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Extraction techniques for analysis of venlafaxine and its metabolites in biological matrices

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Summary

Venlafaxine (VEN), which was introduced into therapy in 1990s is one of the most often used antidepressants. The monitoring of its concentration in the organism is recommended, particularly in the case when a patient suffers of others illnesses and is treated with different drugs, which can interfere with VEN. The most popular diagnostic material for the determination of VEN level is blood. The present study is the review of actual reports on the methods of extraction of VEN and its metabolite from blood and other human diagnostic materials, like saliva and urine, and also from animals tissues. The paper shows the classic extraction methods, such as liquid-liquid extraction and solid-phase extraction. It also contains the modifications of these methods such as liquid-phase microextraction and cloud point extraction. According to the literature it can be stated that the best recovery of VEN and its main metabolite, O-demethylvenlafaxine, was obtained when the liquid-liquid extraction was used. The new, modified methods of extraction, are cost-effective, owing to the reduced use of solvents and also smaller volume of diagnostic material, but the results of the analysis, especially the recovery of the analytes, were lower than those obtained by classic methods of extraction.

Key word: venlafaxine, O-demethylvenlafaxine, SPE, LLE, blood, saliva, urine

Antidepressant drugs have been used since the 1950s, when for the first time the thymoleptic activity of isoniazide, the anti-tuberculosis drug was reported. This caused that iproniazide, a compound of a similar structure, classified as a monoamine oxidase inhibitor, was also introduced as a drug. At the same time it was noticed that imipramine had also thymoleptic activity, and this compound became the first drug from the group of tricyclic antidepressants. Further studies conducted in this direction have shown that similar therapeutic effect can be achieved when the activity was targeted into adrenergic system, which resulted in introducing selective inhibitors of reuptake of adrenaline in the 1970s. The turning point in the treatment of depression was in the 1980s, when selective inhibitors of reuptake of serotonin appeared, which are now the most often used against depression. In the end of the last century, first selective inhibitors of reuptake of serotonin and noradrenalin such as venlafaxine were implemented into treatment [1, 2].

Venlafaxine (VEN), the second generation antidepressant drug, was introduced into treatment in 1993. It was prepared as a racemic mixture, but the two enantiomeric forms have different impact on reuptake of neurotransmitters in the synaptic slit. The (–)-(R) enantiomer inhibits both the noradrenalin and serotonin synaptic reuptake, whereas the (+)-(S) enantiomer inhibits only the serotonin one. From the literature screening it also results that VEN acts as a weak inhibitor of the reuptake of dopamine [3, 4].

VEN is mostly used in the treatment of Major Depressive Disorder and against its recurrences. It is also administered in the therapy of fears, social phobias, sudden fears and agoraphobia [5, 6]. The preparations with VEN can be conventional tablets, or tablets and capsules with retarded release. The dosing depends on a given form of the drug. The conventional tablets with divided dose are given 2-3 times daily, whereas the retarded forms once a day. The range of dosing is usually from 75 to 225 mg/d in depression treatment, and from 150 to 225 mg/d in the therapy of general fears [6].

Pharmacokinetics, interactions, adverse effects

From a single dose, VEN is absorbed at least in 92%, and after absorption it goes through the first-pass effect in the liver. Its total biological availability is within the range from 40 to 45%, depending on the metabolism in an organism [7]. In a blood circulation it is bound by plasma proteins in 27%. VEN is transformed by two enzymes from the group of cytochrome P450, CYP2D6 and CYP3A4, and it is considered as a weak inhibitor of isozyme CYP2D6 responsible for O-demethylation process [8, 9]. Its main and the most important metabolite, O-desmethylvenlafaxine (ODV), is produced in the amount of 56%, and has pharmacological activity and effect on reuptake of monoamines, similar as VEN. Other metabolites, N,O-didesmethylvenlafaxine (16%) and N-desmethylvenlafaxine (1%), are biologically inactive [3].

The average half-life of VEN is 5±2 h, whereas that of its main metabolite, ODV, is 11±2 h. The major part of the drug, about 87%, is eliminated by kidneys within 48 h, including the unchanged form (5%), free ODV (29%), coupled ODV (26%), or inactive metabolites (27%). In persons with impaired kidney functions, the half-life in the elimination phase is much longer, which results in the need to reduce the dose taken by a patient [7].

In spite of the fact that VEN and ODV affected only slightly the activity of liver enzymes, they can interact with drugs metabolized by the same isozymes. When the CYP2D6 inhibitors are applied simultaneously, for instance difenhydramines, the VEN level increases in blood [8]. On the other hand, substances inducing this isozyme, accelerate VEN metabolism and also reduce the time of the drug activity. Similarly, the use of CYP3A4 inhibitors responsible for ODV metabolism, such as ketoconazole, can increase ODV level in blood, and decrease its clearance. This is especially important in the context of ODV half-life, because it is longer than that of VEN [8, 9].

In the literature, special attention is paid to the fact that a serotonin syndrome can occur, when VEN is used in the treatment. This is a life-threatening potential state, especially when the drug is given together with other substances influencing the serotoninergic transmission, such as monoamine oxidase inhibitors (IMAO) [7].

For this reason these drugs cannot be administered together with VEN. The treatment with VEN should not begin sooner, than 14 days after finishing the treatment using IMAOs. A 7-day break is also recommended after ending the treatment with VEN, before starting the administration of MAO inhibitors. The same refers to the treatment with Li salts.

VEN can enhance the risk of blooding through disordering of thrombocytes' activity. It is especially dangerous for patients taking anti-coagulants and inhibitors of thrombocytes. Hence in such cases VEN must be administrated with particular care. VEN should not impair the functions of brain or inhibit motoric activity, this however depends on personal features of a patient. It can enhance the action of ethanol, and that is why it is not recommended to drink any alcohol during the treatment with VEN, similarly as of other substances which have an impact on the Central Nervous System [7].

The most often occurring side effects of VEN therapy identified during clinical trials in more than one person in ten, include nausea, xerostomia, headache, sweating, including night sweating. On the other hand, when the treatment is stopped, it may lead to a withdrawal syndrome, such as vertigo, agitation or fear, paraesthesia, sleep disorders (insomnia, abnormal dreams), nausea, vomiting, convulsions, headache, and symptoms of influenza. These symptoms usually are weak and should vanish by themselves.

Methods of VEN extraction from biological material

The high rank of VEN in depression therapy results in the necessity to elaborate appropriate analytical methods enabling to monitor its level, as well as its metabolites in the organism. These methods should be characterised by such features, which enable determination of VEN and its active metabolite over the concentration range of both analytes used in therapy. The literature data show that therapeutic concentration of VEN ought to be within the range of 0.07 to 0.3 mg/L, whereas that of ODV from 0.2 to 0.5 mg/L. Repeated administration of VEN raises its blood level from 0.07 to 0.27 mg/L, and that of ODV from 0.24 to 0.52 mg/L [10]. Results of pharmacokinetic studies of VEN have shown that its concentration in blood of 1781 patients was found in the range of 0.13-2.50 mg/L (127.6–2496.6 μg/L) [11]. It was also found that in the group of patients aged 65+ and in women, the VEN level in blood was higher, in spite of the treatment with usually applied therapeutic doses. In this situation it is evident that the level of VEN must be monitored, especially in the group of patients mentioned above.

The commonly analysed diagnostic material, in which the concentration of VEN and its metabolites was determined, was blood plasma and serum. There were also several attempts to use saliva and urine for that purpose. Moreover, VEN was determined in animals tissues, as well, for example in rat liver and brain. In this connection, it was decided to review the literature in order to evaluate usefulness of extraction methods used for the preparation of biological material for the determination of VEN and its metabolites in it.

SPE extraction

As it results from the literature data, Solid-Phase Extraction (SPE) is one of the most frequently applied methods for isolation of VEN and its metabolites from biological material. This method is being chosen owing to its selectivity, and it also enables high degree of purification of a sample, as well as a high extraction yield. In comparison with Liquid-Liquid Extraction (LLE), SPE is less labour-consuming, and its application reduces the use of toxic organic solvents, and enables to enhance detection of the investigated compounds.

Mandrioli et al. [12] analysed VEN and its main metabolite, ODV, in blood plasma of patients receiving fixed doses of the drug 75 or 150 mg during a day. For extraction, they used SPE method with type C1 columns, and the determination was carried out by the use of HPLC with spectrofluorimetric detection. The recovery of the method was above 92% for VEN, 93% for ODV, and 97% for the internal standard (citalopram). The linearity of the method was established in the range from 1 to 1000 ng/mL, whereas the limit of detection was estimated as 0.3 ng/mL for both compounds.

In order to optimize the extraction process, other columns were also used. These were as follows: hydrophilic-lipophilic (HLB), cyanopropyl (CN), phenylic (PH), as well as C2 and C8. However, chromatographic peaks obtained using the HLB and CN columns were too low in comparison with the concentrations of the analysed substances. Moreover, PH columns appeared to be not selective enough. Again, columns C2 and C8 did not give satisfactory levels of internal standard recovery, and the use of C8 columns did not allow for the determination of ODV. Moreover, the peak of VEN in the chromatogram was too low in comparison with its concentration. It was also found that better results were achieved, when the columns were flushed with a 30% solution of methanol than with pure water.

Clement et al. [13] have also analysed VEN and ODV in human blood plasma using SPE extraction with columns containing a silicone material with carboxymethyl cellulose. The analysis was performed by HPLC method with coulometric detection. Relatively high recovery values for VEN (74%), and its metabolite (67%) were obtained. The calibration curves for the compounds covered the concentration range from 10 to 200 ng/mL, and the limit of detection for both substances was 0.5 ng/mL. Owing to the application of SPE extraction, the method appeared to be faster and more convenient than that with the use of LLE, and it could be applied for determining analytes in small sample volumes. It was also noticed that the use of a 1 % solution of ammonia in methanol caused an increase in selectivity of the extraction process, whereas higher ammonia concentrations increased elution to extracts of impurities from matrix. This phenomenon had negative effects, because it decreased selectivity of extraction and resulted in appearance of additional peaks in the chromatograms.

He et al. [14] analysed not only VEN in human blood plasma, but also fluoxetine, citalopram and paroxetine. The experiments were conducted using HPLC coupled with mass spectrometry. In order to purify the samples prior to analysis, extraction with the use of hydrophilic-lipophilic columns (HLB1cc) was applied. Total recovery for all four compounds was above 73%, and that for VEN was ranged between 87 and 95%. The

method was linear within the range of 5 to 1000 ng/mL, whereas the detection limit for VEN was 0.1 ng/mL. When comparing the results with those for LLE extraction obtained in previous studies, it was shown that SPE extraction was characterised by better sensitivity and higher recovery.

Kingbäck et al. [15] determined VEN, its metabolites and their enantiomers in human plasma and in whole blood samples. For analysis, they employed liquid chromatography coupled with electrospray tandem mass spectrometric detection, and SPE extraction was carried out in C8 columns. Total recovery for VEN was above 75%, the linearity for VEN and ODV determined in plasma ranged from 1 to 1000 nmol/L, and these values for whole blood were from 10 to 4000 nmol/L, respectively. The figures describing linearity obtained for N-desmethylvenlafaxine (NDV) and N,O-didesmethylvenlafaxine (DDV) were as follows: 0.5-500 nmol/L in plasma and 5-2000 nmol/L in whole blood. The experiments have shown that HPLC with tandem mass spectrometry can be applied for determining concentration of particular enantiomers, both in human plasma and in whole blood, in contrast to HPLC-UV detection method which was less selective.

SPE extraction assures high recovery, which allows to use smaller volumes of samples. This is especially important during application of the method to whole blood analysis, because the matrix of such a sample can lead to quick blocking of the columns.

From toxicological point of view, it is crucial to determine the level of VEN and ODV in a material obtained postmortem. Willie et al. [16] analysed 12 antidepressants in blood, brain and hair of suicides. Prior to isolation of analytes, the brain samples were properly purified and hair samples were washed in order to remove external contaminations from them. Quantification of analytes by GC/MS technique has shown that it was possible to determine the level of VEN and ODV in brain and hair even when it was not possible to do in blood samples. Moreover, it was noticed that the compounds are uniformly distributed in brain, and therefore there was no need to isolate the analytes from a particular part of brain. The analysis of hair provides information of VEN therapy over several previous years.

Kingbäck et al. [17] have isolated VEN, ODV and their enantiomers in postmortem femoral blood in corpses by using C8 columns. These columns were washed first with water, next with the mixture of methanol and water, and finally with acetonitrile, and elution of analytes was performed with a mixture of acetonitrile and trifluoroacetic acid. The analysis by LC/MS/MS method has shown that the average VEN concentration in blood was from 0.1 to 1.0 μg/g. By investigation of VEN metabolism it was found that the rate of this process was highly correlated with the CYP2D6 isozyme genotype of a patient.

LLE extraction

Liquid-liquid extraction (LLE) is another frequently used method along with SPE leading to isolation of VEN and its metabolites from biological matrices. It is often characterised as a technique providing worse results and lower accuracy in compari-

son with SPE. However, its advantage, in contrast to SPE, is that it does not require sophisticated lab equipment and can be used in routine studies [18].

LLE extraction was applied by Luan Vu et al. [3], who quantified VEN and its main metabolite in human blood plasma by using HPLC with fluorimetric detection. A mixture of isoamyl alcohol and hexane (7.5/92.5 v/v) was used for extraction, whereas maprotilline was applied as internal standard. Striving for optimization of the extraction process, it was found that higher concentration of isoamyl alcohol in the mixture improves the recovery of ODV, which results from better solubility of this metabolite than in the case of VEN in that solvent. At the same time this suppresses the recovery of VEN and also enhances extraction yield of endogenous compounds, which can interfere with the determination. It was also established that the applied extraction method assures sufficiently high accuracy during simultaneous assay of VEN and ODV in human blood plasma. The recovery for VEN was about 100%, and for ODV almost 70%. The method is linear for both analytes in the concentration range from 1 to 2000 ng/mL, and the limit of detection is 1 ng/mL for VEN and 5 ng/mL for ODV.

Matoga et al. [19] also analysed VEN and ODV in human blood plasma by HPLC with UV detection. A mixture of isoamyl alcohol and hexane (1/99 v/v) was used for LLE extraction, and opipramole was the internal standard. In order to increase the recovery of VEN and ODV from biological matrix, as well as to purify the sample more effectively, chloroform, ethyl acetate, diethyl ether and hexane were applied. The results show that of the solvents listed above, only hexane enabled appropriate purification of the sample. Chloroform enabled determination of VEN over the studied concentration range, but additional peaks were detected in the chromatograms, which originated from the matrix. The calibration curves were linear for both analysed compounds within the concentration range from 0.2 to 4 μg/mL.

Rudaz et al. [20] applied capillary electrophoresis with DAD detection for assay of VEN, its main metabolite and their enantiomers in human blood plasma. In the investigation charged cyclodextrins were used which were added to the mobile phase. For isolation of analytes by liquid-liquid extraction, a hexane-ethyl acetate mixture was used (80/20 v/v), which enabled purification of samples from impurities originated from the matrix, as well as it assured the best recovery (above 70%) of VEN and its main metabolite. The internal standard was tramadol hydrochloride, and the method was linear in the concentration range from 25 to 500 ng/mL.

A one-step LLE extraction was also applied by Qin et al. [21], who quantified VEN and ODV in human blood plasma using Ultra Performance Liquid Chromatography (UPLC), coupled with tandem mass spectrometry. During optimization of the extraction, ethyl acetate, cyclohexane and hexane were applied, among others, but the best results were obtained when diethyl ether was used, which was characterised by highest volatility and its use shortened significantly the time of samples preparation. As the internal standard, verapamil was applied, and total recovery of VEN and its metabolite was above 88%. The method was linear for both compounds in the concentration range from 0.2 to 200 ng/mL, whereas the limit of detection was 0.2 ng/mL. The method has been found to be very fast and sensitive, and could be applied for VEN and ODV determination in human blood plasma.

Tournel et al. [22] have analysed not only VEN, but also other antidepressants, such as fluoxetine, citalopram, sertraline, paroxetine, milnacipran and fluvoxamine in human blood serum. For the analysis, HPLC with UV detection and clomipramine as an internal standard were used. The compounds were extracted from serum with a mixture of chloroform, 2-propanol and n-heptane (960/14/26 v/v/v), which allowed to obtain the recovery of 86.4% and the linearity of the method in the range of 25-500 ng/mL. This mixture was applied, because it did not produce emulsion during extraction, and assured good recovery of the analytes from the samples.

LLE extraction was applied by Goeringer et al. [10] for the analysis of VEN and ODV in the liver, peripheral blood, bile, urine and vitreous body, the materials originating in the majority of cases from suicides. For homogenization of the liver, ultrasounds were used, and after incubation of the samples in a 10 M NaOH solution, and isolation of the analytes with butyl chloride, they were analysed by LC-MS technique. It was demonstrated that in the postmortem material, both VEN and ODV were present in higher levels in the liver and bile, than in the vitreous fluid and peripheral blood. Moreover, it was shown that in the case of those persons, the VEN to ODV ratio in each of the analysed tissues was around 10:1.

Modified extraction techniques

Among classic extraction techniques applied for the extraction of VEN and its metabolites from biological material, there are numerous their modifications in the literature. These are such techniques as Cloud Point Extraction (CPE), Stir Bar Sorptive Extraction (SBSE) and Liquid-Phase Microextraction (LPME). The modifications are aimed at reducing the use of solvent and volumes of biological material, necessary for analysis.

Qin et al. [23] analysed VEN in human plasma by HPLC with spectrofluorimetric detection. For the extraction of VEN, the CPE method was applied. In this technique a surfactant is added to the sample, then it is heated up to temperature, at which separation of the surfactant's phase from aqueous phase takes place, and the analyte is extracted from aqueous phase into the surfactant's phase. In this research, a non-ionic surfactant Triton X-114 (polyethylene glycol tert-octylphenyl ether) was used and maprotilline as the internal standard. It was found that in comparison with the classic extraction techniques that CPE extraction is easy to do and more effective. Its application does not require using huge volumes of toxic solvents, this restricting pollution of the environment. It was also proved that CPE extraction is characterised by high recovery of VEN, more than 93%, and it is linear in the range of 10-800 ng/mL.

Unceta et al. [24] analysed VEN, as well as fluoxetine and citalopram in the urine and human plasma, and in the rat brains by HPLC with spectrofluorimetric detection. For the extraction of the compounds, the SBSE method was used, and it was carried out in several steps. The first was based on extraction of the analyte into the solid phase, which was a mobile sorbent covered with polydimethylsiloxane (PDMS). Next, thermal desorption of the analyte from the sorbent into the aqueous phase was performed. Total recovery of the studied compounds in this method was within the range of 50-92%,

and it is linear in the range of 1-20000 ng/mL for urine samples, 0.2-2000 for plasma and 2-50000 ng/mL for brain tissue.

When optimizing the extraction, other solvents were also tested in the desorption process, such as methanol, acetonitrile, and the mobile phase: acetonitrile – 0.4% sol. of tetramethylammonium chloride of pH 4 (60/40 v/v). It was found that the best recovery was obtained with acetonitrile. Moreover, the influence of other parameters was studied on the desorption, such as the temperature, time of the process, and the pH of the applied solution. It was noticed that the temperature increase was the reason for the recovery improvement, and by analysing the time of desorption of the analyte in the range of 5-30 min, it was found that 15 min is optimum value. Longer times of desorption did not affect the efficiency of the process. The experiments were performed using the solutions of a pH in the range of 2-11, and the best value was pH 11. In the conclusions, it was shown that method can be applied in forensic research and in controlling of patients' treatment with the drugs.

LPME extraction was applied by Fonseca et al. [4] for the analysis of VEN and its metabolite in the samples of rat liver. For the assays, HPLC with UV detection was used. In the extraction of LPME type, three different solvents are applied. In the first stage, the analyte is extracted from aqueous phase (the donor one, it is the diagnostic material) into organic one, and in the second stage extraction is carried out again into another aqueous phase (the acceptor one). By using this extraction, the recovery of the compounds was above 41% for ODV and above 47% for VEN. These values were within the reference range for this extraction type, and the method was linear in the range of 200-5000 ng/mL.

During optimization of the extraction, the influence on extraction yield was studied of three organic solvents (1-octanol, di-n-hexyl ether, dodecyl acetate), and of acceptor phases (acids: chloric(VII), acetic, trifluoroacetic, of 0.1 M concentration each). The results have shown that the best effect was obtained, when the extraction was performed with 1-octanol-acetic acid, whereas application of chloric(VII) acid did not allow for determination of the compounds.

The extraction yield in LPME depends also in high degree on the partition coefficient of the compounds between particular phases. The highest impact on the extraction yield has the composition of organic phase, which should assure appropriate solubility of the analytes. When the solubility of analyte in organic phase is poor, the compounds will pass to this phase only in limited amounts. On the other hand, when they are highly soluble in the organic phase, these compounds will not be extracted into the acceptor solution.

In these experiments, the time and speed of agitation of the samples during extraction was also considered. It was found that the recovery increased when the extraction lasted longer, however the time of agitation above 20 min did not result in the improvement of recovery. It was also noticed that with an increase in amplitude of agitation, the recovery of the compounds increased.

Determination of VEN and its metabolites enables monitoring of this drug in blood, and therefore optimizing its doses. The literature review concerning extraction methods of VEN and its metabolites from diagnostic material presented above allows for the statement that classic methods of extraction, particularly LLE, provide better recovery of the analytes in comparison with the modified extraction techniques. The use of smaller volumes of solvents or samples in the modified methods is valuable,

especially in the case of application of these methods for pharmacokinetic studies of a drug in blood, and it reduces the costs of analysis. However, the results obtained by these methods are not always satisfying. Among the modified extraction methods the best recovery, above 93%, was obtained when CPE extraction was applied. In the case of other two extraction methods, SBSE and LPME, their recoveries were not so high and depended on the diagnostic material used.

With LLE, the most common mixtures of solvents used, are those containing hexane and isoamyl alcohol in different volume ratios. They allowed for obtaining the highest recovery, above 85%. SPE extraction is considered as the most efficient and more selective method than that of the liquid-liquid extraction. However, in the case of isolation of VEN and its metabolites from biological material, the recovery of these compounds was slightly above 70%. The application of C1 columns allowed for obtaining the recovery exceeding 90%.

Экстракцийные техники в анализе венлафаксина и его метаболитов в биологическом материале

Содержание

Венлафаксин (ВЕН) был введен в лечебную практику в 90. годах прошлого столетия и часто используется в лечении депрессивных состояний. При его использовании показана проверка его содержания в организме, особенно в случае, когда пациент страдает иными заболеваниями, а принимаемые лекарства могут вызывать интеракцию с ВЕН. Наиболее популярным диагностическим материалом является кровь.

В настоящей работе представлен литературный обзор о методах экстракции ВЕН из крови и иных диагностических материалов человеческого роисхождения, м.п. из слюны, мочи, а также из тканей животных. Представлены классические способы экстракции ВЕН таких как экстракция жидкость–жидкость и жидкость–тело постоянное . Учтены также современные техники экстракции, такие как микроэкстракция до жидкой фазы и мицеларная экстракция в пункте помутнения. Цитированная литература указывает, что лучшее получение ВЕН и его главного метаболита О-деметило венлафаксина, получено при применении классической экстракциж жидкость–жидкость. Новые модифицированные методы экстракции, несмотря на то, что позволяют на снижение расходов анализа путем ограничения использования растворителей экстракции, а также значительное уменьшение объема материала для исследований, не характеризуются так хорошим получением аналитов, какие при классических методах экстракции.

Ключевые слова: венлафаксин, О-деметило венлафаксин, SPE, LLE, кровь, слюна, моча

Extraktionsverfahren in Analyse von Venlafaxin und ihrer Metaboliten im biologischen Material

Zusammenfassung

Venlafaxin (VEN) wurde zur Behandlung in der 90ßer Jahren eingeführt, es ist eins der häufiger eingesetzten Antidepressiva. Es ist angebracht, ihren Spiegel im Organismus zu beobachten, insbesondere, wenn der Patient an andere Erkrankungen leidet und die verabreichten Medikamente Interaktionen mit Venlafaxin hervorrufen können. Das populärste Material für die Diagnostik ist Blut. Die vorliegende Arbeit bespricht die Übersicht der aktuellen Literatur zu den Extraktionsmethoden von VEN vom Blut und anderen diagnostischen Stoffen menschlicher Herkunft, u.a. Speichel, Urin und auch vom tierischen Gewebe. Man beschrieb die klassischen Extraktionsverfahren von VEN, wie die Flüssig-Flüssig-Extraktion und Flüssig-Fest-Extraktion. Man berücksichtigte auch die

neuesten Estraktionstechniken, solche wie Mikroextraktion zu Flüssigphase und mizellare Phase durch Cloud-Point-Extraktion. Die zittierte Literatur weist hin, dass die beste Extraktion von VEN und des Hauptmetaboliten, O-Desmenhylvenfaxin, erzielt wurde, wenn die klassische Extraktion Flüssig-Flüssig angewendet wurde. Neue, modifizierte Extraktionsverfahren, obwohl sie die Kosten der Analyse durch die Beschränkung im Gebrauch von Lösemittel und das Volumen des zu Untersuchungen gebrauchten Materials signifikant senken, zeichnen sich nicht mit so einem guten Extrahieren aus, wie man bei den klassischen Extraktionsverfahren erreicht.

Schlüsselwörter: Venlafaxin, O-Demethylvenlaflaxin, SPE, LLE, Blut, Speichel, Urin

Les techniques d'extraction de venlafaxine et de ses métabolites dans le matériel biologique

Résumé

La venlafaxine (VEN), introduite dans la thérapie durant les années 90, est un des antidépresseurs le plus souvent appliqués. On recommande le monitoring de son niveau dans l'organisme, surtout quand le patient souffre encore d'autres maladies et quand ses médicaments peuvent entrer en réaction avec VEN. Le sang est un matériel biologique le plus souvent utilisé pour le diagnostic. Ce article donne une revue de la littérature parlant des méthodes d'extraction de VEN du sang et d'autre matériel biologique (urine, salive, tissu animal). Les auteurs présentent les méthodes classiques d'extraction de VEN telles que l'extraction liquide-liquide et l'extraction en phase solide ainsi que les méthodes les plus nouvelles : microextraction en phase liquide et extraction CPE (cloud point extraction). La littérature citée indique que l'on obtient la meilleure récupération de VEN et de son métabolite O-demethylvenlafaxine en usant l'extraction liquide-liquide. Les méthodes nouvelles, bien qu'elles diminuent les frais en permettant limiter l'usage des solvants et en diminuant le volume du matériel analysé, n'ont pas si bonne récupération des analytes que les méthodes classiques d'extraction.

Mots clés : venlafaxine, O-demethylvenlafaxine, SPE, LLE, sang, salive, urine

References

1. Jarema M. *Psychiatria w praktyce*. Warszawa: Medical Education; 2011, pp 44-51.
2. Jarema M, Rabe-Jabłońska J. *Psychiatria*, Warszawa: PZWL; 2011, pp. 494–503.
3. Luan Vu R, Helmeste D, Albers L, Reist Ch. *Rapid determination of venlafaxine and O-desmethylvenlafaxine in human plasma by high-performance liquid chromatography with fluorimetric detection*. J. Chromatogr. B. 1997; 703: 195–201.
4. Fonseca P, Bonato PS. *Chiral HPLC analysis of venlafaxine metabolites in rat liver microsomal preparations after LPME extraction and application to an in vitro biotransformation study*. Anal. Bioanal. Chem. 2010; 396: 817–824.
5. Brunton LL, Lazo JS, Parker KL. *Farmakologia Goodmana & Gilmana*, Tom I, Lublin: CZELEJ; 2007, pp. 446.
6. Stahl S. *Podstawy psychofarmakologii*, Gdańsk: Viamedica; 2010, pp. 242. .
7. http://leki-informacje.pl/lek/charakterystyka-szczegolowa/2216,efectin-er-37-5.html
8. Spina E, Santoro V, D'Arrigo C. *Clinically relevant pharmacokinetic drug interactions with secondo-generation antidepressants: an update*. Clin. Ther. 2008; 30: 1206–1227.
9. Rotzinger S, Bourin M, Akimoto Y, Coutts RT, Baker GB. *Metabolism of some "second"-"fourth"-generation antidepressants: iprindole, viloxazine, bupropion, mianserin, maprotiline, trazodone, nefazodone and venlafaxine*. Cell. Mol. Neurobiol. 1999; 19: 427–442.
10. Goeringer KE, McIntyre IM, Drummer OH. *Postmortem tissue concentrations of venlafaxine*. Forensic. Sci. Int. 2001; 121: 70–75.
11. Reis M, Aamo T, Spigset O, Ahlner J. *Serum concentrations of antidepressant drugs in a naturalistic setting: Complication based on a large therapeutic drug monitoring database*. Ther. Drug. Monit. 2009; 31: 42-56.

12. Mandrioli R, Mercolini L, Cesta R, Fanali S, Amore M, Raggi MA. *Analysis of the second generation antidepressant venlafaxine and its main active metabolite O-desmethylvenlafaxine in human plasma by HPLC with spectrofluorometric detection*. J. Chromatogr. B. 2007; 856: 88–94.
13. Clement EM, Odontialis J, Franklin M. *Simultaneous measurement of venlafaxine and its major metabolite, oxydesmethylvenlafaxine, in human plasma by high-performance liquid chromatography with coulometric detection and utilisation of solid-phase extraction*. J. Chromatogr. B. 1998; 705: 303–308.
14. He J, Zhou Z, Li H. *Simultaneous determination of fluoxetine, citalopram, paroxetine, venlafaxine in plasma by high performance liquid chromatography-electrospray ionization mass spectrometry (HPLC-MS/ESI)*. J. Chromatogr. B. 2005; 820: 33–39.
15. Kingbäck M, Josefsson M, Karlsson L, Ahler J, Bengtsson F. *Stereoselective determination of venlafaxine and its three demethylated metabolites in human plasma and whole blood by liquid chromatography with electrospray tandem mass spectrometric detection and solid phase extraction*. J. Pharm. Biomed. Anal. 2010; 53: 583–590.
16. Wille SMR, De Letter EA, Piette MHA, Van Overschelde LK, Van Peteghem CH, Lambert WE. *Determination of antidepressants in human postmortem blood, brain tissue and hair using gas chromatography-mass spectrometry*. Int. J. Legal. Med. 2009; 123: 451–458.
17. Kingbäck M, Karlsson L, Zackrisson A-L, Carlsson B, Josefsson M, Bengtsson F, Ahlner J, Kugelberg FC. *Influence of CYP2D6 genotype on the disposition of the enantiomers of venlafaxine and its major metabolites in postmortem femoral blood*. Forensic. Sci. Int. 2012; 214: 124–134.
18. Liu W, Cai H, Li H. *High performance liquid chromatography-electrospray ionization mass spectrometry (HPLC-MS/ESI) method for simultaneous determination of venlafaxine and its three metabolites in human plasma*. J. Chromatogr. B. 2007; 850: 405–411.
19. Matoga M, Pehourcq F, Titier K, Dumora F, Jarry C. *Rapid high-performance liquid chromatographic measurement of venlafaxine and O-desmethylvenlafaxine in human plasma. Application to management of acute intoxications*. J. Chromatogr. B. 2001; 760: 213–218.
20. Rudaz S, Stella C, Balant-Gorgia A, Fanali S, Veuthey J. *Simultaneous stereoselective analysis of venlafaxine and O-desmethylvenlafaxine enantiomers in clinical samples by capillary electrophoresis using charged cyclodextrins*. J. Pharm. Biomed. Anal. 2000; 23: 107–115.
21. Qin F, Li N, Zhang Y, Li F. *Simultaneous quantification of venlafaxine and O-desmethylvenlafaxine in human plasma by ultra performance liquid chromatography-tandem mass spectrometry and its application in a pharmacokinetic study*. J. Chromatogr. B. 2010; 878: 689-694.
22. Tournel G, Houndret N, Hédouin V, Deveaux M, Gosset D, Lhermitte M. *High-performance liquid chromatographic method to screen and quantitate seven selective serotonin reuptake inhibitors in human serum*. J. Chromatogr. B. 2001;761: 147–158.
23. Qin X, Meng J, Li X, Zhou J, Sun X, Wen A. *Determination of venlafaxine in human plasma by high-performance liquid chromatography using cloud-point extraction and spectrofluorometric detection*. J. Chromatogr. B. 2008; 872: 38–42.
24. Unceta N, Ugarte A, Sánchez A, Gómez-Caballero A, Goicolea M, Barrio R. *Development of a stir bar sorptive extraction based HPLC-FLD method for the quantification of serotonin reuptake inhibitors in plasma, urine and brain tissue samples*. J. Pharm. Biomed. Anal. 2010; 51: 178–185.

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