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(Abstracts)

Contents

Long-Lasting Sensory Block Produced by Quaternary Lidocaine Derivatives: Efficacy and Safety of QX-572, QX-222, and QX-314 in Mice

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Introduction: QX-314, one of several quaternary derivatives of lidocaine, produces long-lasting sensory blockade with a delayed onset in animals.[1; 2] These findings indicate a potential of quaternary compounds as long-lasting local anesthetics. However, subsequent animal studies on intrathecal and systemic administration have raised concerns about toxicity due to QX-314.[3; 4] Here, we sought to explore the comparative actions of two other quaternary lidocaine derivatives, QX-572 and QX-222, whose efficacy and toxicity profiles for long-lasting sensory blockade have not been studied. We hypothesized that QX-572 and QX-222, similar to QX-314, produce long-lasting sensory blockade and possess more favorable toxicity profiles.

Methods: Ethics approval was received from the local ACC. We conducted a randomized, double-controlled, and blinded in vivo study in female CD-1 mice. To assess sensory blockade, we used a modified tail flick assay[5] to record tail flick latencies (TFLs) to thermal noxious stimuli (50 °C water). Mice were injected with 40 µL of test solution at the base of the tail. Tail immersion was repeatedly performed to determine sensory blockade (defined as a TFL > 4 s) duration (each concentration, n = 8). To assess local tissue toxicity, tails were collected 24 h post-injection, sectioned, hematoxylin and eosin stained, and prepared for histopathological analyses. Additionally, to quantify systemic absorption, we developed, validated, and utilized a novel liquid chromatography tandem mass spectrometry (LC-MS/MS) method. For analysis, we log-transformed time-to-event data and used ANOVA with Dunnett's post-hoc multiple comparisons test; we calculated potencies from concentration-response curves fitted using non-linear regression.

Results: QX-572 (at ≥ 70 mM) and QX-222 (at ≥ 280 mM) concentration-dependently produced sensory blockade similar to QX-314 (≥ 70 mM), with a delay to onset compared to lidocaine (70 mM [~2%]). The order of potency was QX-572 > QX-314 > QX-222. All quaternary compounds

concentration-dependently produced tissue discoloration, edema and scarring at the site of injection (QX-572, ≥ 70 mM; QX-314; ≥ 140 mM; and QX-222, ≥ 560 mM). Histopathological analyses revealed myofiber degeneration and inflammation. QX-314 at ≥ 140 mM and QX-222 at 560 mM, but not QX-572 (max., 280 mM), produced systemic toxicity that manifested as death. LC-MS/MS indicated a higher magnitude of systemic absorption following peripheral administration of QX-314 and QX-222 compared to lidocaine.

Conclusion: Similar to QX-314, QX-572 and QX-222 produced long-lasting sensory blockade with a delay to onset compared to lidocaine. QX-572 produced no apparent systemic toxicity but its lowest effective concentration was associated with local tissue toxicity; higher concentrations produced irreversible blockade. QX-314 and QX-222 at high concentrations produced local and, counterintuitively, systemic toxicity. While these results suggest a potential for quaternary compounds as long-lasting LAs, toxicity associated with differences in chemical structures is of concern and warrants further study.

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Stability of Reconstituted Remifentanil in Normal Saline Polyvinyl Chloride Bags Stored at Either Room Temperature or 4°C

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Introduction: Remifentanil, a potent synthetic opioid, is reconstituted and diluted to the desired concentration. The manufacturer recommends that reconstituted remifentanil should be disposed of after 24 hours, yet limited data exists regarding the drug's long-term stability. Bevans-Warren et al. recently showed that remifentanil mixed to 100 µg/mL in plastic syringes stored at room temperature (RT) is stable at 45 days[1]. Here, we investigate the stability of remifentanil diluted to 10 µg/mL in 0.9% sodium chloride PVC bags at both RT and 4°C over 30 days.

Methods: Ethics approval was not applicable because the study did not involve human or animal research. 1 mg remifentanil vials were reconstituted with 1 mL of sodium chloride 0.9% and then diluted to 10 µg/mL in 100 mL 0.9% sodium chloride PVC bags. Bags were stored at either RT (23-25°C) or 4°C (3 bags per group). 1 mL aliquots were collected for analysis at 0 hours, 24 hours, 48 hours, and 30 days and frozen at -80°C.

Samples were analyzed via liquid chromatography with tandem mass spectrometry (LC/MS/MS). Remifentanil (100 µg/mL in methanol) and fentanyl (1 mg/mL in methanol) were used to obtain calibration standards over the range 0.02 ng/µL to 1 ng/µL remifentanil. 2 µL of sample solution was injected onto an Agilent Poroshell 120 2.7 µm SB-C18 column at a flow rate of 0.5 mL/min using a gradient of 90% water (0.1% formic acid) 10% acetonitrile (0.1% formic acid). Chromatogram peak areas were used to determine the concentration of remifentanil in each sample.

Data was analyzed using mixed effects modelling (restricted maximum likelihood approach) for within group and between group comparisons with time and temperature as factors. Percent remifentanil degradation was calculated with the starting concentrations as the baseline. The product was deemed stable if there was <10% degradation[2].

Results: The reconstituted remifentanil showed a significant difference in measured concentrations in both groups over time (p=0.001). There was also a significant difference in measured concentrations at baseline [MD (95% CI): 0.017 (0.005, 0.03)] (p= 0.007) but not at other time points between group comparison. The percentage decline in remifentanil concentration was significantly higher at 30 days in RT (-22.47%) compared to 4°C (+5.6%), but

not at 24 or 48 hour timepoints where they did not show any significant degradation (RT: 24h +19.40%, 48h +5.25%; 4°C: 24h +8.85%, 48h +4.19%).

Conclusions: Mixing and dilution of remifentanil by the anesthesiologist may result in inaccurate baseline concentrations when employing routine reconstitution methods in the operating room. Reconstituted remifentanil stored at room temperature may show similar stability to that stored at 4°C but showed significant degradation when stored long term (30 days). This has important environmental and economic implications to practice[3].

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The Comparison Effect of Intravenous Injection of Dexmedetomidine, Ondansetron and Pethidine on Postoperative Shivering Among Patients Under Abdominal Surgery

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Introduction: Postoperative shivering is a common complication of various surgical, so far no acceptable theory has been presented on the prevention of it. The aim of this study was to compare the effect of intravenous injection of, Dexmedetomidine, ondansetron and Pethidine on postoperative Shivering among patients under Abdominal Surgery.

Methods: Ethics approval was obtained from the ethics committee of Isfahan University of Medical Sciences. (IR.MUI.MED.REC. 1398.3.182)

In a double-blind clinical trial study, 128 patients undergoing abdominal surgery were selected and randomly divided into four groups of 32. In the 4 groups 0.5 Mg/kg dexmedmotidine, 0.5 mg / kg pethidine, 0.1 Mg / kg Ondansetron and the same volume of normal saline were injected intravenously when anesthetics were discontinued and the incidence and severity of postoperative shivering were determined and compared in four groups.

Results: The incidence of postoperative shivering was 12.5% in the dexmedmotidine group, 31.3% in the Ondansetron group, 31.3% in the pethidine group and 50% in the control group (P = 0.015). The mean of shivering severity in the four groups was 1.33 ± 0.5, 0.17 ± 0.8, 1.09 ± 0.4 and 1.13 ± 0.39, and the difference between the four groups was significant (P=0.005).

Discussion: The use of all three drugs of Dexmedetomidine, Ondansetron and pethidine are effective in decreasing the incidence of postoperative shivering, but the use of dexmedetomidine is associated with less postoperative shivering, better hemodynamic stability, and fewer other postoperative complications.

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