Does Administration of Non-Steroidal Anti-Inflammatory Drug Determine Morphological Changes in Adrenal Cortex

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Rofecoxib (Vioxx© made by Merck Sharp & Dohme, the USA) is a non-steroid anti-inflammatory drug which belongs to a relatively new group of selective inhibitors of cyclooxygenasis-2, so-called coxibs. Rofecoxib was first registered in the USA, in May 1999. In Poland the drug was registered in the form of 12,5mg and 25mg tablets, as well as 12,5mg/5ml and 25mg/5ml suspension in the same year. Since then the drug was received by tens of millions of patients. As a result of an intensive advertising campaign of this group of drugs and enthusiastic opinions of doctors, coxibs (including Vioxx©) became the most frequently prescribed anti-inflammatory and analgesic drugs in rheumatic diseases. The career of rofecoxib, however, lasted for a short period of time. On September 30, 2004 Merck Sharp & Dohme company announced the withdrawal of Vioxx© drug from the market due to occurring dangerous adverse effects (an increase in the number of thrombotic-embolic incidents and sudden deaths of circulatory system diseases in the group of patients receiving rofecoxib) [1, 2,].

It was expected that drugs of this group would exhibit an increased therapeutic action and no adverse effects on the alimentary track mucosa or nephrotoxicity, or intensifying of susceptibility to bleeding, typical of other NSAIDs. In addition, there were expectations concerning the possibilities of their application, at least as auxiliary drugs, in the treatment of neoplasms, due to intensifying of apoptosis [3].

Rofecoxib administerd in the therapeutic doses of 12,5, 25 or 50 mg once a day is well absorbed in the alimentary track. The tablets and suspension have the same biological availability of about 93% [4, 5, 6].

At present it can already be said that coxibs did not entirely fulfill the hopes placed on them in relation to eliminating major adverse effects, which was expected due to their selective affinity to COX-2 [7, 8].

In relation to the withdrawal of Vioxx© preparation (rofecoxib) from the pharmaceutical market, an attempt was made to conduct microscopic-electron evaluation of the cortical part of the adrenal gland in preparations obtained from animals under influence of the drug.

The tests were performed on male white rats of Wistar strain, with body mass of 250 – 300g, which remained in the same conditions and received standard diet and drinking water ad libitum during the experiment.

The control group consisted of animals (10 rats) which did not receive any other substance except standard granulated fodder and drinking water.

Every morning the animals from the experimental group (15 rats) were administered, through a tube intragastrically, the preparation (suspension in physiological saline) rofecoxib – a non-steroid anti-inflammatory drug (Vioxx© preparation, Merck Sharp and Dohme, the USA) in the dose of 1,25 mg during 8 weeks, which constituted 10-times the maximum human therapeutic dose.

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After finishing the examination cycle the rats were decapitated and sections including the cortical part (zona fasciculata) of the adrenal gland were obtained for ultrastructural evaluation.
In the central part of the cytoplasm there was a cell nucleus. Chromatin mainly concentrated near the nucleus areola, in which nucleopores were noticeable. In the nucleus located in the middle part of large multiangular cells an electron-dense, irregular in shape, nucleolus was visible. In the evaluated material, compared to the preparations from the control group animals, there was found a greater number of secretory (Fig.1) vacuoles and large, containing cholesterol and other lipids as well as generated glucocorticoids lipid drops in the cytoplasm containing prominent endoplasmic reticulum. There were also found cells with a diluted structure of cytoplasm - dilutions of cytoplasm in the apical and basal parts of the cells. Mitochondria occasionally demonstrated features of delicate swelling.
The observed changes which occurred on the cellular level, with the application of large doses of the drug, result from the mobilization of adaptation mechanisms of the organism. Explaining of the nature of the observed ultrastructural changes requires broadening of the studies with the methods of molecular biology, and also monitoring of the endocrine function of the adrenal gland.
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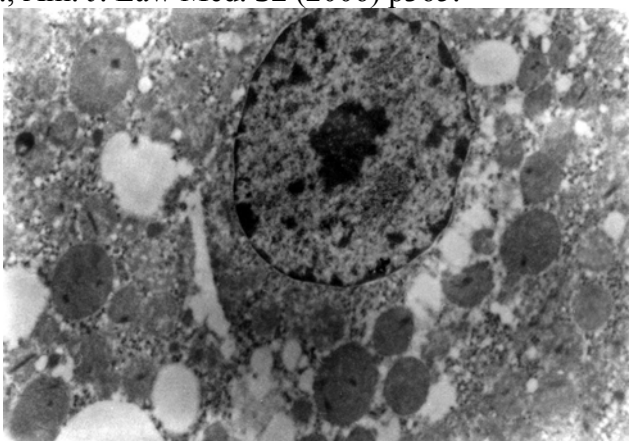

Figure 1. Cell of zona fasciculata of adrenal cortex.
Numerous secretory vacuoles present in cytoplasm. Magn. 12000x.

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