Comparative Analysis of Acute Toxicity of Amino Acid-Containing Antiarrhythmics

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Acute toxicity of amino acid-containing antiarrhythmic agents is experimentally studied in mice. Introduction of amino acids into the antiarrhythmic molecules always reduces their toxicity. However, the same amino acids unequally modulate toxicity of different antiarrhythmic drugs.

Key Words: *toxicity; amino acids*

Pharmacotherapy of heart rhythm disturbances is an important medical and social problem. Of particular interest is the development of new antiarrhythmic drugs, derivatives of some amino acids, for instance, glutamic, aspartic, and γ-amino butyric acids. Being natural metabolites or metabolite-related substances, these agents exhibit pronounced antiarrhythmic effect and are characterized by low toxicity and allergenicity. These substances play now an increasing role in the medicine, since they act as bioregulators of physiological and neurochemical processes in the organism, prevent hypoxia, improve tissue respiration, and act as inhibitory and excitatory transmitters in the CNS [2-6].

The aim of the present study was to investigate the effect of amino acid residue on the toxicity of antiarrhythmic drugs.

MATERIALS AND METHODS

Toxicity of 3 amino acid-containing trimecaine analogs containing glycine, magnesium L-aspartate, and N-acetylglytamic acid (laboratory codes LKhT-1-97, LKhT-2-97, LKhT-3-97, respectively) and diazo derivatives of arylpentanes containing DL-aspartic acid, magnesium L-aspartate, and glycine (laboratory codes LKhT-11-91, LKhT-53-91, and LKhT-20-92, respectively) was evaluated (Table 1).

Diazo derivatives of arylpentanes in the form of bases were synthesized in the reaction between aminoketones and formamide; the products then interact (mol/mol) with the corresponding amino acids in ethanol-water solution. The structure of final products was confirmed by proton magnetic resonance (Tesla BS 584A) and infrared spectroscopy (Specord IR-75), and their purity was verified by elemental analysis and thin layer chromatography (Table 1).

Experiments were carried out on 260 albino mice weighing 18-20 g. The drugs were injected intraperitoneally, LD_{50} was calculated as described previously [1] using probit-analysis.

Structural precursors trimecaine, its morpholine analog, and LKhT-2-86 were used as the reference drugs. Before injection the diazo derivatives of arylpentanes were dissolved in distilled water acidified with hydrochloric acid, derivatives of trimecaine morpholine analog LKhT-1-97 and LKhT-2-97 in 20% ethanol, and LKhT-3-97 in distilled water.

RESULTS

LKhT-2-97 containing magnesium L-aspartate was the most toxic derivative of trimecaine morpholine analog; however, LD_{50} of this agent was 2-fold higher than that of trimecaine (Table 2). LKhT-3-97 containing N-

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TABLE 1. Physicochemical Properties of Amino Acid Derivatives of Diazoarrylpentanes and Trimecaine Morpholine Analog

Agent	Molecular weight*	T_m, °C**	Infrared spectrum, cm^{-1}	Yield, %
LKhT-11-91	516.72	105-107	1635, 1520	94
LKhT-53-91	643.89	64-66	3260, 1660	92
LKhT-20-92	458.56	91-93	3250, 1670	96
LKhT-1-97	337.17	133-136	1660	70
LKhT-2-97	353.54	115-120	1640	65
LKhT-3-97	451.27	135-140	1640	65

Note. *Molecular weight is expressed in carbon units. **T_m is melting temperature.

acetylglutamic acid characterized by minimum toxicity, its LD_{50} 4-fold surpassed that of trimecaine. LD_{50} for LKhT-1-97 containing glycine also 3-fold surpassed that for trimecaine.

Thus, amino acids attached to morpholine trimecaine analog markedly reduced its toxicity. This effect was most pronounced in N-acetylglutamic acid and glycine, which can be attributed to their detoxifying activity and improvement of the nonspecific organism's resistance.

Introduction of DL-aspartic acid and magnesium L-aspartate into LKhT-1191 and LKhT-53-91 molecules reduced their toxicity about 1.5-fold in comparison with their structural precursor LKhT-2-86. Glycine attached to LKhT-2-86 (agent LKhT-20-92) also reduced its toxicity.

Thus, toxicity of diazo derivatives of arylpentanes was maximally reduced when the molecule was conjugated with DL-aspartic acid.

1,4-Naphthoquinone derivatives containing aspartic and glutamic acids and glycine exhibited lower toxicity in comparison with the unmodified molecule (LD_{50} increased 60-80-fold). The aspartic acid-containing compound possessed minimal toxicity, while glutamic acid and glycine produced practically the same detoxifying effects.

Conjugation with amino acids always reduces the toxicity of antiarrhythmic drugs. This effect can be attributed to detoxifying and membrane-stabilizing activity of amino acids and to improvement of the nonspecific organism's resistance. However, the same amino acids unequally modulate toxicity of different antiarrhythmics. This effect probably depends on the strength of chemical bond between amino acids and the corresponding nitrogenous bases, which is determined by electron density on the nitrogen atom, the length of amino acid chain (spatial factor), and the presence of Mg^{2+} in the molecule. All Mg^{2+}-containing agents were more toxic than Mg^{2+}-free drugs.

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TABLE 2. Acute Toxicity of Amino Acid-Containing Antiarrhythmics ($M \pm m$)

Agent	Amino acid	LD_{50}, mg/kg
Trimecaine	—	200±16
Trimecaine morpholine analog	—	275±19
LKhT-1-97	Glycine	612±42
LKhT-2-97	L-Aspartic acid+Mg^{2+}	450±37
LKhT-3-97	N-Acetylglutamic acid	800±35
LKhT-2-86	—	99±3
LKhT-11-91	DL-Aspartic acid	174±7
LKhT-20-92	Glycine	112±4
LKhT-53-91	L-Aspartic acid + Mg^{2+}	126±3
1,4-Naphthoquinone	—	6.5±0.3
I	DL-Aspartic acid	538±14
II	Glutamic acid	401±12
III	Glycine	415±8

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