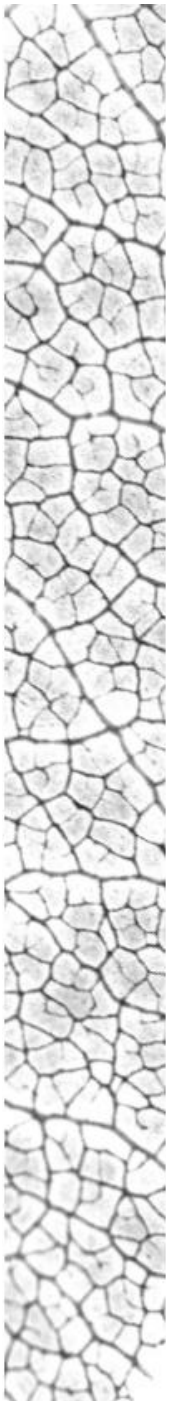

EurAsian Journal of BioSciences
Eurasia J Biosci 14, 3069-3072 (2020)

Pharmacological correction of changes in the chemical and mineral composition of rat's skeletal bones by Mexidol after 60-day of Tartrazine administration

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Abstract
Currently, the yellow synthetic azo dye tartrazine is widely used in such industrial fields as pharmy, food and cosmetology. The effects of tartrazine on morphological and functional state of bones as well as ways of correction of changes insufficiently studied. The aim of the study was to establish the possibilities of using Mexidol as a pharmacological corrector for changes in the chemical and mineral composition of skeletal bones in mature rats after 60 days of using tartrazine. The research was carried out on 175 white mature male rats, divided into 5 groups. 1st group - control; 2nd and 3rd groups - 1 ml of tartrazine solution was administered to rats daily intragastrically at dose 750 and 1500 mg/kg body weight respectively for 60 days; 4th and 5th groups - 1 ml of tartrazine solution was administered to rats daily intragastrically at dose 750 and 1500 mg/kg body weight respectively for 60 days and intramuscularly 5% solution of mexidol at dose 50 mg/kg body weight. The periods of observation were 3, 10, 15, 24 and 45 days after the end of 60-days tartrazine administration. The chemical and mineral composition of the humerus, hip bones, and the third lumbar vertebra were studied by gravimetric method. Also the spectrophotometry was used. The application of mexidol is accompanied by smoothing out the negative effect of 60-day tartrazine administration at dose of 7500 and 1500 mg/kg body weight on the mineral and chemical composition of the rat's skeletal bones from the 15th to the 45th days of observation. The mineral and chemical structure of bones was recovered to control values more quickly in group with the use of tartrazine at dose of 750 mg/kg body weight.

Keywords: bones, chemical and mineral composition, tartrazine, mexidol

Luzin VI, Fastova ON, Tverskoi AV, Morozov VN, Morozova EN, Tverskaya AV (2020) Pharmacological correction of changes in the chemical and mineral composition of rat's skeletal bones by Mexidol after 60-day of Tartrazine administration. Eurasia J Biosci 14: 3069-3072.

INTRODUCTION

Food additive E102 - yellow synthetic azo dye tartrazine is currently widely used in such industrial fields as pharmacy, food and cosmetology (Sarafanova, 2004, Merinas-Amo, et al. 2019). However, recent studies show controversial results of the effect of this food additive on the body. According to some data, tartrazine does not cause any statistically significant morphological and functional changes in the body. According to others it has an adverse effect, in particular, on the blood, the immunological status of the body, embryonic development, growth and development of cognitive functions, etc (Amin, Hameid & Abd Elsttar, 2010. El-Sakhawy, Mohamed, & Ahmed, 2019. Bhatt, yas, Singh, John & Soni, 2018. Gao, Shen, Yin, An, & Jin2011. Hashem, et al. 2019).

Currently, the effect of tartrazine on the morphological and functional state of the skeletal system has not been adequately studied. There are only incomplete and fragmentary data that do not give a full picture of the skeleton changes. In our previous work, it was found that intragastric administration of tartrazine at a dose of 750 and 1500 mg/kg body weight for 60 days to mature rats is accompanied by the disbalance development of the chemical, macro- and microelement

Received: July 2019
Accepted: March 2020
Printed: September 2020

Table 1.

№	Name of group	Description
1.	Control	Animals daily intragastrically was injected 1 ml of 0.9% isotonic sodium chloride solution for 60 days
2.	Experimental 1.	1 ml of tartrazine solution was administered to rats daily intragastrically at dose 750 mg/kg body weight for 60 days
3.	Experimental 2.	1 ml of tartrazine solution was administered to rats daily intragastrically at dose 1500 mg/kg body weight for 60 days
4.	Experimental 1+corrector	1 ml of tartrazine solution was administered to rats daily intragastrically at dose 750 mg/kg body weight for 60 days and intramuscularly 5% solution of mexidol at dose 50 mg/kg body weight
5.	Experimental 2+corrector	1 ml of tartrazine solution was administered to rats daily intragastrically at dose 1500 mg/kg body weight for 60 days and intramuscularly 5% solution of mexidol at dose 50 mg/kg body weight

composition of the proximal tibial epiphysis. The hydrophilicity of the ash studied was increased whereas the percentage of organic and mineral substances was decreased with a proportional change of macro- and microelements (Luzin, Fastova, Morozov, Morozova, 2019; Putri, et al, 2018)

The changes revealed require the search for correction paths, including pharmacological ones, in order to reduce the negative effect of tartrazine on the body. Taking into account that tartrazine is able to initiate the development of oxidative stress in the body due to the ability of its cleavage products in the intestine to form reactive oxygen species (Dermirkol, Zhang, & Ercal, 2012. El-Desoky, et al. 2017). the mexidol was chosen. It inhibits the processes of lipid peroxidation of biomembranes, actively reacts with lipid peroxides, primary and hydroxyl radicals of peptides, and increases the activity of antioxidant protection enzymes (in particular superoxidedismutase) (Voronina, 2012).

Purpose

The aim of the study was to establish the possibilities of using mexidol as a pharmacological corrector for changes in the chemical and mineral composition of skeletal bones in mature rats after 60 day of using tartrazine.

MATERIAL AND METHODS

The research was carried out on 175 white mature male rats weighing 200-210 g. The distribution of animals into groups is shown in **Table 1**.

The periods of experiment were 3, 10, 15, 24, and 45 days after completion of the 60-day administration of tartrazine.

The handling of laboratory animals and all interventions were carried out in accordance with existing norms and regulations (Tkachenko, et al. 2019).

To study the chemical and mineral composition, the humerus, hip bones, and the third lumbar vertebra were taken. These bones were subjected to drying in a dry oven and ashing in a muffle furnace, followed by determination of the percentage of water, organic and mineral substances by gravimetric method (Kolb, et al. 1976)The content of macro- and microelements in the ash obtained was determined by spectrophotometry using generally accepted methods (Polujektov, et al. 1967. Pupyshev, et al. 2009). The received digital data were subjected to statistical processing in the program “STATISTICA 5.11” (Rebrova, et al. 2002).

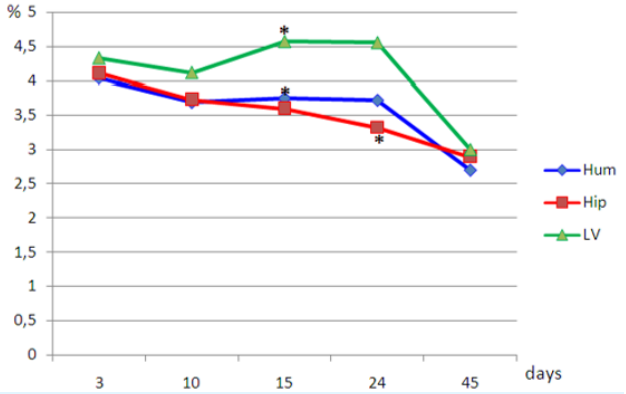

Fig. 1. Dynamics of changes of contents of minerals in the ash of humerus, hip bone and the third lumbar vertebra in the group with intragastric administration of tartrazine at a dose of 750 mg/kg body weight and intramuscular injection of 5% mexidol solution at dose of 50 mg/kg body weight (in % to the values of control group)
*-significant changes, compared with control values (p<0,05).

RESULTS

Intragastric administration of tartrazine at a dose of 750 mg/kg body weight and intramuscular injection of 5% mexidol solution at dose of 50 mg/kg body weight, the water content was less than the values of control group without the using of corrector from 15 to 45 days: in the humerus - by 7.55%, 7.12% and 7.89%, in the hip bone - by 5.30%, 6.19% and 5.70%, in the third lumbar vertebra - by 7.59%, 7.89% and 4.02%. Also, the contents of minerals were greater by 3.75%, 3.72% and by 4.57%, 4.55%, on the 15th and 24th days of experiment in the humerus and the third lumbar vertebra respectively and in the hip bone - by 3.32% on 24th day (**Fig. 1**).

Moreover, the calcium content in the ash of the humerus and hip bones was higher than the values of the 2nd group by 5.39% and 4.07% on the 15th day of experiment and by 4.64%, 5.05% in the third lumbar vertebra on the 15th and 24th days. Finally, the content of sodium, potassium and magnesium in the humerus was lower by 5.25%, 5.98% and 6.63% on 15th day respectively, and the sodium content in the third lumbar vertebra by 5.31% on 45th day.

Intragastric administration of tartrazine at dose of 1500 mg/kg body weight and intramuscular injection of 5% mexidol solution at dose of 50 mg/kg body weight, the water content in the third lumbar vertebra was less than the same indicators of the group without the use of

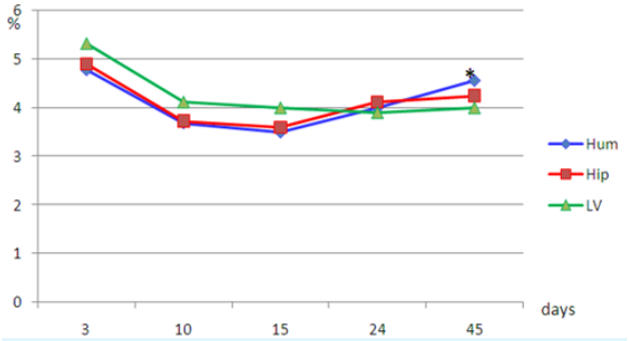

Fig. 2. Dynamics of changes of zinc content in the ash of humerus, hip bone and the third lumbar vertebra in the group with intragastric administration of tartrazine at a dose of 1500 mg/kg body weight and intramuscular injection of 5% mexidol solution at dose of 50 mg/kg body weight (in % to the values of control group)
*-significant changes, compared with control values ($p<0,05$).

corrector by 7.02%, 6.69% and 5.20% from the 15th to 45th days of experiment respectively and by 6.92%, 8.16% and by 6.42%, 6.83% in the humerus and hip bones respectively on the 24th and 45th days. Also, the mineral content was higher than the values of 3rd group by 5.12%, 4.41% in the third lumbar vertebra on the 15th and 24th days of experiment, by 3.11% in the humerus on the 24th day and by 3.81% in the hip bone on 45th day.

The proportion of calcium in the mineral component of the third lumbar vertebra was higher than the values of 3rd group by 4.40% on the 15th day of experiment and the phosphorus content in the hip bone by 4.19% on 45th day. Also, the potassium content in the humerus was less by 5.89% on 45th day of experiment. Finally, the zinc content in humerus was higher than that of the comparison group by 4.56% on 24th day (**Fig. 2**).

The positive changes of the chemical and mineral composition of skeletal bones during the mexidol using can be explained by its membrane-protective and antioxidant effects.

Under conditions of oxidative stress, mexidol increases the stability of the cell membranes in bone tissue.

Oxygen reactive species (radical anion superoxide, hydrogen peroxide, hydroxyl radical), which are formed during the breakdown of tartrazine in the intestine, are bound by mexidol (Mazurov, Bolotova, 2008)

Also, mexidol increases the activity of antioxidant enzymes such as superoxidedismutase, catalase, glutathione (Mazurov, Bolotova, 2008).

CONCLUSIONS

1. The mexidol using against the background of the tartrazine administration at dose of 7500 and 1500 mg/kg body weight is accompanied by smoothing out the negative effect of the experimental conditions on the mineral and chemical composition of the bones from the 15th to the 45th days of observation.

2. The increase of proportion of calcium and the ratio of calcium/phosphorus and a decrease of hydrophilic elements - sodium, potassium and magnesium in the ash of the bones were registered.

3. The chemical and mineral structure recovery of skeletal bones in mature rats was faster in the group with the tartrazine using at dose of 750 mg/kg body weight.

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