EXAMINING THE INFLUENCE OF THREE INCREASING DOSES OF SULPHAMETHASINE SODIUM ON THE MASS OF KIDNEYS IN RATS WISTAR STRAIN

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In this work the toxicity of sulphamethasine sodium, given during 8 weeks, was examined. In water for white rats three increasing doses (0.066%, 0.2% and 0.6) were given. In strictly controlled laboratory conditions influence of this treatment was observed on the mass of kidneys and their anatomic changes, as well as changes in organoleptic character of urine. The trial was performed on 96 female rats Wistar strain, body weight ranging from 172.6 to 179.5 g. The rats were divided in 4 equal groups, out of which one was control. The control group was given pure potable water. For the purpose of observing the parameters, once in two weeks 6 rats from the control group were slaughtered. Based on the trials and the obtained results it may be concludes that sulphamethasine sodium given in drinking water in therapeutic, but also two times lower and higher concentration, effected the rats. The intensity of its effect depended from the dose. In the rats that received the highest doses of drugs in all examined time, there was notable cachexia and atrophy of kidneys. Urine was dark yellow colour with specific (unpleasant) odor.

Key works: sulphamethasine sodium, rat, kidneys

Wide application of sulphonamide in chemotherapy of animals, besides their direct biopositive effect, brought into the interest of the question of unwished, even toxic effect on microorganism. The most important toxic reactions that appear due to administration of sulphonamide have, in their nature, mostly chronic character. Chronic intoxication caused by sulphonamide includes both renal damages as a consequence of crystallization of slightly soluble sulphonamide and even less soluble acetylated derivates in kidney tubules, kidney pelvis and uterus. Crystallization may occur any time in the first ten days of administration of sulphonamide (1, 2, 5). The level of renal damages depends on solubleness of sulphonamide, quantity of urine, quantity of excreted sulphonamide, pH value of urine, degree of sulphonamide acetylation and individual dispositions (6, 7). Crystals of sulphonamide, in the shape of needles, are punctuated and enter into tissue of urinary tract. Every sulphonamide forms characteristic crystals that help their identification. Formed crystals may damage tubule epithelium or epithelial coat of kidney pelvis or prevent flow of urine - obstructive effect on urinary tract (3, 10).

Signs of chronic intoxication in some animals have specific characteristics. In big ruminants symptoms are diarrhoea, dehydration, exhaustion, loss of appetite and reduced milk yield, due to suppression of gut flora in digestive tract and reduced synthesis of Vitamin B complex. In other animals prolonged administration of sulphonamide causes reduced weight gain, depression, loss of appetite, nausea.
vomiting. Chronic toxicity in poultry is characterized by reduced egg production and production of eggs with thin shell. These symptoms appear two weeks after administration of sulphonamide (5, 6).

Materials and methods

The effect of sulphonamide on rats has not been enough researched, so before we decided to make a detailed research on toxicological features of sulphadimidine sodium. This research would provide at least three moments: (1) closer determination of toxic effect of this chemotherapeutics in controlled laboratory conditions; (2) closer insight of registered changes to the length of exposure of the organism examined on sulphonamide; (3) detection of changes in kidney of treated animal.

These experiments were carried out on white male rats, Wistar strain, and at the beginning of the experiments their body weight ranged from 172.6 to 181.0 g. From the time when they were brought forth until the beginning of experiment, they were kept under the same conditions of nutrition and care. During the experiment the rats were fed with food for laboratory animals, and watered ad libitum. In the experiment was used preparate "Sulphadimidin sodium" ad. uv. vet., that contains 16% of active substance.

At the beginning of the experiment, by the random method, a group of 10 animals was formed. They were sacrificed for the purpose of obtaining the beginning value of the observed parameter. Remaining 96 rats were divided in 4 equal groups, out of which one was untreated, control group (C). The experiment groups received drinking water with sulphadimidine sodium during 8 weeks in concentration of 0.066% (experimental group O-I), 0.2% (O-II) and 0.6% (O-III). In intervals of 2 weeks (week 2, week 4, week 6 and 8 of the experiment) six rats from control and experimental groups were sacrificed. Kidneys were examined pathoanatomic, taken out and measure on computerized scale "SARTORIUS".

Results

In control, untreated group of rats absolute mass of kidneys continually grew (Table 1), while in week 6 and 8 there was a statistically important value above the beginning one (p<0.001). In the first six weeks of the experiment in rats from O-I group absolute kidney mass, as a rule, grew relatively faster so that, starting from week 4, it was significant (p<0.001) above the beginning value, but only in week 4 they were same with findings in group C (p<0.01) (Table 1).

In the experiment where rats received three time larger concentration of sulphadimidine sodium in drinking water (O-II), absolute kidney mass grew even faster in the first three quarters of the experiment, so already in week 2 (p<0.01), as well in weeks 4 and 6 (p<0.001), it was significantly above the beginning value. In week 4 (p<0.05%) and week 6 (p<0.01) it was significantly higher comparing to the findings from control group (Table 1) However, during the experiment there was not significant difference comparing to the findings from group O-I.

The average absolute kidney mass of rats that received 0.6% of sulphadimidine sodium in drinking water (O-III) there was practically no difference in first three quarters of the experiment, so in week 6 it was significantly lower from the findings in group C (p<0.01) in the same time, O-I (p<0.01) and rats were
treated with 0.2% concentration of tested drug (O-II) \((p<0.001)\), but at the end observation period it was statistically important \((p<0.01)\) below the findings in group C, O-I and O-II (Table 1). Beside this, absolute mass of organs in rats from group O-III was statistically important below the beginning values (Table 1).

### Table 1.

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Control group</th>
<th>0.066 % (O-I)</th>
<th>0.2 % (O-II)</th>
<th>0.6 % (O-III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.66±0.16</td>
<td>1.66±0.16</td>
<td>1.66±0.16</td>
<td>1.66±0.16</td>
</tr>
<tr>
<td>2</td>
<td>1.8±0.2</td>
<td>1.7±0.3</td>
<td>1.97±0.1</td>
<td>1.6±0.1</td>
</tr>
<tr>
<td>4</td>
<td>1.9±0.3</td>
<td>2.3±0.3 a a</td>
<td>2.3±0.5 a</td>
<td>1.6±0.2</td>
</tr>
<tr>
<td>6</td>
<td>2.08±0.2 **</td>
<td>2.2±0.1 ***</td>
<td>2.50±0.1 ** a a</td>
<td>1.7±0.2 ce</td>
</tr>
<tr>
<td>8</td>
<td>2.5±0.4</td>
<td>2.3±0.2 ***</td>
<td>2.5±0.3</td>
<td>1.9±0.2 cc</td>
</tr>
</tbody>
</table>

- statistically important difference comparing to the beginning values \(p<0.01; ** p<0.001\)
- a - statistically important difference comparing to control finding \((a - p<0.05; a a - p<0.01)\)
- b - statistically important difference comparing to the findings from group O-I \((b b - p<0.01)\)
- c - statistically important difference comparing to findings from group O-II \((c - p<0.05; c c - p<0.01; c c c - p<0.001)\)

Middle tested doses of sulphadimide sodium caused oliguria and changes in organoleptic features of urine (dark yellowish color and specific, sharp odor) of animals treated form week 4, while in group O-III changes occurred in all the observed time. Sacrificed animals from the control, untreated group of rats (C), as well from rats in treated groups (O-I, O-II), that received two lower concentration of sulphadimidine sodium in drinking water, in none of the period showed obvious macroscopic pathoanatomic changes. In group O-III, where the rats were treated with the highest doses of sulphadimidine sodium in drinking water (0.6%), already after the first sacrifice of animals (week 2) cachexia and atrophy of the kidneys was obvious. These changes were even greater during the experiment.

**Discussion**

As it can be seen from the results, toxic effect of sulphadimidine sodium on the kidneys were the most expressed in groups that received highest doses of the drug. Our results are partially in accordance with the results registered on other animal kinds. The signs of developed intoxication in mammals are haematuria, albuminuria, renal colic, anuria, frequent need for urinating, precipitation of white crystals around vulva and prepuce, peripheral neurite and at the end swelling of kidneys with probable nephrosis \((4, 9)\).

When sulphonamide is given to female rats in late gestation, what causes almost total loss of calcification in fetus, this is the result of inhibited activity of
phosphatase. Continual administration of sulphadimidine to male rats results in atrophic changes in testis, vesicles seminalis and prostate, what may be the lack of folic acid. Also, cancerogenic and teratogenic effect of sulphonamide was proved in the experiments with the rats and chicken embryo (8).

Conclusion

Sulphadimidine sodium, continually administered in drinking water as a therapeutic mean in three times lower and three time higher concentration, effected the organism of rats, but the intensity of its effect depended of doses. Besides this, the appeared changes we registered in group O-III, according to data from literature, could be a consequence of this chemoterapeutics on suppression of saprophyte microflora and consequent reduction of Vitamin B complex synthesis (especially folic acid), but "on the other hand direct harm of kidneys is a consequence of crystallization of sulphadimidine sodium in kidney tubule, kidney pelvis and uterus.

Literature