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RESEARCH ARTICLE

Theoretical Rationale for the Combined Use of Gabapentin and Fingolimod for the Treatment of Multiple Sclerosis Using *In Silico* Methods

Vitaly LARIONOV[*], Olexandr NEFEDOV[**], Igor BELENICHEV[***], Olexandr KALBUS[****], Olena NEFEDOVA[*****], Iryna SAMURA[******°], Nina BUKHTIYAROVA[*******]

Theoretical Rationale for the Combined Use of Gabapentin and Fingolimod for the Treatment of Multiple Sclerosis Using In Silico Methods

SUMMARY

Chronic neuropathic pain in multiple sclerosis is found in 25-90 % of patients. Optimal pharmacotherapy should include both disease-modifying agents and medications that affect neuropathic pain. Taking into account that the development of multiple sclerosis is based on a chronic demyelinating inflammatory process (foci of demyelination), the rational treatment of relapsing-remitting multiple sclerosis should include both disease-modifying therapy and symptomatic therapy, in particular, medications affecting neuropathic pain. The study showed that under physiological conditions, ionic interaction between fingolimod and gabapentin is possible with the formation of salts capable of reversible dissociation without changing the molecule's structure, and with the formation of the corresponding protonated forms. The acid-base properties of the compounds were analyzed using the ACD/pKaDB and ChemAxon programs. At the pharmacokinetic level, no interaction is expected between finngolimod and gabapentin as they use different transport systems, and different metabolic enzymes. Fingolimod and gabapentin differ significantly in the extent of plasma proteins binding, which excludes their interaction during absorption, distribution, metabolism, and excretion. Therefore, the synergistic combination of fingolimod and gabapentin can be a promising therapeutic alternative for the effective treatment of multiple sclerosis. Its positive additive effects are expected to relieve symptoms of the disease, reduce the intensity of inflammatory processes in the central nervous system, produce a neuroprotective effect, contribute to remyelination due to the action of fingolimod, and relieve symptoms of neuropathic pain under the influence of gabapentin.

Key Words: *Multiple sclerosis, combination therapy, fingolimod, gabapentin.*

Multipl Skleroz Tedavisinde Gabapentin ve Fingolimodun Birlikte Kullanım Olasılığının In Silico Metotlarla Teorik Olarak Doğrulanması

ÖZ

Multipl sklerozda kronik nöropatik ağrı hastaların %25-90'ında bulunur. Optimal farmakoterapi, hem hastalığı değiştirici ajanları hem de nöropatik ağrıyı etkileyen ilaçları içermelidir. Multipl skleroz gelişiminin kronik demiyelinizan inflamatuvar sürece (demiyelinizasyon odakları) dayandığı göz önüne alındığında, tekrarlayan-düzelen multipl sklerozun rasyonel tedavisi, hem hastalığı modifye edici tedaviyi hem de semptomatik tedaviyi, özellikle nöropatik ağrıyı etkileyen ilaçları içermelidir. Çalışma, fizyolojik koşullar altında fingolimod ve gabapentin arasındaki iyonik etkileşimin, molekülün yapısını değiştirmeden geri dönüşümlü ayrışma yeteneğine sahip tuzların oluşumu ve karşılık gelen protonlanmış formların oluşumu ile mümkün olduğunu gösterdi. Bileşiklerin asit-baz özelliklerinin analizi ACD/pKaDB ve ChemAxon programları kullanılarak yapıldı. Sonuçlarımız, fingolimod ve gabapentin için fizyolojik koşullar altında, molekülün yapısını değiştirmeden ters ayrışma yeteneğine sahip tuzların oluşumu ve karşılık gelen protonlanmış formların oluşumu ile iyonik etkileşimin mümkün olduğunu ortaya koydu. Farmakokinetik düzeyde, fingolimod ve gabapentin arasında herhangi bir etkileşim beklenmemektedir; çünkü bunlar ortak taşıma sistemlerini ve metabolik enzimleri kullanmazlar, ayrıca emilim, dağılım, metabolizma ve eliminasyon sırasındaki etkileşimleri hariç tutan değişen derecelerde protein bağlamaya sahiptirler. Bu nedenle fingolimod ve gabapentinin sinerjistik kombinasyonu, multipl sklerozun etkili tedavisi için umut verici bir terapötik alternatif olabilir. Olumlu katkı etkilerinin hastalığın semptomlarını hafifletmesi, merkezi sinir sistemindeki inflamatuvar süreçlerin yoğunluğunu azaltması, nöroprotektif etki oluşturması, fingolimodun etkisine bağlı olarak remiyelinizasyona katkıda bulunması ve gabapentin etkisi altında nöropatik ağrı semptomlarını hafifletmesi beklenmektedir.

Anahtar Kelimeler: *Multipl skleroz, kombinasyon tedavisi, fingolimod, gabapentin.*

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[*] ORCID: 0000-0003-2678-4264, Department of Medical Chemistry, Laboratory of Physico-Chemical Pharmacology, A.V. Bogatsky Physico-Chemical Institute of National Academy of Sciences of Ukraine, Odessa, Ukraine.
[**] ORCID: 0000-0002-5796-1852, Clinical Department, INTERCHIM, Additional liability company, Dnipro, Ukraine.
[***] ORCID: 0000-0003-1273-5314, Department of Pharmacology and Medical Formulation with the Course of Normal Physiology, Medical Faculty No. 1, Zaporizhzhia State Medical University, Ukraine.
[****] ORCID: 0000-0003-0796-4825, Department of Neurology, Medical Faculty, Dnipro State Medical University, Ukraine.
[*****] ORCID: 0000-0002-1665-9032, Department of Human Anatomy, Clinical Anatomy and Operative Surgery, Medical Faculty, Dnipro State Medical University, Ukraine.
[******] ORCID: 0000-0001-5352-3209, Department of Pharmacology and Medical Formulation with the Course of Normal Physiology, Medical Faculty No. 1, Zaporizhzhia State Medical University, Ukraine.
[*******] ORCID: 0000-0003-3499-3111, Department of Clinical Laboratory Diagnostics, Medical Faculty No.2, Zaporizhzhia State Medical University, Ukraine.

[°] Corresponding Author; Iryna Samura
E-mail: irinasamura77@gmail.com

INTRODUCTION

Multiple sclerosis (MS) is the the most prevalent chronic inflammatory disease of the central nervous system (CNS), and is one of the leading causes of disability, especially among young adults of working age. Up to 80 % of all MS patients have a relapsing-remitting MS phenotype (Walton et al., 2020). Neuropathic pain may develop in many pathologies, including metabolic disorders (Nefedov & Kalbus, 2022), mechanical damage to the peripheral nervous system (Burlaka, Belenichev, Nefedov, Aliyeva, & Bukhtiyarova, 2020), inlammation, and autoimmune processes (Duffy, Lees, Perera, & Moalem-Taylor, 2018), and its therapy is not always effective because it must affect several parts of this pathological process. Lesions of the peripheral and central nervous systems are leading factors in the development of neuropathic pain in patients with MS. Inflammation is one of the most essential factors in the development of neuropathy, and its complex pharmacotherapy should include an anti-inflammatory component (Duffy et al., 2018; Nefedov & Kalbus, 2022). Central sensitization in MS is based on increased activation of N-methyl-D-aspartate (NMDA) receptors. Glutamate plays a critical role in the toxic neuronal and myelin damage in MS. Glutamate is formed in large quantities in the brain under the influence of proinfammatory cytokines (interleukin-1β, TNF-α) and encephalitogenic T-lymphocytes, which are induced in the central nervous system in MS and anti-NMDAR encephalitis (Gulec et al., 2020; Sinari et al., 2020). The concentration of glutamate in the cerebrospinal fluid increases, and the activity of enzymes responsible for the degradation of glutamate decreases during the period of exacerbation of MS (Huang et al., 2020). Suppression of inhibitory reactions mediated by glycine and Gamma-aminobutyric acid (GABA) plays an essential role in the mechanisms of formation of aggregates of hyperactive neurons in the structures of the CNS (Cawley et al., 2015). Chronic neuropathic pain in MS is found in 25-90 % of patients; therefore, rational pharmacotherapy of MS should include both disease-modifying agents and medications that affect neuropathic pain (Nefodov et al., 2018).

Essential antinociceptive therapy for pain in MS includes analgesics, anti-inflammatory medications, long-acting prostaglandins; and membrane stabilizing medications, which reduce neuronal excitability and ephaptic transmission (Racke, Frohman, & Frohman, 2022). *In vivo* studies demonstrated that GABA-A and GABA-B agonists and modulators ıncreased preservation of myelinated sensitive fibers, and diminished axonal damage in the CNS. Further, decreased mononuclear inflammatory infiltration, pro-inflammatory cytokines reduction, and reduced levels of reactive oxygen species were also reported (Stamoula et al., 2023). Thus, GABA modulators, especially Gabapentin, can be considered promising agents for combination therapy of pain in MS.

Gabapentin is efficacious in numerous clinical studies, case reports, and chart reviews in a variety of neuropathic pain syndromes of central origin (Nicholson, 2001).

Among the wide range of disease-modifying medications for treating MS, oral forms are often preferred. In particular, Fingolimod, the first oral disease-modifying drug, is commonly used to treat active MS. The mechanism of action of Fingolimod is to affect the function of leukocytes through the sphingosine-1-phosphate signaling system (Bennett et al., 2004). Fingolimod is effective in experimental autoimmune encephalomyelitis, an animal model of MS; and it was subsequently investigated in two phase III clinical trials in relapsing-remitting MS. These studies demonstrated that Fingolimod is a safe and effective medication (Ayzenberg, Hoepner, & Kleiter, 2016). It was also found that in a model of convulsive seizures, Fingolimod produced a positive effect on the GABA system and increased the concentration of GABA in the CNS (Abd El-Kader, Moursi, Khaleefa, Noureldin, & Shoala, 2021). All this suggests the possibility of a rational combination of gabapentin and fingolimod.

Given the potential benefits of combination therapy with gabapentin and fingolimod for patients with MS, the purpose of the study was to assess the possibility of combined use, effectiveness, and safety of gabapentin and fingolimod in the treatment of relapsing-remitting MS.

MATERIAL AND METHODS

Potential chemical reactions of the compounds were predicted based on the presence and reactivity of the functional groups that are part of their structure.

The acid-base properties of the drugs were analyzed using ACD/pKaDB program (ACD/pKaDB Web site, 2001), and ChemAxon software (ChemAxon Web site, 2010). Molecular weight, lipophilicity (logP and logD), and solubility were calculated by additive methods of these programs. Biological targets (receptors, enzymes, and transporters) were obtained from the relevant sources and databases DrugBank, PubChem (PubChem, 2001). Available data on the probability of interaction of the compounds with one or another isoform of cytochrome, transporters, or pharmacological targets were calculated by the admetSAR program and are freely available on the website https://www.drugbank.ca/.

RESULTS AND DISCUSSION

The ability of fingolimod and gabapentin to interact with the specific enzyme systems involved in the transport and metabolism of drugs was predicted with the help of the admetSAR program on the website https://www.drugbank.ca/ (Table 1.) Accurate data on the involvement of specific enzyme systems in the metabolism of fingolimod were also included in the analysis (Lipinski, Lombardo, Dominy, & Feeney, 2001).

In the structures of fingolimod and gabapentin, potential reaction centers were identified, namely functional groups for further analysis of the possibility of physicochemical interactions (Figure 1.), as well as protolytic forms depending on pH with the corresponding physicochemical parameters (ionization constant, logP and logD, solubility, etc.) (Figures 2 and 3; Tables 2 and 3.). The balance between the benefits of combined pharmacological action and the potential risk of side effects and incompatibilities determines the appropriateness and possibility of combination therapy.

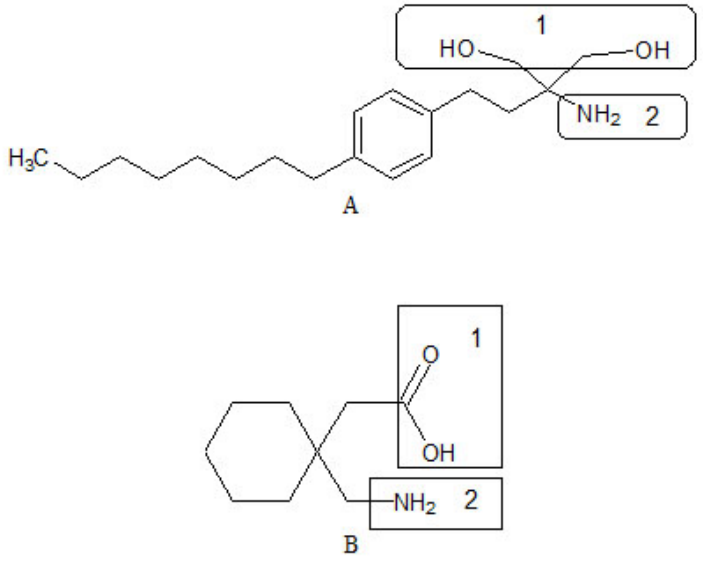


Figure 1. Structural formulas of fingolimod (A) and gabapentin (B) with specific functional groups.

Table 1. Predicted properties of fingolimod and gabapentin for interaction with specific enzyme systems.

Property	Fingolimod		Gabapentin	
	Value	Probability	Value	Probability
Absorption in the gastrointestinal tract	+	0.9884	+	0,941
Permeability through GEB	+	0.5779	+	0.9382
Substrate Pgp	Substrate	0.6975	Not a substrate	0.6557
Inhibitor Pgp I	Not an inhibitor	0.9505	Not an inhibitor	0.9789
CYP450 2C9 substrate	Not a substrate	0.8251	Not an inhibitor	0.7982
CYP450 2D6 substrate	Not a substrate	0.6702	Not a substrate	0.893
CYP450 3A4 substrate	Not a substrate	0.7685	Not a substrate	0.8124
CYP450 1A2 substrate	Inhibitor	0.5519	Not a substrate	0.7612
CYP450 2C9 inhibitor	Not an inhibitor	0.8526	Not an inhibitor	0.9409
CYP450 2D6 inhibitor	Inhibitor	0.6567	Not an inhibitor	0.9273
CYP450 2C19 inhibitor	Not an inhibitor	0.8152	Not an inhibitor	0.9418
CYP450 3A4 inhibitor	Not an inhibitor	0.7348	Not an inhibitor	0.9547

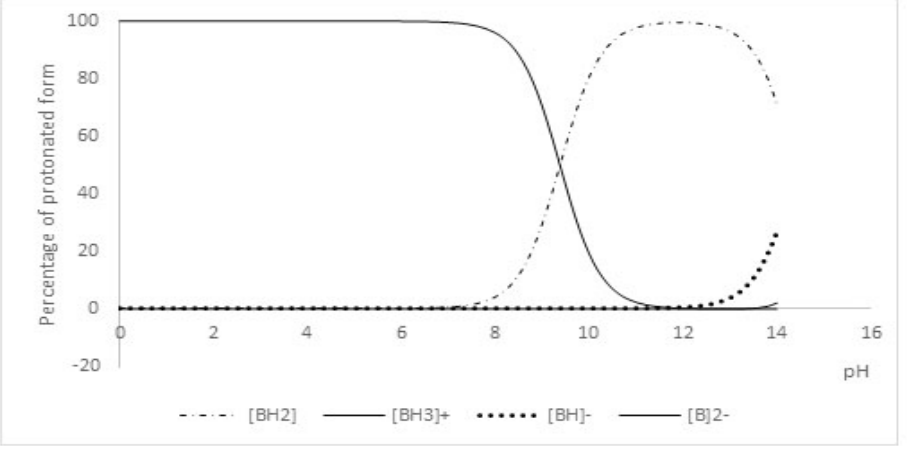
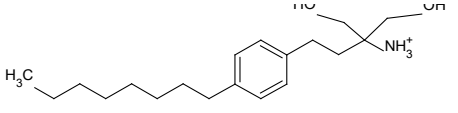
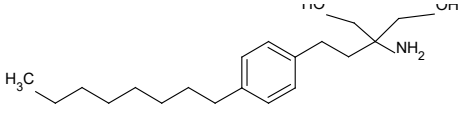
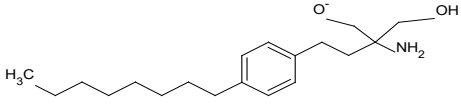
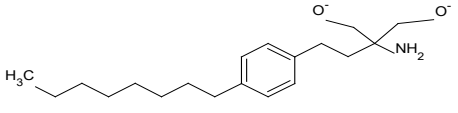


Figure 2. Percentage correlation between protonated forms of fingolimod depending on pH.

Table 2. Protolytic forms of fingolimod and calculated physicochemical parameters.

Protolytic form	Physicochemical parameters				
	pKa	LogP (LogD)	Solubility, g/L	Proton donors	Proton acceptors
 $[BH_3]^+$	8.7±0.3	2.15±1.0	8.68	3	0
 $[BH_2]$	–	5.25±0.61	0.015	2	1
 $[BH]^-$	12.2±0.2	1.15±1.0	0.012	1	2
 $[B]^{2-}$	13.3±0.2	0.8±0.3	0.11	0	3

Note: * – calculated for non-ionized form.

The theoretical basis for substantiating this medication combination is to analyze possible interactions at different levels: the pharmaceutical, pharmacokinetic, and pharmacological. Interactions at the pharmaceutical level determine the possibility of creating a stable and effective combination medication. The pharmacokinetic level takes into account the characteristics of absorption, distribution, metabolism, and excretion of administered medications to propose optimal pharmacotherapy regimens. Potential positive and negative effects of medication interaction at the levels of receptors, enzymes, and systems are studied at the pharmacological level. All of the aspects mentioned above determine the need for a step-by-step analysis of possible interaction between fingolimod and gabapentin.

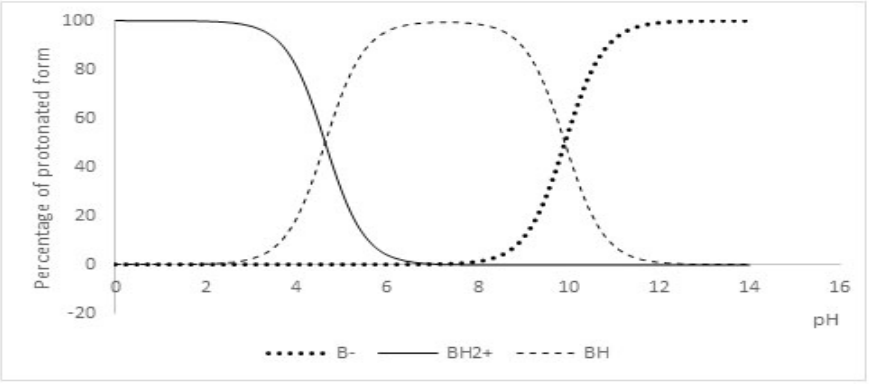


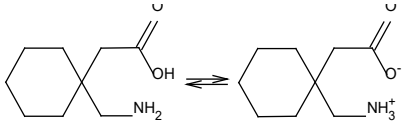
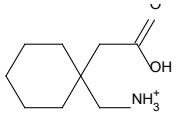
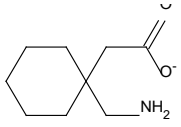
Figure 3. Percentage correlation between protonated forms of gabapentin depending on pH.

Interactions at the pharmaceutical level

Pharmaceutical interaction is due to a set of properties of compounds, and their possibility can be characterized based on the presence and reactivity of functional groups and physicochemical parameters (theoretically calculated, or empirically determined), such as ionization constants, tendency to salt and complex formation, solubility and others. The molecule of fingolimod has two types of functional groups: primary alcohol hydroxy groups (1) and primary amino group (2) (Figure 1A). Under physiological conditions, only amino groups can be reversibly ionized, and can form salts, whereas hydroxy groups form alkoxy anions only at highly alkaline pH.

Salt formation, while hydroxy groups form alkoxy anions only at strongly alkaline pH. Since the balance between protonated forms depending on pH is determined by the values of dissociation constants, the corresponding indicators for different forms of fingolimod (Table 2.) and the percentage of these forms depending on pH (Figure 2.) were calculated.

Table 3. Protolytic forms of gabapentin and calculated physicochemical parameters.

Protolytic form	Physicochemical parameters				
	pKa	logP (logD)	Solubility, g/L	Proton donors	Proton acceptors
 [BH]	–	1.19*	90.8	1*	2*
 $[BH_2]^+$	3.68±0.1	-1.52	16.23	2	1
 $[B]^-$	10.3±0.3	-1.6	16.33	1	2

At significantly high pH, anions $[BH]^-$ (pKa = 12.2 ± 0.2) and $[B]^2$ (pKa = 13.3 ± 0.2) can theoretically be formed. Still, this process is not significant because these conditions do not occur in the body, or dosage forms. The gabapentin molecule (Figure 1B.) combines both acidic (1) and alkaline (2) functional groups, due to which the compound exhibits amphoteric properties and can also exist as a double-charged internal bipolar ion (zwitterion). The isoelectric point of gabapentin is 7.14 (Drug Future Chem Data Web site, 2022), and at physiological pH, it exists almost entirely in the form of zwitterion [BH] (Figure 3.). The percentage of cation $[BH_2]^+$ (pKa = 3,68 ± 0,1) is highest at pH below 3 (Figure 3.), which may have some value in the acidic environment of the stomach. In contrast, the formation of the anion $[B]^-$, which is present in significant quantities only at pH >10 (pKa = 10.3 ± 0.3), is not substantial. In general, based on the ionization constants of fingolimod and gabapentin, it can be expected that under physiological conditions, only ionic interaction between compounds is possible with the formation of salts capable of reversible

dissociation without changing the structure of the molecule, with the formation of corresponding protonated forms.

According to the protonated state, the characteristics of compounds, such as lipophilicity (logP or logD – lipophilicity at pH 7.4) and solubility in water that are related to the number of proton donors and acceptors, change and affect the ability of compounds to overcome histohematic barriers. Thus, fingolimod in non-ionized form has a high value of lipophilicity (logP 5.25±0.61) and the lowest solubility in water. In contrast, its ionized forms ($[BH_3]^+$, $[BH]^-$ and $[B]^{2-}$) are more water-soluble (Table 2.). A similar trend was observed for gabapentin (Table 3.). It should be noted that the value of lipophilicity (logP 1.19) is calculated for the non-ionized form, while the natural solubility in water is due to zwitterion. The reversible ionization ability is due to the presence in the molecule of donors and acceptors, which number naturally varies depending on the ionization (protonation/deprotonation) of the medication (Tables 2 and 3.).

Interaction at the pharmacokinetic level

At the pharmacokinetic level, drug interaction can occur at the stages of absorption, metabolism, distribution, or excretion, and occur primarily through the use of the same transport or biotransformation mechanisms. Absorption of various drugs from the gastrointestinal tract occurs with involving many mechanisms, such as passive and facilitated diffusion, and active transport. Medications with low molecular weight (up to 300 Da), uncharged medications (or those capable of reversible ionization – organic bases and acids), and structures with optimal lipophilicity are mainly transferred through biological barriers (Leo, Hansch, & Elkins, 1971). In addition, the number of hydrogen bond acceptors or donors should not be too large (up to five) so as not to create difficulties in transitioning from hydrophilic to lipophilic phases when crossing biomembranes (Lipinski et al., 2001). Active transport, on the contrary, ensures the transport through the cell membrane of those compounds that do not meet these requirements. Active transport requires energy consumption, special transport systems, and some structural similarity to endogenous substrates transported in this way.

Active transport systems are represented in the gastrointestinal tract by various transporters, which primary function is to increase the absorption of compounds to be included in the processes of energy or plastic metabolism. Interactions with these systems can be expected if the investigated compounds are similar to endogenous compounds or have specific functional groups that determine the possibility of their interaction with such systems. Thus, organic anion transporters (OAT1, OAT3, OAT4, OATP1A2) can participate in the absorption of organic acids (in the form of anions); organic cation transporters (OCT1, OCT2, family SLC-transporters) promote the transfer of organic positively-charged ions, and also take part in the transfer processes of non-specific transporters of reversible transport (mainly Pgp). They can also reduce the concentration of the compounds in some tissues (brain), or accelerate the excretion of foreign compounds of a particular chemical structure. These transporters are expressed not only in the intestinal wall, but also in other organs (kidneys) and tissues (hematoencephalic, hematotesticular barriers), where their functioning strives to maintain homeostasis. Although facilitated diffusion does not expend energy on the transfer of compounds, it attracts specific transport systems and experiences saturation effects. Both fingolimod and gabapentin are low molecular weight compounds (307.4 and 171.23 Da, respectively), the number of proton donors and acceptors in them does not exceed five (Tables 2 and 3.). In addition, lipophilicity values of their ionized forms existing at intestinal pH prove the theoretical possibility of their absorption by simple diffusion, in which the compounds do not have mutual influence on the mass transfer of each other. Gabapentin has an active transport mechanism – L-amino acid transport (Berry, Beran, Plunkeft,

Clarke, & Hung, 2003; Stewart, Kugler, Thompson, & Bockbrader 1993), which limits its absorption, but that applies only to its use in high doses (1,200-4,800 mg/day). Fingolimod, present as a cation and structurally similar to endogenous compounds, could theoretically use OCTs, but it is described to be absorbed slowly but almost completely (Zollinger et al., 2011). It is likely that fingolimod, which is prone to reversible ionization, forms a highly lipophilic non-ionized form that dissolves well, accumulates in the lipophilic regions of cell membranes, and enters the systemic circulation for a long time. Therefore, the mutual influence of these agents used at therapeutic doses on the absorption processes is not expected.

Drug interactions at the pharmacokinetic level include competition for transport systems at the level of distribution between tissues, or for enzyme systems that metabolize compounds. To consider this, the ability and likelihood of whether fingolimod and gabapentin are substrates or inhibitors of shared enzyme systems were predicted (Table 1.). The findings indicate a high probability of no interaction between fingolimod and gabapentin at the levels of shared enzyme systems. Thus, with the predicted ability to overcome hemato-intestinal and blood-brain barriers (high absorption and entry into the brain), they are not substrates or inhibitors of the Pgp transporter and the most common systems. In addition, gabapentin is practically not metabolized *in vivo*, whereas fingolimod undergoes intensive metabolism using the CYP 4F2 system, which metabolizes some medications (Lipinski et al., 2001).

Analysis of pharmacokinetic parameters of fingolimod and gabapentin requires special attention (Table 4.). First, the medications differ significantly, by 2-3 orders of magnitude, in dosages recommended to achieve a therapeutic effect that may be a problem when creating a combined drug (uneven dosage per unit, analytical quality control, etc.). Secondly, the medications have significant differences in such pharmacokinetic parameters as absorption and elimination. Fingolimod is a compound with a long time of absorption and elimination ($t_{1/2}$ 163 ± 56.3 hours), whereas gabapentin is characterized by both rapid absorption and relatively rapid elimination from the body. Thirdly, although fingolimod and gabapentin have relatively similar clearance values, there is a big difference in their volumes of distribution (1,200 ± 260 L/kg for fingolimod and 0.8 L/kg for gabapentin) that may result in their long elimination period. Finally, due to differences in physicochemical properties (including lipophilicity), fingolimod and gabapentin bind to plasma proteins to varying degrees, which precludes their interaction during the distribution phase (transport in albumin-bound form). Given the above, the interaction between fingolimod and gabapentin at the metabolic system level is unexpected. It is also possible to exclude their mutual influence on distribution and transportation in a state bound to plasma albumin, although significant differences in pharmacokinetic parameters preclude their use in the combined dosage form.

Table 4. Some pharmacokinetic parameters of fingolimod and gabapentin.

Parameter	Fingolimod (David et al., 2012; David et al., 2018)	Gabapentin (Tjandrawinata et al., 2014; Goa & Sorkin, 1993)
The usual dose, mg	0.125-5	800-1200
Absorption constant, $hour^{-1}$	0.043	0.86
Elimination constant, $hour^{-1}$	0.0042	0.14
Time to reach maximum concentration, Tmax, hours	12 (6-36)	2,5
Elimination half-life, hours	163 ± 56.3	5-9
Volume of distribution, L/kg	1200 ± 260 (PubChem, 2001)	0.8
Degree of binding to blood plasma proteins, %	99.7 (PubChem, 2001)	< 3
Clearance, L/hour	6.3 ± 2.3 (GILENYA, 2001)	13.5

Interaction at the pharmacological level

Pharmacological interaction, as an indicator of the final total effect of a combination of drugs, is a necessary point to assess their effectiveness and safety. Pharmacological interactions can be direct (realized at the levels of target molecules, secondary messengers and mediator systems), or indirect (realized at the levels of target cells, organs and functional systems). In the body, fingolimod is converted to an active metabolite fingolimod phosphate by the enzyme sphingosine kinase (EC 2.7.1.91). Fingolimod and fingolimod phosphate have a high (< 0.2 nM) affinity for sphingosine-1-phosphate receptors subtype 1 (S1PR1). The therapeutic activity of fingolimod requires phosphorylation *in vivo* by sphingosine kinases to form the active moiety fingolimod phosphate (Brinkmann et al., 2010). Fingolimod phosphate binds to lymphocytic receptors S1PR1, causing internalization and degradation of the receptors. Functional antagonism at the receptors S1PR1 mediates the therapeutic effects of fingolimod, such as reducing inflammation and supporting structural restoration of the CNS parenchyma in patients with multiple sclerosis (Brinkmann et al., 2010; Matloubian et al., 2004). Initially, fingolimod acts as a potent S1PR1 agonist, primarily binding to and activating S1PR1. However, this effect is temporary, as excessive stimulation of S1PR1 effectively attracts β-arrestins to the receptor complex, promoting receptor internalization, and detaching the receptor from G protein and signaling pathways. This β-arrestin-controlled endocytic regulation reduces signaling through S1PR1, whereas chronic exposure to fingolimod causes a decrease in the amount of S1PR1 on the cell surface and long-term modulation of S1PR1 signaling. Downregulation of S1PR on lymph node T cells affects lymphocytes so that they do not respond to the output signal preventing infiltration of T cells (including proinflammatory Th17 cells) into the CNS, thereby reducing the risk of developing inflammation. Recent data also suggest that fingolimod may promote neuronal survival through microglial production of brain-derived neurotrophic factors.

The most commonly reported side effects of fingolimod are a temporary decrease in heart rate, and delayed atrioventricular conduction at the beginning of the treatment. Occurring bradycardia may be mediated by activation of the intra-rectifying potassium channel or G-protein activated by the intra-rectifying K^+ channel (IKACh/GIRK), and vasoconstriction is likely mediated by Rho-kinase-dependent (EC 2.7.11.1), and calcium-dependent mechanisms. The use of fingolimod in patients with MS is associated with an increased risk of infections, especially lower respiratory infections; herpes virus infections, herpes simplex virus infections, and mycosis due to a weakened immune system.

Gabapentin is a structural analog of GABA, a mediator that performs an inhibitory function. Its mechanism of action differs from the mechanism of action of other drugs that interact with GABA receptors. Gabapentin was found not to interact with $GABA_A$ or $GABA_B$ receptors of GABA uptake carriers of brain, as well as with benzodiazepine, glutamate, glycine or NMDA receptors (Taylor, 1997). The exact mechanism of action of gabapentin is still being determined. It is established that gabapentin binds to voltage-sensitive calcium channels, in particular the α2δ-1 subunit of Ca^{2+} channels, which may provide its analgesic effect. In vitro, gabapentin modulates the action of glutamic acid decarboxylase (GAD), an enzyme that synthesizes GABA. Results with human and rat brain nuclear magnetic resonance (NMR) spectroscopy show that gabapentin increases GABA synthesis. Gabapentin enhances non-synaptic GABA responses from neuronal tissues and reduces the release of several monoamine neurotransmitters (Shrivastava, Triller, & Sieghart, 2011). Adverse reactions when taking gabapentin are rare, and even when taking the drug at a dose of 49 g/day, their manifestation does not have serious consequences. Symptoms of overdose included dizziness, double vision, slurred speech, drowsiness, loss of consciousness, lethargy, and mild diarrhea (Goldenberg, 2010).

Given the mechanisms of realization of the target pharmacological effects of fingolimod and gabapentin, the summative (additive) action on the symptoms of MS is expected: a reduction of the intensity of inflammatory processes in the central nervous system, neuro-

protective effect, and remyelination due to fingolimod, combined with the relief of symptoms of neuropathic pain under the influence of gabapentin. The absence of common receptor and physiological systems in the mechanisms of their action mediates the absence of risk of exacerbations of adverse reactions (Khan & Smith, 2014; Sternberg et al., 2018; Racke, Frohman, & Frohman, 2022). Analysis of the physicochemical, pharmacokinetic, and pharmacodynamic properties of of fingolimod and gabapentin suggests that this drug combination can be successfully used in the treatment of multiple sclerosis. At the same time, the urgent question is about creating a dosage form based on a fixed combination of fingolimod and gabapentine.

CONCLUSION

Our results suggest that under physiological conditions for fingolimod and gabapentin, ionic interaction is possible with the formation of salts capable of reverse dissociation without changing the molecular structure with the formation of the corresponding protonated forms. At the pharmacokinetic level, no interaction is expected between fingolimod and gabapentine, as they do not use shared transport systems, metabolic enzymes, and have different degrees of protein binding that prevent their interactions during absorption, distribution, metabolism, and elimination. Therefore, the synergistic combination of fingolimod and gabapentine can be a promising therapeutic alternative for the effective treatment of MS. Their positive summative (additive) effect would be expected to relieve the symptoms of MS, reducing the intensity of inflammatory processes in the central nervous system, producing neuroprotective action, and contributing to remyelination due to the action of fingolimod, and ease the symptoms of neuropathic pain under the influence of gabapentine. The urgent question is about creating a dosage form based on a fixed combination of fingolimod and gabapentine.

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AUTHOR CONTRIBUTION STATEMENT

Developing the concept and doing a majority of the literature search (VL, ON and IB), designing the analyses methodology for estimation of the reactivity of functional groups (IB and OK). Carrying out some of the analysis and interpretation (ON), carrying out data collection and processing (ON, IS and NV). Suggesting the use of synergistic combination of fingolimod and gabapentin for the treatment of MS (ON and IF). The manuscript preparation, editing and review (IB and IS).

CONFLICT OF INTEREST

All the authors of this article declare that there is no conflict of interest.

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