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MEDICINE AND PHYSIOLOGY

ANALYSIS OF THE POSSIBLE INTERACTION BETWEEN AMANTADINE AND GLYCINE

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Annotation. *Interaction of drugs is the change in the effectiveness and safety of a single drug, compared with its simultaneous or consistent application with others. The purpose of this work is to determine the possible interaction of amantadine and glycine in the consistent use for Parkinson's syndrome pharmacotherapy. Thus, the same as in case of the pharmacodynamic phase, one should not expect a negative interaction of amantadine with glycine in the pharmacokinetic one, that makes their combined administration for treatment of parkinsonian syndrome scientifically grounded.*

Key words: *chemical and physico-chemical interaction, Amantadine, Glycine, pharmacodynamic drug interaction.*

It is known that extrapyramidal disorders are traditionally referred to as motor disturbances caused by lesions of basal ganglia or associated structures that are part of the extrapyramidal system. The classification of extrapyramidal disorders includes both extrapyramidal syndromes and extrapyramidal diseases. The latter include diseases that selectively affect the basal ganglia and are predominantly manifested by extrapyramidal syndromes (for example, Parkinson's disease, or essential tremor). Parkinson's disease is characterized by akinesia (hypokinesia) or rigidity (akinetic-rigorous syndrome), which are often accompanied by resting tremors and postural instability. Approximately 80% of Parkinsonian cases is the Parkinson's disease itself, for which clinically distinct one-sided or asymmetric symptoms at the onset of the disease, a pronounced reaction to levodopa's agents, the presence of a resting tremor and pathomorphological changes – degeneration of neurons of the the substantia nigra with the formation in intact neurons of intracellular inclusions – Lewy bodies [1].

Amantadine is one of the drugs that start treatment for parkinsonism. This medicine contributes to the synthesis of dopamine, reducing its back capture, while there is protection of neurons of the substantia nigra by blocking glutamate receptors. Therefore, for the correction of modeling extrapyramidal disorders that are consistent with parkinsonian syndrome, we considered it expedient to use amantadine as a basic therapy. It is important to note that Parkinson's syndrome is not only a violation of the extrapyramidal system. So in 70-80% of patients are observed neurotropic disorders – sleep disturbance, depression, cognitive deficiency, and others. Approximately half of patients with Parkinson's disease without dementia have mild cognitive impairment,

even in the early stages of the disease, and sometimes even before the development of mnemonic deficiency. This, in particular, violation the executive (planning and memory), visual-spatial and linguistic functions. It is known that among the drugs of nootropic action, we note a very wide range of drugs that are used to reduce and eliminate cognitive deficits, but not all of them are safe [2].

Glycine has a mild psychoactive effect, improves blood circulation, due to normalization GABA level, has anticonvulsant and antihypoxic properties. It is indicated when memory is reduced after an injury, stroke on the background of chronic diseases, etc.

Therefore, in our opinion, the research of glycine for reducing the manifestations of cognitive deficits on the background of anti-parkinsonian therapy is very important and relevant. We have previously studied the antiparkinsonial action of glycine in association with amantadine in catalepsy manifestations in rats and tremors in mice, and now it is interesting to determine the possibility of interactions of glycine and amantadine with simultaneous use.

Interaction of drugs is the change in the effectiveness and safety of a single drug, compared with its simultaneous or consistent application with others. Simultaneous use of xenobiotics, food, alcohol and smoking is the important aspect of the drug's interaction. Interaction of drugs that change the effectiveness and safety of pharmacotherapy has a clinical significance [3]. The interaction of medications, which leads to increased efficiency and safety of pharmacotherapy, underlies the rational combination of drugs. The combination of drugs which can result in a decreased effectiveness of pharmacotherapy is called irrational. Potentially dangerous combinations of drugs are a serious clinical problem. According to various authors, from 17 to23% of drugs combinations, prescribed by physicians, are potentially dangerous. So in 16-18% of patients receiving such dangerous combinations, side effects are developed. In addition, the side effects arising from the application of potentially dangerous combinations also represent a serious economic problem, as the cost of their treatment is half the cost of therapy for all medical complications. The study of the mechanisms of drug interactions is one of the possible ways to increase the effectiveness of combination therapy and its safety.

The reason for the undesirable effects of interaction may be, firstly, physical, chemical or physico-chemical incompatibility and, secondly, pharmacodynamic and pharmacokinetic interactions.

The purpose of this work is to determine the possible interaction of amantadine and glycine in the consistent use for Parkinson's syndrome pharmacotherapy [4].

The first stage of research was the study of chemical and physico-chemical interaction of amantadine and glycine. This inconsistency arises from the chemical reactions (oxidation, reduction, hydrolysis, double exchange, etc.) of substances with each other. Possible interactions at the physico-chemical level in the combination of amantadine and glycine are developed due to the peculiarities of the structure and the presence of functional groups. Thus, amino group (functional group (1)) is the most

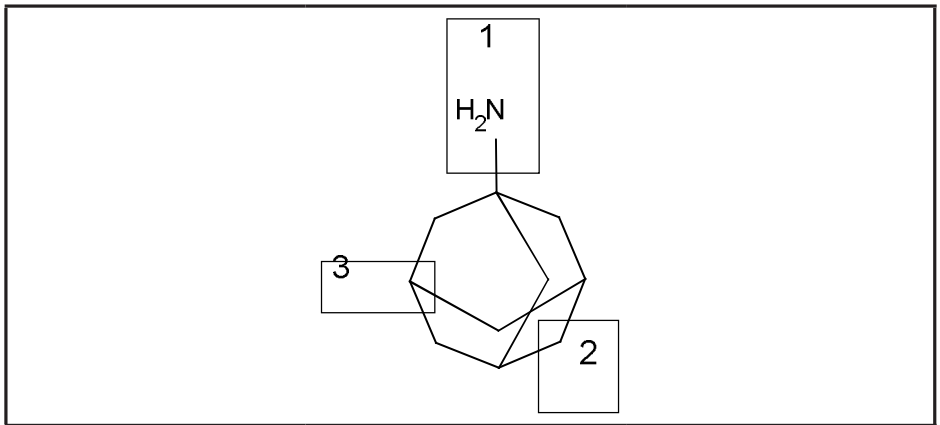
reactive in amantadine (Table 1), where protonation and deprotonation (depending on the pH of the medium) occurs first of all. As is evident from the rate of pKa (10.76 ± 0.2) in physiological conditions (pH = 7.4), the compound is a cation in an ionized form which goes under deprotonation at a high pH level only. This determines the high solubility in the aqueous medium (the estimated value is 6.61 mol / L) and low lipophilicity at pH = 7.4 (logD = -0.88 ± 1.0). The ability of the nitrogen atom to reverse protonation also determines the formal number of proton donors, but for the protonated form of amantadine, this process occurs only at high pH values as stated above. However, since this process is equilibrium and there is always a certain amount of non-ionized form with high lipophilicity (logP = 2.22 ± 0.24), the compound is notable for effectively overcoming a biological barriers by passive diffusion.

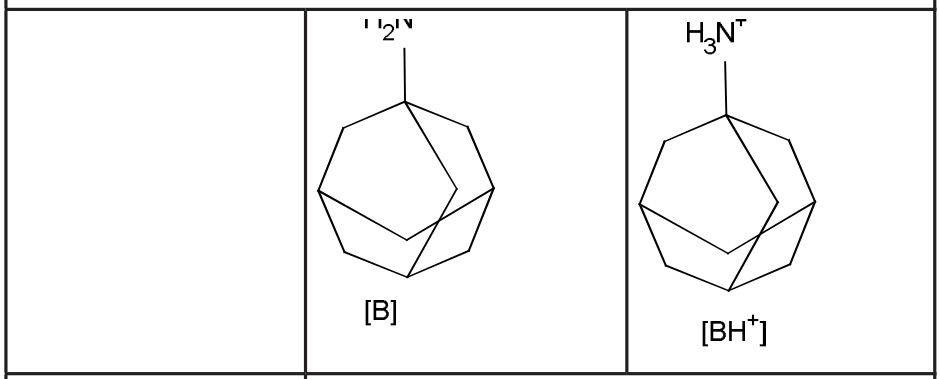
Other possible reactive centers of the molecule include the secondary (2) and tertiary (3) carbon atoms of the adamantane structure. It is known that the tertiary carbon atom is more reactive than the secondary one. Due to the weak inductive effect of aliphatic groups and the partial stabilization of free radicals, which is usually formed as an intermediate, these reactions are oxidative-reducing and can occur only in reactions with strong oxidizing agents. Thus, the amantadine reactivity is limited by the amino group only, where the most probable is the salivation reaction (protonation with the formation of salts). Formation of amid derivatives and Schiff alkali are the other inherent to the aliphatic amino group reactions. However, the first of these reactions can take place only under the conditions of salt and carboxylic acid dehydration (for example, at elevated temperature), but the conditions of the second one are necessity of the aldehyde or ketone derivative in a weakly acidic medium.

Glycine is a bifunctional compound which contains both amino (1) and carboxyl groups (2) in the structure (Table 2). Since the nitrogen of the amino group is a donor of unbound electronic dyad (basic properties), and the hydroxyl of the carboxyl group is capable of dissociation (acidic properties), glycine exists in the form of a bipolar ion (zwitterion) which polarity (polar surface of glycine) is 63.32 Å2. Consequently, it determines the high solubility in water (102.3 g / l theoretically calculated and 250 g / l according to experimental data). Due to the amphotericity of glycine, it exhibits both acidic and alkaline properties depending on pH and exists as a zwitterion (pKa amino group 2.43 ± 0.1, whereas for carboxyl 9,64 ± 0,13). The isoelectric point is an another amino acids characteristic where the number of positively charged particles in a solution equals the number of negative ones. Therefore, as pI rate for glycine is 6.1, a certain fraction of glycine exists in the form of a carboxylic anion under physiological conditions. The presence of charge in glycine determines not only its pressure in water solubility, but also the insignificant ability to overcome biological barriers through passive diffusion (in particular, hydrophobic regions of lipid membranes) and enters the internal environment, mainly through active or facilitated transport.

Table 1

Structure of amantadine molecule





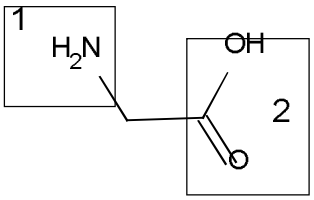
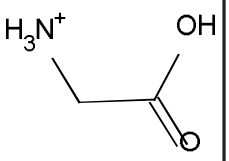
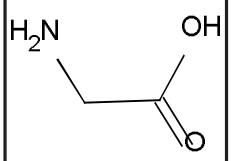
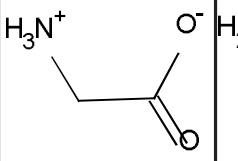
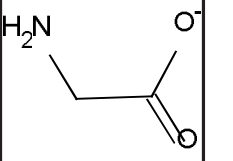
Polar surface area, (PSA), Å^2	26,02	
pKa	-	10,76 ± 0,2
Solubility, g/l (25 °C)	6,61 mol/l (pH 7,4)	
logD (logP)	2,22 ± 0,24	-0,88 ± 1,0
Proton donors number	0	1
Proton acceptors number	1	0

The reactivity of glycine is provided due to the presence of these two functional groups. So, besides the ability to form salts, which is primarily realized by the formation of carboniferous acid, glycine is capable of forming amides (from amino groups) and esters (with hydroxyl groups). It should be noted that these reactions occur only in case of water removal, in the presence of which, on the contrary, the hydrolysis of amides or esters takes place. Consequently, in conditions of the organism (in particular, the gastrointestinal tract) they are exceptions. Therefore, only ionic interactions between amantadine and glycine that result in the formation of an ionic compound

(aminoadamantane) are possible to be expected at the physicochemical level first of all. In the interest of this, the fact that amantadine amino group is deprotonated only at high pH values (higher than 10,76 ± 0,2), and the carboxyl group of glycine (due to the presence of an amino group) has high acidity - protonation of carboxylic acid occurs only at a pH below 2.43 ± 0.1. In favor of this is the fact that amantadine amino group is deprotonated only at high pH rates (higher than 10,76 ± 0,2), and the carboxyl group of glycine (due to the presence of an amino group) has high acidity - protonation of carboxylic acid occurs only at a pH below 2.43 ± 0.1. However, taking into account that the amino group of glycine also acts as an acceptor of protons and is in close proximity to the carboxyl group, as well as the fact that amantadine, as a pharmaceutical substance, is used as a hydrochloric salt, it can be concluded that the chemical interactions between these compounds are excluded, and the combination may be stable.

Table 2

Structure of glycine molecule

				
	 [LH^+]	 [LH]	 [LH]	 [L-]
Polar surface area, (PSA), Å²		63,32		
pKa	2.43 ± 0.1			9.64 ± 0.13
Solubility, g/l (25 °C)	102.3 g/l (250 g/l – experimental values)			
logD (logP)		(-1,03 ± 0,28)	-3,53 ± 1,0	
Proton donors number	2	1	1	0
Proton acceptors number	0	1	1	2

The next stage of our study was the determination of pharmacodynamic drug interaction. This type of interaction develops when two medicinal products with a summation or antagonistic effect at the cellular, physiological or physico-chemical levels are administered at same time. Although this type of interaction is often used for therapeutic purposes, there may be unwanted results as well. If the interaction is carried out at the receptor level, it mainly concerns agonists and antagonists of different receptors types. In case of synergism, the interaction of substances is accompanied by an increase in the final effect. Synergism of drugs can be manifested by simply summing or potentiation of the final effect. Summarized (additive) effect is observed with simple addition of effects of each component. When the overall effect exceeds the sum of the separate effects of both substances after combined administration of these substances, it indicates potentiation.

It has been established that the anti-parkinsonian effect of amantadine is realized by increasing the synthesis of dopamine in presynaptic terminals, increasing the release of dopamine in the synaptic cleft, inhibition of reuptake of dopamine in the presynaptic terminal, stimulation of expression of D2-dopamine receptors in striatum, and indirect anticholinergic action. A new mechanism of amantadine pharmacological effect was discovered recently: ability to block glutamate NMDA receptors predominantly at the level of striatum. It expands the range of the use of these drugs not only with secondary Parkinsonism, but also with other forms of central motor disorders. Currently, it is widely recognized that glutamate NMDA receptor antagonist of amantadine sulfate subtype, which inhibits neurotoxic effects of glutamate, has a neuroprotective effect [5].

Glycine is a substituted amino acid that has the properties of a metabolism regulator. Glycine is an inhibitive neurotransmitter, a regulator of metabolism in the brain. The biological targets of glycine are glycine and GABA receptors that regulate the activity of glutamate receptors. Due to these properties glycine is able to reduce conflict, psycho-emotional stress, aggressiveness, improve mood, and increase social adaptation.

Consequently, the pharmacodynamic action of amantadine and glycine depends on different mechanisms of interaction with the corresponding biological targets, therefore, one should not expect side effects while receiving them simultaneously. Particular attention should be paid to the features of pharmacokinetic interaction - the change of one or several characteristics of the drug: absorption, distribution, metabolism or excretion. These types of interaction are usually determined by the following parameters: serum concentration, half-life, binding to proteins, the amount of free drug in the blood, and the rate and amount of the drug excretion. Amantadine is well absorbed from the gastrointestinal tract after oral administration. Cmax is 5 hours; amantadine sulfate T1/2 - 12-13 hours, amantadine hydrochloride - 30 hours. It is eliminated by the kidneys in the unchanged form. Amantadine metabolism in the organism under the action of enzymes of the monooxygenase system of hydroxylated derivatives was not fixed, and almost the only way of its biotransformation is amino conjugation i.e. acetylation

Unlike amantadine, glycine is not absorbed by simple diffusion, but by the specific carriers GlyT1 and GlyT2 [6]. The processes of glycine metabolism are characteristic

of amino acids and do not affect the enzymes that catalyze medications of xenobiotic origin.

Conclusions. Thus, the same as in case of the pharmacodynamic phase, one should not expect a negative interaction of amantadine with glycine in the pharmacokinetic one, that makes their combined administration for treatment of parkinsonian syndrome scientifically grounded.

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