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The eye lens evaluation of the atorvastatin-treated white rat

The aim of this study is to determinate potential cataractogenic activity of atorvastatin (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor). HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin-statins) are the most potent cholesterol and LDL-C lowering drugs. Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase are effective lipid--lowering agents, extensively used in medical practice. The mode of action is stimulation of the LDL receptor activity in addition to reduction of the assembly and biosynthesis of lipoproteins in the liver. Statins differ in many aspects, such as pharmacological properties (hydrophilic vs. lipophilic, elimination half-time, cytochrome P-450 metabolism, etc.), their kind and intensity of side effects (2, 7, 14). The most potent in their inhibitory action on the HMG-CoA reductase enzyme are atorvastatin and simvastatin. Atorvastatin (Lipitor, Sortis) was developed as an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase for treatment of serum lipid disorders. It is possible that some hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) therapy is associated with cataract occurrence (2, 13). Since Atorvastatin has been only recently introduced, we have relatively small experience in respect of its side-effect. The purpose of these studies was to focus on the potential cataractogenic contribute of atorvastatin.

The cataract is relatively frequent eye lens complication and is the most frequent reason of blindness (15). The etiology of cataract is still not explained. There are theories of genetic, immunological, or metabolic disorders trying to explain the genesis of cataract (8). The nature of cataract is lens' chemical composition changes, Specially reduction of soluble proteins (cystein, glutation), which are necessary to lens' "internal respiration", and excess of non soluble ones. There is observed excess of lipids (cholesterol) and inorganic substances (calcium and phosphorus) concentration in the lens. The shortage of glutation results in reduction of hydrogen out of lens' transportation (being the equivalent of oxygen availability in other tissues). That implies fault carbohydrate oxidization

and lactic acid excess in aqueous (1). Also water presence reduction, resulting in lens' fiber induration, protein disturbances (reduction of gamma and alfa excess, molecular weight excess, aggregation) (8) and red-ox processes disturbance, sulfhydryl group oxygenation, proteolitic enzymes presence (15) are observed. There is the possible role of capsula active membrane transport disorder. That results in glycolysis reduction and sorbitol way of carbohydrates metabolism. Now the role of free radicals is discussed (9). The cataract may be result of metabolic disorders (diabetes, hipocalcemia, galactokinase shortage, Lowe syndrome, morbus Fabry), injury, congenital (chromosome aberrations, rubella), or toxic (steroids, chlorpromazine, cholinesterase inhibitors, Busulfan, Amiodarone, aurotherapy) (5).

The study provides evidence that long-term use of therapeutic statin doses does not increase the risk of developing cataract (12), but the concomitant use of some drugs (e. g. erythromycin and simvastatin) may increase the cataract risk (11).

MATERIAL AND METHODS

The studies were carried out on white Wistar rats – of ca 300 g of body weight. Fifty-six eyes of 28 rats were studied. Animals were given the inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (Sortis – Parke-Davis, USA) in two doses: group I (10 animals) – 1.14 mg/kg mg/day, group II (10 animals) – 11.4 mg/day. The above-mentioned doses correspond to doses of 10 mg (maximal therapeutic dose) and 100 mg/day. The drug was administered intragastrically through a stomach tube, in the form of water suspension (1 ml). The control animals were given respectively distilled H_2O. The drug was applied for the period of 2 weeks. After 2 weeks of drug application 5 animals of every group were sacrificed in ether narcosis and their eyes were taken up. Next 5 animals of every group were sacrificed after 6 weeks (4 weeks after last doses drug administration) and eyes were taken for observation in the microscope. Sixteen eyes of 8 healthy animals were enucleated as a control group. The eye preparations were formalin fixed. The anterior segment of each eye was cut and the lens were taken up for observation. Lens structure was observed in stereoscopic, dark-filed and in optic microscopy.

RESULTS

The cataract was observed in the examined preparations. In group I (1.14 mg/kg) cataract occurred in 5 lens (2 in 2-week group and 3 in 6-week group) – Fig. 1. In group II (11.4 mg/kg) we noticed cataract in 9 lens (5 in 2-week group and 4 in 6-week group) – Fig. 2. Control group: 2 lens had cataract changes. Rat's eye turned out to be reacting to atorvastatin, specially to high doses administered. In the experimental groups we ob-

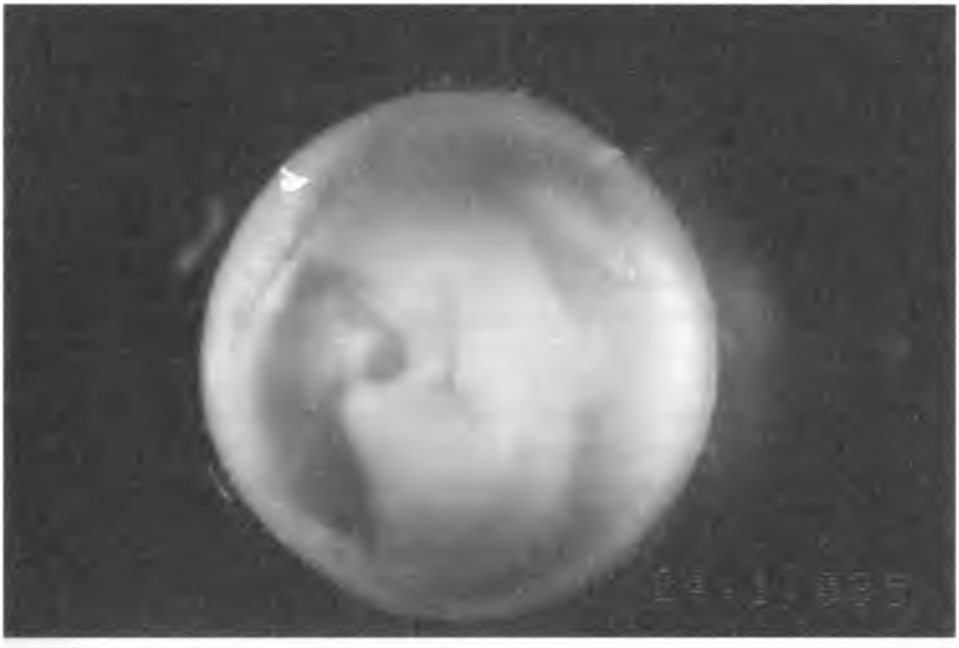

Fig. 1. Experimental group 1.14 mg/kg. Cataract presence in lens

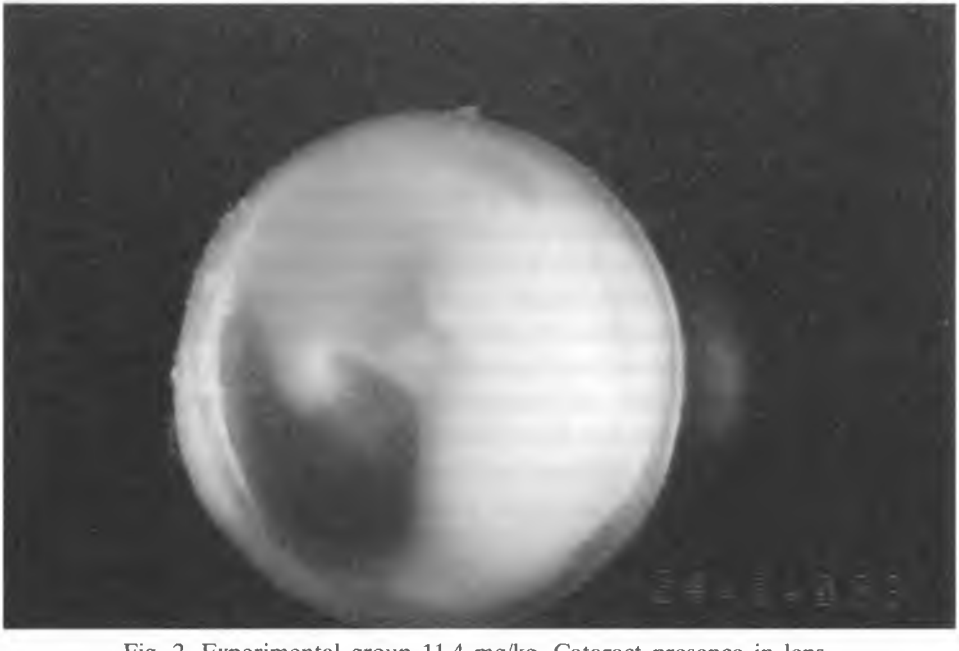

Fig. 2. Experimental group 11.4 mg/kg. Cataract presence in lens.
Duration more significant compared to group 1.14 mg/kg

served dose-related increase in the number and duration of cataract episodes. Changes were more significant in the experimental groups given 11.4 mg/kg. Alterations in the examined lens design may be the result of atorvastatin effect.

DISCUSSION

The studies showed that some hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are associated with cataract in dogs (2). Reductase inhibitors (RIs) except other side-effects, induce cataracts in dogs exposed to relatively high levels of the drugs for extended periods of time (12). Clinical safety data of statins regarding cataract development in humans have been of limited value (13). Some publications inform, that long-term use of therapeutic statin doses does not increase the risk of developing cataract, but the concomitant use of some drugs (e. g. erythromycin) and some statins (simvastatin) may increase the cataract risk (13). The role of cytohrome P450 enzyme system in drug--drug interactions involving HMG-CoA reductase inhibitors has been extensively studied (4). There are also informations about possible differences in possible cataractogenic activity of atorvastatin in this regard (12). However, different statins have different pharmacokinetic properties and variable effectiveness with potential clinical implications and side-effects profile. Differences are also connected with the type of lipophilic or hydrophilic nature and are determinated by the age of the rat (11). Atorvastatin is the last one discovered and there is no sufficient evidence of possible complications. The drug producer informs that atorvastatin application differs in cataract risk compared to other statins. However, because of some cases of other statin-induced cataract in dog's eye there is recommended oculistic examination before application and subsequently each year therapy (6).

The mechanism of potential cataract is not quite known. There is possible the influence of atorvastatin on cholesterol synthesis, cytochrome P450 metabolism. Some evidences of myopathy (common statin therapy complication) and cataract, both caused by the R120G mutation in alphaB-crystallin can be seen. Such desmin-related myopathy is one of several diseases characterized by the coaggregation of intermediate filaments with alphaB-crystallin, and it identifies intermediate filaments as important physiological substrates for alphaB-crystallin (10). Atorvastatin therapy *in vivo* leads to apoptosis (programmed cell death) (3). It may be a possible reason for cataract complications (2). There is also possible the influence of statin on membrane transport in capsule of the lens or oxygen reactive species and red-ox processes disturbance.

CONCLUSIONS

The possibility of lens opacification presence caused by therapeutic and higher doses of atorvastatin were examined in this experiment. As the result of experiment we observed the presence of cataract in atorvastatin treated rats. The duration of cataract related to the drug dose was significant in rats atorvastatin treated with the of 11.4 mg/kg (10 times higher than maximal therapeutic dose of atorvastatin).

The results may contribute to the efficacy and security of atorvastatin therapy, and may add to wider knowledge about the potential risk of statins use, but extensive long-term studies should be performed.

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SUMMARY

The aim of this study is to determine potential cataractogenic activity of atorvastatin the 3-hydroxy-3-methylglutaryl coenzyme A (HMG -CoA) reductase inhibitor. HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin) (statins) are the most potent cholesterol and LDL-C lowering drugs. Statins differ in many aspects e.g. intensity of side-effects. It is possible that some hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) therapy is associated with cataract occurrence. The purpose of these studies was to focus on the potential cataractogenic contribution of atorvastatin. The studies were carried out on white Wistar rats. The animals were given atorvastatin (Sortis – Parke-Davis, USA) in two doses: 1.14 mg/kg mg/day, and 11.4 mg/day. Lens structure was observed in stereoscopic, dark-filed and in optic microscope, the cataract was observed in the examined preparations, specially high doses administered. We concluded that lens turned out to be reacting to atorvastatin. Drug dose coresponded to increase in the number and duration of cataract episodes (changes were more significant in the experimental groups 11.4 mg/kg). Alterations in the examined lens design may be a result of atorvastatin effect.

Wpływ atorwastatyny na zmiany w soczewce oka szczura

Celem niniejszego doświadczenia jest ocena potencjalnego wpływu atorwastatyny – inhibitora reduktazy 3-hydroxy-3-methylglutaryl koenzymu A (HMG -CoA) na powstawanie zaćmy. Inhibitory reduktazy HMG-CoA (atorwastatyna, lowastatyna, simwastatyna, prawastatyna, fluwastatyna, ceriwastatyna) – statyny – są lekami silnie obniżającymi poziom cholesterolu i LDL-C. Statyny różnią się między sobą pod wieloma względami, m. in. nasileniem i rodzajem działań ubocznych. W przebiegu terapii statynami możliwe jest wystąpienie m. in. zaćmy soczewki oka. Celem obecnej pracy jest zbadanie potencjalnego pojawienia się zaćmy w przebiegu stosowania atorwastatyny. Badanie przeprowadzono na szczurach rasy białej Wistar. Zwierzętom podano atorwastatynę (Sortis – Parke-Davis USA) w dawce 1,14 mg/d oraz 11,4 mg/d. Zmiany w soczewce obserwowano w mikroskopie świetlnym i stereoskopowym. Zaobserwowano zaćmę w badanych preparatach, zwłasz-

cza w grupie większej dawki leku. Potwierdzono hipotezę, że atorwastatyna może wywoływać zmiany w soczewce oka. Liczba zmienionych soczewek i nasilenie zmian korespondowały z dawką leku (zmiany były bardziej nasilone w grupie wyższej dawki). Zaobserwowane zmiany w obrazie soczewek mogą być efektem działania atorwastatyny.