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Anti-inflammatory and anti-oxidant properties: Is there a link?

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BACKGROUND: It is believed that the anti-inflammatory activity of medicines is closely related to their antioxidant activity. However, in clinical practice rigorous evidence-based medicine approach fails to reveal important effects of antioxidants on patient important outcomes in inflammatory disorders, as has been shown by a number of Cochrane reviews [1–3].

OBJECTIVE: To evaluate anti-inflammatory and antioxidant effects of newly developed pharmacological agents: dimephosphone and its structural analogues ephorane and mephoprane, and xymedon, in comparison with prednisolone and etidronate in experimental animal model of adjuvant arthritis.

METHODS: Experiments were conducted in 64 white mongrel rats of both sexes weighing 180–200 g, which were divided into 8 groups 8 rats each (4 males and 4 females each), kept under standard vivarium conditions with certified feeding ration (kombikorm). The study was approved by the local ethics committee. We induced adjuvant arthritis by administration under the plantar aponeurosis of the left hind paw of 0.1 ml of Freund's adjuvant (Sigma) in rats of 7 study groups. The groups were as follows: 1st group - intact animals (control); 2nd group – animals to whom the solvent (distilled water) was administered with intra-gastric tube in corresponding volume (control of the model); 3rd – 8th study groups, in which animals were administered with study agents each at a dose of 1 mmol/kg body weight: dimephosphone, ephorane, mephoprane, xymedon, etindronate and prednisolone. The intensity of the modeled arthritis was determined by measurements of paw volumes with plethysmometer (UgoBasile). We calculated the difference in rat paw volume before the administration (baseline) and after administration of Freund's adjuvant at 3, 7, 11, 15, 20, 27, 31, 38, 41 days. The development of secondary arthritis was documented by the increase in volume of both hind and fore paws and tails. On the 41st day of the experiment the animals were sacrificed under light ether anesthesia and exsanguinated. The blood was used to determine the activity of catalase and peroxidase, the content of the total, reduced and oxidized glutathione, the level of ceruloplasmin, conjugated dienes of unsaturated fatty acids (DC), TBA-interacting products (MDA), and the total antioxidant activity of serum (AOA). The results were processed statistically using the Student's *t*-test.

RESULTS: The primary reaction to the Freund's adjuvant in a form of swelling of the ankle joint of the left hind paw was observed at 24 hours after its injection. External clinical manifestations of the modeled disease were more pronounced on the third day: local inflammatory reaction (redness, swelling, ulceration) was seen in all the animals at the injection site with the increase of the paw volume. On the 11th day of the experiment 20% of the animals developed secondary arthritis. The study agents

dimephosphone, ephorane, and prednisone exerted anti-inflammatory effect decreasing the volume of left hind paws by 45%, 46% и 27% respectively on the 40th day of experiment. Mephoprane did not affect the primary inflammatory response to the Freund's adjuvant (rats' left hind paws), however it reduced the volume of the contralateral right paw (secondary arthritis) by 90% on the 20th day of the experiement. This ant-inflammatory effect was accompanied by documented antioxidant activity in case of dimephosphone, ephorane, prednisolone, but not mephoprane. Dimephosphone reduced the levels of lipid peroxidation products in rats blood by 46% (DC) and by 25% (MDA). Ephorane also reduced the levels of lipid peroxidation products in the blood by 46% (DC) and by 25% (MDA), increasing the level of glutathione by nearly half, both the total and the reduced form. Prednisolone reduced the level of lipid peroxidation products in blood by 61% (DC), but not the TBA-interacting products. Mefopran did not affect the blood level of lipid peroxidation products. Xymedon and etidronate showed no anti-inflammatory effect. Xymedon demonstrated anti-oxidant properties, decreasing the blood levels of lipid peroxidation products, while etidronate seemed to behave in pro-oxidant mode, increasing the blood levels of lipid peroxidation products.

CONCLUSIONS: The effects of studied agents on the intensity of inflammation and lipid peroxidation were inconsistent. The results of the study did not show a clear link between anti-inflammatory and anti-oxidant activity. Further research in potential anti-inflammatory activity of new drugs exhibiting antioxidant properties needs to be done before recommending their use in clinical practice.

Keywords: Anti-inflammatory, anti-oxidant, rat paw oedema, arthritis

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