

COMPARATIVE STUDY OF THE INFLUENCE OF MONO-AND DITHIOL ANTIDOTES UPON RENAL STRUCTURAL CHANGES AND UREA LEVEL IN ACUTE MERCURY INTOXICATION

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Key-words: thiol antidotes — mercury intoxication — renal morphology — urea

The increasing production and use of mercury and its derivatives in various industrial branches and agriculture enhances the risks of contact and even poisoning of large population groups. This circumstance supports the interest in detailed investigation of various aspects of toxic action of mercury and its compounds with many animal species and man (3, 7, 9). At the same time one studies the effects, tolerance and side effects of familiar mercury antidotes and searches for new drugs and substances with eventual antidote action (6, 8, 10).

At the present work we study comparatively the influence of dithiol antidotes Unithiol (U) and 2,3-dimercaptopropranolol (BAL) and monothiol antidote D-penicillamin on nephrotoxic effect of mercuric chloride in acutely intoxicated rats. This antidotic action in case of application at dosages providing equally fourfold bigger amount of sulfhydryl groups was compared with that of introduced mercury ions (double molar ratio of dithiol antidotes and fourfold molar ratio of monothiol one).

According to the central part of renal lesions in the picture of acute mercury intoxication (5) the presumption is made that the comparison of antidotes concerning their influence upon the renal alterations caused by mercuric chloride can be a reliable criterion for their relative effectiveness.

Material and methods

The experiments were carried out on 55 white male rats divided into 5 groups: 1st — control — animals injected with physiological saline s. c.; IInd — injected with 7,5 mg/kg mercuric chloride s. c. The dose is LD₅₀ of the same compound for the same animal and way of application (2); IIIrd — treated with mercuric chloride, in the way the animals of the IInd group are treated, combined with applying of U 12 mg/kg i. m.; IVth — treated with mercuric chloride in the way the animals of the IInd group are treated, combined with BAL 7 mg/kg i. m.; Vth — treated with mercuric chloride like the animals of the IInd group and given D-penicillamin 16,5 mg/kg orally.

The antidotes were introduced twofold — 30 min and 8 h after intoxication with mercuric chloride. The mentioned single doses provided an introduction of sulfhydryl groups in a ratio 4:1 to the introduced mercury cations.

The serum urea level of 11 animals of each group was determined 24 hours after intoxication. The urease-method (urea-test H1) was used. The material for histological study was taken from the kidneys of each animal and prepared after

the paraffin method. The preparations were stained with hemalaun-eosin. PAS-reaction of McMannus was done to detect the neutral mucopolysaccharides and Bracheau-reaction to establish RNA.

Results and discussion

The data obtained show that under the influence of applied lethal dose mercuric chloride the serum urea level increases more than 7 times (mean value of control animals $24,56 \pm 1,81$ mg % and of intoxicated ones $180,71 \pm 14,30$ mg % (table 1). U shows the strongest effect. In this way of application it leads to a considerable diminution (about 2,5 times) of the serum urea level in comparison with that of the animals given only mercuric chloride (table 1). BAL and D-penicillamin display a weaker influence upon the urea level than U. After their

Table 1

Urea serum concentrations in rats treated with mercuric chloride alone and in combination with thiol antidotes

Physiological saline	Treatment with			
	Mercuric chloride	Merc. chlor. + Unithiol	Merc. chlor + BAL	Merc. chlor + penicillamine
24,56 $\pm 1,81$	180,71 $\pm 14,30$	70,32 $\pm 7,10$	141,97 $\pm 17,52$	143,47 $\pm 16,67$

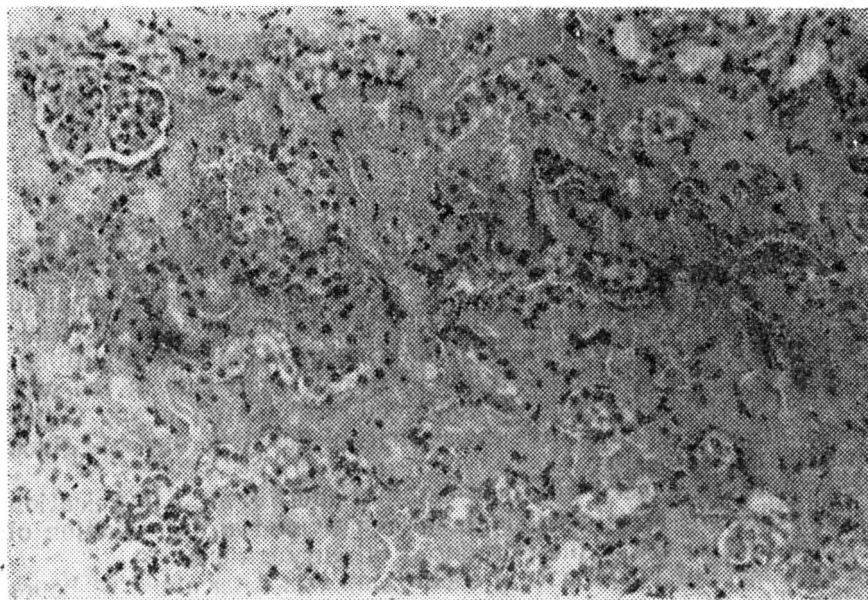


Fig. 1. Animal with mercuric chloride intoxication. Severe dystrophic and necrotic changes in the epithelial cells of renal proximal tubules. Staining HE, magn. $\times 250$

application the urea level of intoxicated animals decreases with about 40 per cent (table 1). The differences between the urea values of animals treated with mercuric chloride alone and combined with these antidotes are statistically unreliable.

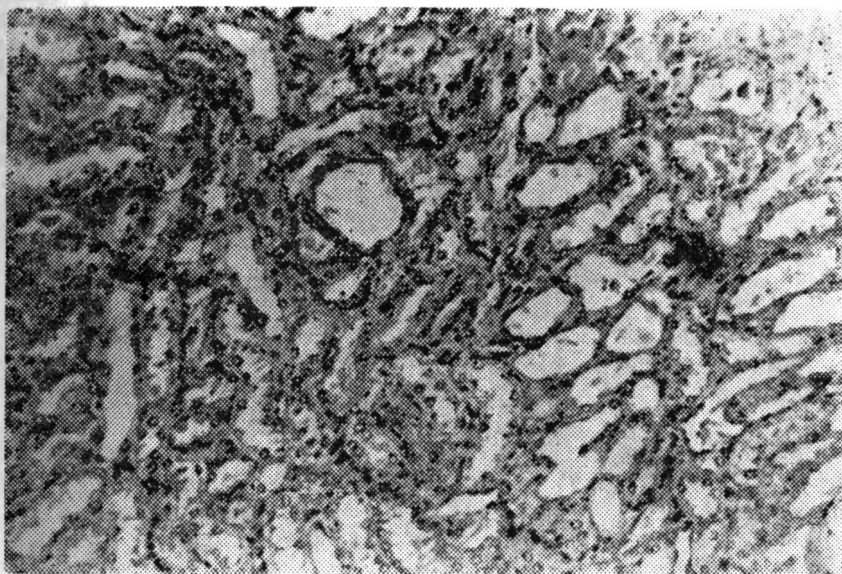


Fig. 2. Kidney of an animal treated with both mercuric chloride and Unithiol. Proximal tubules covered with low epithelial cells. Staining HE, magn. $\times 250$

The morphologic investigation of the kidney of intoxicated animals reveals some alterations corresponding to severe necrotic upper nephron nephrosis. The epithelial cells in most proximal tubules are scaled-off into the lumens. The basal membrane is naked, or even destroyed in some of them (fig. 1). In the apical part of the cytoplasm of intact cells the quantity of PAS(+) nonglycogenic substances is increased. In almost every tubular lumen protein substances and cylinders can be seen. The interstitium is edematous with scarce lymphoid-plasmocyte infiltration at certain places. The glomerules are anaemic, the basal membrane of capillaries is thickened and soaked with PAS(+) nonglycogenic substances. The medullar blood vessels are widely dilated and their lumens are filled with erythrocytes. A well expressed perivascular oedema is also observed. In the proximal tubules of animals treated with both mercuric chloride and U there are regeneration signs. At the places with intact basal membrane one can establish low epithelial cells which have clear cytoplasm (fig. 2). There are binuclear cells with mitoses in the nuclei and an increased DNA and RNA content in them. A protein substance is established in a few tubular lumens. Partially, the haemodynamic disturbances still persist — the glomerules are still anaemic, the medullar blood vessels are still dilated and filled with erythrocytes. A slightly expressed interstitial oedema can be also observed.

The necrotic upper nephron alterations induced by the mercury intoxication still persist in animals treated with both mercuric chloride and BAL. Most epithelial cells of proximal tubules are scaled-off into the lumens (fig. 3). The retain-

ing cells display severe dystrophic lesions. The basal membrane of some tubules is destroyed. Here and there initial regeneration signs can be found out. RNA content in the cytoplasm and nuclei of regenerating cells is slightly increased. The haemodynamic disorders still persist as observed after single mercuric chlo-

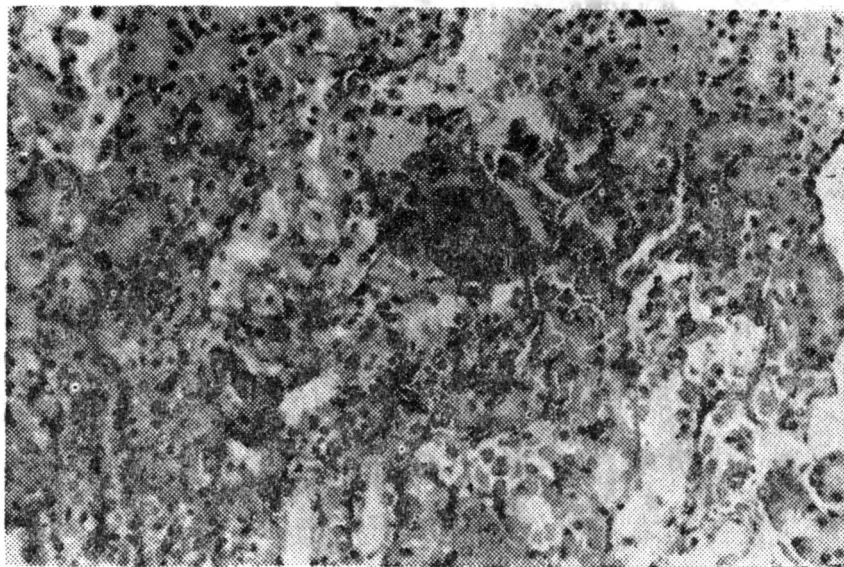


Fig. 3. Kidney of an animal treated with both mercuric chloride and BAL. Epithelial cells of proximal tubules are necrotically altered, some of them are scaled-off into the lumens of the tubules

ride treatment. The regeneration signs are most slightly expressed in animals treated with both mercuric chloride and D-penicillamin. The picture doesn't differ considerably from that after single application of mercuric chloride. Only in isolated cases certain signs of initial regenerative process are established in some proximal tubules with intact basal membrane.

The findings of the comparative study of the protection of thiol antidotes U, BAL, and D-penicillamin upon renal structural and functional changes after mercuric chloride intoxication present a certain interest having in mind the lack of any literature data about this problem. Our data show that in comparison with the other mentioned antidotes introduced at doses providing the introduction of equal number of sulfhydryl groups towards mercury cation U possesses the highest effect. It is expressed in relation to the structural lesions of renal parenchyma induced by mercuric chloride, as well as to the increased serum urea level. This is in concordance with the high U antidotic activity in renal lesions due to mercury intoxication which is reported by other authors (1, 4). Our data allow us to suppose that besides active groups (in this case the sulfhydryl ones) the molecule — carrier of these groups has an essential importance for the effectiveness of a given chemical antidote. It determines to a great extent the physico-chemical relationships of the compound and the related to them resorption, distribution, speed of elimination, etc. In this meaning, U has the highest activity as compared with the studied compounds which are carriers of sulfhydryl groups, too.

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**СРАВНИТЕЛЬНОЕ ИССЛЕДОВАНИЕ ВЛИЯНИЯ МОНО- И ДИТИОЛОВЫХ
АНТИДОТОВ НА СТРУКТУРНЫЕ ИЗМЕНЕНИЯ ПОЧЕК
И НА УРОВЕНЬ МОЧЕВИНЫ ПРИ ОСТРОЙ
РТУТНОЙ ИНТОКСИКАЦИИ**

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РЕЗЮМЕ

Исследовано влияние дитиоловых антидотов унитиола и 2,3-димеркаптопропанола (БАЛ) и моноитиолового антидота Д-пеницилламина на структурные изменения почек и на уровень мочевины в сыворотке. Исследование проводилось 24 часа после интоксикации летальной дозой хлористой ртути (7,5 мг/кг веса подкожно). Антидоты применялись в дозах, обеспечивающих введение сульфгидрильных групп в количестве 4:1 по отношению к введенным катионам ртути. В этих экспериментальных условиях влияние унитиола как на морфологические изменения, так и на повышение сывороточного уровня мочевины, оказывается наиболее благоприятным.