What's New

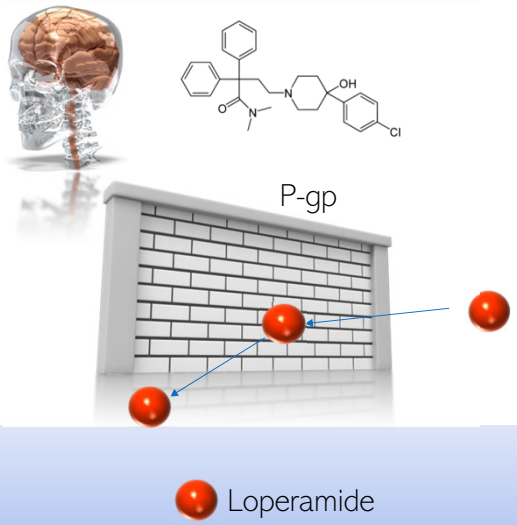
- Pain -

Liverpool University Hospitals NHS Foundation Trust
Dr Andrew Dickman
Consultant Pharmacist

1

Loperamide

- Loperamide is a peripheral μ-opioid
- Almost completely metabolized in the liver:
  - CYP2C8 and CYP3A4
  - usually resulting in very small, negligible, plasma level
- Oral bioavailability ≈ 0.3%
- P-gp actively extrudes loperamide from the CNS



2

Loperamide

Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

Topical loperamide for the treatment of localized neuropathic pain: a case report and literature review

Kopsky DJ, et al. Topical loperamide for the treatment of localized neuropathic pain: a case report and literature review. J Pain Res. 2019; 12:1189-1192.

3

Loperamide

- N=1
- Intractable local neuropathic pain
- 5% loperamide cream
- Onset of the analgesic effect was within 30 mins
- OD – BD for symptomatic relief
- Effect lasted for ≈ 2.5 hrs following each application

Kopsky DJ, et al. Topical loperamide for the treatment of localized neuropathic pain: a case report and literature review. J Pain Res. 2019; 12:1189-1192.

4

Loperamide

Randomized Crossover Study

Morphine Versus Loperamide with Intrasite Gel in the Treatment of Painful Dermal Ulcers: A Randomized, Crossover Study

B. Jyothi, MD[1], Milon V. Mitragotri, MD[1], Mahesh D. Kurugodiyavar, MD[2], Safiya I. Shaikh, MD[1], and Vishwajeet V. Korikanthimath, MBBS[1]

Jyothi B et al. Morphine Versus Loperamide with Intrasite Gel in the Treatment of Painful Dermal Ulcers: A Randomized, Crossover Study. Pain Physician. 2021 Jan;24(1):E37-E44.

5

Loperamide

- N=9
- 0.06% w/w loperamide in Intrasite gel
- 0.06% w/w morphine in Intrasite gel
- Applied daily
- Morphine and loperamide were equivocal in pain relief
  - after 12 and 24 hours
- Satisfaction scores better morphine

Jyothi B et al. Morphine Versus Loperamide with Intrasite Gel in the Treatment of Painful Dermal Ulcers: A Randomized, Crossover Study. Pain Physician. 2021 Jan;24(1):E37-E44.

6

Resiniferatoxin (RTX)

- A toxin found in a Moroccan cactus *Euphorbia resinifera*
- Resin by the inhabitants of Morocco over 1000 years ago

- King Juba II of Mauretania (50 BC - 23 AD)
- Discovered medicinal purposes
- Used as a nasal irritant – similar to smelling salts

7

Resiniferatoxin (RTX)

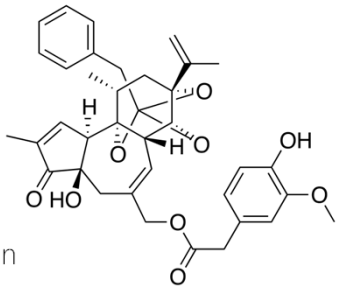
- During the Renaissance, Euphorbium was used to provoke sneezing
- 18th century - first descriptions of it use as an analgesic for chronic pain

- Disappeared from medical practice
  - to toxic?
  - variability in composition of resin?

8

Resiniferatoxin (RTX)

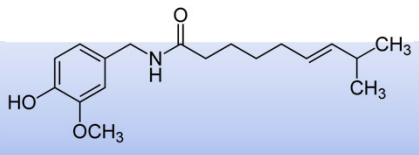
- 1975 – resiniferatoxin (RTX) isolated (by Germans!)
- Is a phorbol-related diterpene
  - phorbol esters are tumour promotors
  - mimic diacyl glycerol, which is an activator of protein kinase C
  - RTX does not promote tumour formation!
- 1989 – discovery that RTX is an ultrapotent analogue of capsaicin



9

Resiniferatoxin (RTX)

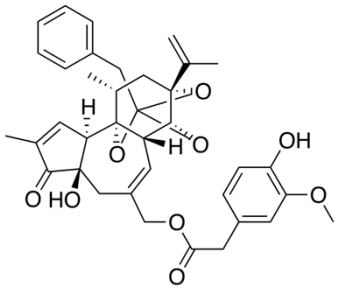
- Jalapeño pepper – 8000
- Carolina reaper pepper – 2million
- Pure capsaicin 16m
- RTX – 16 billion



10

Resiniferatoxin (RTX)

- Is a highly selective TRPV1 agonist
- May be able to deliver permanent, local pain relief with a single intrathecal injection
- Effect of peripheral application may persist for weeks
- Sensations of mechanical pinch and pressure are largely intact following administration, as are sensations of vibration and cold temperature



11

Resiniferatoxin (RTX)

- Has been tested in pet dogs that suffer from osteosarcoma (useful human model)
- Prior to RTX administration, the dogs would not bear weight
- Intrathecal RTX administration
  - effective pain relief and improve function
  - without long-term side effects
- Unblinding if dog had an unacceptable level of discomfort

Brown DC, Agnello K, Iadarola MJ. Intrathecal resiniferatoxin in a dog model: efficacy in bone cancer pain. Pain. 2015 Jun;156(6):1018-1024

12

Resiniferatoxin (RTX)

- Chicago, April 2014
- 39th Annual Regional Anaesthesia and Acute Pain Meeting
- Preliminary data from Phase 1 trial
- 6 patients with advanced cancer and severe refractory pain
- 13 or 26 mcg injection of RTX into the intrathecal space
- Patients achieved, on average, a 20% reduction in pain intensity NRS score at 2 weeks
- The drug was well tolerated with no unexpected side effects

sorrento THERAPEUTICS

13

A Multicenter, Open-Label, Phase 1b Study to Assess the Safety and Define the Maximally Tolerated Dose of Epidural Resiniferatoxin (RTX) Injection for Treatment of Intractable Pain Associated with Cancer

SS Nedeljkovic[1], S Narang[2], E Rickerson[3], RC Leviff[4], DB Horn[5], DJ Paltin[2], N Albares-Ibarra[6], A Nahama[6], T Zhao[6], P Bharathi[6], M Luchi[6], H Minkowitz[6], D Solanki[6], D Leiman[6,*]
[1]Brigham and Women's Hosp., Boston, MA; [2]Univ. of Miami, Miami, FL; [3]ND Res., Houston, TX; [4]Univ. of Texas at Houston, Dept of Surgery, Houston, TX; [5]Sorrento Therapeutics, Inc., San Diego, CA

Sponsored by Sorrento Therapeutics, Inc.

Introduction

- Derived from Euphorbia (cactus-like plant).
- Ultrapotent agonist of TRPV1 receptor.[1]
- RTX vs. capsaicin
  - RTX ~18 billion Scoville units
  - Capsaicin ~16 million Scoville units
- Highly specific - affects only TRPV1 expressing nerves (Aδ and C fibers).
- RTX activates TRPV1 receptor inducing influx of calcium, resulting in lysis of pain-sensory neurons.
- Cancer-related pain is one of the most common and troublesome symptoms and is reported by more than 70% of patients with cancer.
- Despite the availability of effective treatments, cancer-related pain may be inadequately controlled in up to 50% of patients.[2]

Methods

- Phase 1b, open-label, single-dose RTX, 3 + 3 dose escalation design.
- Subjects with intractable chronic pain (NPRS worst pain ≥ 6) due to advanced cancer.
- Dose levels: 0.4, 1, 2, 4, 8, 15, 25 mcg in 3 mL saline.
  - First 2 dose levels may advance after first subject dosed if no DLTs.
- Administered epidurally as interlaminar injection at midline L2-L3, L3-L4, L4-L5, L5-S1, or via caudal catheter L5 to S4 under anesthesia.

Demographics & Baseline Characteristics

Demographics, Baseline Characteristics	RTX n=17
Female: n (%)	11 (64.7%)
Male: n (%)	6 (35.3%)
Age, Median (min, max)	58.0 (28, 82)
Baseline Worst NPRS, Mean (SD)	7.8 (1.26)
Baseline Average NPRS, Mean (SD)	6.8 (1.66)
Baseline Worst NPRS <6: n (%)	1 (5.9%)
Baseline Worst NPRS ≥ 6, <8: n (%)	8 (47.1%)
Baseline Worst NPRS ≥ 8: n (%)	8 (47.1%)

Cancer Diagnosis	n=17
Breast	2 (11.8%)
Lung	2 (11.8%)
Multiple Myeloma	2 (11.8%)
Rectal	2 (11.8%)
Renal cell	2 (11.8%)
Bladder	1 (5.9%)
Endometrial	1 (5.9%)
Gastrointestinal Stromal Tumor	1 (5.9%)
Large-B-cell Lymphoma	1 (5.9%)
Myxoid Liposarcoma	1 (5.9%)
Neuroblastoma	1 (5.9%)
Rectosigmoid	1 (5.9%)

Results

Safety

- No DLTs were reported.
- Serious AEs were attributed to progression of underlying cancer.
- Most common treatment-related AE was transient procedural pain, typically described as burning sensation in both lower extremities, which diminished over several hours and then resolved.

Safety – Treatment Emergent Adverse Events		
TEAE	Severity	RTX Treated (n=17)
Procedural pain	Moderate	8 (47.1%)
Back Pain	Moderate	1 (5.8%)
Burning sensation	Mild	1 (5.8%)
Bradycardia	Mild	1 (5.8%)
Hypertension	Mild	1 (5.8%)
Increased blood pressure	Moderate	1 (5.8%)
Nausea	Mild	1 (5.8%)
Paraesthesia	Mild	1 (5.8%)
Groin pain	Mild	1 (5.8%)

Pharmacokinetics

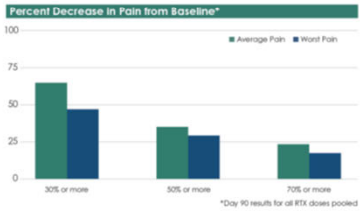
- Only 2 of 17 subjects at any dose level had detectable (>50 pg/mL) RTX in plasma following injection.
  - Dose at 15 mcg: plasma level peaked at 97 pg/mL RTX at 0.5 hour and was not detectable by 2 hours after injection.
  - Dose at 25 mcg: plasma level peaked at 76 pg/mL RTX at 1 hour and was not detectable at other time points.

Efficacy

- Clinical efficacy assessed at 3 levels: 30%, 50%, and 70% decrease in pain from baseline NPRS score.
- Dose-response relationship observed for majority of responders at 15 mcg and 25 mcg levels.
- Eleven of 17 subjects achieved a 30% decrease in pain using NPRS scores.

Efficacy				
Percent Decrease in Pain from Baseline	Average Pain		Worst Pain	
30% NPRS reduction	15 mcg	100%	15 mcg	66.7%
	25 mcg	66.7%	25 mcg	66.7%
	All Dose Levels	64.7%	All Dose Levels	47.1%
50% NPRS reduction	15 mcg	33.3%	15 mcg	66.7%
	25 mcg	66.7%	25 mcg	33.3%
	All Dose Levels	35.3%	All Dose Levels	29.4%
70% NPRS reduction	15 mcg	33.3%	15 mcg	33.3%
	25 mcg	33.3%	25 mcg	33.3%
	All Dose Levels	23.5%	All Dose Levels	17.6%

Percent Decrease in Pain from Baseline*



*Day 90 results for all RTX doses pooled

Conclusion

Resiniferatoxin (RTX) has the potential to alleviate severe pain in patients who have intractable cancer pain.

- RTX was tolerable at all doses tested (with concomitant analgesics administered for procedural pain on Day 1).
- PK data showed undetectable drug in plasma in 15/17 subjects.
- A dose-dependent decrease in pain scores was detected.

1. Moran MM, Szallasi A. Targeting nociceptive transient receptor potential channels to treat chronic pain: current state of the field. Br J Ph. 2018; V175, 2185-2203.
2. Neufeld NJ, Elnahal SM, Alvarez RH. Cancer pain: a review of epidemiology, clinical quality and value impact. Future Oncology. 2017; V13, 833-841.

https://www.clinicaltrials.gov/ct2/show/NCT03226574

14

Extended Duration CSCI?

15

What's New

- BD and Liverpool University
- International survey of practice
- Identify average duration of CSCI prescription
  - range of settings
- Common combinations

UNIVERSITY OF LIVERPOOL

BD

16