PRE-CLINICAL STUDY OF ACUTE TOXICITY AND HYPOGLYCEMIC ACTION OF N,N/-(ETHANE-1,2-DYYIL)BIS(QUINOLINE-2-CARBOXAMIDE)

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The relevance of studying the problems of diabetes mellitus (DM) is determined by extremely rapid growth of morbidity as well as high degree of disability. The ambiguity of certain aspects of the pathogenesis of diabetes and its complications, together with complexity of pharmacotherapy requires constant studying of this problem and searching for new antidiabetic drugs.

N,N'-(ethane-1,2-dyyil)bis(quinoline-2-carboxamide), a compound containing the fragments of the chemical structure of imidazoline receptors type I_2 blocker – (2-(4,5-dyhidroimidazol-2-yl) quinoline hydrochloride), known by BU 224 code, has attracted our attention. There are no hypoglycemic drugs of such chemical structure now. There is no data about the impact of the investigated compound on carbohydrate metabolism. However, on the basis of chemical structure, it may be assumed that N,N'-(ethane-1,2-dyyil)bis(quinoline-2-carboxamide) can affect imidazolin receptors and, consequently, influence the mechanisms of carbohydrate metabolism regulation. In literature there are data concerning anticancer properties of this compound in vitro, due to the strengthened apoptosis and activation of caspase-3.

(N,N'-(ethane-1,2-dyyil)bis(quinoline-2-carboxamide) was synthesized by Candidate of chemical sciences Paponov B.V. (V.N. Karazin Kharkiv National University).

Objective. This study aimed to investigate the hypoglycemic action of N,N'-(ethane-1,2-dyyil)bis(quinoline-2-carboxamide) as a prospective hypoglycemic agent on the model of alloxan-induced diabetes and on the normoglycemic rats to determine the "dose of effect" dependence as well as acute toxicity in different routes of administration.

Materials and methods. The acute toxicity of N,N'-(ethane-1,2-dyyil)bis (quinoline-2-carboxamide) was determined on the white rats using intraperitoneal and intragastric administration of the investigated substance. LD_{50} was calculated by the method of Litchfield-Wilcoxon using the probit analysis. Hypoglycemic effect was investigated on the white random-bred male rats with the body mass equal to 0.20±0.02 kg. DM was modelled by the subcutaneous administration of alloxan monohydrate (Sigma, USA) once at a dose of 150 mg/kg as a 5% solution in the acetate buffer, pH 4,5. Animals previously were devoided of food for 24 h, but had

free access to water. After 10 days the rats with the basal glucose level higher than 11 mg/dl were selected. Glucose was determined in the blood samples which were taken from the vessels of tip of the tail, by the glucose oxidase method using diagnostic kits ("Filicit", Ukraine).

In order to study pharmacological activity, N,N'-(ethane-1,2-dyyil)bis (quinoline-2-carboxamide) was administered as an aqueous suspension, stabilized by polysorbate 80 at a dose of 1.5 mg/kg intraperitoneally. This dose possesses an antitumor effect. Intragastrically N,N'-(ethane-1,2-dyyil)bis(quinoline-2-carboxamide) was given in a broad range of doses as the aqueous suspension stabilized by polysorbate 80. As a reference drug metformin (Sigma, USA) at a dose of 100 mg/kg was used. Plasma glucose content was determined by glucose oxidase method before and 90 min after drug administration. ED_{50} was calculated by the method of G.N. Pershyn. Statistical differences were analysed using Wilcoxon criterion Ť and Student t test.

Results and discussion. By the classification of Hodge H.C., Sterner J.H., N,N'-(ethane-1,2-dyyil)bis(quinoline-2-carboxamide) administrated intraperitoneally belongs to moderately toxic substances (III grade of toxicity, LD_{50} = 10.005 mg/kg), administrated intragastrically – to low-toxic compounds (IV grade of toxicity, LD_{50} = 633.45 mg/kg).

As to pharmacological activity, N,N'-(ethane-1,2-dyyil)bis(quinoline-2-carboxamide), at a dose of 1.5 mg/kg intraperitoneally has pronounced hypoglycemic effect, lowering the level of glycemia at 57.2% that exceeds the antidiabetic effect of metformin that equal 44.0% at a dose of 100 mg/kg. In the intragastric administration N,N'-(ethane-1,2-dyyil)bis(quinoline-2-carboxamide) has a dose-dependent hypoglycemic effect in range of doses 7.92-31.67 mg/kg, with non-linear dependence "dose-effect". The maximal hypoglycemic effect is provided by the dose of 15.84 mg/kg. ED_{50} equals 11.64 mg/kg.

The therapeutic index at intragastric administered equals 54.42, indicating a wide therapeutic window and the respective safety of the compound. In normoglycemic rats N,N'-(ethane-1,2-dyyil)bis(quinoline-2-carboxamide) at a dose of 15.84 mg/kg statistically significantly lowers blood glucose by 24,9%, while at doses of 3.96-7.92 mg/kg hypoglycemic effect is absent.

Thus, the effect of N,N'-(ethane-1,2-dyyil)bis(quinoline-2-carboxamide) can be defined as antihyperglycemic in significantly lower dose compared with metformin both in intraperitoneal and intragastric administration with a sufficiently high level of safety. The latter is verified by the therapeutic index that was calculated using the results of effective dose and acute toxicity determination in intragastric administration.