A Multifaceted Approach to Post Operative Adhesion Prevention

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Statement of Purpose: Use of bioactive agents in absorbable gel-forming liquid copolyesters for post-operative adhesion prevention (PAP) was reported earlier [1,2]. Until recently, most studies focused on using gel formers as protective barriers and a pharmacological adjuvant to interfere with deposition of fibrous tissue about the surgical site[2]. Results of the studies led to the identification of promising systems for PAP based on a combination of A-B-A block copolyesters of polyethylene glycols (PEG) and the anti-angiogenic lanreotide (LN) or the non-steroidal anti-inflammatory naproxen (NP) as an adjuvant [2]. This and recent interest in multifaceted PAP systems[3] prompted the pursuit of present study, which deals with using an optimized gel forming barrier with selected combinations of LN and NP in rats and rabbits.

Methods: LN and NP were procured and two A-B-A copolymers (W3 and W4) of end grafted PEG 600 with a mixture of trimethylene carbonate (TMC) and glycolide (G) were prepared. Sprague Dawley rats and New Zealand white rabbits were used in sets of at least five animals per experiment.

The block copolymers were prepared by end-grafting PEG 600 with a mixture of TMC and G as described earlier[1-3] to produce W3 and W4 as moderately and highly hydrophilic copolymers, respectively, by adjusting the PEG/cyclic monomer ratio. Combinations of NP and LN with W3 and W4 were mixed as described earlier[2] to produce the desired formulations, one of which was selected for use in the present study. This consists of a mixture of 80/20 (wt %) W3/W4 copolymers containing 2.5 mg LN and 0.5 mg NP per gram of polymers. LN was dispersed in the gel formulations used in rats and pilot rabbit studies. However, for the final rabbit study, LN was dissolved in sterile H_2O and added to the mix. The NP was used as a 50/50 mixture of its sodium salt and free acid dissolved in W4. For rat surgical procedure, abdominal cavity was opened and inner abdominal wall exposed. Using a scalpel, a 1 cm^2 area of mucosal lining of the inner abdominal wall was delaminated and peeled off. The area was lined with 6-0 silk suture and covered with 0.1 mL formulation, irrigated with saline, and then allowed to set for 3 minutes. Abdominal cavity was then closed and the rat recovered. After one week the rat was euthanized and examined for adhesions. The pilot rabbit surgical procedure was similar to that of the rat with the exception of using four 1 cm^2 defects in the abdominal wall (two on each side), each of which was covered with 0.2mL of gel-forming formulation for a total dose of 8 times that used in rats. Due to absence of discernable adhesions in both sets of rabbits treated with active formulation as well as untreated controls, the pilot surgical protocol was modified significantly as follows: The rabbit abdominal cavity was opened along linea alba one inch below rib cage and opened in order to expose the inner abdominal sidewall. An area of ~ 3cm by 5 cm with the long axis parallel to incision is chosen for the site. The area is lined with 4-0 silk suture by placing a knot at one corner and then running a continuous suture line to the next corner and knotting it. The rectangle is completed with a knot at each corner and two knots at the original point. The area in rectangle is brushed with a stiff brush to disturb the mucosal membrane and two interrupted silk knots are spaced between each corner. After placing the silk, a cross in center of rectangle was made with 2-0 plain gut suture with knots at intersection of rectangle perimeter. A single interrupted gut knot is placed in center of cross. This procedure is repeated on opposite side of abdominal cavity. The cecum is then externalized and brushed with surgeon scrub brush on both sides (15 strokes each). The colon is externalized and two areas of approximately six segments receive 15 strokes on each side. The cecum, colon, and related structures are placed back into cavity and the silk lined rectangle is exposed. One mL of formulation is placed evenly on the rectangle, irrigated with saline, and held open for two minutes. The abdominal wall is released and this process is repeated on the other side. The abdominal cavity is closed with 2-0 vicryl and the subcutaneous tissue is closed with 4-0 PDS. The skin was closed using Tissumend II Sterile tissue adhesive. The rabbits recovered and after one week the rabbit were euthanized and examined for presence of adhesions. In the absence (control) and presence of active formulations substantial and practically no adhesions were observed, respectively.

Results / Discussion: Using the rat surgical protocol and associated formulation, with the solid LN dispersed in the gel former indicated that combined dosage form is effective in reducing significantly the incidence of adhesion using rat side wall model as compared to controls. Applying same surgical protocol to the rabbit side wall using an enlarged defect area failed to result in any discernable signs of adhesion in both treated and untreated animals. However, using the modified, more aggressive surgical protocol led to substantial adhesion formation in untreated animals. Preliminary results on the use of combined agents (with LN pre-dissolved prior to mixing into the formulation) appear to significantly reduce incidence of adhesion formation.

Conclusions: Available results using the side wall model suggest that (1) development of adhesion in rabbits is more difficult than in rats and (2) the multifaceted approach to PAP is effective in a simple rat and a more aggressive rabbit model.

References:

1.Shalaby, S. W. U.S. Patent 5,714,159 (1995).
2. Corbett, J.T., et al. Trans. Soc. Biomat, 25, 141, 2002; 26, 99 (2003).
3. Shalaby, S.W. U.S. Patent 6,551,610 (2003).

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