The model of acute cold trauma in rats was reproduced by placing the rats in a freezer "NordInter-300" at a temperature of -18 ° C for 2 hours in individual plastic boxes (without limiting air intake). Oligopeptides were administered by intranasal introduction at a dose of 20 μg/kg for 30 minutes prior to cold exposure. The reference drug "Semax" (CJSC "Innovative Scientific and Production Centre "Peptogen", the Russian Federation) was administered at a dose of 20 μg/kg in the same terms. The frigoprotective effect was evaluated by changing the rectal temperature in animals, which was measured by a WSD-10 thermometer before cooling and 10 minutes after the acute cold exposure.

Results and discussion. In the course of our investigational studies, it was found that lifetime of mice was 70.57 minutes in the control group affected by acute total cooling. The administration of the investigated substances and reference drug resulted in acceleration of mice's lifetime. Thus, the frigoprotective activity of the KK-1 peptide was 6.5%, the KK-5 peptide was 36.5%, and Semax 8.2%. However, statistically significant acceleration of animals` lifetime against the reference group was observed only under the affect of the KK-5 peptide (by a factor of 1.4). In addition, in regards of frigoprotective activity, the KK-5 peptide of was higher than the reference drug (for 28%) and the KK-1 peptide (for 29.7%).

Analysis of rectal temperature indices in rats 2 hours after acute cold stress testifies to the development of hypothermia (in the control group of animals the rectal temperature was decreased by 8%). KK-1, KK-5 peptides and Semax were contributed to a rise in temperature by 6%, 5.5% and 7% respectively.

Also, the rates of animals receiving study medicines did not statistically differ from the markers of the intact group, indicating the ability of the medicines to prevent the development of hypothermia and further pathophysiological manifestations of hypothermia.

Conclusions. The frigogrotective properties of peptides - homologues of the fragment of $ACTH_{(15-18)}$ and Semax reference drug were determined on the model of acute total cooling of mice and cold trauma in rats.

The frigogrotective activity of Acetyl (D-Lys) -Lys-Arg-Arg-amide peptide was 6.5%, of Acetyl-(D-Lys) -Lys- (D-Arg) -Arg-amide peptide was 36.5%, Semax reference drug was 8.2%. Acetyl-(D-Lys)-Lys-(D-Arg)-Arg-amide peptide in regards of frigogrotective activity reaches higher heights than Acetyl-(D-Lys)-Lys-Arg-Arg-amide peptide and Semax reference drug.

Peptides - homologues of the fragment $AKTG_{15-18}$ under the names KK-1 and KK-5 under the conditions of acute cold stress prevent the decrease in rectal temperature of rats, not inferior to the Semax.

Today it is important to carry further investigation of mechanisms of frigoprotective effect of peptides - homologues of the fragment of $ACTH_{(15-18)}$.

DOXEPIN LETHAL POISONING: PROBLEMS OF ANALYTICAL DIAGNOSTICS

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Introduction. Doxepin (3-(dibenz[b,e]oxepin-11(6H)-ylidene)-N,N-dimethylpropylamine) is a tricyclic antidepressant, which is recommended in medical practice for the treatment of depression, which is accompanied by anxiety. According to literature review, the toxic and lethal of Doxepin concentration in the blood is in the range from 0.5 or 0.7 to 29 mg/l.

Aim of the study is analyze of lethal cases of Doxepin poisoning over the past 10 years and identify of factors that contributed to this.

Materials and methods are the search and bibliographic analysis of literature on the causes of antidepressant lethal poisoning, as well as an analysis of factors that increase the likelihood of tricyclic antidepressant Doxepin poisoning.

Results and discussion. Andrea Dettling' study only 9 cases of fatal isolated Doxepin poisoning was found and the concentration of antidepressant was measured in blood samples from peripheral vessels.

The results are in range from 1.5 to 7.0 mg/l, which is the lowest quarter of linear lethal concentrations of the substances mentioned in the literature without specific place of sampling blood. The question of whether concentrations of Doxepin and its metabolite, Nordoxepin, were found to be sufficient to establish that deadly poisoning from intoxication was raised in the case under consideration.

Doxepin concentration in the blood of the heart was in 5 times higher than in the venous blood of the thigh. This difference can be explained post-mortem redistribution, which may cause of false interpretation of the results. Therefore, it is difficult to determine the absolute or standardized value for lethal doxepin intoxication.

Anna Koski' study was expressed suggested that CYP2D6 gene polymorphism may contribute to development of fatal adverse effects of tricyclic antidepressants. The cases of fatal Doxepin poisoning whiz undetermined etiology of death, which were accompanied by a completely non-functional genotype CYP2D6 were detected. This indicates about a complete absence of the enzyme CYP2D6 and shows poor metabolic phenotype. Chance that defective genotype contributes to death, possibly associates with high, repeated dose of Doxepin.

Doxepin concentration was 2.4 mg/l, Nordoxepin concentration was 2.9 mg/l and Doxepin/Nordoxepin correlation was 0.83. This is the lowest rate in 35 deaths which were analyzed during 2002.

M.A. Neukamma clarifies the question of which poisoning (acute or chronic) was the cause of the case of fatal Doxepin poisoning. In the study special attention was given the way of Doxepin biotransformation by enzymes CYP2D6, CYP2C9 and CYP2C19, and how the intake of other drugs (Amlodipine, Diazepam, Metoprolol and Ibuprofen, etc.) effects on biotransformation and smoking.

In cases of intoxication, which include combinations drugs that act on the central nervous system, should consider not only such drug-drug interaction as increased side effects, but also the possible mutual influence on metabolism of drugs and habits such as smoking (Figure 1).

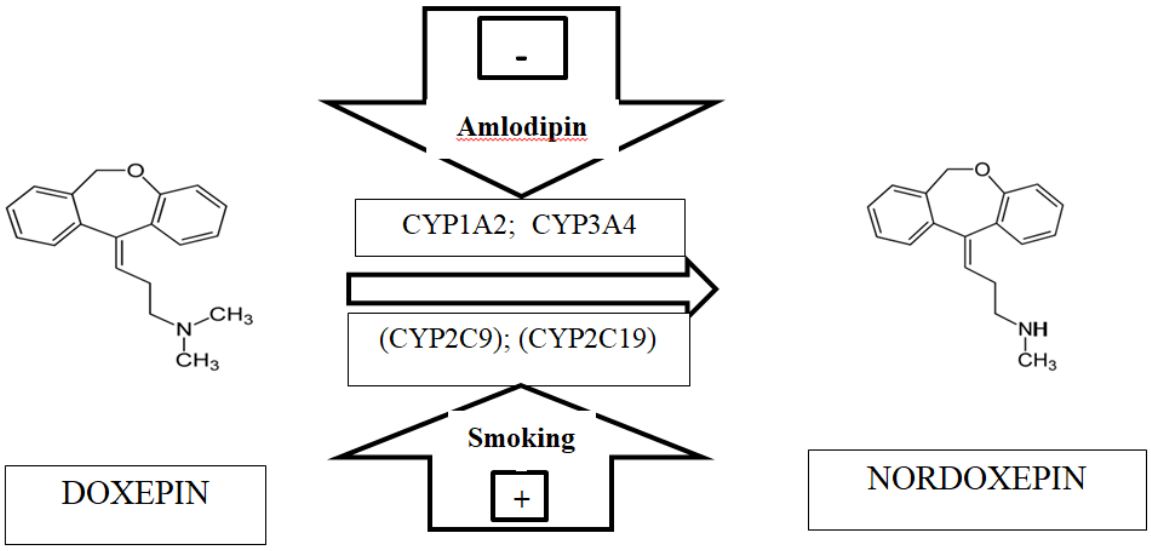

Figure 1. Metabolism of Doxepin: induction (+) and inhibition (−) of cytochrome P450 isoforms (CYP) when taking medicines and smoking

Given all the circumstances, it seems likely that death was caused by an inconspicuous gradual intoxication.

Conclusions. Literature review of Doxepin poisoning can determine the possible causes that play a major role in the poisoning of this antidepressant (gene polymorphism and impact on Doxepin biotransformation parallel use of other drugs and smoking), as well as phenomena that can lead to wrong results of chemical-toxicological analysis (post-mortem redistribution effect).