DRUGS FOR THE TREATMENT OF NEUROPATHIC PAIN

We continue our series on drugs for the treatment of neuropathic pain. Part 4 of the series examines evidence on topical agents for neuropathic pain.

Part 4 – Topical Agents

Apart from anticonvulsants and tricyclic antidepressants, topical local anaesthetics are also often recommended and prescribed as first-line pharmacological therapy for certain neuropathic pain conditions.[1,2] Topical anaesthetics provide analgesia by blocking voltage-gated neuronal sodium channels thereby preventing the generation and transmission of nerve impulses.[3]

The most commonly used topical agent is lidocaine, available as a patch containing 5% lidocaine. It exerts analgesic effect directly to the skin area in contact without causing local anaesthesia.[4] In placebo-controlled clinical trials, lidocaine effectively relieved allodynic pain in postherpetic neuralgia (PHN).[5-7] Moreover, patients with PHN or diabetic neuropathy, who were partial responders to gabapentin treatment, showed significant improvements in pain intensity and pain relief with the addition of lidocaine patch to continuing gabapentin treatment.[8]

The lidocaine patch permits convenient, titration-free, once-daily dosing (12 hours on, 12 hours off, maximum 3 patches per day).[2,4] It is well tolerated with minimal skin reactions (rash or redness at the application site) and insignificant systemic absorption, even with extended dosing.[5,7,9] Therefore, the risk of drug interactions and systemic adverse effects is very low, making this a good alternative for patients who cannot tolerate systemic agents, in particular the elderly.[1] The lidocaine patch is not yet available for use in Hong Kong.

The eutectic mixture of local anaesthetics (EMLA) is another useful topical agent that is easy to apply and is not associated with any major adverse effects.[10] It contains 2.5% lidocaine and 2.5% prilocaine. The EMLA cream has been shown to be effective in the treatment of PHN.[11-13]

Other topical medications in neuropathic pain management include capsaicin (0.075%) and nonsteroidal anti-inflammatory drugs. There is variable evidence for the efficacy of these agents in PHN patients.[14,15] Moreover, the unpleasant, burning sensation often associated with capsaicin is not tolerated by many patients.

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Parts 1 to 3 of this series were presented in issues 10 to 12, respectively, and can be found at www.neuropainhk.org/newsletter.asp.

LITERATURE REVIEW

Attal N, Cruccu G, Haanpää M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol *2006;13:1153-1169.*

The lack of consensus on suitable pharmacological treatment for neuropathic pain conditions led to the development of these guidelines by the European Federation of Neurological Societies (EFNS) task force. The overall aim was to evaluate all randomized controlled trials (conducted in outpatient treatment settings) performed in the various neuropathic pain conditions and make appropriate pharmacological treatment recommendations. Studies were classified by level of evidence according to EFNS standards. The authors considered the effect of treatments on pain signs and symptoms, and also considered other factors such as quality of life, effect on sleep and adverse events. The Table summarizes the EFNS recommendations.

The EFNS task force has also made recommendations for the less studied neuropathic pain conditions, and proposes a number of new strategies for future trials that would allow objective comparisons of different pharmacological options for the management of neuropathic pain.

Table. EFNS recommendations for drug treatments in neuropathic pain conditions

Pain condition	First-line treatments	Second- or third-line treatments
Painful polyneuropathy, eg, painful diabetic neuropathy	Gabapentin Pregabalin TCA	Duloxetine* Venlafaxine* Lamotrigine Opioids Tramadol
Postherpetic neuralgia	Gabapentin Pregabalin Lidocaine (topical)# TCA	Capsaicin Opioids Tramadol Valproate
Trigeminal neuralgia	Oxcarbazepine Carbamazepine	Surgery
Central pain	Amitriptyline Gabapentin Pregabalin	Cannabinoids Lamotrigine Opioids

TCA, tricyclic antidepressant
* preferred to TCA in patients with cardiovascular risk factors
\# for patients with a small area of pain and allodynia, particularly the elderly

Approved indications in Hong Kong for some of the recommended drugs: *gabapentin*, neuropathic pain; *pregabalin*, peripheral neuropathic pain; *carbamazepine*, trigeminal neuralgia, glossopharyngeal neuralgia, diabetic neuropathy; *clomipramine*, chronic painful conditions.

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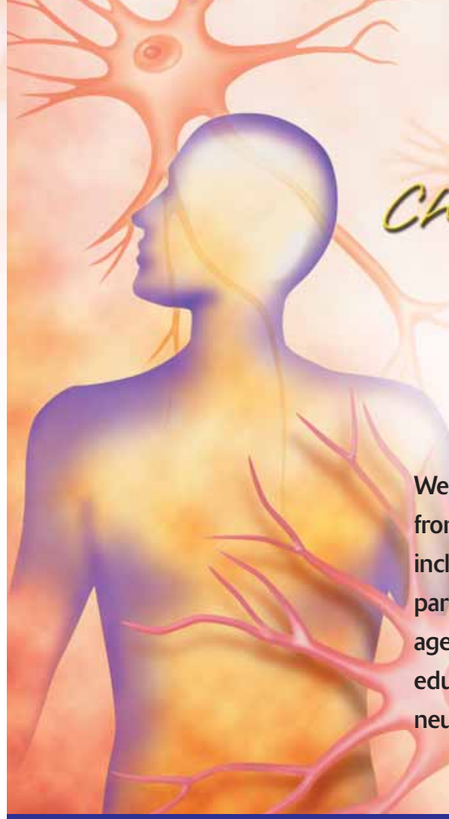

Challenges in Neuropathic Pain

Welcome to the 13th issue of *Challenges in Neuropathic Pain*, a newsletter from the Multidisciplinary Panel on Neuropathic Pain (MPNP). This issue includes an overview of the role of central sensitization in chronic pain and part 4 of the series on drugs for neuropathic pain – a discussion on topical agents. Previous issues of *Challenges in Neuropathic Pain*, as well as patient education materials and recommendations from the MPNP on various neuropathic pain conditions, are available at www.neuropainhk.org.

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Contact the Panel
Forward any comments on this newsletter to the Multidisciplinary Panel on Neuropathic Pain at mpnp@asia.cmpmedica.com.

Role of Central Sensitization in Chronic Pain

The mechanisms underlying the development of chronic pain are not yet fully understood. Several mechanisms, including peripheral and central sensitization processes, are believed to play key roles in the pathogenesis of chronic pain.[1] The following is an overview of the role of central sensitization in chronic inflammatory pain and neuropathic pain.

The term 'central sensitization' refers to the process by which sustained or repeated stimulation of primary afferent fibers results in prolonged neuronal hyperexcitability in the dorsal horn of the spinal cord.[1]

In chronic inflammatory conditions, such as osteoarthritis and rheumatoid arthritis, pain is initiated by tissue damage or inflammation. In neuropathic conditions, pain results from lesions in the nervous system.[2] Hypersensitivity at the site of damage and in adjacent normal tissue is common in both these conditions.[3] Moreover, spontaneous pain, hyperalgesia (increased response to noxious stimuli), allodynia (painful response to non-noxious stimuli), exaggerated temporal summation (repeated stimuli of constant intensity that result in an increase in pain perception) and enlarged areas of referred pain may also develop.[3,4] There is evidence in the literature that central sensitization may be involved in the manifestation of these symptoms.[1,4]

Mechanisms of central sensitization

Central sensitization has both presynaptic and postsynaptic components (Figure).[1] When the nociceptive system is sensitized, there is increased release of neurotransmitters from the spinal terminals of afferent neurons.[5] This represents the presynaptic component. The enhanced release of neurotransmitters then causes the activation of receptors and secondary messenger systems and ultimately leads to increased excitability of spinal cord neurons. This process represents the postsynaptic component of central sensitization.[5]

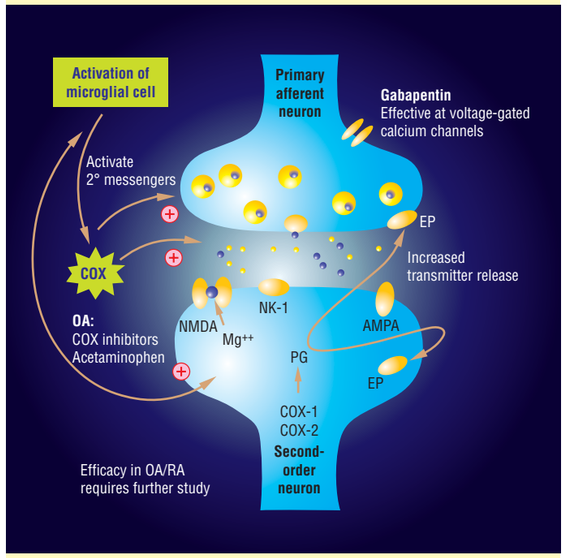
The potential neuronal mediators, their target receptors and outcome responsible for the development and maintenance of central sensitization are listed in the Table.

Table. Neuronal mediators and receptors involved in central sensitization[1,5,7-10]

Neurotransmitter/mediator	Target receptors	Outcome
Glutamate	AMPA and NMDA	Opening of receptor channels
Neuropeptides Substance P NKA CGRP	 NK-1 NK-2 CGRP	Enhanced glutamatergic synaptic transmission
Prostaglandin E_2	EP (pre- and postsynaptic)	Enhanced nociceptor sensitivity
Pro-inflammatory cytokines IL-1β TNF-α	 Type 1 IL-1 TNF types 1 & 2	 COX-2 upregulation Sensitization of nociceptive neurons
Second messenger systems Nitric oxide	 –	 Sensitization of spinothalamic tract cells

AMPA, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; NMDA, N-methyl-D-aspartate; CGRP, calcitonin gene-related peptide; NK, neurokinin; EP, prostanoid receptors; IL-1β, interleukin-1β; TNF-α, tumour necrosis factor-α; COX-2, cyclooxygenase-2

Figure. Mechanisms of central sensitization common to chronic inflammatory pain and neuropathic pain[1]



AMPA, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; NMDA, N-methyl-D-aspartate; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; EP, PGE_2 family of prostanoid receptors; Mg^{++}, magnesium ions; NK-1, neurokinin-1; OA, osteoarthritis; PG, prostaglandin; RA, rheumatoid arthritis

Glutamate is the major neurotransmitter in the spinal dorsal horn,[1] and acts on AMPA (α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid) and NMDA (N-methyl-D-aspartate) receptors.[5] The NMDA receptors, in particular, are thought to play a key role in the development and maintenance of central sensitization.[6] Several other neuromodulators enhance central sensitization, including neuropeptides,[5] prostaglandins,[5,7] pro-inflammatory cytokines[8,9] and second messengers.[10]

Normally, spinal hyperexcitability is counteracted by descending inhibitory systems in the central nervous system.[11,12] A number of endogenous substances, including opioids, cannabinoids, norepinephrine and adenosine, are released to counteract the development of the central sensitization process. Dysfunction in these inhibitory systems may also contribute to increased spinal hyperexcitability in some musculoskeletal disorders.[13]

Even though inflammatory pain and neuropathic pain have some common mechanisms leading to central sensitization (Figure), it is worth noting that some differences do exist. This will have important implications for the efficacy of drugs used to treat these conditions. Since nerve damage induces inflammatory events that lead to the development of neuropathic pain, at the peripheral level these two conditions are similar.[14] However, when it comes to the maintenance of these pain conditions, inflammatory hyperalgesia appears to rely mainly on peripheral input, while neuropathic pain seems to depend on enhanced descending facilitation from the brainstem in addition to peripheral contribution.[15,16]

Targeting central sensitization with drug therapy

Drugs used for the treatment of inflammatory pain generally target various mediators or receptor sites in the central sensitization pathway. Drugs that have demonstrated efficacy in the treatment of inflammatory pain include selective nonsteroidal anti-inflammatory drugs (NSAIDs),[17-19] tumour necrosis factor-α (TNF-α) blockers[20] and interleukin-1 (IL-1) receptor antagonists.[21] NMDA-receptor antagonists also have great potential in preventing and reducing central sensitization, but they only have limited therapeutic use as they can impair essential motor functions.[22]

In neuropathic pain, no distinct targets have yet been identified in the central sensitization pathway.[23] However, a number of therapeutic agents (including antidepressants, anticonvulsants, topical anaesthetics and opioids) are effective in the management of neuropathic pain. Some of these agents are also effective in treating arthritis pain. The tricyclic antidepressants, phenytoin and lidocaine all act on sodium channels[1,24,25] whereas gabapentin and pregabalin act on the $\alpha_2\delta$-subunit of calcium channels.[26]

As the mechanisms underlying the central sensitization process become clearer, more effective targeted therapies are likely to emerge.

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CASE PRESENTATION

In this issue, a case of neuropathic pain associated with Tolosa-Hunt syndrome is presented.

Tolosa-Hunt syndrome

Presenting symptoms

A 67-year-old woman presented with intermittent paroxysmal sharp pain (sometimes provoked by touch) over the right frontal area for 2 months followed by sudden onset of right eye ptosis. She had constant numbness over her right upper face, and was nonresponsive to analgesics.

Objective findings

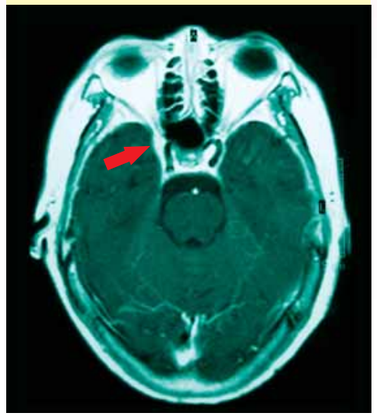
Clinical examination revealed no rash or scar on the affected area of the face. However, the patient had impaired pinprick and touch sensation over the area supplied by the right trigeminal nerve, as well as transient sharp shooting pain provoked by tactile stimulation on the right frontal area. She also had near complete right eye ptosis with impaired adduction and moderate restriction in upward right eye movement. Movement of her left eye was normal. Both pupils were reactive to light and of equal diameter (3 mm). No neck rigidity or any other neurological deficit was observed. Brain CT scan was normal.

The clinical diagnosis was Tolosa-Hunt syndrome with partial right III and V nerve palsies and neuropathic pain.

Management

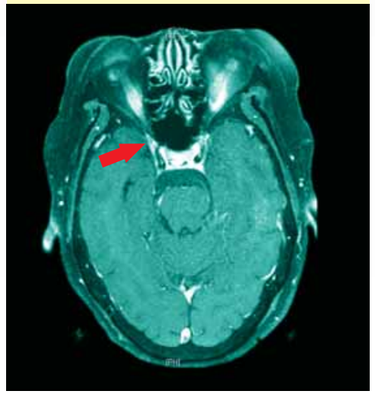
Urgent brain CT and angiogram of the Circle of Willis were performed, and no abnormality was found. Blood tests were normal. MRI of the brain showed a small enhancing lesion at the right cavernous sinus (Figure 1).

Figure 1. MRI showing small enhancing lesion in the right cavernous sinus



High-dose prednisolone (1 mg/kg/d) and gabapentin (300 mg tid) relieved the paroxysmal sharp pain, but the unpleasant numbness persisted. The right third nerve palsy completely resolved after 6 weeks. Steroid therapy was then tapered off over the next 2 months. A follow-up brain MRI, 4 months later, showed substantial resolution of the enhancing lesion (Figure 2).

Figure 2. Post-treatment MRI showing substantial resolution of the enhancing lesion



Discussion

Tolosa-Hunt syndrome is an uncommon cause of painful ophthalmoplegia and is characterized by prompt response to steroid therapy. In patients with acute painful third nerve palsy, it is important to rule out the diagnosis of ipsilateral posterior communicating artery aneurysm with or without subarachnoid haemorrhage. Accurate diagnosis of Tolosa-Hunt syndrome relies on high quality MRI with contrast, as demonstrated in this case.

Source: MPNP members

Q & A

Forward any questions on neuropathic pain to the MPNP at mpnp@asia.cmpmedica.com.

What is the role of cognitive behavioural therapy in treating neuropathic pain?

Cognitive behavioural therapy (CBT) is one of many nonpharmacological approaches to pain management and has been widely used for more than 30 years.[1] It involves three basic components[2]:

- The first component helps patients understand that the pain experience can be affected by cognitions and behaviour, and stresses the important role patients can play in controlling their own pain.
- The second component is coping skills training. Patients are trained how to effectively cope with their pain through a variety of cognitive and behavioural pain coping strategies. These include relaxation techniques, activity pacing, pleasant activity scheduling and distraction techniques. Through cognitive restructuring, patients are taught to replace negative, pain-related thoughts with more adaptive, coping thoughts.
- The third component of CBT encourages patients to apply and maintain the learned coping skills.

A number of randomized, controlled trials have demonstrated the efficacy of CBT in treating painful conditions, including chronic low back pain,[3] rheumatoid arthritis,[4] osteoarthritic knee pain[5] and cancer-related pain.[6] However, limited evidence exists for the benefits of using CBT in neuropathic pain management. In one randomized trial, CBT reduced pain intensity, pain-related functional interference and distress in patients with HIV-related peripheral neuropathy.[7]

The available evidence for the effectiveness of CBT in many chronic pain conditions provides much hope for its use in the management of neuropathic pain. CBT can be included as part of a multidisciplinary approach to yield the greatest chance of relieving pain in patients with neuropathic pain.

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