ENA-001, a Novel BK-channel Blocker, Enhances Hypoxic Ventilatory Sensitivity and Alleviates Propofol-induced Respiratory Effects in Healthy Volunteers

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BACKGROUND

Procedural sedation carries an elevated risk of respiratory depression and blockage of the airway due to drug interference with ventilatory control. It is not possible to predict the onset, duration, or severity of deleterious respiratory events due to a number of contributing factors, including individual differences in drug sensitivity, pulmonary and central nervous system dysfunction, underlying disease (e.g., pulmonary or cardiac disease) and concomitant medications. Given that there is no specific antagonist available for commonly used anesthetics, such as propofol, the appropriate use and management of medication during procedural sedation is crucial to ensure patient safety. A major paradigm aiming to minimize the risks associated with these medications and improve patient outcomes includes the use of agnostic respiratory stimulants.

ENA-001 is being developed as an agnostic respiratory stimulant for the treatment of postoperative respiratory depression. ENA-001 is a fast acting and short-duration intravenous (IV) agent acting partially by blocking the BK_{Ca2+} (Maxi K channels) in the carotid body to stimulate respiration. It has been previously reported that ENA-001 produced clear ventilatory stimulation in healthy subjects and partly attenuated suppression of ventilation by the opioid alfentanil.

CONCLUSIONS

- ENA-001 was safe and well tolerated in healthy participants at the two dose levels administered in this study
- Treatment with ENA-001 increased hypoxic sensitivity compared to placebo, both with and without coadministration of clinically relevant plasma concentrations of propofol
- Administration of ENA-001 did not impact the level of propofol-induced sedation

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METHODS

This was a randomized, double-blinded, placebo-controlled, three-period crossover phase 1b study, the effect of two intravenous doses of ENA-001 on propofol-induced respiratory depression was investigated in 14 healthy volunteers. In each period, ENA-001 or placebo was intravenously infused continuously for 270 minutes (ENA-001 low dose 33.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 10 min followed by a continuous infusion of 6.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 260 min; ENA-001 high dose 33.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 20 min followed by a continuous infusion of 18.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 250 min). During each period, the loading dose of ENA-001 or placebo was followed by three back-to-back blocks in which participants received IV propofol dosages or placebo over 70 minutes in a predetermined order (open label): placebo – propofol low dose – propofol high dose (targeting plasma concentration of 600 and 1200 ng/mL, respectively).

The primary endpoint of the study was the acute hypoxic ventilatory response (AHR) defined as (minute ventilation (V_E) in hypoxia – V_E in normoxia)/(SpO_2 in normoxia - SpO_2 in hypoxia) in L/min/%. The AHR was tested during each propofol block at normal and high end-tidal CO_2 concentration (i.e., 6 short hypoxic episodes per study period) (Figure 1). Safety parameters were included as secondary endpoints.

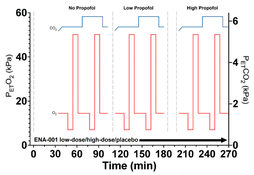


Figure 1: Overview of study design

Schematic representation of a treatment period with continuous infusion of ENA-001 high/low dose or placebo, three blocks of placebo or propofol (separated by vertical dotted lines) and two hypoxic runs per block (red lines). Each hypoxic run consisted of a hypoxia/hyperoxic exposure (corresponding left Y-axis). In each block there were two runs, one at normocapnia followed by one at hypercapnia (blue lines with corresponding right Y-axis).

RESULTS

Table 1: Demography

Characteristic	All Participants (N=14)
Sex, n (%)	
Female	6 (42.9%)
Male	8 (57.1%)
Race, n (%)	
Asian	1 (7.1%)
Black or African American	1 (7.1%)
White	12 (85.7%)
Age (y), mean (SD)	27.1 (7.6)
Weight (kg), mean (SD)	71.4 (11.7)
Height (cm), mean (SD)	178.8 (9.71)
BMI (kg/m^2), mean (SD)	21.94 (2.23)

BMI: body mass index

Figure 2: Summary graphs of the minute ventilation, SpO_2 and AHR per treatment

Vertical blue shading indicates the hypoxic runs at normocapnia, red shading at hypercapnia. The propofol dosing blocks are separated by vertical dotted lines.

Panel A: Minute ventilation (mean [SD]) on the left Y-axis and corresponding SpO_2 values on the right Y-axis at timepoints directly prior to and during each hypoxic run.

Panel B: Acute Hypoxic Response in L/min per % desaturation (mean [SD]).

- ENA-001 high dose resulted in a significant treatment effect versus placebo on AHR
- Propofol inhibited the AHR and had an even greater effect on the hypercapnic response
- Concurrent administration of a high dose of ENA-001 caused the AHR to remain comparable to pre-propofol values

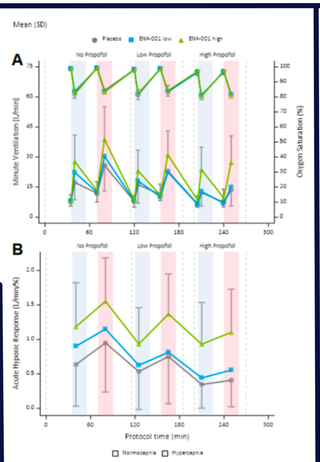


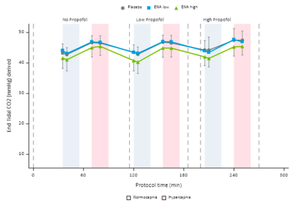
Table 2: Analysis results Acute Hypoxic Response (L/min/%) under clamped $P_{ET}CO_2$ conditions

Treatment	Propofol and Hypoxia	LSM	95% CI Lower	95% CI Upper
Placebo	Overall	0.604	0.295	0.912
	No Propofol Normocapnia	0.635	0.294	0.975
	No Propofol Hypercapnia	0.949	0.608	1.289
	Low Propofol Normocapnia	0.534	0.194	0.874
	Low Propofol Hypercapnia	0.751	0.410	1.091
	High Propofol Normocapnia	0.346	0.006	0.686
	High Propofol Hypercapnia	0.407	0.066	0.747
ENA low dose	Overall	0.747	0.439	1.056
	No Propofol Normocapnia	0.901	0.560	1.241
	No Propofol Hypercapnia	1.150	0.809	1.490
	Low Propofol Normocapnia	0.624	0.284	0.965
	Low Propofol Hypercapnia	0.813	0.473	1.154
	High Propofol Normocapnia	0.442	0.101	0.782
	High Propofol Hypercapnia	0.554	0.214	0.895
ENA high dose	Overall	1.179	0.870	1.488
	No Propofol Normocapnia	1.185	0.844	1.525
	No Propofol Hypercapnia	1.552	1.212	1.893
	Low Propofol Normocapnia	0.934	0.593	1.274
	Low Propofol Hypercapnia	1.368	1.027	1.708
	High Propofol Normocapnia	0.930	0.590	1.271
	High Propofol Hypercapnia	1.104	0.764	1.444

LSM: Least Squares Mean

- Propofol decreased AHR during placebo infusion
- Propofol high dose diminished the additional effect of hypercapnia
- Concomitant administration of ENA-001 high dose resulted in the AHR remaining similar to pre-propofol values
- Increases in minute ventilation induced by hypercapnia during high dose propofol was greater in the ENA-001 high dose group

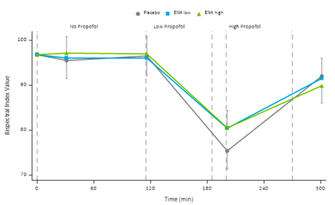
Figure 3: Summary of Graph Mean (SD) End Tidal CO_2 (mmHg)



CO_2 = carbon dioxide; SD = standard deviation; ENA low = ENA001 low dose; ENA high = ENA001 high dose; min = minutes

- Mean unclamped PETCO2 values recorded for ENA-001 high dose were lower at timepoints prior to the hypoxic measurements at isocapnia compared to ENA-001 low dose and placebo

Figure 4: Estimated means (95% CI) Bispectral Index Value (BIS)



- Administration of ENA-001 did not result in a significant effect versus placebo on the BIS value

DISCLAIMER: ENA-001 is for research use only and it's not been approved by the FDA for human use.

SAFETY

- No deaths or serious adverse events occurred during the study
- The most common adverse events (AEs) during the study were infusion site pain only reported for treatment with ENA-001
  - No dose dependent increase in occurrence was observed after treatment with ENA-001
- The incidence of all other AEs was similar after each of the three treatments
- The mean changes in clinical laboratory values, vital signs, and ECG were similar across the three treatments