

Bupivacaine Extended Release Liposome Injection Does Not Prolong QTc Interval in a Thorough QT/QTc Study in Healthy Volunteers

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Keywords: EXPAREL; bupivacaine; moxifloxacin; clinical trial; healthy subject; QTc

Journal of Clinical Pharmacology, XXXX;XX:xxx-xxx
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Following surgery, effective postsurgical pain management is essential because most patients experience pain that often persists for several days or even weeks. For a wide range of surgical procedures, local anesthetics administered via an epidural injection, peripheral nerve blocks, or local infiltrations are commonly used to provide postoperative analgesia. However, the duration of analgesic action of local anaesthetics is typically less than 12 hours.¹ Bupivacaine is among the most widely used long-acting local anesthetics with its moderate onset and long duration of action demonstrated in preclinical and clinical studies.^{2,3} However, longer acting local anesthetics are known to induce systemic toxicity, mostly in relation to the central nervous system (excitation) and cardiovascular system (depression).^{2,3}

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DOI: 10.1177/0091270011419853

The cardiotoxicity of bupivacaine and its effects on the QTc interval have been demonstrated in preclinical studies. Besides its known sodium channel-blocking properties, it has been shown to block calcium and potassium channels. The effects of bupivacaine on human cloned cardiac delayed rectifier potassium channels have been described by Gristwood.³ Blocking potassium channels can lengthen cardiac action potential, leading to serious arrhythmias.³ One study in dogs showed that administration of 4 mg/kg bupivacaine significantly prolonged the QTc interval by more than 25%.⁴ Cardiovascular effects of bupivacaine were also demonstrated in clinical studies. In one such study, patients were administered 40 mL of bupivacaine 5 mg/mL for scheduled shoulder arthroscopy. A significant prolongation of the PQ interval was seen 125 minutes postapplication of bupivacaine, which remained significantly prolonged until 6 hours post-dose.⁵ Double-blind crossover studies in healthy human volunteers have demonstrated that a maximum dose of 48 mg bupivacaine (maximum plasma concentration of 2.25 mg/L) significantly increased the QTc interval by 26.9 ms.⁶ Another study showed that in subjects receiving more than 75 mg bupivacaine, the maximum increase in the QTc interval was 24 ms ($P = .022$).⁷

EXPAREL, a new formulation of bupivacaine, given as a single injection after surgery, could provide adequate, continuous, and extended pain relief,