homogenized liver samples preliminary incubated in 10 M sodium hydroxide solution [19]. The GC-MS, HPLC-UV detection, LC-MS, respectively, were used as analytical methods [19].

In the national practice of forensic toxicology research, the general isolation methods the most widely applied for the pre-treatment of biological tissues studied for the presence of drugs are based on the extraction by such hydrophylic solvents as acidified water and acidified ethanol [20-22]. Particularly, according to the Guideline of the Main Bureau of Forensic Medical Examination of the Ministry of Health of Ukraine the acidified water and acidified ethanol should be used provided that their effectiveness is confirmed [20]. No such literature data have not been found on Venlafaxine.

The aim of this study was to determine the Venlafaxine recovery from biological tissues using generally accepted methods of drug isolation by the extraction with acidified water and acidified ethanol.

Materials and methods. *Reagents and Equipment*. Venlaxor (75 mg) tablets containing Venlafaxine hydrochloride were purchased from Grindex (Riga, Latvia). The extraction of Venlafaxine from commercial tablets was performed as described in the article [18]. All other chemicals were of analytical grade or better. Absorption of the solutions in the UV region of the spectrum was measured using a spectrophotometer (SF-46), the spectral measurement range was 190-1100 nm. A pH-meter 5123 (Elvro, Wroclaw, Poland), a water-bath LW-4 (Bytom, Poland), Merck chromatographic plates (Silica gel 60 F254, size 10×20 cm, Germany), volumetric flasks of 10 mL, 25.00 mL, 50.00 mL, volumetric pipettes, Class A (Simax, Czech Republic) were also used.

Sample preparation. 20 g of the ground animal liver were spiked with 1 mL of the Venlafaxine aqueous solution containing 2000 μg of the drug-base, the model sample obtained was stirred and left for 24 hours. The blank experiment was carried out with the same biological tissue.

Venlafaxine was isolated from the model liver sample by the extraction with water acidified with oxalic acid (according to the A. O. Vasylieva method), ethanol acidified with oxalic acid (according to the Stas-Otto method), water acidified with sulphuric acid (according to the V. P. Kramarenko method) according to the generally accepted methods [21, 22].

The chloroform extract obtained was subjected to the additional cleanup procedure by the back-extraction and TLC. The chloroform extracts were placed into a porcelain cup, evaporated in a water bath at a temperature not higher than 40°C, and a dry residue was dissolved in 20 mL of a 0.1 M solution of hydrochloric acid (pH 1). Then the content of the cup was mixed thoroughly, placed into a separatory funnel and shaken twice with hexane (10 mL each), discarding the organic solvent phase. The acidic aqueous residues were combined, alkalified with a 20 % sodium hydroxide solution to pH 10-11, and Venlafaxine was extracted three times with 10 ml of hexane each time. The combined organic extract was filtered through a paper filter containing 0.5 g of anhydrous sodium sulfate. The resulting hexane extract was evaporated, placed into a 25 mL volumetric flask and reconstituted with hexane to the appropriate volume.

T*he thin layer chromatography (TLC) analysis of the extract*. 10 μL of the reference chloroform solution (the drug concentration was 1 mg/mL or 10 μg in the sample) was spotted on two Merck chromatographic plates using a microsyringe, next 0.5-3.0 mL aliquot of the extract resulted after the back extraction (previously evaporated to a minimum volume of ~0.05 mL) was applied as a band. Another 2.0-5.0 mL aliquot of the biological extract evaporated to the minimum volume was applied additionally on the chromatography plate, which then was developed in the mobile phase of methanol-25 % ammonium hydroxide solution (100:1.5). Then the zone on the chromatogram corresponding to this band was not be treated by the location reagent. Further, 0.5-3.0 mL aliquot of the blank biological extract was applied.

At first, chromatograms were developed in chloroform as a mobile phase to separate the drug and matrix components, herewith concomitants migrated from the solvent front to the finish line and the analyte located on the start line. Then chromatograms were eluted in one of three other mobile phases. An acidified iodoplatinate solution was used for visualization, Venfaxine was detected by blue-violet spots. The analyte was eluted from the chromatogram strip untreated by the location reagent twice each time with 2 mL of methanol.

The UV spectrophotometric detection and the quantitative determination of Venlafaxine in the eluate. The UV-spectrum of Venlafaxine in the methanol eluate was measured in the wavelength range of 200-350 nm; a 10 mm light pathway cuvette was used. The quantitative determination of Venlafaxine was performed at 277 nm by the calibration curve. The reference solution was eluate in the blank experiment.

Standard solution (SS) of the drug was prepared by dissolving 0.01695 g of Venlafaxine hydrochloride (it corresponded to 0.01500 g of the Venlafaxine base) in methanol using a 50.00 mL volumetric flask; the resulting concentration was 300 μg/mL of the drug base. To prepare standard working solutions (SWS), the aliquots of 0.40; 1.00; 2.00; 3.00; 4.00; 5.00; 6.00; 8.00 and 9.00 mL of SS were placed into 10 mL volumetric flasks and diluted to the appropriate volume with methanol. The concentration of SWS obtained were 12.0; 30.0; 60.0; 90.0; 120.0; 150.0; 180.0; 240.0 and 270.0 μg/mL. The absorbance of SS and 9 SWS was measured against methanol as *Reference solution*. The linear regression model described in the general form as $y = b \times x + a$ was applied to obtain the equation of the calibration curve.

Results and discussion. The cleanup procedure by the back-extraction, which was incorporated into the sample preparation process, was optimized based on the previously obtained data on the extraction yield of the drug depending on the nature of the organic solvent and the pH of the aqueous media.

The maximum extraction yield (62-64 %) was obtained for hexane at pH 10-11. The lowest amount of the analyte (0.3 %) was extracted with hexane pH 1.

The methanol-25 % ammonium hydroxide solution (100:1.5) and cyclohexane-toluene-diethyl amine (15:3:2) mobile phases (No. 1 and 2), which were recommended by the International Association of Forensic Toxicologist (TIAFT) for systematic toxicological screening of drugs by TLC [13], and the toluene-acetone-ethanol-25 % ammonium hydroxide solution (45:45:7.5:2.5) mobile phase (No. 3), which was also widely used in the national practice of forensic toxicological studies [21, 22], were applied for detecting Venlafaxine isolated from the liver tissue by TLC.

The R_f values of Venlafaxine in the biological extracts and the drug in the reference solution coincided and were 0.65 ± 0.03, 0.57 ± 0.03 and 0.71 ± 0.05 in mobile phases 1, 2 and 3, respectively (the mean of five measurements). Blank extracts did not give the spots with the corresponding R_f values. The sensitivity of acidified iodoplatinate as a location reagent was 2.0 μg per sample. It was previously found that the elution recovery of Venlafaxine from the plates with methanol was 98.2 %.

The UV-spectrum of Venlafaxine isolated from the liver and Venlafaxine in the standard methanol solution coincided and had three principal peaks at wavelengths of 226 ± 2, 277 ± 2 and 284 ± 2 (Fig.). The UV-spectrum of the blank eluate did not have principal peaks at the corresponding wavelengths.

The quantitative determination of Venlafaxine in the eluates was performed using calibration curve described by the equation: $y = (0.00368 \pm 2 \times 10^{-5}) \times x$ ($r = 0.999$; $S_o^2 = 7 \times 10^{-5}$; $S_a = 0.004$; $S_b = 2 \times 10^{-5}$). The significance of the intercept in a regression model was checked using the *F*-test, and the conclusion was drawn that it was possible to transfer to the equation in the form of $y = b' \times x$. The calibration curve showed linearity in the range of 25.00-300 μg/mL. Detection Limit (*DL*) and Quantification Limit (*QL*) were calculated from the calibration

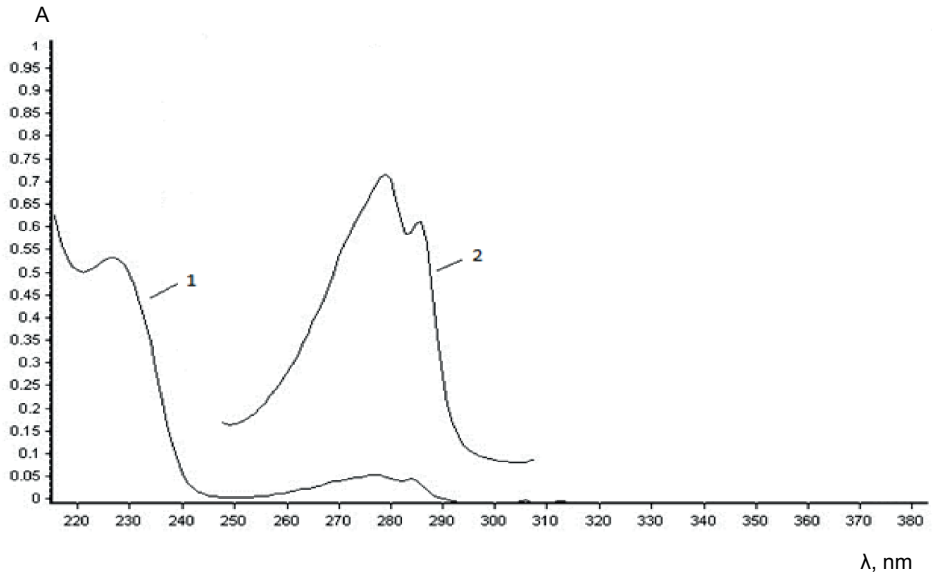

Fig. The UV-spectrum of Venlafaxine in methanol (1 – concentration 5×10^{-5} mole/L; 2 – concentration 5×10^{-4} mole/L)

Table 1

Recovery of the isolation methods of Venlafaxine from the liver tissue by the A. O. Vasylieva, Stas-Otto, V. Ph. Kramarenko methods

Venlafaxine added to 20 g of the liver, μg	Recovery ($\bar{X}$), %	Metrological characteristics			
		S	$S_{\bar{X}}$	$\Delta\bar{X}$ (n = 5; P = 0.95)	ε, %
A. O. Vasylieva method					
2000	44	1.8	0.8	2	5
Stas-Otto method					
2000	36	2.4	1.1	3	9
V. P. Kramarenko method					
2000	28	2.4	1.1	3	11

Table 2

The values of the background response (A_{min}), *DL* and *QL* of the UV-spectrophotometric determination of Venlafaxine in the biological extracts obtained by various isolation methods

The extract obtained by the specified method	The value of the background response (A_{min})	S	RSD, %	ΔA_{min} (n = 10; P = 0.95)	ε	*DL*, μg/mL	*QL*, μg/mL
by A. O. Vasylieva	0.024	0.0037	15.4	0.003	11.0	3.3	10.1
by Stas-Otto	0.020	0.0024	12.0	0.002	8.6	2.2	6.5
by V. P. Kramarenko	0.025	0.0031	12.4	0.002	8.9	2.8	8.4

curve parameters: the standard deviation of *y*-intercept S_a and slope *b* [23]; they were 3.5 μg/mL and 10.9 μg/mL, respectively. Thus, the working region of the UV-spectrophotometric method developed for the Venlafaxine quantitative determination satisfied the analytical task concerning the determination of the pre-treatment procedure recovery of the model liver sample. The recovery values of the range of isolation methods being tested are given in Table 1.

Thus, the highest recovery was obtained while extracting with water acidified with oxalic according to the A. O. Vasylieva method, which was 44 ± 2 %. This was slightly lower than the efficiency of the special isolation method by the chloroform extraction followed by a cleaning step with hexane, which was developed for lipophilic substances, in particular Venlafaxine (recovery was 51%). The important parameters determining the lipophilicity of the drug were the partition coefficient log P (octanol/water) for its hydrochloride equaled to 0.43, and the volume of distribution (V_d) was 4-12 L/kg. The practical value of the recovery assessment for general isolation methods is that they are recommended as a pre-treatment step in conducting non-directed forensic toxicological examinations [20].

In accordance with the recommendations relatively to sample preparation methods for forensic toxicology studies, the degree of the analyte isolation should not necessarily be maximum, a value of about 50 % is sufficient with a reproducibility of the specified parameter for different concentrations of the analyte in the sample studied higher than 20 % [13, p. 181]. In this case, the extraction of endogenous impurities should be minimized. Thus, the A. O. Vasylieva method may be useful as a pre-treatment step for the non-directed toxicological research, while the isolation method by chloroform should be used in directed toxicological studies of the biological material for the presence of lipophilic drugs.

The influence of endogenous biological matrix components on the results of the quantitative determination by the UV-spectrophotometric method was evaluated. For this purpose, *DL* and *QL* of Venlafaxine in the extracts were calculated using the absorption values of the corresponding blank extracts at λ_{max} = 277 nm according to the equations [23]: $DL = 3.3 \times S/b$ and $DL = 10 \times S/b$ where *S* was the standard deviation of the absorption value of the background response of the corresponding number of blank samples; *b* was the slope of the calibration curve of the analytical method applied (Table 2).

As can be seen from Table 2, the *DL* and *QL* values calculated from the model based on the standard deviation of absorbance of blank samples did not exit the corresponding validation characteristics obtained from the parameters of the calibration curve. This indicated the lack of the biological matrix component influence on the UV-spectrophotometric determination of the analyte in the eluates. In addition, the pre-treatment process developed provided a sufficient recovery for application of the UV-spectrophotometric method, which showed the working area within the level of the expected lethal concentrations of Venlafaxine in the biological material.

Conclusions and prospects for further research. 1. The recovery values of Venlafaxine from the biological material using generally accepted methods have been determined. The highest recovery was obtained while extracting with water acidified with oxalic acid, which was 44 ± 2 %, which provided its suitability for the sample preparation during the non-directed toxicological examination.

2. The inclusion of the additional cleanup procedure by the back-extraction and TLC into the pretreatment process made possible to apply the UV spectrophotometric method, which was linear within the range of the expected lethal concentrations of Venlafaxine in the biological material.

3. The method of the Venlafaxine isolation from the liver tissue by extracting with acidified water with oxalic acid followed by the additional optimized cleanup procedure can be recommended for the forensic toxicological examination of the biological material for the presence of Venlafaxine.

Taking into account the lipophilic properties of Venlafaxine it is interesting to study acetonitrile and acetone as amphiphilic solvents for extracting the antidepressant under study from the biological material.

Conflict of interests: authors have no conflict of interests to declare.

ПЕРЕЛІК ВИКОРИСТАНИХ ДЖЕРЕЛ ІНФОРМАЦІЇ

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