Opioids in treated and untreated obstructive sleep apnea: Remifentanil pharmacokinetics and pharmacodynamics

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Background: Patients with obstructive sleep apnea (OSA) are considered more sensitive to opioids and at increased risk of opioid-induced respiratory depression. Whether OSA treatment (continuous positive airway pressure, CPAP; or bilevel positive airway pressure, BIPAP) modifies this risk remains unknown. Greater opioid sensitivity may arise from altered pharmacokinetics or pharmacodynamics. This preplanned analysis of a previous cohort study of remifentanil clinical effects in OSA tested the hypothesis that pharmacokinetics and/or pharmacodynamics of remifentanil, a representative μ-opioid agonist, are altered in adults with treated or untreated OSA.

Methods: A single center, prospective, open-label, cohort study (ClinicalTrials.gov, NCT02898792) administered a stepped-dose, target-controlled remifentanil infusion (target effect-site concentrations 0.5, 1, 2, 3, 4 ng mL^{-1}) to awake adult volunteers (median 52 yr, range 23-70) without OSA (n=20), untreated OSA (n=33), and treated OSA (n=21). Type III (in-home) polysomnography verified OSA. Remifentanil plasma concentrations, end-expired CO_2, thermal heat tolerance, and pupil diameter (miosis) were assessed. Population pharmacokinetic (clearance, volume of distribution) and pharmacodynamic (miosis, thermal heat tolerance, end-expired CO_2) models were developed.

Results: Remifentanil clearance (median) was 147, 143, and 155 L h^{-1} (P=0.472), and volume of distribution was 19.6, 15.5, and 17.7 L (P=0.473) for subjects without OSA, untreated OSA, and treated OSA, respectively. Total body weight was an influential covariate on both remifentanil clearance and central volume of distribution. There were no statistically or clinically significant differences between the three groups in miosis EC_{50} or Emax, or the slopes of thermal heat tolerance or end-expired CO_2 vs remifentanil concentration. At a plasma remifentanil concentration of 4 ng mL^{-1}, in participants without OSA, untreated OSA, and treated OSA,

respectively model-estimated pupil area (12, 13, and 17% of baseline, P=0.086), thermal heat tolerance (50, 51 and 51°C, P=0.218) and end-expired CO_2 (47, 48, and 50 mmHg, P=0.257) were not statistically different between groups.

Conclusions: OSA (untreated or treated) did not influence remifentanil pharmacokinetics or pharmacodynamics (miosis, analgesia, respiratory depression). Results do not support the hypothesis that pharmacokinetics and/or pharmacodynamics of remifentanil, a representative μ-opioid, are altered in adults with treated or untreated OSA. Remifentanil dosing may not need adjustment for pharmacokinetic or pharmacodynamic considerations in OSA.