in vitro and in vivo Studies of Silica Xerogels for the Controlled Release of Bupivacaine

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Statement of Purpose: Bupivacaine is an amino-amide local anesthetic commonly used for pain control in patients undergoing elective and emergent surgery. Direct injection bupivacaine solution provides local analgesia for approximately 2-3 hr [1]. Bupivacaine delivered continuously is a very attractive goal for both acute and chronic pain management. With the ultimate goal of reducing morbidity and decreasing post-operative narcotic use, we have been pursuing prolonged controlled release of bupivacaine. Herein we used room temperature processed sol-gel silica-based xerogels, a novel class of controlled-release materials, as the carrier material and determined *in vitro* release kinetics. These data then formed the basis for a first *in vivo* dose response study.

Methods: Bupivacaine contained silica xerogel was prepared at room temperature via a one step acid catalyzed sol-gel process [2]. Tetraethoxysilane (TEOS, Strem Chemicals), de-ionized water and hydrochloric acid were mixed and stirred to form an acid-catalyzed sol. Bupivacaine was dissolved in methanol first and the bupivacaine-methanol solution was added to the sol. The concentration of added bupivacaine to the final silica xerogels was 9.1 or 13 wt%. Upon mixing, the sol was cast into cylindrical polystyrene vials. The vials were sealed and the sols were allowed to gel, age and dry at 37°C. The dried xerogel disks were then crushed into granules. The crushed silica granules were sieved by nylon meshes to obtain granules in the range 20-150 μm.

In vitro study: The *in vitro* release kinetics was studied using phosphate buffered saline (PBS). Twenty five mg of bupivacaine-loaded xerogel granules were immersed in triplicate in 5 ml PBS (pH=7.4, Gibco) at 37°C (5 mg/ml) and the solutions were exchanged daily up to seven days. The concentration of released bupivacaine was measured using a UV-Vis spectrophotometer (Ultrospec Plus) at 265 nm.

In vivo study: The rat model of (hindpaw) incisional pain described by Brennan et al. [3] was used for studying tactile hypersensitivity. Male Sprague Dawley rats (220-240 g, Ace Laboratories) were acclimated to individual Plexiglas observation boxes. The floor of each box consisted of smooth wire mesh so that a series of von Frey monofilaments could be presented (perpendicularly) to the plantar surface of both hindpaws immediately before isoflurane inhalation and surgery. Two experimental groups (n=8) received different doses xerogel containing bupivacaine, via a small syringe, directly in the incision. Two control groups (n=8) received either sham surgery or surgery with implantation of silica xerogel lacking bupivacaine. Tactile sensitivity was evaluated at +0.5, 1, 1.5, 2, 3 and 18hr and paw withdraw thresholds were calculated by the method of Chaplan et al. [4]

Results: The *in vitro* results (Figure 1) show that bupivacaine was continuously released from silica xerogel granules in a controlled manner for 7 days. Higher concentrations of bupivacaine were released within the first day as drug load in the particles increased.

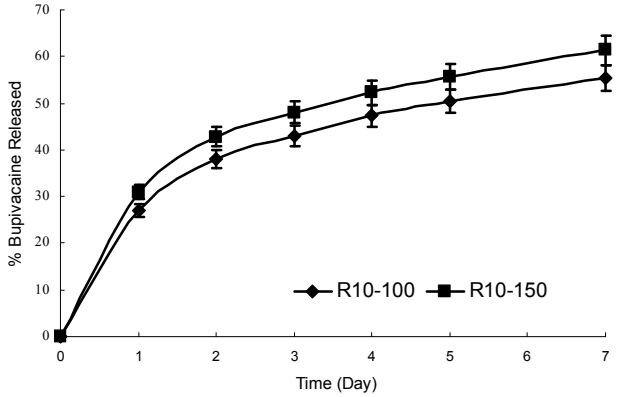

Figure 1 The cumulative release patterns of bupivacaine from xerogel granules.

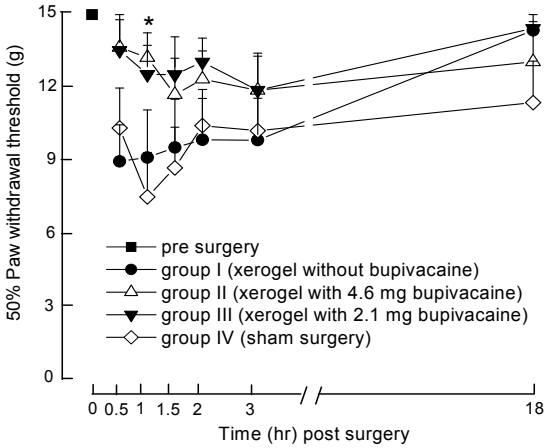

Figure 2. Attenuation of mechanical hypersensitivity in rats receiving bupivacaine loaded xerogel granules (groups II and III) relative to control groups I and IV ($p<0.05$, ANOVA and Newman-Keuls)

Conclusions: The in vitro and in vivo studies have shown that sol-gel derived silica xerogel is a promising controlled release carrier for the local anesthetic bupivacaine.

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References:

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