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# *Histological changes of white rat kidney after experimental administration of ethanol and cephalexin*

Despite the fact that the toxicity of cephalosporins is small (14), it was stated that they can cause necrosis of the proximal convoluted tubules in the case of the concomitant administration with aminoglycosides or loop diuretics. In dehydrated patients with impaired kidney function this potential toxic combination should be used with caution and the indications regarding their dosage in the renal insufficiency should be rigorously observed. Psychotic reactions were described in patients with the renal insufficiency treated with cephalosporins, including cephalexin (8). Cephalexin action changes in the case of the interaction with ethacrynic acid, furosemide, pyretanide and gentamycin. Antybiotic toxicity increases in these cases (10).

The aim of our experiments was to check whether nephrotoxic changes appear in the case of interaction of ethanol and cephalexin, which can take place in practice.

## MATERIAL AND METHODS

The experiment was carried out on Wistar rat males weighing about 200g. The animals were divided into two control groups and two experimental groups, including five animals each.

Rats from control group I received standard granulated fodder and water *ad libitum*. Rats from control group II received 20% ethanol *ad libitum* instead of water. Each animal from this group drank about 20ml of ethanol for 24h. Animals from experimental group I received cephalexin (Lilly, Florence, Italy) in the single dose of 42mg/24h, which corresponds to ten fold of the minimal therapeutic dose in human. The drug was administered each morning by means of intragastric bougie as suspension in 0.9% NaCl.

Animals from experimental group II received cephalexin like animals from experimental group I. Moreover, instead of water they received 20% ethanol *ad libitum*. Each animal from experimental group I drank about 15ml of ethanol for 24h. Animals were guillotined. The kidneys were fixed with 4% formaldehyde, dehydrated in alcohol, cleared with xylene and embedded in paraffin. The routine H+E staining and PAS reaction for the detection of neutral mucopolysaccharides were made on 7μ thick paraffin slices. The pictures were taken with the use of the Carl Zeiss Jena microscope and photo camera.

## RESULTS AND DISCUSSION

Regarding a lack of complete data about the influence of the new cephalosporins on kidneys, the investigation of cephalexin influence on this organ is very purposeful. Despite small drug toxicity, its elimination is an agent that loads kidneys and requires participation of the transport proteins (4). However, kidneys play a significantly smaller role in ethanol metabolism in comparison with the liver (1).

In our experiment in all animals receiving ethanol (the control group II) we observed hyperemia of the renal parenchyma in the form of the dilatation of capillaries surrounding tubules in the cortical and medullary part and also the dilatation of the glomerular capillary loops. In some animals these changes occured simultaneously, in others separately. The capillary dilatation exerts direct influence on the blood pressure and through the juxtaglomerular apparatus also on the aldosteron secretion. Former et al. (5) reported that ethanol concentration in the blood of about 300mg/l inhibits aldosteron secretion, while the concentration three times lower stimulates this hormon secretion. Different appearance of the renal glomeruli, namely a lack of the space between two layers of the Bowman's capsule in the renal glomeruli of the proper cortex and a dilatation of this space in the renal corpuscles of the juxtamedullary nephrons suggest their differentiated participation in the filtration and different sensitivity to ethanol. It may be concluded that ethanol administrated for a short time causes only functional changes manifestated as lower diuresis in some glomeruli and more intensive diuresis in others.

In our investigations we concentrated mainly on the renal corpuscle and the proximal convoluted tubule because cephalexin is secreted by the main part of the nephron (6). It shows high affinity for oligopeptide carrier – symporter $H^+$ (7). It is dependent on the presence of alpha-amino groups characteristic of cephalosporins (3, 4). The drug absorption takes place in the small intestine in a similar way (9, 11, 12, 13).

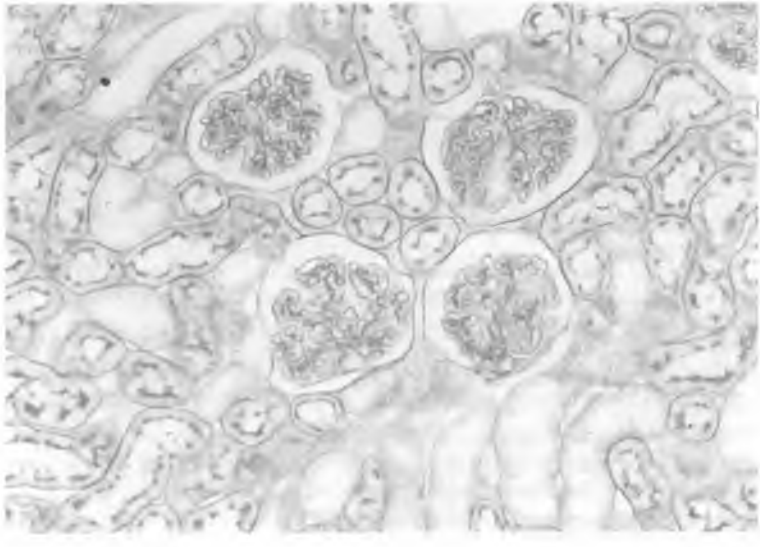

Fig. 1. The kidney of a rat from experimental group I. The dilated spaces between two layers of the Bowman's capsule in renal corpuscles and dilated lumen of tubules are visible. PAS method. Magn. 400x

Our observations revealed that cephalexin administered in the dose of 42mg/24h for 10 days did not exert nephrotoxic influence. However, it stimulates diuresis. A distinct dilatation of the

space between two layers of the Bowman's capsule and a dilatation of the lumen in the main nephron tubules were observed (Fig. 1). The differences in the intensity of the brush border stainability and the thickness of basal membranes were observed in comparison with the control animals. Donaubauer et al. did not observe the signs of histological damage of the proximal convoluted tubule epithelium after 14-day intraperitoneal administration of cefpirone HR 810 in the dose of 1500mg/kg/24h. However, they observed proteinuria and the lysosomal enlargement after 90-day administration of this drug in the dose of 400–1600mg/kg/24h.

The concomitant administration of cephalexin and ethanol caused a stronger hyperemia of the renal parenchyma than in the case of ethanol itself. The dilated arteries, capillaries surrounding tubules and glomerular capillaries were observed. The functional picture of the renal corpuscles, especially those located in the proper cortex was highly differentiated. A dilatation was observed in some of them and complete lack of the space between two layers of Bowman's capsule was observed in others (Fig. 2). Degenerative changes were observed in some corpuscles of the proper cortex. However, the majority of the juxtamedullary corpuscles did not show any morphological

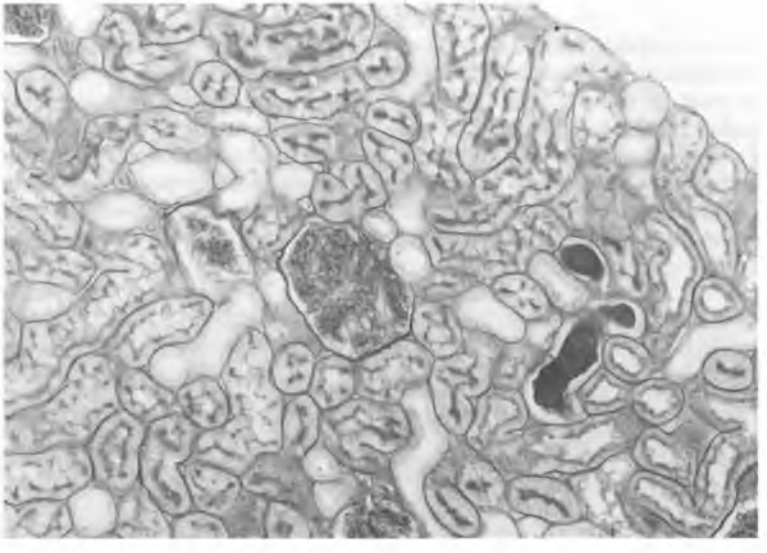

Fig. 2. The kidney of a rat from experimental group II. A lack of the spaces between two layers of the Bowman's capsule and changes in the vascular loops of the proper cortex glomeruli, shrunken tubular lumen and the presence of fluid in some collecting tubules are visible. PAS method. Magn. 400x

changes. The urine retention was observed in many tubules, especially collecting ones, in the renal medulla (Fig. 3). So, it may be stated that the interchange between the tubular lumen, vascular stroma and blood vessels underwent functional disturbance. However, a differentiated activity of plasma filtration was a consequence of different functional activity of renal corpuscles. Examinations of the concomitant influence of cephalexin and ethanol conducted by Barrio-Lera et al. (2) revealed that ethanol decreases this antibiotic excretion with the urine through its influence on the transport mechanisms.

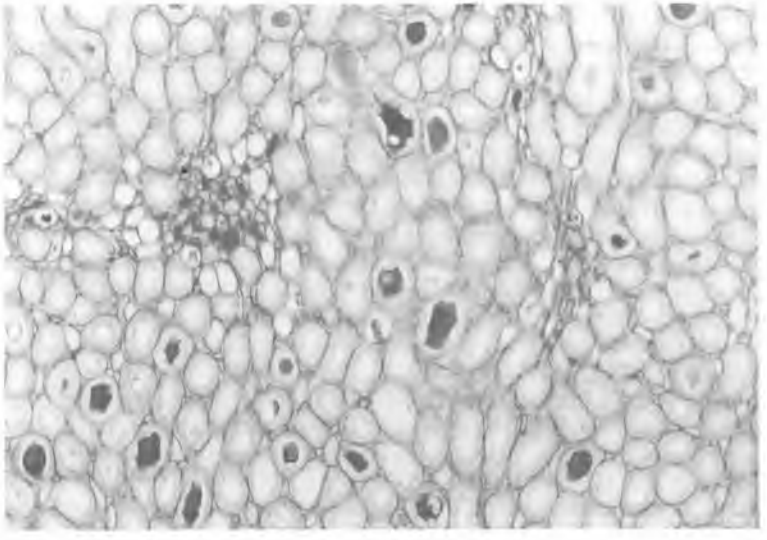

Fig. 3. The kidney of a rat from experimental group II. The presence of the urine in the collecting tubules of the medullary part. PAS method. Magn. 400x

## CONCLUSIONS

1. 20% ethanol administered ad libitum for 10 days causes hyperemia of the parenchyma in the rat kidney and the functional decrease of filtration in the glomeruli of the proper cortex and the increase of filtration – in the juxtamedullary glomeruli.

2. Cephalexin administered in the dose of 42mg/24h for 10 days does not act nephrotoxically but it stimulates diuresis.

3. The concomitant administration of ethanol and cephalexin in the same doses causes strong hyperemia of the parenchyma, functional changes in the glomeruli of the proper cortex in the form of decreased diuresis, degenerative changes in some of them and the urine retention in numerous collecting tubules.

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## SUMMARY

The experiment was carried out on Wistar rat males weighing about 200g. Animals from the control group received water and standard granulated fodder ad libitum. Animals from control group II received 20% ethanol *ad libitum* instead of water. Animals from experimental group I received cephalexin in the single dose of 42mg/24h, Animals from experimental group II received cephalexin in the dose of 42mg/24h and 20% ethanol ad libitum. After 10 days animals were decapitated. Histological examinations (H+E staining and PAS reaction) were made on 7μ thick paraffin slices. It was stated that ethanol causes hyperemia of the renal parenchyma and cephalexin stimulates diuresis. However, concomitant administration of ethanol and cephalexin causes functional changes (inhibition of diuresis) and degenerative changes in capillary loops of some renal corpuscles apart from hyperemia.

## Histologiczne zmiany nerki szczura białego po doświadczalnym podawaniu etanolu i cefaleksyny

Badania wykonano na szczurach samcach rasy Wistar o masie ciała ok. 200 g. Zwierzęta grupy kontrolnej otrzymywały wodę i standardową paszę granulowaną. Zwierzęta grupy kontrolnej II otrzymywały zamiast wody 20% etanol *ad libitum*. Zwierzętom grupy doświadczalnej I podawano cefaleksynę w dawce 42 mg/dobę. Zwierzętom grupy doświadczalnej II – cefaleksynę w dawce 42 mg/dobę i 20% etanol *ad libitum*. Po 10 dniach zwierzęta dekapitowano. Na skrawkach nerek o grubości 7 μ wykonano badania histologiczne (H+E i reakcję PAS). Stwierdzono, że etanol wywołuje przekrwienie miąższu nerek, a cefaleksyna ma działanie stymulujące diurezę. Natomiast łączne podawanie antybiotyku i etanolu poza przekrwieniem wywołuje zmiany czynnościowe (hamowanie diurezy), a w pętlach naczyń niektórych ciałek zmiany degeneracyjne.