NEW FORMULATIONS FOR THE CONTROLED LOCAL ANESTHETICS IN DENTISTRY: FROM DEVELOPMENT TO CLINICAL TESTS

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The structure and physicochemical features of local anesthetics (LA) are determinant for their potency and toxicity. Water solubility is, for instance, an essential parameter for the transport of the anesthetic molecule to the nerve fibers as well as to the ionization equilibrium that guarantees the existence of both ionized and non-ionized LA forms on the site of action. On the other hand lipid solubility is also crucial for drug partitioning into the axon, so that enough amounts of LA molecules will sit inside that membrane in order to keep the sodium channel in its non-conducting state. The development of new LA formulations is nowadays a challenge in dentistry. Liposomes are interesting drug-delivery systems for LA since they enhance the availability of compounds, reduce their systemic toxicity and increase their half-life in vivo. Similar advantages have been claimed for cyclodextrin formulations of poorly water-soluble anesthetics, for hydrogel formulations and, more recently, for LA in polymers. We intend in this project to develop new pharmaceutical forms for the controlled release of classic LA molecules, in vehicles such as liposomes, cyclodextrins, gels and polymers. Our aim is to enhance the pharmacological actions and to reduce the local and systemic toxicity of LA, looking forward to a future application in dentistry. The potentiality of this kind of project can be understood by the dimensions of the local anesthetics market in Brazil: ca. US$ 12.5 billion per year, according to the Brazilian Pharmaceutical Industry Association. Researches designed to develop new pharmaceutical forms have, necessarily, an interdisciplinary approach such as ours, due to the different stages of the research involved: technological development, physicochemical characterization, scale up and clinical steps. The development of these stages is the focal point of this thematic research.
**SUMMARY OF RESULTS TO DATE AND PERSPECTIVES**

In this first year of the thematic research project we have obtained results with different approaches, reflecting the multidisciplinary vocation of the project: molecular details on the interaction of local anesthetics and membranes; development (preparation, physicochemical characterization); *in vitro* toxicity tests, biologic activity tests in animals and clinical tests; all of which were carried out with new pharmaceutical forms substitute for classic local anesthetics.

a) On the mechanism of action of local anesthetics – By using Nuclear Magnetic Resonance (NMR) we have demonstrated the interaction of benzocaine and lidocaine with a peptide belonging to the inner cytoplasm linker between helices S4-S5, domain IV, of the voltage-gated sodium channel. Those LA interact with specific residues of the linker are known to be important for the stabilization of the protein in its inactivated (non-conducting) state. In a similar approach we have employed different spectroscopic techniques such as NMR, Electron Paramagnetic Resonance and Fluorescence to detect changes in the organization and dynamics of the lipid phase of model membranes after treatment with LA. The results allowed us to propose the existence of transient sites, specific for each LA molecule (lidocaine, etidocaine, mepivacaine, bupivacaine), that should determine their access to the sodium channel site.

b) Development and physico-chemical characterization of drug-delivery systems (liposomes, cyclodextrin, liposome gels) of local anesthetics – We have developed liposome local anesthetic formulations for mepivacaine, lidocaine and prilocaine. In this period we have also characterized the formation of supramolecular complexes between beta-cyclodextrins and LA such as bupivacaine, ropivacaine, lidocaine, tetracaine and benzocaine by employing diverse techniques. We have also developed gel formulations of local anesthetics (within or without liposomes) for topical use (pre-anesthesia) in dentistry, which resulted in the application of a patent report to the INPI/Brazil. Finally, we have also started studies for the future development of polymeric nanoparticles to carry local anesthetics.

c) Biologic activity tests – The anesthetic effect of the new formulations was evaluated through the infraorbital nerve blockage test in animals. The results for lidocaine, mepivacaine, prilocaine and ropivacaine revealed an increase in the time of anesthesia for all the liposome formulations. The *in vitro* toxicity of the formulations was tested in cell cultures. The *in vivo* local toxicity was evaluated through histological analysis in muscles and nerve tissues (Cereda et al, submitted).

d) Pre-clinical / clinical trials – With the approval of the Ethical Committee of Piracicaba School of Dentistry, University of Campinas, Brazil, up to now we have finished two clinical trials with healthy volunteers, showing an increase in time of anesthesia with liposomal formulations of ropivacaine and benzocaine (Silva et al, submitted), for topical use.

**MAIN PUBLICATIONS**


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