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

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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 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 in assessing the potential inhibitory action of clinically-known molecules, having an antioxidant activity. Propofol, 2,6-diisopropylphenol, which is used as intravenous anesthetic agent, meets these requirements. Besides its anesthetic action employed to induce 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 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-benzquinone (PPFQ) and 3,5,3',5'-tetraisopropyl-(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 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 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

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