The safety evaluation of DepoBupivacaine™ administered by incision wound infiltration in rabbits and dogs

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Bupivacaine is used widely for infiltration analgesia, but local and systemic effects occurring from this route of administration may impact its use. DepoBupivacaine (DB; bupivacaine extended-release liposome injection) using multivesicular DepoFoam™ technology (Angst et al., 2006) is in development for prolonged postoperative analgesia following wound infiltration. Studies were conducted in rabbits and dogs, according to Good Laboratory Practices, to evaluate the potential local and systemic toxicity and any effect on wound healing after local infiltration of DB into a surgical wound (incision) site. Groups of New Zealand White rabbits (body weight: 2.6-3.7kg) and beagle dogs (body weight 6.2-9.7kg) (4/sex/group) received DB 9, 18, or 30 mg/kg, conventional (nonliposomal) bupivacaine HCl solution (Bsol; 7.5 mg/mL, 9 mg/kg), or saline control. Two concentrations of DB were tested (25 mg/ml, 15 mg/ml) with the higher concentration included to achieve a systemic exposure level of 30 mg/kg. Pre-operative medications included atropine sulfate, ketamine and/or propofol. General anesthesia was induced via isoflurane inhalation. In order to simulate a hernia, a skin incision was made over the left inguinal canal, the external and internal inguinal rings were located, and a blunt dissection performed into the canal all the way into the peritoneal cavity. The hernia was closed by a layered closure of the fascia/aponeuroses of the muscles plus the inguinal ligament. All treatments were administered once on day 1. Each dose was divided into eight equal volumes. Four injections were administered in the muscle fascia around the surgical mesh, and four more injections were given in the area surrounding the incision repair. Endpoints included body weights, food consumption, clinical pathology, and histopathology examination of a full range of tissues, and toxicokinetic analysis on day 1. Histopathology examination of a full tissue list including surgical sites was performed on day 3 or day 15 (2/sex/group per period). Macroscopic examinations of wound healing were measured and recorded from day 2 through day 15. No group differences were detected that would indicate local toxicity. There were no DB-related adverse findings in either species. In rabbits, surgical site histological findings at day 3 and day 15 were typical of surgical wound healing. Except for granulomatous inflammation (GI), which was observed in 8 of 24 animals receiving DB, there were no differences in overall incidence or severity of histologic changes in the surgical site between animals receiving DB and the saline or Bsol groups. With the low severity, GI was considered most likely a reaction to the liposomes, and not adverse. In dogs, surgical site histologic changes at day 3 and day 15 were indicative of normal wound healing across the groups. There was no adverse effect on wound healing or immune competence in either species. The attenuation of Cmax with DB vs. Bsol was ~ two- to sixfold, i.e., Cmax = 107±27.6 vs. 620±89.9 ng/mL (rabbit) and 536±484 vs. 931±396 ng/mL (dog) (n=4, combined data for sexes; mean and standard deviation, p<0.05, Student’s t test). This suggests a safety factor of the same magnitude for DB as compared with Bsol at the same dose. The data reported here are the first demonstration of the safety of DB in infiltration models in relevant toxicology species. Based on preclinical data, DB does not produce a burst release of bupivacaine, and poses no risk beyond that of Bsol. DB has a low potential for producing adverse local or systemic effects when administered as a single dose.