**Improved Safety of Opioid Analgesic Oliceridine Compared to Morphine Assessed by Utility Function Analysis**

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**BACKGROUND**

- Opioids produce potent pain relief and therefore remain the cornerstone of treatment of moderate to severe pain.¹
- Among the many opioid side effects, respiratory depression may complicate adequate dose-exposure for analgesia, and in rare instances can be potentially life-threatening.¹
- In the context of the ‘opioid crisis’, there is an ongoing search for potent opioid analgesics with reduced adverse effects.
- Full µ-receptors agonists provoke analgesia, by activation of the G-coupled signaling pathway, and dose-dependent respiratory depression (with apnea at high doses) by activation of the β-arrrestin pathway.²
- Recent focus has been on the development of biased ligands, which are µ-receptors agonists that selectively engage the G-coupled signaling pathway while avoiding the β-arrestin pathway.²

**OBJECTIVE**

Here we ran an analysis data from the above study and performed a population pharmacokinetic-pharmacodynamic (PK/PD) analysis, which allowed us to construct safety or utility functions U, which give an integrated profile on the probability of drug harm in the light of its benefit.

**METHODS**

- We performed a PK/PD analysis that gives parameter estimates an indication of inter-individual variabilities (ω²).
- The population PK/PD analyses were performed in NONMEM.
- Utility functions are objective and precise assessments of the probability of analgesia relative to the probability of respiratory depression (R).
- We created the classical utility function (benefit minus harm): $U = P(A) − P(R)$, where A is analgesia and R is respiratory depression.

**RESULTS**

**PK/PD analysis**

- The morphine steady-state plasma concentration causing 25% RD was $11 ± 2$ ng/mL (median ± SEM) and for concentration causing a doubling of the pain tolerance $34 ± 10$ ng/mL.
- The equivalent values for oliceridine were $27 ± 4$ ng/mL (ventilation) and $28 ± 5$ ng/mL.
- These values are indicative of a 2.5-fold greater morphine respiratory potency compared to olicerdine while equiopency was observed for the analgesic efficacy of the two opioids.
- Additionally, oliceridine equilibrates more rapidly than morphine within its effect compartment.

**Utility Functions**

- The two utility curves that were constructed, i.e. the probability of analgesia minus the probability of RD and the probability of analgesia without RD, were all in favor of oliceridine compared to morphine (Figure 3 and Figure 4).
- This indicates that following treatment with oliceridine the probability of analgesia exceeds that of RD, over the dose range studied, in contrast to morphine, where the probability of RD exceeded that of analgesia.

**CONCLUSION**

- The PK-PD analysis revealed a more than 2-fold greater potency of morphine compared to oliceridine in producing respiratory depression at doses where the two opioids were equianalgesic.
- Oliceridine has a greater analgesic probability combined with a lesser probability of respiratory depression.
- The clinical respiratory events occurred in clinical practice when the utility P(A) NOT R < 0.2. The experimental utility may well be translated into clinical practice.
- Compared to the prototypical opioid analgesia morphine, the G-protein selective µ agonist, oliceridine, has a favorable safety profile when considering both analgesia and respiratory depression.

**Reference:**


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