Concept of neuropathic pain and its management

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Key words Neuropathic pain, 10% lidocaine gel, Na+ channel blocker

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Neuropathic pain, a major factor of difficult pain problems, has greatly advanced in both fields of research and management. First nociceptive pain, that is, normal, physiological pain should be mentioned. Physiological pain, originally, has an important protective function, especially on the body surface, to prevent organs from over heat, cold and mechanical stimuli. This pain is usually a short but indispensable, as a body sensor. Touch sensation is conducted by a large axon. Pain fibers consist of small-diameter myelinated (Aβ) and unmyelinated (C) axons. Mechanical, hot, cold and chemical stimuli are picked up by free nerve endings of these axons. At free nerve endings, these stimuli lead to electrical activity to be transferred to the central nervous system, and pain is thus transmitted. All stimuli are picked up only on free nerve endings.

On the other hand, neuropathic pain occurs under pathological conditions such as nerve injuries occurring with surgery, trauma, spinal cord injuries, stroke, cancer, diabetes, herpes zoster and so on. The mechanism behind neuropathic pain differs entirely from the usual physiological pain that depends on a labeled line system. Neuropathic pain ranges from mild and dysesthetic to excruciating torture. The conditions are usually chronic and very often fail to respond to current therapies. Bennett GJ1 showed estimated incidence of neuropathic pain in inhabitants of U. S. A. (Table 1), but this did not include postoperative retarded pain which is estimated to occur in 10% of cases, these cases are neuropathic2.

I Clinical features of neuropathic pain3-5

In neuropathic pain, sensory nervous systems are damaged, peripherally or centrally, and the lesioned area easily becomes depolarized and spontaneous activity occurs. The mechanisms of this type of pain generation differ from normal and the patient feels a strange and dysesthetic pain. Neuropathic pain syndromes and signs are showed here.

Sensory deficit and pain

A cardinal feature in neuropathic pain is a partial or complete loss of afferent sensory function and the paradoxical presence of certain hyperphenomena in the painful area.

Allodynia and hyperalgesia

Allodynia refers to a situation where a normally innocuous stimulus produces a sensation of pain, the quality of which is inappropriate for the stimulus, for example, when lightly touching the skin with a wisp of cotton or an ice cube produces a burning pain sensation6.

Hyperalgesia refers to a painful sensation of abnormal severity following noxious stimulation6.

Hyperpathia

The term given to this condition: abnormal pain evoked from an area where there is an increased threshold for sensory detection6. Hyperpathic pain

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can be evoked by normally innocuous stimuli, by normally noxious stimuli, or by both. The pain is often felt after a remarkable delay and it may only appear after repeated stimulation\(^7\). Hyperpathic pain is described as having an "explosive" onset and a greatly exaggerated severity.

Abnormal prolongation of pain and abnormal spread of pain

In neuropathic pain the duration may be increased and may be associated with an abnormal spread of the pain. Psychophysical and neuronal recordings have shown that pain intensity is related to impulse discharges and numbers of neurons activated. Wide dynamic range (WDR) neurons are in part characterized by small receptive zones that can be excited by non-noxious stimuli (touch, gentle pressure) surrounded by a much larger zone from which noxious stimuli can evoke neuronal discharges. These large receptive field zones are overlapping, extend over several dermatomes and their receptive fields are a reflection of synaptic propriospinal interconnections in the spinal dorsal horn that extend over several segments. Therefore a noxious stimulus will in contrast to a non-noxious stimulus activate several WDR neurons and increasing the stimulus intensity will result in activation of further WDR neurons which are rostrocaudally dispersed\(^4\).

Wind-up-like pain and after sensations

In normal skin repeating a stimulus that activates C-fibre nociceptors causes burning pain sensations whose perceived intensity increases with each successive stimulus, provided that the stimuli are presented no more than 3 seconds apart. This perceptual phenomenon (pain summation) has an exact parallel in an electrophysiological effect known as wind-up: an increased response of spinal dorsal horn neurons to repeated C-fibre input\(^3\).

The persistence of pain long after termination of a painful stimulus. This is another characteristic feature of neuropathic pain\(^8\). WDR neurons show the same phenomenon of persistent discharges following noxious recruitment suggesting that after sensations may be a reflection of such neuronal discharges\(^9\).

Table 2 shows the main clinical features that are common in neuropathic patients. There are many different types of neuropathic pain and it is rare for one patient to manifest them all. Any of the features listed should raise the suspicion that a patient’s pain is neuropathic.

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**Table 1** Estimated incidence of neuropathic pain in the United States (based on a population of 270 million)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful diabetic neuropathy</td>
<td>600,000</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>500,000</td>
</tr>
<tr>
<td>Cancer-associated</td>
<td>200,000</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>120,000</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>51,000</td>
</tr>
<tr>
<td>Causalgia and reflex sympathetic dystrophy</td>
<td>100,000 ??</td>
</tr>
<tr>
<td>Phantom pain</td>
<td>50,000 ??</td>
</tr>
<tr>
<td>Poststroke (central pain)</td>
<td>30,000</td>
</tr>
<tr>
<td>HIV-associated</td>
<td>15,000</td>
</tr>
<tr>
<td>Tic douloureux (10% of 21 million cases)</td>
<td>15,000 ??</td>
</tr>
<tr>
<td>Low back pain associated</td>
<td>2,100,000</td>
</tr>
<tr>
<td>Total (excluding back pain)</td>
<td>1,681,000 (0.6%)</td>
</tr>
<tr>
<td>Total (including back pain)</td>
<td>3,781,000 (1.4%)</td>
</tr>
</tbody>
</table>

Table 2  Clinical features of neuropathic pain

1. Spontaneous, continuous and paroxysmal pain
2. Sensory deficit and pain
3. Alldynia and hyperalgesia
4. Hypoesthesia
5. Abnormal prolongation of pain and abnormal spread of pain
6. Wind-up-like pain and after sensations

II Clinical cases

Case 1: Neuropathic pain after nephrolithotomy
(Fig. 1)

A 69 year old woman came to our pain clinic on February 7th, 1996. She had sustained for 3 years the stabbing pain under surgery-related scarred skin in left upper lateral quadrant. The pain had continued since the left nephrolithotomy had been done.

Hypesthesia on the scarred region was noted in warm, cool and tactile sensory tests, but there was no allodynia on the same region, and otherwise normal results was seen. 10% lidocaine gel on the scarred skin or lidocaine (4 mg/kg) drip infusion for 60 minutes provided no relief. The antidepressant of amitriptyline 10~25 mg/day, only at bed time, was prescribed, was effective and was continued for 18 months until she experienced epigastralgia due to cholelithiasis. Amitriptyline was then discontinued, but neuropathic pain in left upper quadrant was not aggravated, and she is now in stable condition.

Case 2: Postthoracotomy pain syndrome

A 57 year old man seen in our pain clinic on April 1, 1997, complained of numbness and dull aching pain in the right chest with paroxysmal cramping pain in upper right chest. These pain had persisted since a right total pneumonectomy has been done in December, 1996.

Examinations revealed the right operated lung cancer state without malignant recurrence and hypesthesia on right operative chest field (Th3-7 front) but no allodynia. Low backache and disc hernia L₄₋₅ were evident on MR-examination. Amitriptyline 10 mg was prescribed to be given at bed time. Effect on the right chest dull aching pain was recorded on the 4~5th day after start of the medication, and the right postthoracotomy pain gradually

Fig. 1  69 year old woman
Left Nephrolithotomy on Feb. 5, 1993. Stabbing and piercing pain along the old operation scars had continued since left nephrolithotomy had been done. NSAIDs was prescribed but was not effective. Stabbing pain: VAS was 82 mm on the first visit. 10% lidocaine gel on the operation scars was not effective. Lidocaine 4 mg/kg drip infusion was not effective on the first visit.

[Dept. of Anesthesiology, Fukuoka University Hospital, 1997]
subsided. In June, 1997, laminectomy was done. Amitriptyline was discontinued during the hospitalization for disc hernia and the neuropathic pain in the right chest did not recur. In August, 1997, the patient was discharged in an ambulatory condition.

**Case 3: Neuropathic pain after brain haemorrhage**

A 62 year old man came to our pain clinic in a wheelchair, complaining of pain and stiffness in the right arm and shoulder plus insomnia. He had had a brain haemorrhage 6 months before, and right hemiplegia and dysphasia were present since the haemorrhage had occurred. He complained of stiff and aching pain, especially at night time. In the outpatient department, the lidocaine test (0.4 mg/kg and the saline single blind test) were done and Visual Analogue Scale (VAS) decreased from 40 mm to 20 mm only after the lidocaine injection. Mexiletine 3 mg/kg was prescribed and the pain decreased but without patient satisfaction. Amitriptyline 10 mg was then prescribed to be given at bed time, together with mexiletine. Much improvement followed and he was discharged.

**Case 4: Postoperative pain with allostynia, hyperpathia and sensory deficit at the area related to the tympanoplasty (Fig. 2, 3, Table 3)**

A 44 year old woman was transferred to our pain clinic on January the 14th, 1997 from the ear, nose and throat department of our university hospital, because of severe allodynia on the right auricle and referred pain to the tongue, which could be evoked by non-noxious stimulus to the right auricle or right external auditory canal. This situation gradually developed during the six months after tympanoplasty reoperation on September, 1992. She has sustained this pain for 4 years, despite various pain treatments. (Dept. of Anesthesiology, Fukuoka University Hospital, 1997)
alldynia decreased gradually. Two weeks later, examination revealed allodynia (warm, cool and tactile) on the operative scars at the region of the retroauricle, external auditory canal and also on the right tongue mucus membrane.

Valproic acid 200 mg/day or amitriptyline 10 mg/day was prescribed for 4 weeks, but she could not tolerate the sleepy state and discontinued the medication by herself. 10% lidocaine gel local application (only auricle) was continued. She improved gradually day by day while on the application of 10% lidocaine gel to the right auricle and 40 days after the initiation of 10% lidocaine gel, the VAS was 10 mm. However, she complained of re-aggravation of pain when she was active and had had insufficient sleep, and lidocaine drip infusion therapy (4 mg/kg/hr) was started once a week. In April, 1997, she worked as a cook, with no problems of pain, and is doing well. Application of 10% lidocaine to the right ear is made only at night time. Sensory examination (warm, cool and tactile test) showed allodynia on the right surface of the tongue and tasteless on that region, but otherwise she is doing well.

Case 5: Postherpetic neuralgia (Fig. 4)

A 69 year old man came to our pain clinic, complaining of terrible pain (VAS 70 mm) on the right T5 skin segment with a herpetic eruption which healed a week before (the visiting day was the 22nd day after
eruption). He complained of pain and insomnia on the first visiting day. He was admitted to hospital and continuous epidural infusion to T5 segment with 2% mepivacaine 0.7 ml/hr was initiated but his pain remained. On the 3rd admission day, epidural patient controlled analgesia (PCA) pump therapy was started and VAS decreased to 20 mm. Amitriptyline 10 mg/day, Mexiletine 150–300 mg/day were prescribed but the allodynia remained. 10% lidocaine gel was applied to the local skin for 14 days. Despite of all this treatment, the PCA pump to the epidural space had to be continued until the 32nd admission day (VAS 10 mm). The continuous epidural infusion therapy with 2% mepivacaine and 0.5% bupivacaine seems to be effective for such cases. This device alone can control the unbearable postherpetic pain state.

III Treatment of neuropathic pain

In the recent 5 years, the development of animal models of nociception showed that pain may be considered to have multiple components, even at the spinal level and that these mechanisms may reflect distinct pharmacologies. Evolution of these animal models has provided the clinical development of surprisingly novel agents targeted at pain control. Yaksh TL indicated the following drugs for neuropathic pain treatment.

Alpha 2 adrenoreceptor agonists

Preclinical studies have shown that alpha 2 adrenergic receptor agonists are effective in opioid insensitive models of nerve injury pain. While related mechanisms are not clear, alpha 2 agonists can diminish sympathetic outflow, either by a direct preterminal action on postganglionic fibers or by acting spinally on preganglionic sympathetic outflow. Consistent with this observation, it has been shown that clonidine can attenuate neuropathic pain in humans8,10.

NMDA antagonists

Systemic ketamine reduces the allodynia, hyperalgesia and after sensation present in patients with PHN11. Dextromethorphan has been shown to reduce the after sensation induced by repetitive stimuli in human observers12. Adenosine A1 agonists

Systemic delivery of adenosine can reduce spontaneous pain and increase touch-evoked pain13. Intrathecal delivery of a selective adenosine A1 agonist was shown to abolish the allodynia otherwise observed in a neuropathic patient14. The mechanism of A1 agonist activity is believed to be due to inhibition of spinal glutamate release.

N-type Ca++ channel blocker

An intrathecal N-type Ca++ channel antagonist (SNX-111) will attenuate neuropathic pain condition in patients with neuropathic and cancer pain. Gabapentin (1-(aminomethyl) cyclohexane acetic acid)

This was synthesized to be a systemically active GABA analogue and was found to have anticonvulsant activity, although initially given to humans as an adjuvant therapy to control seizures. Recent clinical case series indicated that the agent had efficacy in treating human neuropathic pain states15. Preclinical studies16 have demonstrated that systemic and intrathecal delivery of the agent is able to reverse, in a dose dependent fashion, the tactile allodynia in the Chung model, the thermal hyperalgesia in the Bennett model, and the second phase of the formalin test and so on. The mechanism of this action is not understood, but several points can be made. (1) The agent has a potent spinal action. (2) Binding studies fail to show affinity for either GABA A or B sites, although Gabapentin can increase the rate of GABA synthesis and release. (3) Binding studies have shown no affinity of Gabapentin for NMDA, AMPA or no-strychnine sites, but its effects are reversed by D-serine (an agonist at the NMDA–glycine site). (4) Gabapentin has moderate inhibitory effects on branched chain amino acid transferase (BCAA–T), a primary enzyme that metabolizes cystolic amino acids to form glutamate17. (5) Finally it has been shown that Gabapentin binds to the alpha 2 delta subunit of calcium channel18. Which, if any, of these elements are important to the actions of Gabapentin is not known. However, in view of the developing structure activity relationship, it seems clear that drugs may
represent a novel class of antihyperalgesic/allodynic agents, the gabapentinoids.

Na⁺ channel blocker

10% lidocaine gel (Table 4, Fig. 5)

Peripheral nerve injury is followed by a massive discharge in damaged sensory fibers, and spontaneous activity can arise subsequently in the neurona and persist for several weeks. Such ongoing discharges may be involved in the development of neuropathic pain. Na⁺ channel blockers work, in this situation, attenuate ectopic discharges in primary afferents. 10% lidocaine gel (pH = 8.7) penetrates the skin and it was found effective in an uncontrolled study of 11 PHN patients. We have used 10% lidocaine gel made by Fukuoka University Hospital Pharmacy for PHN patients for 4 years and good results were evident in PHN patients with allodynia. Table 4 indicated 10% lidocaine gel application that all patients were in severe pain (VAS 70−50). They all (case 3−6) complained of allodynia on the affected skin, the case 3 patient had had angina pectoris and warfarin was prescribed. The case 4 patient had had a myocardial infarction and cardiac failure. The case 5 patient was a 92 year old woman. The case 6 patient had had pulmonary tuberculosis and right lung abscess, with a thoracoplasty history. These patients were not considered for continuous epidural infusion with bupivacaine even though the pain was severe. In this situation, 10% lidocaine gel is useful and proved to be very effective. However, first two patients did not respond to 10% lidocaine gel application. The case 1 patient did not have allodynia, and a tricyclic antidepressant was effective. The case 2 patient had severe pain despite the local application of 10% lidocaine gel, but continuous epidural perfusion with 0.5% bupivacaine was effective. The pain in the case 2 patient was considered to relate to a peripheral

**Table 4** Effects of 10% lidocaine gel on PHN

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Region</th>
<th>Months after eruption</th>
<th>Allodynia</th>
<th>VAS on visit</th>
<th>VAS after treatment</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>F</td>
<td>Th left</td>
<td>2</td>
<td>(−)</td>
<td>70−80</td>
<td>70−80</td>
<td>applied continuous epidural infusion therapy</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>F</td>
<td>Th2a left</td>
<td>2</td>
<td>(++)</td>
<td>70</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>M</td>
<td>Th right</td>
<td>2</td>
<td>(++)</td>
<td>63 − 10−5</td>
<td>Warfarin (−)</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>M</td>
<td>Th2a right</td>
<td>1.5</td>
<td>(+)</td>
<td>70</td>
<td>10−5</td>
<td>MI, Cardiac failure</td>
</tr>
<tr>
<td>5</td>
<td>92</td>
<td>F</td>
<td>Trig 1 left</td>
<td>1</td>
<td>(++)</td>
<td>70</td>
<td>5</td>
<td>Antipyrine 10 mg 4 weeks</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>F</td>
<td>Th right</td>
<td>1</td>
<td>(+)</td>
<td>40−50</td>
<td>10−5</td>
<td>Old lung abscess Thoracoplasty</td>
</tr>
</tbody>
</table>

[Dept. of Anesthesiology, Fukuoka University Hospital, 1997]

![Fig. 5 Effect of 10% lidocaine gel for PHN Patients (n=29) (Dept. of Anesthesiology, Fukuoka University Hospital, 1997)](Fig. 5 Effect of 10% lidocaine gel for PHN Patients (n=29) (Dept. of Anesthesiology, Fukuoka University Hospital, 1997)
neuroma and dorsal root ganglion and continuous epidural perfusion therapy blocked both impulses from the peripheral neuroma and DRG. We have found 10% lidocaine gel to be effective for PHN patients with alldynia. The pain source seems to be near the skin surface.

IV Drip infusion of lidocaine (4~8 mg/kg)\textsuperscript{20-26} (Fig. 6, Table 5)

Intravenous lidocaine, at plasma concentrations that do not block axonal conduction, diminishes facilitated states induced by tissue and nerve injury without altering the acute nociceptive threshold. In humans, systemic lidocaine can be effective in treating certain neuropathic pain disorders at doses that do not produce frank anesthesia and at plasma concentrations less than those required to block axonal conduction. Fig. 6 shows the effects of repeated lidocaine drip infusions for patients who sustained PHN on 1st division of right trigeminal nerve for over 20 years. The VAS value at the start point was 90 mm. Lidocaine drip infusion was repeated 9 times during 2 months and the VAS value decreased to below 10 mm and the patient greatly improved. We have prescribed lidocaine infusion therapy (4~8 mg/kg for 60 min.) for 15 PHN patients. Excellent means that the VAS decreased to under 10 mm within 5 infusions. Good means that the VAS became about 10 mm after 5 or more infusions, fair means patient felt improvement after the treatments (Table 5).

Continuous epidural infusion therapy with 0.5% bupivacaine\textsuperscript{27,28}

For a severe grade of PHN, we have prescribed continuous epidural infusion therapy with 0.5% bupivacaine 0.5~0.75 ml/hr for 2~3 weeks. The principle of this regimen is to abolish the severe pain and maintain a good attenuated state for 2~3 weeks, but, the patient should be ambulatory during this 2~3 weeks, therefore, 0.5% bupivacaine 0.5~0.75 ml/hr was prescribed.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Lidocaine drip infusion therapy (4~8 mg/kg/60 min.) for PHN patients (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent (+++)</td>
<td>Good (+++)</td>
</tr>
<tr>
<td>&lt; 5 times</td>
<td>&gt; 5 times</td>
</tr>
<tr>
<td>Lidocaine 8 mg/kg</td>
<td>0</td>
</tr>
<tr>
<td>Lidocaine 4 mg/kg</td>
<td>1</td>
</tr>
<tr>
<td>5/15 (33%)</td>
<td></td>
</tr>
<tr>
<td>11/15 (73%)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 6 77 year old man, Trig. I (Rt.) 20 years and 6 months after eruption [Dept. of Anesthesiology, Fukuoka University Hospital, 1997]
Tricyclic antidepressants

Apart from the NSAIDs and the opioids, antidepressants are probably the most commonly prescribed class of drugs for the treatment of chronic pain. The first generation tricyclic antidepressants, amitriptyline, imipramine, clomipramine, desipramine, nor-triptyline and doxepin have been used, and amitriptyline, imipramine and clomipramine are the most widely used. However, pain relief from these drugs is often modest in degree and can be accompanied by side effects such as sedation, postural hypotension, and cholinergic blockade. Max MB indicated that from data on 60 controlled clinical trials. (1) Tricyclic antidepressants with balanced inhibition of 5HT and NE reuptake, amitriptyline, imipramine and clomipramine, appeared to be the most effective agents, and (2) The selective NE reuptake blocker desipramine was also effective. (3) Dose-responsive study or concentration-responsive study was done on neuropathic patients, and a significant relation to dose dependent efficacy was noted. (4) But considering the side effects, tricyclic antidepressant (amitriptyline, imipramine or clomipramine) should probably be prescribed 10 mg/day for patients over age 65 years and 25 mg/day for those under 65 years.

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References

7) Noordenbos W : Pain, Elsevier, Amsterdam, 1959
25) Tanelian DL, Brose WG : Neuropathic pain can be relieved by drugs that are use-dependent sodium channel blockers : lidocaine, carbamazepine, and mexiletine. Anesthesiology 74 : 949-951, 1991