

C-Jun N-Terminal Kinases Inhibition: A New Approach to the Regulation of Venlafaxine Pharmacokinetics

*Gleb Zyuz`kov*¹, Yuliya Zyuz`Kova¹, Olga Bryushinina¹, Nataliya Abdrashitova¹,
Alexandr Lakeev¹, Darya Tsuran¹, Galina Frelikh¹, Vladimir Udut¹*

¹ Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia.

ABSTRACT

The effect of the c-Jun N-terminal kinases (JNK) inhibitor 'IQ-1' on the pharmacokinetics of the antidepressant venlafaxine was studied. An acceleration of the metabolism of this psychotropic agent was revealed when a modifier of intracellular signal transduction was administered to experimental animals in vivo. The JNK blockade was accompanied by a decrease in the plasma level of the antidepressant without changes in the concentration of the pharmacologically active metabolite O-desmethylvenlafaxine. The results obtained indicate a modification of the pattern of venlafaxine biotransformation, involving a change in metabolic pathways with an increase in the formation of other metabolites, or a correction of its distribution in the body. The revealed properties of the JNK inhibitor can be used to develop fundamentally new approaches to improve the effectiveness of antidepressant therapy with venlafaxine within the framework of implementing the 'Strategy for Targeted Regulation of Xenobiotic Metabolism and Drug Pharmacokinetics'.

Keywords: Metabolism, Pharmacokinetics, Antidepressant Therapy, Intracellular Signal Transduction, JNK.

INTRODUCTION

The functioning of all cell types relies on the participation of the intracellular signal transduction system [1-6]. However, the specific roles of individual signal transduction pathways in regulating the xenobiotic-metabolizing function of cells competent in this regard are largely unknown. Simultaneously, uncovering the involvement and distinct roles of particular signaling molecules in the biotransformation of pharmacologically active substances can form the basis for the development of innovative approaches to personalized pharmacotherapy [7-11]. Therefore, it is pertinent to investigate the potential for controlling the intensity and

nature of substance transformation within the body by regulating intracellular signal transduction in metabolizing cells and creating 'Targeted Regulators of Xenobiotic/Drug Metabolism' [7, 12].

In recent years, pharmacologists have increasingly focused on modifiers affecting the activity of mitogen-activated protein kinase known as c-Jun N-terminal kinase (JNK). It has been demonstrated that JNK plays a role in regulating various functions of different cellular components, and inhibitors targeting this signaling molecule have been identified to possess neuroprotective, anti-inflammatory, hemostimulatory, and several other pharmacological properties [2]. Additionally, the significant role of JNK in regulating the metabolism of the antidepressant venlafaxine by liver cells is well-documented [7, 12].

Venlafaxine, a widely used antidepressant, exists as a

*Corresponding author: Gleb Zyuz`kov

zgn@pharmso.ru

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racemate of R- and S-enantiomers, effectively blocking the reuptake of serotonin, norepinephrine, and dopamine [13, 14]. However, its effectiveness is sometimes compromised due to variations and individual characteristics in the pathogenesis of depressive disorders. Venlafaxine is primarily metabolized in liver cells with the assistance of cytochrome P450 enzymes [9, 15]. The CYP2D6 isoenzyme, in particular, converts it into the sole pharmacologically active metabolite, O-desmethylvenlafaxine (O-DVLF) [13, 16]. Additionally, CYP2C19, CYP3A4, and CYP2C9 contribute to the formation of inactive metabolites, including N, O-didesmethylvenlafaxine, and their glucuronide conjugates [9, 17]. Developing specific methods to modify the pharmacokinetics and pharmacodynamics of this drug holds the potential to significantly enhance the quality of psychiatric care for patients with depression.

We have previously demonstrated the potential for accelerating the conversion of venlafaxine to O-DVLF using a JNK inhibitor *in vitro* [7, 12]. However, the precise nature of the modification of this antidepressant's metabolism with selective JNK blockade *in vivo* and the resulting alterations in its pharmacokinetics remain unknown.

The objective of this study was to investigate the impact of a JNK inhibitor on the pharmacokinetic profiles of venlafaxine and O-desmethylvenlafaxine in blood plasma.

MATERIALS AND METHODS

Animals and experimental design

The study was conducted on 114 C57BL/6 mice aged 2-2.5 months, weighing 20-22 g, at E.D. Gol'dberg Tomsk NIMC. All experimental procedures followed ethical principles for the humane treatment of animals and received approval from the local Ethics Committee of the Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center, Russian Academy of Sciences (protocol

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The animals were randomly assigned to two groups: control and experimental, with 48 mice in each group. The experimental group received venlafaxine (supplied by Aarti Industries, India) via intragastric tube at a dose of 120 mg/kg (2.4 mg/mouse), selected based on literature data from a pharmacokinetic study of venlafaxine in small rodents. Fifteen minutes before venlafaxine administration, the experimental group of mice was intraperitoneally injected with the JNK inhibitor "IQ-1S" (11H-indeno[1,2-b]quinoxalin-11-one oxime sodium salt, from Montana State University, Bozeman, Montana, USA) at a dose of 30 mg/kg (0.6 mg/mouse), a dose commonly used in the study of the pharmacological properties of "IQ-1S" in mice. The control group received an equivalent volume (0.2 ml) of solvent intraperitoneally.

Blood samples were collected at 0.25, 0.5, 1, 2, 3, 4, 8, and 24 hours (n=6 for each observation period in both control and experimental groups) after the administration of venlafaxine. The blood was obtained from the heart under deep anesthesia in a CO₂ chamber, in a volume of 0.5 ml. Plasma was then obtained by centrifugation at 1660×g for 10 minutes, and the levels of venlafaxine (VLF) and O-desmethylvenlafaxine (O-DVLF) were determined [13, 17].

VLF and O-DVLF definition

The sample preparation method was based on the principle of liquid-liquid extraction using an organic solvent. Initially, 200 µl of thawed plasma was combined with 100 µl of an internal standard solution, which contained fluvoxamine hydrochloride at a concentration of [C] = 50 ng/ml. To this mixture, 50 µl of 12.5% ammonia solution, 300 µl of 0.9% sodium chloride solution, and 800 µl of ethyl acetate were added. The resulting mixture was then vigorously stirred using an MSV-3500 tube vortexer (Biosan, Latvia) at 2100 rpm for 8 minutes. Subsequently, the phases were separated by centrifugation in an SL 16L centrifuge (Thermo Scientific, USA) at 12000×g for 8 minutes at 4°C. The upper organic fraction, comprising

650 µl, was carefully transferred into a colorless glass vial for subsequent chromatographic and mass spectrometric analysis.

The quantitative determination of VLF and O-DVLF in mouse plasma was conducted using HPLC-MS/MS, employing an LC-20 Prominence liquid chromatograph from Shimadzu in conjunction with an AB Sciex QTrap 3200 tandem mass spectrometer featuring electrospray ionization.

The equipment setup included an LC-20AD high-pressure mobile phase pump, SIL-20A auto-injector, and CTO-20A column thermostat. The analytical column used was a Phenomenex Luna C18, with a particle size of 5 µm, measuring 100 × 4.6 mm, and it was accompanied by a pre-column cartridge. The mass spectrometry analysis was performed using the AB Sciex QTrap 3200 tandem chromatograph-mass spectrometer. Data acquisition was carried out with Analyst 1.6.3 software, while chromatographic data processing was accomplished using Multi Quant 2.1.

The fragmentation and detection of analytes were achieved through electrospray ionization in the specified reaction monitoring mode, where positively charged ions were recorded. This process was based on the following transitions, measured as m/z (mass-to-charge ratio): for VLF, 278.0 (parent ion) to 58.0 (VLF fragment ion), and for O-DVLF, 264.1 (parent ion) to 57.90 (fragment ion).

Chromatographic analysis was conducted in an isocratic mode, utilizing a mobile phase composed of acetonitrile (eluent B) and 5 mM aqueous ammonium formate, pH 2.93 (eluent A), at a ratio of 85:15 (v/v) and a flow rate of 0.65 ml/min. A 2 µl aliquot was injected, and the column was maintained at a constant temperature of 40°C. The average retention time for VLF and O-DVLF was 1.49±0.01 and 1.44±0.02 minutes, respectively, and the entire analysis process took no longer than 3.50 minutes. As an internal standard, fluvoxamine (m/z, 319.1 → 71.1) was employed, with an average retention time of 1.50±0.02 minutes.

Calibration curves were constructed by plotting the ratio

of analyte peak area to the internal standard peak area against the nominal sample concentration, using a weighted least squares method with a weighting factor of $1/x^2$, where x represents the nominal analyte concentration. The calibration curve range was 0.5 to 105,000 ng/ml for VLF ($n = 6$, $y = 0.0132x + 0.0100$, $R^2 = 0.9937$) and 0.5 to 500 ng/ml for O-DVLF ($n = 6$, $y = 0.0130x + 0.0101$, $R^2 = 0.9930$). A total of 18 mice were used for method validation and calibration curve construction

The extramodel method of statistical moments was calculated using Phoenix WinNonlin® version 8.3 (Certara, USA): time to reach maximum concentration (T_{max} , h), maximum plasma concentration (C_{max} , ng/ml), area under the plasma concentration-time curve from the moment of taking the drug to 24 h (AUC_{0-24} , h×ng/mL), area under the plasma concentration-time curve from the moment of drug administration to infinity ($AUC_{0-\infty}$, h×ng/mL), mean residence time of the compound in the systemic circulation (MRT , h), half-life ($T_{1/2}$, h), apparent volume of distribution (V_d/F , ml), total clearance (plasma volume that is completely cleared of the drug per unit time, Cl/F , ml/h).

Statistical analysis

The results obtained were analyzed using the method of variance statistics with the STATISTICA 6.0 analysis package. To compare all pharmacokinetic parameters, except for T_{max} , the Student's t-test was applied after logarithmic data transformation. For T_{max} , the nonparametric Mann-Whitney U test was used. The values are presented as the arithmetic mean and standard error of the mean ($M \pm SEM$), and the significance of differences in indicators between groups was considered at $p < 0.05$.

RESULTS AND DISCUSSION

Pharmacokinetics of venlafaxine

Following a single intragastric administration of venlafaxine to mice, rapid absorption into the bloodstream occurred, with peak concentrations reached at 0.25, 0.5, and 1 hour of observation (Table 1, Fig. 1). The time to

reach maximum concentration was 0.5 hours (Table 2). Subsequently, there was a notable decline in circulating VLF levels, reaching their lowest point at the 24-hour

mark in the experiment. These results align closely with the pharmacokinetic characteristics of the studied antidepressant, as reported in.

Table 1: Dynamics of the concentration of venlafaxine (VLF) and its metabolite O-desmethylvenlafaxine (O-DVLF) in the blood plasma of C57BL/6 mice after the single administration of venlafaxine (1) and with the combined use of an antidepressant with the JNK inhibitor (2), ng/ml (M±SEM)

Time, h	VLF		O-DVLF	
	1	2	1	2
0.25	3521.45±562.38	2539.72±416.43	473.03±12.38	464.89±19.44
0.5	3962.16±795.01	2937.10±622.79	395.17±31.43	363.99±43.76
1	3863.39±297.82	2713.83±189.37*	244.08±20.93	257.63±15.42
2	1067.61±98.21	613.98±55.08*	99.94±11.20	85.51±7.67
3	1116.86±100.18	1539.15±210.43	62.48±5.40	61.45±12.52
4	710.37±41.2	511.27±49.68*	71.94±7.03	61.92±8.70
8	62.93±10.6	63.58±11.64	13.03±2.17	8.64±2.31
24	5.11±1.25	8.91±1.41	0.73±0.13	0.99±0.43

* - the differences in the indicator with the control (Group1) at $p < 0.05$

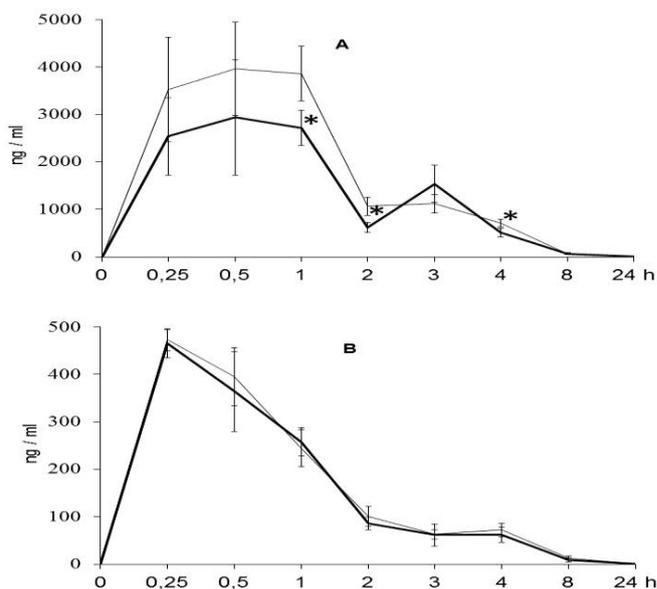


Fig. 1. Mean pharmacokinetic profiles of venlafaxine (A) and its metabolite O-desmethylvenlafaxine (B) in blood plasma of C57BL/6 mice after a single administration of venlafaxine (thin lines) and the antidepressant with the JNK inhibitor (thick lines). Confidence intervals at $p=0.05$; * - the significance of differences in indicators with control was noted at $p < 0.05$.

Prior oral administration of the JNK inhibitor significantly influenced the studied pharmacokinetic parameters. In the initial phase of the study, the plasma concentration of VLF remained comparable to control values, indirectly suggesting a limited impact of the JNK activity modifier on the drug

absorption process. However, at 1, 2, and 4 hours of observation, there was a statistically significant reduction in the VLF concentration in plasma, reaching levels of approximately 70.2%, 57.5%, and 71.9% of the corresponding control values, respectively (Table 1, Fig. 1).

Table 2: Pharmacokinetic parameters of venlafaxine (VLF) and its metabolite O-desmethylvenlafaxine (O-DVLF) following the single administration of venlafaxine (1) and co-administration of the antidepressant with the JNK inhibitor (2) in C57BL/6 mice, (M±SEM)

Parameters	VLF		O-DVLF	
	1	2	1	2
Tmax (h)	0.70±0.12	1.15±0.29	0.30±0.05	0.25±0.00
Cmax (ng/ml)	4283.19±522.55	3730.45±401.12	476.08±12.41	464.89±19.44
AUC 0-24 (h×ng/ml)	9700.97±490.46	8035.53±485.71*	927.91±47.55	842.08±49.82
AUC 0-∞ (h×ng/ml)	9724.39±494.94	8082.55±490.34*	931.26±47.82	847.52±49.92
MRT (h)	2.27±0.14	2.49±0.12	2.79±0.15	2.54±0.25
T 1/2 (h)	2.86±0.12	3.45±0.16*	3.12±0.11	3.27±0.32
Vd/F (ml)	1026.59±37.74	1557.42±131.37*	-	-
Cl/F (ml/h)	256.61±14.68	287.22±26.63	-	-

* The differences in the indicator with the control (Group1) at p<0.05

The analysis of the calculated pharmacokinetic parameters in this case indicated a decrease in both AUC 0-24 and AUC 0-∞ (reducing to 82.2% and 83.1% of the control levels, respectively) (Table 2). Simultaneously, there was an increase in the half-life of VLF (by 20.1% from the initial values) and a notable expansion in the volume of distribution of the agent, reaching 151.7% of the control level. The estimated total clearance of VLF did not show significant differences between the control and experimental groups.

The examination of the content of the primary metabolite of the antidepressant in blood plasma also revealed interesting phenomena concerning the drug's targeted effect on its pharmacokinetics. Specifically, Tmax for O-DVLF was just 0.5 hours, with MRT at 2.79 hours and a half-life of 3.12 hours (Table 2, Fig. 1). These characteristics align with literature data concerning the rapid first-pass metabolism of venlafaxine, resulting in the formation of the active metabolite O-desmethylvenlafaxine [16, 17].

The administration of the JNK inhibitor before venlafaxine did not lead to statistically significant changes in the O-DVLF concentration throughout the entire observation period (Table 1, Fig. 1). No corrections in the calculated parameters were observed. It's important to note that dose-dependent parameters such as Cl/F (clearance) and Vd/F (apparent volume of distribution) are not typically calculated for metabolites. However, in this context, it seems reasonable to anticipate an accelerated uptake into tissues under the influence of the JNK inhibitor, not only for VLF (as suggested earlier) but also for O-DVLF. This is because an increase in the intensity of venlafaxine biotransformation into O-DVLF under the influence of a JNK inhibitor [7, 12] should logically result in an increased plasma concentration of this metabolite.

Overall, the results obtained indicate a significant alteration in the pharmacokinetics of venlafaxine when influenced by the JNK inhibitor. The observed decrease in plasma concentration of VLF, while O-DVLF remains present, may be associated with several mechanisms.

First, it could be linked to the previously identified acceleration and alteration in the metabolic pathways of venlafaxine, resulting in a new metabolic pattern, particularly an increase in the formation of N, O-didesmethylvenlafaxine through the activation of CYP2C19, CYP3A4, and CYP2C9 [7, 12].

Secondly, this phenomenon could be rooted in redistribution mechanisms affecting both VLF and O-DVLF, involving their rapid penetration into tissues. It's likely that the observed increase in VLF's half-life ($T_{1/2}$) is

associated with this process. With a higher substance intake into tissues, less of it can be immediately excreted from the body, as there is a reduced amount of VLF circulating in the bloodstream at any given time. The removal of VLF becomes possible only when the substance re-enters the bloodstream from the tissues.

Moreover, the confirmation of the involvement of this mechanism (rapid tissue penetration of VLF) in the observed patterns could serve as a foundation for developing a fundamentally new approach to enhancing the efficacy of antidepressant therapy with venlafaxine. Given the relatively high affinity of both VLF and O-DVLF for nervous tissue [8], this opens up prospects for increasing the concentration of both venlafaxine itself (which possesses independent psychotropic pharmacological activity [13]) and its active metabolite (O-DVLF) [7, 17] in the brain. This is particularly significant considering their relatively high affinity for nervous tissue, especially venlafaxine [18].

As a result, there is the potential not only to enhance therapeutic efficacy but also to reduce the overall xenobiotic burden on the body, consequently lowering the risk of drug-related side effects, all while maintaining therapeutic effectiveness.

CONCLUSION

The findings indicate the need for further investigation into the potential of JNK inhibitors to modify the pharmacokinetics of venlafaxine, as part of the development of the 'Strategy for Targeted Regulation of Xenobiotic Metabolism and Drug Pharmacokinetics' [7, 12].

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مثبط JNK: نهج جديد لتنظيم الحرائك الدوائية لفينلافاكسين

جليب زيوزكوف^{1*}، يوليا زيوزكوف¹، أولغا بريوشينينا¹، ناتاليا عبراشيتوفا¹، ألكسندر ليكيف¹،
داريا تسوران¹، غالينا فريليك¹، فلاديمير أودوت¹

¹معهد غولدبرغ لبحوث الصيدلة والطب التجديدي، مركز تومسك الوطني للبحوث الطبية، الأكاديمية الروسية للعلوم، تومسك، روسيا.

ملخص

تمت دراسة تأثير مثبط "IQ-1" JNK على الحرائك الدوائية لمضاد الاكتئاب فينلافاكسين. تم الكشف عن تسارع عملية التمثيل الغذائي لهذا العامل المؤثر عقلياً عندما تم إعطاء معدل نقل الإشارة داخل الخلايا لحيوانات التجارب في الجسم الحي. ترافق حصار JNK مع انخفاض في مستوى البلازما لمضاد الاكتئاب دون تغييرات في تركيز المستقلب النشط دوائياً. O-desmethylvenlafaxine تشير النتائج التي تم الحصول عليها إلى تعديل نمط التحول الحيوي للفينلافاكسين (والذي يتكون من تغيير في المسارات الأيضية مع زيادة تكوين المستقلبات الأخرى) أو تصحيح توزيعه في الجسم. يمكن استخدام الخصائص التي تم الكشف عنها لمثبط JNK لتطوير مناهج جديدة بشكل أساسي لتحسين فعالية العلاج المضاد للاكتئاب باستخدام فينلافاكسين في إطار تنفيذ "استراتيجية التنظيم المستهدف لعملية التمثيل الغذائي للأجسام الحيوية وحركية الدواء".

الكلمات الدالة: التمثيل الغذائي، الحرائك الدوائية، العلاج بمضادات الاكتئاب، نقل الإشارات داخل الخلايا، JNK.

* المؤلف المراسل: جليب زيوزكوف

zgn@pharmso.ru

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