World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:15, No:05, 2021

Spectroscopic Study of the Anti-Inflammatory Action of Propofol and Its Oxidant Derivatives: Inhibition of the Myeloperoxidase Activity and of the Superoxide Anions Production by Neutrophils

Authors : Pauline Nyssen, Ange Mouithys-Mickalad, Maryse Hoebeke

Abstract : Inflammation is a complex physiological phenomenon involving chemical and enzymatic mechanisms. Polymorphonuclear neutrophil leukocytes (PMNs) play an important role by producing reactive oxygen species (ROS) and releasing myeloperoxidase (MPO), a pro-oxidant enzyme. Released both in the phagolysosome and the extracellular medium, MPO produces during its peroxidase and halogenation cycles oxidant species, including hypochlorous acid, involved in the destruction of pathogen agents, like bacteria or viruses. Inflammatory pathologies, like rheumatoid arthritis, atherosclerosis induce an excessive stimulation of the PMNs and, therefore, an uncontrolled release of ROS and MPO in the extracellular medium, causing severe damages to the surrounding tissues and biomolecules such as proteins, lipids, and DNA. The treatment of chronic inflammatory pathologies remains a challenge. For many years, MPO has been used as a target for the development of effective treatments. Numerous studies have been focused on the design of new drugs presenting more efficient MPO inhibitory properties. However, some designed inhibitors can be toxic. An alternative consists of assessing the potential inhibitory action of clinically-known molecules, having antioxidant activity. Propofol, 2,6-diisopropyl phenol, which is used as an intravenous anesthetic agent, meets these requirements. Besides its anesthetic action employed to induce a sedative state during surgery or in intensive care units, propofol and its injectable form Diprivan indeed present antioxidant properties and act as ROS and free radical scavengers. A study has also evidenced the ability of propofol to inhibit the formation of the neutrophil extracellular traps fibers, which are important to trap pathogen microorganisms during the inflammation process. The aim of this study was to investigate the potential inhibitory action mechanism of propofol and Diprivan on MPO activity. To go into the anti-inflammatory action of propofol in-depth, two of its oxidative derivatives, 2,6-diisopropyl-1,4-p-benzoquinone (PPFQ) and 3,5,3’,5’-tetra isopropyl-(4,4’)-diphenoquinone (PPFDQ), were studied regarding their inhibitory action. Specific immunological extraction followed by enzyme detection (SIEFED) and molecular modeling have evidenced the low anti-catalytic action of propofol. Stopped-flow absorption spectroscopy and direct MPO activity analysis have proved that propofol acts as a reversible MPO inhibitor by interacting as a reductive substrate in the peroxidase cycle and promoting the accumulation of redox compound II. Overall, Diprivan exhibited a weaker inhibitory action than the active molecule propofol. In contrast, PPFQ seemed to bind and obstruct the enzyme active site, preventing the trigger of the MPO oxidant cycles. PPFQ induced a better chlorination cycle inhibition at basic and neutral pH in comparison to propofol. PPFDQ did not show any MPO inhibition activity. The three interest molecules have also demonstrated their inhibition ability on an important step of the inflammation pathway, the PMNs superoxide anions production, thanks to EPR spectroscopy and chemiluminescence. In conclusion, propofol presents an interesting immunomodulatory activity by acting as a reductive substrate in the peroxidase cycle of MPO, slowing down its activity, whereas PPFQ acts more as an anti-catalytic substrate. Although PPFDQ has no impact on MPO, it can act on the inflammation process by inhibiting the superoxide anions production by PMNs.

Keywords : Diprivan, inhibitor, myeloperoxidase, propofol, spectroscopy
Conference Title : ICI 2021 : International Conference on Inflammation
Conference Location : Amsterdam, Netherlands
Conference Dates : May 13-14, 2021