Pharmacokinetic and Analgesic Properties of Inhaled Remifentanil

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Introduction: Anesthesia practice could benefit from availability of a conveniently deliverable, non-invasive, short-acting, highly efficacious, and easily titratable analgesic/sedative. Remifentanil is clinically advantageous due to its rapid elimination profile. Dosing via spontaneous, respiration would inherently and safely control duration and level of analgesia via patient minute ventilation. For the first time, patients could benefit from an inhaled opioid for routine, but uncomfortable, clinical procedures.

Methods: Using a whole-body rat exposure chamber, a dose-response relationship was established for inhaled remifentanil. Aerosol concentrations (0-2mg/mL) were compared using a tail flick meter to objectively measure analgesic response. Fixed exposure time (5 min) was used to quantify the depth of analgesia. Pharmacokinetic analysis was performed to quantitate remifentanil and metabolites in rat blood using liquid chromatography/mass spectrometry. Blood sample esterase activity was immediately ceased by mixing blood with n-butyl chloride, followed by remifentanil and metabolite extraction for analysis.

Results: Inhaled remifentanil produced a dose-dependent increase in analgesia in rats. Statistical difference in pain responses occurred using 500 and 750mcg/mL aerosol concentrations compared to saline control ($p<0.01$, $n=4$, ANOVA with Bonferroni's multiple comparison testing). Statistical difference was also found between saline control and 1 and 2mg/mL ($p<0.001$ $n=4$). 1mg/mL was found to be dose of maximal analgesic response using the tail flick meter. Onset of action was rapid (2 min) with recovery within 5 minutes after cessation of the aerosol delivery. Remifentanil, the de-esterified metabolite (GI-90291), and the N-dealkylated metabolite (GI-94219) were detectable in rat blood drawn 5 min after pulmonary exposure to remifentanil using LC/MS^2.

Discussion/ Conclusion: Remifentanil is bioavailable and efficacious via inhalation. Rats achieved maximal analgesia within 2 min of a 5 min exposure period to an aerosol concentration generated from 1mg/mL solution. Recovery occurred within 3-5 min after exposure. Remifentanil and metabolites were detectable and quantifiable in rat blood following pulmonary exposure using LC/MS^2. Rats appeared unaffected by repeated exposures, as body weights were comparable among control and exposed animals. The animals continued to socialize and behave normally. No deaths or apparent illness occurred. Histology appeared normal.

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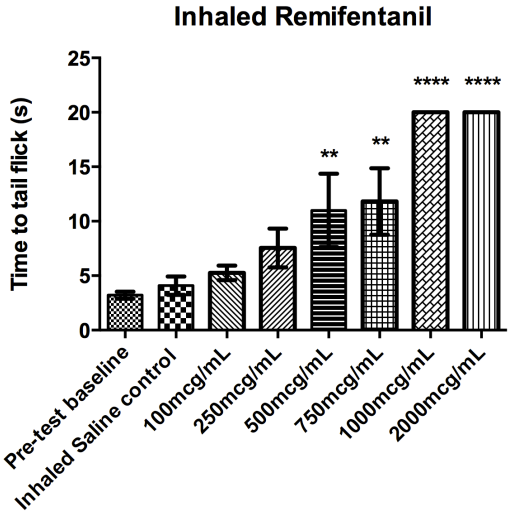

Maximum test duration 20 s. ****Indicates significant difference from baseline and saline control, $p<0.0001$. **Significant difference from pre-test baseline and inhaled saline compared to 2000mcg/mL $p<0.01$. n=4 in all groups.