The New Types of Pharmacological and Other Treatments of Pain

Prof. Richard Rokyta MD, PhD, DSc, FCMA

Charles University in Prague, Third Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague

SPOLEČNOST PRO VĚDY A UMĚNÍ, USA

Tábor 2010
Neuromodulatory methods are nondestructive and reversible techniques of chronic pain treatment.

Neurosurgery destructive – and reconstructive.
Neuromodulatory methods
1) stimulation methods (nervous tissues stimulation)
2) intraspinal and nitraventricular application of remedies.

A) Neurostimulatory methods:
- peripheral nerve stimulation – PNS
- spinal cord stimulation or posterior and anterolateral spinal cord pathways – SCS –
- deep brain stimulation – DBS
- motor cortex stimulation - MCS
- repetitive transcranial cortex stimulation – rTMS

B) Intraspinal application: epidural, subarachnoidal and intracerebroventricular remedies application.
Use of neurostimulation in pain therapy
• tested method for introducing motor cortex brain stimulation
• reducing of chronic pain pains after ictus
• deafferentation pain – avulsion of brachial plexus
• phantom pain
• stump pain
• thalamic pain
• neuropathic pain – postherpetic neuralgia
PRIALT®▼ (ZICONOTIDE)
When to Consider Intrathecal Analgesia

• Many classes of systemic drugs used for chronic pain

• Neuropathic pain¹
  – Anti-depressants (tricyclics SSNRIIs)
  – Calcium channel $\alpha_2\delta$ ligands (gabapentin, pregabalin)
  – Opioids

• When analgesia is inadequate despite
  – Opioid rotation
  – Adjuvants
  – Co-analgesics

... consider using intrathecal analgesia
## A Very Brief History of Intrathecal Analgesia and the PAC

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>Intrathecal opioids used in humans</td>
</tr>
<tr>
<td>1980s</td>
<td>1st “permanent” catheter for intraspinal drug delivery</td>
</tr>
<tr>
<td>1990s</td>
<td>Intrathecal bupivacaine and/or clonidine often co-administered with opioids for neuropathic pain</td>
</tr>
<tr>
<td>2000</td>
<td>1st PAC algorithm for intraspinal drug delivery¹</td>
</tr>
<tr>
<td>2003</td>
<td>2nd PAC algorithm for intrathecal analgesia²</td>
</tr>
<tr>
<td>2005</td>
<td>Ziconotide a new class of intrathecal analgesic</td>
</tr>
<tr>
<td>2007</td>
<td>3rd PAC algorithm for intrathecal analgesia³</td>
</tr>
</tbody>
</table>
## Intrathecal Polyanalgesic Therapy Algorithm 2007

<table>
<thead>
<tr>
<th>Line</th>
<th>Drug Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line 1</td>
<td>morphine ↔ hydromorphone ↔ ziconotide</td>
</tr>
<tr>
<td>Line 2</td>
<td>fentanyl ↔ morphine/hydromorphone ↔ morphine/hydromorphone + ziconotide ↔ bupivacaine/clonidine</td>
</tr>
<tr>
<td>Line 3</td>
<td>clonidine ↔ morphine/hydromorphone/fentanyl + bupivacaine/clonidine + ziconotide</td>
</tr>
<tr>
<td>Line 4</td>
<td>sufentanil ↔ sufentanil + bupivacaine/clonidine + ziconotide</td>
</tr>
</tbody>
</table>
From *Conus magus* to Ziconotide (PRIALT®)

- *Conus magus* is a marine snail
- Uses a highly poisonous mixture of different conotoxins to paralyse and kill fish within seconds
- Ziconotide is a synthetic analogue of ω-conotoxin MVIIA from *Conus magus*
The Ziconotid Molecule

Synthetic equivalent of ω-conotoxin MVIIA from the marine snail *Conus magus*

H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-

Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH₂
The Ziconotide Molecule

• Large molecular weight 2639 vs 285 morphine
• Permanently charged at physiological pH
  – Low tissue penetration
• Metabolised by peptidases
• Methionine amino acid susceptible to oxidation
Programmable Implanted Pumps for Use With Ziconotide

- Medtronic SynchroMed® II or CE marked equivalent
- Implanted, programmable, battery-powered
- 20- and 40-ml Reservoirs
Ziconotide Recommended for All Pain Types

- **Ziconotide** recommended as a first-line therapy for nociceptive, mixed and neuropathic pain in the 2007\(^1\) PAC guidelines on the use of intrathecal agents

- Guidelines published in 2000\(^2\) and 2003\(^3\) did not include use of **ziconotide** as it was under development
Transmission of Pain Signals

Pre-synaptic terminal

Na\(^+\) channel

N-type Ca\(^{2+}\) channel

Post-synaptic projection neuron
Ziconotide Inhibits N-Type Calcium Channels

• Exact mechanism of action of ziconotide in humans is not known

• Electrophysiological studies have shown ziconotide to be a selective inhibitor of the N-type calcium channel\(^1\)

• N-type calcium channels are concentrated in the superficial laminae (I-II) of the dorsal horn – the pain processing region of the spinal cord\(^2\)

Radiolabelled ziconotide binding in the dorsal horn of the rat spinal cord\(^2\)
Ziconotide Mechanism of Action

Pre-synaptic terminal

N-type Ca\(^{2+}\) channel

Post-synaptic projection neuron

ziconotide

ziconotide
Efficacy of Ziconotide in Animal Models of Nociceptive Pain

- **Formalin/Hot plate**
  - Ziconotide • Anti-nociceptive with minimal tolerance\(^1\)

- **Acute inflammation**
  - Ziconotide • Attenuated heat-hyperalgesia\(^2\)

- **Post-operative pain**
  - Ziconotide • IT but not IV alleviated pain\(^3\)
Pharmacodynamics of Ziconotide: Extrapolation of Rat Data to Humans

Radiolabelled ziconotide binding in the dorsal horn of the rat spinal cord

Hypothesis: Inhibition of N-type calcium channels leads to analgesia

Radiolabelled ziconotide binding in the sagittal section of rat brain. High-density binding in neocortex, basal ganglia, basal forebrain, hippocampus, olfactory glomerulus and dorsal grey matter

Hypothesis: Inhibition of N-type calcium channels leads to neurological side effects
Criteria for Intrathecal Analgesia (Ziconotide) Therapy

- Patients with chronic severe pain where
- Definitive treatment for pain is not available or has failed
- Analgesia is inadequate with either optimal systemic medication or non-pharmacological therapies
- Analgesia treatment side effects are unmanageable or intolerable
- No contraindications to neuraxial drug delivery exist
- The patient has had appropriate psychological assessment
- The patient can give informed consent based on provision of appropriate information about the benefits and risks of treatment
Ziconotide Can Be Used in Neuropathic, Nociceptive and Mixed Pain

Cancer pain
- Refractory mixed nociceptive/neuropathic pain
- Visceral tumours or autonomic dysfunction resulting in gut dysmotility
- Chemotherapy-induced painful peripheral neuropathy
- Bone metastases

Non-cancer pain
- Failed back surgery syndrome
- Axial spinal pain
- Peripheral polyneuropathy
- AIDS-related pains
- Complex regional pain syndrome
- Brachial plexopathy
- Central pain syndromes
  - Post-stroke pain
  - Spinal cord injury pain
Lidokain - Versatis
The Dr Hind Story –
Background of the Product

- Dr. H Hind, pharmacist, 83, tried to help his wife Diana, 81, after she developed very painful postherpetic neuralgia in 1989.
- Several oral medications had been insufficient or intolerable for her. Weekly injections of lidocaine were painful, but pain relief was about 6 hours.
- Dr. Hind developed a topical lidocaine solution, applied it to the painful area and covered it with a plastic wrap. Surprisingly the combination worked, with pain relief for several days.
- The idea of a lidocaine plaster for painful postherpetic neuralgia was born!
- The prototype of a plaster delivering lidocaine was developed by Dr. Hind and finalized in collaboration with Teikoku Seiyaku Co.
Onset of Action I

Clinical Efficacy

Rapid pain relief
- Cooling effect
- Mechanical protection

Sustained analgesia
- Lidocaine effect

Grunenthal

Versatis
Handling and Combination of Versatis®

- Easy handling
  - Once daily plaster application
  - 12h-on / 12h-off regimen (24h pain relief)
  - Can be cut according to the painful area
  - Up to 3 plasters can be used at one time
  - No titration necessary

- Easy combination
  - When combination is useful, current treatment habits must not necessarily be changed
Conclusion

Efficacy

Excellent safety profile

Easy handling and combination

Unique and innovative treatment approach for localised neuropathic pain symptoms (like burning, stabbing, shooting)
Topical agents

Lidocaine plasters (5%) are effective based on 5 class I or II RCTs in PHN with brush-induced allodynia, but the therapeutic gain is modest against placebo, and the level of evidence is lower than for systemic agents [7,53]. The largest recent trial including patients with or without allodynia (with enriched enrolment design) was negative on the primary outcome (time-to-exit), but the groups were not balanced at baseline, and many patients withdrew prematurely from the study [54]. In an enriched-design open-label trial, lidocaine plaster was better tolerated than pregabalin [55]. Lidocaine plasters are safe because of their low systemic absorption and well tolerated with local adverse effects only (mild skin reactions) [54–56].

Randomized controlled trials have reported benefit from topical capsaicin 0.075% [7], but as a result of the burning effect of capsaicin, blinding was probably compromised. A one-off application of high concentration (8%) capsaicin patch applied to the skin for 60 min was more effective than a low concentration patch (0.04%) during 12 weeks [57]. Although a post hoc analysis suggests that blinding was successful, patient randomized to the high concentration patch required more rescue medication immediately after application. Adverse effects were primarily attributable to local capsaicin-related reactions at the application site (pain, erythema). Efficacy of capsaicin patches was demonstrated in two other studies reported in a systematic review [47].
Market Experience in the US with LIDODERM® in 2006 [1]

- 6% Zoster
- 8% Other neurop. pain
- 9% Osteoarthritis
- 10% All others
- 13% Injuries – Trauma
- 39% Back pain
- 13% Joint pain
- 2% Diabetic polyneuropathy

[1] IMS data MAT 09/06
Capsaicin - Qutenza
• Qutenza 179 mg cutaneous patch
• QUALITATIVE AND QUANTITATIVE COMPOSITION
• Each 280 cm² cutaneous patch contains a total of 179 mg of capsaicin or 640 micrograms of capsaicin per cm² of patch (8 % w/w).
  – Excipient
• Each 50 g tube of cleansing gel for Qutenza contains 0.2 mg/g butylhydroxyanisole (E320).
• For a full list of excipients, see section 6.1.
  – 3. PHARMACEUTICAL FORM
• Cutaneous patch.
• Each patch is 14 cm x 20 cm (280 cm²) and consists of an adhesive side containing the active substance and an outer surface backing layer. The adhesive side is covered with a removable, clear, unprinted, diagonally cut, release liner. The outer surface of the backing layer is imprinted with ‘capsaicin 8%’.
  – 4. CLINICAL PARTICULARS
  – 4.1 Therapeutic indications
• Qutenza is indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.
- **Contraindications**
- Hypersensitivity to the active substance or to any of the excipients.
- **Special warnings and precautions for use**
• **Mechanism of action**
  Capsaicin, or 6-nonenamide, N-[(4-hydroxy-3-methoxyphenyl) methyl]-8-methyl, (6E), is a highly selective agonist for the transient receptor potential vanilloid 1 receptor (TRPV1). The initial effect of capsaicin is the activation of TRPV1-expressing cutaneous nociceptors, which results in pungency and erythema due to the release of vasoactive neuropeptides.

• **Pharmacodynamic effects**
  Following capsaicin exposure, cutaneous nociceptors become less sensitive to a variety of stimuli. These later-stage effects of capsaicin are frequently referred to as “desensitization” and are thought to underlie the pain relief. Sensations from non TRPV1-expressing cutaneous nerves are expected to remain unaltered, including the ability to detect mechanical and vibratory stimuli. Capsaicin-induced alterations in cutaneous nociceptors are reversible and it has been reported and observed that normal function (the detection of noxious sensations) returns within weeks in healthy volunteers.

• **Clinical Efficacy**
  Efficacy of a single 30-minute application of Qutenza to the feet has been shown in controlled clinical trials conducted in patients with painful HIV-AN. Efficacy of a single 60-minute application of Qutenza to locations other than the feet has been shown in controlled clinical trials conducted in patients with PHN. Pain reduction was observed as early as Week 1 and was maintained throughout the 12-week study period. Qutenza has been shown to be effective when used alone or when used in combination with systemic medicinal products for neuropathic pain.
Instranasal fentanyl - Instanyl
Definition of breakthrough pain (BTP)

Breakthrough pain is defined as:
‘transitory exacerbation of pain that occurs on a background of otherwise stable persistent pain’

Other terms used:
episodic pain, transient pain, pain flare
Current management of cancer BTP

The current treatments used are:

• Oral morphine (commonly used but not registered as a treatment of BTP)

• Oral Transmucosal Fentanyl (registered as treatment of BTP):  
  – Actiq®: Fentanyl lozenge  
  – Effentora®: Fentanyl buccal tablet  
  – Abstral®: Fentanyl sublingual tablet
Current BTP treatments have limitations

Actiq®, Effentora® and Abstral® are new BTP treatments but have limitations:

- Their onset of action is too long
  - Their duration of action exceeds the duration of the vast majority of BTP episodes leading to potential overmedication
  - Actiq and Effentora are difficult to administer (have to be held in mouth for around 15 minutes to dissolve)
  - Oral transmucosal formulations are not suitable in cancer patients with dry mouth syndrome, mucositis, nausea/vomiting
Instanyl® is the first intranasal treatment for BTP in cancer patients

Instanyl® is indicated for the management of BTP in adults who already receive maintenance opioid therapy for chronic cancer pain

- Instanyl® is the first and only approved formulation of fentanyl for intranasal administration.
- Instanyl® has a profile that is particularly suitable for the treatment of BTP in patients with cancer and addresses many unmet medical needs.
The profile of Instanyl® mirrors the typical time profile of a BTP episode

- Instanyl® has rapid absorption and fast onset of action
- Median time to onset of meaningful pain relief was 11 minutes in cancer patients and 7 minutes in non-cancer patients.
- Instanyl® has short duration of action (median duration: 56 minutes)
Instanyl® is safe and well-tolerated

As demonstrated in trials:

- Instanyl® does not increase risk of respiratory depression or bring additional safety issues to the management of BTP in cancer
- Instanyl® does not induce tolerability problems (incidence is similar to that of control group in clinical trials)
Instanyl® has the greatest efficacy of BTP treatments in cancer: MTC results summary

- Instanyl® provides greater reduction of pain at 15 minutes and throughout 60 minutes after treatment administration than Actiq®, Effentora® and oral morphine
  - Instanyl® had probability >99% of being the best treatment
  - Instanyl® was superior to oral morphine at all timepoints
  - Instanyl® was superior to Actiq® at 15, 30 and 45 minutes
  - Instanyl® was superior to Effentora® at 15 and 30 minutes
- Oral morphine was not more effective than placebo in providing pain relief until 45 minutes post administration
Summary

- BTP in cancer has an enormous impact on patients and requires appropriate treatment.
- Instanyl® has an optimal profile for the treatment of BTP in cancer patients.
- Instanyl® is clinically superior to other treatments of BTP in cancer patients.
- Instanyl® is better value for money than other treatments of BTP in cancer patients.
Sublingual fentanyl - Lunaldin
Schematic model of the disintegration, bioadhesion and drug dissolution of the new sublingual tablet system.

Tablet → Disintegration into ordered units. → The units adhere to the sublingual mucosa. → The carrier particles dissolve and release the active substance, which dissolves and is absorbed over the mucosa.
Schematic model of the mixing and tableting procedures for the sublingual fentanyl tablets and the tablet components.
Plasma concentration–time profiles of fentanyl in one cancer patient following a sublingual dose of 100 g (●), 200 g (■) and 400 g (▲) fentanyl base.
• Thank you for your attention!