CEBRANOPADOL: A NOVEL FIRST-IN-CLASS ANALGESIC IN DEVELOPMENT FOR CHRONIC PAIN CONDITIONS - EFFECTS ON RESPIRATION IN HEALTHY HUMAN VOLUNTEERS

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INTRODUCTION

Opioid analgesics are commonly used and are effective treatments in patients with moderate to severe acute or chronic pain. However, their use is limited by side effects such as respiratory depression, constipation, sedation, and nausea/vomiting. Respiratory depression is potentially life-threatening, and is the main cause of opioid-related deaths [1]. Thus, there is a need for analgesics that are as effective as typical opioids but with a better safety profile.

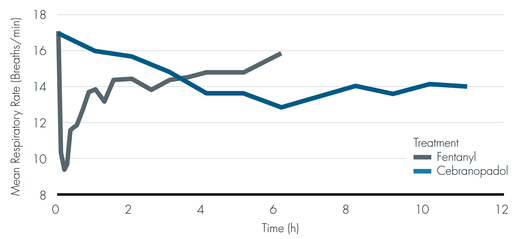
Cebranopadol is a novel first-in-class analgesic. It acts as a nociceptin/orphanin FQ peptide (NOP) and opioid peptide (OP) receptor agonist with central analgesic activity. Cebranopadol is currently in clinical development for the treatment of chronic pain conditions.

It is expected that combining a classical OP receptor agonist with a NOP receptor agonist, ideally in the form of a single small molecule, offers the potential to enhance analgesia and reduce side effects like respiratory depression compared with classical opioids [2]. A ceiling effect to respiratory depression has been linked to the activation of NOP receptors [3].

BACKGROUND

In a Phase 1 trial with 12 healthy male subjects, the effects of a single oral dose of cebranopadol 600 µg (solution in Macrogol 400) on respiratory function (respiratory rate and oxygen saturation) were compared to a single intravenous dose of fentanyl (3.5 µg/kg). Results showed that cebranopadol demonstrated a less pronounced effect upon respiratory parameters (respiratory rate and ventilation) than fentanyl (Figure 1; respiratory rate). The effect of cebranopadol on oxygen saturation was negligible.

Figure 1: Arithmetic mean respiratory rate values vs. time by treatment



Following up on the above mentioned findings, a thorough evaluation of the respiratory depression potential of cebranopadol was performed by means of a population pharmacokinetic (PK) – pharmacodynamic (PD) modeling study. The results of this PK-PD modeling study are presented in this poster.

PK-PD MODELING STUDY

OBJECTIVES

This PK-PD study quantifies cebranopadol's respiratory effects in male volunteers.

METHODS

Study design

- The following main endpoints were obtained at regular time intervals during 10 - 11 hours following cebranopadol administration: ventilation at an elevated clamped end-tidal partial pressure of carbon dioxide, pain threshold and tolerance to a transcutaneous electrical stimulus train, and cebranopadol plasma concentrations.

Data analysis

- The data were analyzed using sigmoid maximum effect (E_{MAX}; respiration) and power (antinociception) models.
- The PK-PD data were analyzed with the statistical package NONMEM VII (ICON Development Solutions, Hanover, Maryland). 1st stage (PK analysis): Empirical Bayesian estimates of the PK parameters were obtained. 2nd stage (PD analysis): The PK parameters were fixed to those obtained in the first stage.
- PK analysis: Multiple compartment models were fitted to cebranopadol PK data.
- PD analysis: To eliminate a possible hysteresis between plasma concentration and effect, an effect compartment was postulated that equilibrates with the plasma compartment with a half-life $t½k_{e0}$ (i.e., the blood-effect-site equilibration half-life).

Ventilation was modeled as [4]:

$$\mathbf{Effect(t) = E_{MAX} + (E_{MIN} - E_{MAX}) \times [(C_E(t)/C_{50})^{\gamma} \times (1 + [C_E(t)/C_{50}]^{\gamma})^{-1}]}$$

Effect = effect at time t (minute ventilation); E_{MAX} = maximum or predrug effect (baseline ventilation); E_{MIN} = minimum effect (E_{MIN} = 0 indicates that apnea may be reached); $C_E(t)$ = effect-site concentration at time t; C_{50} = effect-site or steady-state concentration causing 50% depression of ventilation.

Pain responses were modeled as [4,5]:

$$\mathbf{Pain\ response(t) = Baseline\ response \times [1 + 0.25 \times (C_E(t)/C_{25})^{\gamma}]}$$

Pain response(t) = stimulus intensity at which a pain threshold or pain tolerance response occurs at time t; Baseline response = the predrug stimulus intensity at which a pain threshold or pain tolerance response occurs; C_{25} = the effect-site or steady-state concentration causing 25% stimulus intensity for a response (threshold or tolerance). Pain threshold and tolerance were simultaneously analyzed.

- Utility of drug effect (utility function, UF) was defined as the probability of obtaining the desired effect minus the probability of obtaining a side effect [4].

  The UF of cebranopadol as function of its effect-site concentration is presented here as:

$$\mathbf{UF(C_E) = P(A > \alpha) - P(R > \beta)}$$

P(A) = probability for analgesia, P(R) = probability for respiratory depression, α and β = threshold values.

So, the utility function for at least 50% respiratory depression and an increase in current of at least 50% above baseline (i.e., an increase in analgesia by 50%) equals P(A >50%) - P(R >50%).

RESULTS

The blood-effect-site equilibration half-life for respiratory depression and analgesia was 1.2 ± 0.4 h (median ± standard error of the estimate [SEE]) and 8.1 ± 2.5 h, respectively. The estimated effect site concentration causing 50% respiratory depression was 62 ± 3.6 pg/mL reaching a significant ceiling at 4.9 ± 0.7 L/min from a baseline ventilation of 20 ± 0.5 L; the equivalent concentration causing a 25% increase in currents to achieve the pain threshold and tolerance was 97 ± 29 pg/mL (Table 1).

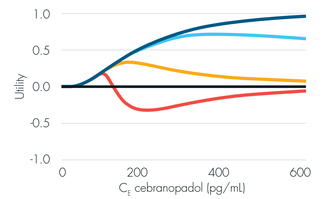
Table 1: Pharmacodynamic model parameters

	Typical value ± SEE	ω² ± SEE
Ventilation		
$t½k_{e0}$ (h)	1.23 ± 0.38	1.10 ± 0.76
E_{MAX} (L/min)	20.0 ± 0.50	0.004 ± 0.001
E_{MIN} (L/min)	4.94 ± 0.72	0 (fixed) *
C_{50} (pg/ml)	61.95 ± 3.55	0 (fixed) *
γ	1 (fixed) *	0.15 ± 0.05
σ	1.03 ± 0.04	
Pain Response		
$t½k_{e0}$ (h)	8.13 ± 2.53	0 (fixed) *
Baseline tolerance (mA)	23.5 ± 2.4	0.13 ± 0.03
Baseline threshold (mA)	17.1 ± 1.9	0.006 ± 0.004
C_{25} (pg/ml)	97.3 ± 29.3	0.56 ± 0.33
σ	1.97 ± 0.23	

Table presents typical values of medians ± standard errors of the estimate (SEE).
C_{25} and C_{50} = effect-site concentrations causing 25% and 50% of effect; E_{MAX} and E_{MIN} = maximum (baseline) and minimum effects; $t½k_{e0}$ = blood-effect-site equilibration half-life; * = SEE could not be estimated; σ = residual error; γ = shape parameter; ω = inter-subject variability (in the log-domain).

The UF for P(A >50%) and P(R) at a range of thresholds (from >50% to >80%) are given in Figure 1. The higher the threshold for respiratory depression is, the more positive is the UF, which is due to the ceiling in respiratory depression (Table 1). At 50% threshold values (red line in Figure 2), the UF becomes negative at cebranopadol concentrations >130 pg/mL with a nadir of -0.32 at 220 pg/mL after which it slowly returns towards 0. At higher threshold values for respiratory depression (β), the UF becomes positive with values approaching 1 at a threshold for respiratory depression >80%. This is due to the ceiling effect (Table 1) which precluded respiratory depression >70% (Figure 2).

Figure 2: Cebranopadol utility function as function of the effect-site concentration at C_{50} value of 62 pg/mL



SAFETY EVALUATIONS

Cebranopadol 600 µg as a single oral dose was safe and well-tolerated by all 12 subjects. No deaths, other serious adverse events, or adverse events leading to discontinuation occurred during this trial. Overall, the most commonly reported treatment emergent adverse events after administration of cebranopadol were sedation with 8 subjects (66.7%), somnolence with 3 subjects (25.0%), as well as nausea, dizziness, and headache with 2 subjects (16.7%) each.

CONCLUSIONS

- This PK-PD modeling study suggests that cebranopadol produces ceiling effects in respiratory depression at 25% of baseline ventilation, in contrast to pure μ-opioid peptide receptor agonists like fentanyl that produce apnea at high concentrations [4].
- Cebranopadol might offer a beneficial effect that may prevent development of apnea even at high concentrations.

DISCUSSION

- Due to the nature of the pain model used in this investigation, cebranopadol's analgesic potency might be underestimated.
- Although cebranopadol displays some features of typical opioids such as adverse events mentioned above, it also distinguishes from typical opioids by the ceiling effect in respiratory depression as described in this PK-PD study.

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