**INTRODUCTION**

Opioid effects are potentiated by cannabinoids by synergistic interactions at the receptor and/or signal transduction. Anandamide, an endocannabinoid, is degraded by the enzyme Fatty Acid Amide Hydrolase coded by gene FAAH. We recently reported associations of FAAH variants with respiratory depression (RD) and PONV after outpatient tonsillectomy surgery. Since RD is the most serious adverse effect of opioids in postoperative patients, the aim of this study was to evaluate FAAH variant effects on clinical RD as well as experimental carbon dioxide (CO2) respiratory response, an objective and sensitive measure of subclinical RD.

**METHODS**

After institutional IRB approval and informed consents, we enrolled children aged 10-18 years, ASA 1-2, undergoing spine fusion for idiopathic scoliosis (under standard intravenous anesthesia) in a prospective, genotyping blinded study. All received morphine PCA after surgery. Respiratory responses to inspired 5% CO2 in room air (tidal volume, respiratory rate, minute ventilation (MV), end tidal CO2 and pulse oximetry), was obtained at baseline (before surgery, before morphine) and after morphine (after spine surgery). They were followed for 48 hours postoperatively for RD, defined as respiratory rate<8/minute for >3 minutes, morphine use, nausea/vomiting and pain scores. Blood was collected for genotyping FAAH variants using Illumina Human Omni5 array, Taqman for specific variants and morphine pharmacokinetics. A population PK model was developed for morphine using nonlinear, mixed effects modeling approach (NONMEM; version 7.2, ICON Dev. Soln., MD, USA). Logistic regression was used to test association between genotypes and clinical outcomes; mixed models including morphine concentration, genotype, ETCO2 and ETCO2-genotype interaction to test association between CO2-MV response and genotypes, adjusted for morphine conc.

**RESULTS:**

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<th>Patients with Clinical RD had more depressed MV-CO2 response</th>
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<td>Patients were followed for 48 hours postoperatively for RD, defined as respiratory rate&lt;8/minute for &gt;3 minutes, morphine use, nausea/vomiting and pain scores. Blood was collected for genotyping FAAH variants using Illumina Human Omni5 array, Taqman for specific variants and morphine pharmacokinetics. A population PK model was developed for morphine using nonlinear, mixed effects modeling approach (NONMEM; version 7.2, ICON Dev. Soln., MD, USA). Logistic regression was used to test association between genotypes and clinical outcomes; mixed models including morphine concentration, genotype, ETCO2 and ETCO2-genotype interaction to test association between CO2-MV response and genotypes, adjusted for morphine conc.</td>
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**CONCLUSIONS**

- Specific FAAH variants with regulatory function significantly affect ventilatory response to hypercarbia which may be an early indicator of risk for opioid related RD in children receiving morphine.
- They also are associated with morphine associated clinical RD and PONV after surgery.
- These genotype-phenotype associations contribute to better understanding of the interindividual variability in individual response to opioids.
- The associations point to important interactions between opioid and cannabinoid actions, which need to be further explored, and have predictive as well as targeted drug development potential.

**REFERENCES**


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