Leucine-Enkephalin as a Novel Analgesic: Efficacy and Safety in Pre-Clinical Models.

J Gudin[1,2], S Mathias[2], I Uchegbu[3]

INTRODUCTION:

Endogenous peptides with analgesic potential include endorphins via the mu receptor, dynorphins via the kappa receptor and enkephalins via the delta receptor.

Kappa and delta opioid agonists have been shown to provide analgesic benefit while sparing toxic mu agonist toxicity[1].

Preclinical data supports analgesia from enkephalin without significant opioid tolerance, or drug liking. Unfortunately, exogenous enkephalins are rapidly degraded and have difficulty accessing the CNS[2]

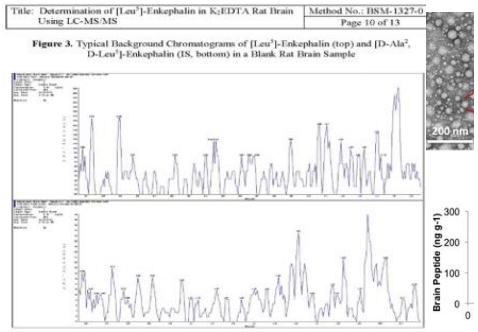
Using a novel encapsulation method known as Molecular Envelope Technology (MET), leucine-enkephalin, or L-ENK can be delivered via an intranasal formulation of "protected" nanoparticles. MET increases dwell time in the nares promoting delivery via the olfactory route across the blood brain barrier and into the central nervous system.

PRECLINICAL DATA[3]

When studied in rats, polymer nanoparticles were able to transport MET encapsulated L-ENK to the brain via the intranasal route.

METHODS:

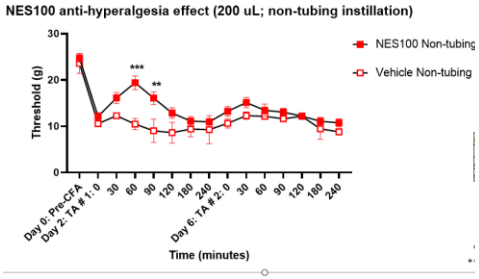
MET is a modified chitosan derivative also known as GCPQ (N-palmitoyl-N-monomethyl-N, N-dimethyl-N, N, N-trimethyl-6-Oglycolchitosan). NES100 is a microparticulate dosage form of L-ENK encapsulated in MET. Initial studies supported by HEAL initiative have focused on formulation, determination of L-ENK and MET in rat plasma and brain samples, dose range finding studies and anti-hyperalgesic efficacy assessments of the MET-LENK formulation.



LC-MS/MS L-ENK in Rat Brain

RESULTS:

LC-MS/MS Determination of L-Enkephalin and MET was successfully completed in rat plasma and brain samples. Dose range finding (DRF) studies were performed in 2 species, rat and dog. The rat 14 Day DRF study showed no treatment related clinical signs or mortality. In addition, there was no related findings in hematology, coagulation and serum chemistry data. The dog 14 Day DRF study also showed no treatment related mortality or findings in body temperature, body weight, food consumption, and ophthalmic exam. From an efficacy perspective, a dose-response with intranasal MET-LENK was noted in a Complete Freund's Adjuvant (CFA) anti-hyperalgesia model versus intranasal placebo and subcutaneous morphine. Administration of the high dose MET-LENK (30 mg/kg) significantly decreased hypersensitivity in treated animals compared to CFA control.



Rat MET-LENK Antihyperalgesic Effect

DISCUSSION:

There is a significant unmet need for effective analgesics with limited or no abuse potential. Our research on Leucine-enkephalin suggests that, in pre-clinical models, there is a clear efficacy signal with minimal adverse effects noted in animals. Using a novel encapsulation method known as Molecular Envelope Technology (MET), leucine-enkephalin can be delivered via an intranasal formulation of "protected" nanoparticles. MET increases dwell time in the nares promoting delivery via the olfactory route and may prevent degradation in the CNS. If data confirms analgesic benefit without respiratory depression or addiction, this enkephalin formulation may represent a potential broad-spectrum molecule to treat multiple types of acute and chronic pain and potentially other CNS disorders. We will continue to move this drug through preclinical development leading up to first in human trials.

REFERENCES

1. Pain. 2001 Sep;93(3):207-212.
2. Mol Pharm 2014, 11, 1081-93
3. Jrnl of Controlled Release Vol 270, 28 Jan 2018, p135-144

1. Department of Anesthesiology and Pain Medicine, University of Miami, Miller School of Medicine.
2. Virpax Pharmaceuticals
3. University of London, School of Pharmacy. Nanomerics Ltd.