13.10 Acute neuropathic pain

13.10.1 General considerations

Owing to its severity and persistence (considered as chronic pain), neuropathic pain has a high morbidity and often results in disability.

Nociceptive pain differs from neuropathic pain. Neuropathic pain is usually described as being sharp, aching or throbbing. It usually occurs in the area of injury, is proportional to the extent of injury, and decreases as healing takes place.

Neuropathic pain may remain constant, but usually changes in character (i.e. distribution, triggers, severity, duration and frequency of attacks). It often persists even after healing or after the original stimulus has disappeared. The pain is dysfunctional since it no longer has a protective role, namely to protect the person from real or potential tissue harm:

- The person experiences pain in a body part that is not present anymore (*phantom pain*).
- Pain may be experienced in the absence of a stimulus (*dysaesthesia*).
- Pain may be experienced in response to nonharmful stimuli, such as touch (*allodynia*).
- The pain may be a disproportionate response to a stimulus that is painful (*hyperalgesia*).
- Pain may be accompanied by inappropriate sensations, such as pins and needles, crawling and tingling (*paresthesia*).
- Pain or other sensations are experienced in a different part than the part that is stimulated (*alachaesthesia*).
- Pain is experienced in a numb area (*anaesthesia dolorosa*).

Neuropathic pain is caused by lesions in the CNS or the peripheral nervous system (PNS). Injury of the CNS and PNS cause severe acute neuropathic pain (ANP) and may evolve into chronic pain complex regional pain syndromes.

13.10.2 Central neuropathic pain

Central neuropathic pain (CNP) is caused by pathology in the somatosensory tracts involving the spinothalamic tract, or trigeminothalamic tracts and the sensory cortex. Stroke, brain surgery and spinal cord injury are the most common causes of CNP. It affects approximately 8% of stroke victims and about 70% of patients with spinal cord injury. CNP also complicates multiple sclerosis, vascular malformations, tumours and infections (tuberculosis, syphilitic myelitis, abscesses, HIV).

Spinal cord injury can cause severe ANP, which is often complicated by chronic pain. Pain can develop weeks, months or years following spinal cord injury. Pain is experienced at the level or above the level of injury.

Stroke-related CNP appear soon, months or years after the *stroke*. It usually involves large parts of the body and is characterised by a sensation or mixture of sensations of aching, burning (*causalgia*), cold, crushing, shocking, stabbing, numbness, allodynia, hyperalgesia, alachaesthesia and hip pain. Other symptoms include intolerance to temperature change, fatigue, a vague numb sensation, hyperalgesia, allodynia, allachaesthesia and visceral pain. Nociceptive pain can also develop.

CNP is difficult to treat, and is resistant to many options. Treatment of the condition follows the principles used for the management of chronic neuropathic pain.

13.10.3 Peripheral neuropathic pain

Peripheral neuropathic pain (PNP) occurs after injury of the dorsal root ganglion, a peripheral nerve, or nerve plexus. Common aetiologies include metabolic disease (diabetes mellitus), infection (postherpetic neuralgia [PHN] following herpes zoster), ischaemia, injury (postsurgical, brachial plexus avulsion), entrapment (carpal tunnel syndrome, disc herniation with compression of a spinal nerve causing radicular pain, trigeminal neuralgia), autoimmune connective tissue disease (due to neurovasculitis), malignancy, drugs (antineoplastic agents, antiepileptic agents, vitamin deficiencies) and toxins (lead, mercury, arsenic, thallium, organic solvents [including glue sniffing]).

Approximately 1% of patients experience PNP after nonamputation surgery. In about half of these patients, pain persisted for at least a year. Procedures that carry a higher risk to develop ANP include limb amputation, thoracotomy, and mastectomy with axillary lymph node dissection. The mechanism of ANP in all these procedures involve peripheral nerve injury. Severity of postoperative pain may be the first indication of nerve injury and is a predictor of long-term pain. Insufficient postoperative analgesia is also complicated by prolonged postoperative pain.

Nerve injuries that are renowned for the most severe ANP include spinal cord injury, brachial plexus avulsion, burn injury and herpes zoster. Thermal injury and herpes zoster damage cutaneous nerves. This progresses to ANP and is often described as intense burning dysaesthesia (hot pain), stinging or pricking, beating and itching. These sensations often persist long after the lesions have healed.

Patients suffering from a neuropathic pain (CNP and PNP) often experience pain-related sleep disturbance, and vice versa. This aspect should be kept in mind when treating neuropathic pain.

At the end of this section, two very common ANP syndromes will be discussed, namely herpes zoster- and HIV-related pain.

13.10.4 General management of acute neuropathic pain

- If possible, manage the primary process that has led to ANP and prevent further damage (e.g., management of fractures, wound care and early adequate multimodal analgesia).
- Early pharmacological therapies to address the initiating process should be started as soon as possible. Once the doctor has missed the early therapeutic window, the risk of chronicity increases, which responds far less favourable to medication (e.g. herpetic neuralgia).
- Psychological support should be offered since psychological stress aggravates pain.

13.10.5 Pharmacological management of acute neuropathic pain

Several drugs have been tested and recommended for the management of CNP and PNP, irrespective of the causes. Although different drugs demonstrate better analgesic effects in some conditions, part of its beneficial effects may be ascribed to the effect on sleep and mood.

The efficacy of drugs in some painful neuropathies is unclear. For some conditions, a drug may be the 'first-line recommendation', while it may be an 'add-on' for another condition. However, several algorithms have been suggested, which can be applied (tried) in most conditions.

The difference in effects of drugs in different conditions may be ascribed to different pain mechanisms, different levels of pain, pharmacogenetic factors, etc. For example, pregabalin is useful in several conditions, but ineffective in the treatment of HIV-associated distal sensory polyneuropathy and radiculopathy. Apart from surgery, the best treatment option for trigeminal neuralgia is carbamazepine.

Regarding the influence of pathophysiology on treatment, painful neuropathies may have different mechanisms of injury, which may influence the efficacy of particular drugs in particular neuropathies. For example, neuropathies may be caused by either compression or noncompression mechanisms (toxic, trauma, ischaemic or infective). Compression neuropathy (e.g. radicular pain following disc herniation) has a different pathophysiology and is often not

successfully treated by the conventional drugs (e.g. the gabapentanoids). The same may apply to trigeminal neuralgia caused by vascular compression at the brain stem.

The efficacy of drugs is usually measured according to a global effect on pain (e.g. the VAS). However, the effect of analgesic used in neuropathic pain may be determined by the effect of the drug on a particular pain entity (e.g. the effect on mechanical [touch] allodynia and thermal allodynia). If these different aspects (total pain, differential pain) were tested, so-called responders to a particular agent reported in most studies, would not be real responders. For example, in central and peripheral nerve injury, IV lignocaine is not equally effective to suppress all the pain components, since patients experience relief of spontaneous pain and mechanical allodynia and hyperalgesia, but not thermal allodynia and hyperalgesia.

The recommendations in this section are based on the conclusions of several trials, review articles and meta-analyses. The recommendations include 'should be offered', 'should be considered', 'less robust evidence', or 'no better than placebo'. These recommendations are based, for example, on meta-analyses that grouped recommendations on the size of the difference between treatment options, risk difference (reduction in pain in the active group minus that in the control group) and numbers needed to treat (NNT). For a difference in the proportions of patients with a pain reduction > 30–50%, a risk difference of > 20% is regarded as a large effect (NNT < 5), a risk difference of > 10–20% (NNT 5–10) as a moderate effect, and a risk difference of < 10% (NNT > 10) is regarded as a small effect. When reporting the mean reduction of pain from baseline on a Likert scale or VAS as compared to an alternative drug or placebo, a reduction difference of > 30% is considered a large effect, > 15–30% is a moderate effect, and < 15% is a small effect.

Several drugs are used off-label to treat neuropathic pain. This must be explained to the patient. Moreover, the patient must be aware that the drug does not change disease progression.

The following drugs are used to alleviate ANP: antidepressants, antiepileptic agents, membrane stabilisers, ketamine, opioids and capsaicin.

Antidepressants

These include the TCAs (e.g. amitriptyline, nortriptyline) and the SNRIs (e.g. venlafaxine and duloxetine).

Both TCAs have several adverse effects, including dizziness, insomnia or sedation, dry mouth, blurred vision, hypertension and tachycardia. These should not be used within two weeks of MAOIs and should not be used together with antihistamines, antihistamine-like agents (such as antipsychotic drugs) and antiemetics. TCAs have antimuscarinic effects and should be avoided in patients with glaucoma and prostate enlargement. These should also not be used with other serotonin reuptake inhibitors, including the SSRIs and tramadol.

Early amitriptyline reduces the development of PHN and has been used for relief of phantom limb pain, pain following hip surgery and painful diabetic peripheral neuropathy pain. However, amitriptyline is not beneficial in the treatment of HIV-related neuropathic pain. The dose of amitriptyline is a low dose (10 mg) at night, which is increased gradually up to 75 mg.

Blood levels of amitriptyline are increased by the inhibitors of cytochrome enzyme inhibitors, such as the protease inhibitor antiretroviral agents (e.g. ritonavir, lopinavir and atazanavir). Blood levels are decreased by the enzyme inducer carbamazepine.

Two SNRIs are recommended for neuropathic pain, namely venlafaxine and duloxetine. Neuropathic pain following chemotherapy and painful diabetic peripheral neuropathy can be treated with venlafaxine and duloxetine, while gabapentanoids are ineffective. Venlafaxine and duloxetine have a safer CV profile than the TCAs and these should not be prescribed within two weeks after stopping an MAOI.

Extended-release venlafaxine 75 mg daily for 2–6 weeks has been used with success. The dose of duloxetine is approximately 0.8 mg/kg at bedtime.

Duloxetine has several drug interactions: SSRIs (serotonin syndrome), neuroleptics (prolonged QT interval, dysrhythmias), anticoagulants (increased bleeding) and the triptans. The dose should be decreased in patients with decreased renal function. (See the SAMF for more complete information.)

Antiepileptic drugs

Antiepileptic agents, gabapentanoids (gabapentin and pregabalin), carboxamides (carbamazepine and oxcarbazepine), lamotrigine and topiramate have been used for ANP. Lamotrigine, topiramate and phenytoin have been used for trigeminal neuralgia.

- *Gabapentin* and *pregabalin* have been recommended as first-line treatment of several neuropathic pain syndromes. These drugs are GABA analogues with a structure similar to that of the amino acid leucine, but are inactive at $GABA_A$ (the benzodiazepines) and $GABA_B$ receptors (baclofen). Like opioids and ketamine, these agents inhibit the release of glutamate and aspartate from the dorsal root neurons to stimulate the sensory neuron in the spinal cord. The gabapentanoids affect the α2-δ-1 subunit of neuronal calcium channels on presynaptic membranes. Pregabalin has a higher affinity for the alpha-2-delta protein. Therefore, the dose of pregabalin is approximately six times lower than that of gabapentin.

Expression of calcium channels occurs in central and peripheral neurons following nervous system injury. The effect of the gabapentanoids on the α2-δ-1 subunit of these neuronal calcium channels may explain the efficacy of these drugs in CNP (spinal cord injury) and PNP (postherpetic neuralgia and diabetic peripheral neuropathy, trigeminal neuralgia). Although pregabalin is useful in several conditions, it is ineffective in the treatment of HIV-associated

distal sensory polyneuropathy. Little evidence from randomised control trials support the use of gabapentanoids for the management of radicular and chemotherapy-induced neuropathic pain.

Apart from its effect on neuropathic pain, pregabalin improves sleep. This effect occurs within the first two days of treatment and contributes to its analgesic effect.

The adverse effects of gabapentin and pregabalin are similar and include sedation, fatigue, dizziness, irritability, cerebellar signs (dysarthria, tremor, ataxia, vertigo) and ocular symptoms (blurred vision, diplopia). Patients who experience adverse effects from one gabapentinoid usually experience the same effects from the other.

The gabapentanoids use the L-amino acid transporters in the gut for absorption. This transport system of gabapentin is saturable, while that of pregabalin is not saturated by large doses. The gabapentanoids are not metabolised by cytochrome enzymes and is excreted mainly by the kidneys. Therefore, the doses of these agents must be adjusted according to renal function tests.

The starting dose of *gabapentin* is approximately 2 mg/kg 12-hourly and may be increased gradually to a maximum of 20 mg/kg 12-hourly. The dose of pregabalin is approximately 1 mg/kg 12-hourly and may be increased gradually to 4 mg/kg 12-hourly. Pregabalin should not be stopped abruptly but withdrawn over no less than a week.

- *Oxcarbazines carbamazepine* and *oxcarbazepine* are the first-line drugs for the management of trigeminal neuralgia. However, the most successful treatment of trigeminal neuralgia is surgery to decompress the nerve in the brainstem.

The dose of *carbamazepine* is approximately 1.5 mg/kg (100 mg) 12-hourly. This dose is increased by 1.5 mg/kg 12-hourly until pain is relieved. The maximum dose is approximately 16 mg/kg/day (1 200 mg). The MD is 5–10 mg/kg/day (400–800 mg).

Carbamazepine is not a 'clean' drug. It induces its own metabolism in the liver, necessitating an increase in doses. Therefore, blood levels should be monitored. It has several drug interactions, which should be investigated before prescribing the drug. Interactions occur with other anticonvulsants, antiretroviral drugs, TCAs, neuroleptics, MAOIs, lithium, SSRIs, cimetidine, erythromycin, tetracycline, rifampicin, calcium channel blockers (verapamil, diltiazem decrease metabolism of carbamazepine), oral contraceptives and glucocorticosteroids. Several of these drugs are also used for other pain conditions, and the necessary adjustments should be made.

Adverse effects of carbamazepine include drowsiness, nausea, dizziness, diplopia, ataxia, elevation of liver enzymes, lymph adenopathy, bone marrow suppression (agranulocytosis, thrombocytopaenia, aplastic anaemia), and syndrome of inappropriate vasopressin secretion

(hyponatremia). Therefore, blood levels, blood count and blood biochemistry should be performed after initiation of therapy.

Oxcarbazepine is a derivative of carbamazepine. It is cleaner than carbamazepine as it is converted into an active metabolite, which does not induce liver enzymes significantly. It has less adverse effects than carbamazepine, but also interact with calcium channel blockers, oral contraceptives, antiretrovirals and MAOIs.

The initial dose of *oxcarbazepine* is 4 mg/kg 12-hourly. This dose is increased gradually to effect weekly, up to a maximum of approximately 16 mg/kg/day. The effective dose is then decreased. The MD is 4–8 mg/g/day.

- *Lamotrigine* inhibits the release of glutamate (ketamine-like). Lamotrigine reduces pain experienced from HIV-related peripheral sensory neuropathy and trigeminal neuralgia. The dose is approximately 0.3 mg/kg/day, increased by 0.3 mg/kg/day after two weeks, and then increased by 1.5 mg/kg every two weeks if necessary. The total dose is divided and taken 12-hourly with a target dose of 3–4 mg/kg/day. Lamotrigine levels are decreased by enzyme inducers (carbamazepine and phenytoin) and by protease inhibitors (lopinavir, ritonavir). Adverse effects include sedation, insomnia, cerebellar signs, diplopia, blurred vision (myopia), dizziness, nausea, severe skin rash (Stevens-Johnson syndrome), desquamation and bone marrow suppression. This drug inhibits dihydrofolate reductase.
- *Topiramate* is a glutamate antagonist and GABA agonist. It is also a carbonic acid anhydrase inhibitor. The dose is the same as that for lamotrigine (i.e. approximately 0.3 mg/kg/day, increased by 0.3 mg/kg/day after two weeks, then increased by 1.5 mg/kg every two weeks if necessary). The total dose is divided and taken 12-hourly with a target dose of 3–4 mg/kg/day. Adverse effects are similar to that of lamotrigine. However, it also has several troubling adverse effects, including cognitive decline, dysgeusia, acral paraesthesiae, metabolic acidosis, acute narrow-angle-glaucoma, renal calculi and it is **teratogenic**.
- *Phenytoin* may be used to manage a trigeminal neuralgia crisis. A dose of 14 mg/kg is administered intravenously over 20 minutes. This dose may be effective for up to two days, allowing other drugs to take effect.

Membrane stabilisers

Peripheral nerve injury increases expression of sodium channels, leading to a more positive membrane potential, which makes the nerves more excitable. Two sodium channel blockers have been tried, namely *mexiletine* and *lignocaine*. Evidence regarding the efficacy of *mexiletine* is lacking. Lignocaine is not absorbed orally, but the efficacy of IV lignocaine and lignocaine 5% patches have been used with success in PHN and trauma-related neuropathy. Several IV lignocaine 'tests' have been used. In CNP and PNP, lignocaine 5 mg/kg over 30 minutes improve spontaneous and mechanical allodynia and hyperalgesia for up to 6 hours (and for days

in some patients). Lidocaine 3 mg/kg over 3 minutes followed by 4 mg/kg over 60 minutes were effective in CNP and PNP. Although not investigated, these modalities may be useful in the management of an acute attack of neuropathic pain. Lignocaine 5% patches are used for herpes zoster- and HIV-related neuropathic pain.

Opioids

Despite several adverse effects, addiction potential and overuse pain syndromes, opioids may be used in the management of chronic nonmalignant neuropathic pain. Morphine, oxycodone and tramadol may be considered, but these have moderate effect sizes.

Although there is no firm evidence for its efficacy in neuropathic pain, tramadol is considered a second-line drug for ANP and exacerbations of neuropathic pain. It should not be used with SSRIs and TCAs.

Tapentadol is a newer, weak μ-receptor agonist and norepinephrine reuptake inhibitor. It has been used for painful diabetic peripheral neuropathy.

N-Methyl D-aspartate receptor antagonists: ketamine

Ketamine 0.4mg/kg IVI has shown some efficacy in the treatment of ANP. This may be used for relief of acute exacerbations of neuropathic pain.

Capsaicin receptor stimulation

Capsaicin stimulates transient receptor potential vanilloid 1 (TRPV1) channels (capsaicin receptors) on nociceptors at the peripheral sensory nerve endings. TRPV1 is activated by exogenous and endogenous stimuli. These channels are activated by temperature higher than 43 °C, a low pH and substances in spices (e.g., capsaicin in chili peppers, and allyl isothiocyanate in mustard and wasabi). TRPV1 is involved in the detection of high temperature and thermoregulation. Stimulation of TRPV1 channels causes an intensely painful, burning sensation. Application of a high concentration causes overstimulation of nociceptors followed by a reversible reduction in nerve fiber density and extinguishing of nociceptor sensitivity. The capsaicin 8% patch does not have any systemic adverse effects, and a single application can provide pain relief for up to three months. It is useful in herpetic neuralgia as well as some painful HIV-related neuropathies.

13.10.6 Algorithm for the pharmacological management of acute neuropathic pain

- *First-line:* TCAs, gabapentanoids, SNRIs, topical agents (lignocaine, capsaicin)
- *Second-line:* opioids (tramadol), combinations of first-line agents (taking into account drug interactions)
- *Third-line:* antiepileptic agents, SNRI antidepressants, NMDA antagonists

13.10.7 Acute herpetic neuralgia

Acute herpetic neuralgia (AHN) results from reinfection by herpes varicella viruses that were dormant in a dorsal root ganglion or trigeminal ganglion for several years. The incidence of AHN increases with age. The pain of AHN often starts as paraesthesia, allodynia, hyperalgesia and dysaesthesia (aching, severe itching, burning and electric shock-like pain). These symptoms often precede the typical dermatomal herpes zoster vesicular rash. In approximately 15% of patients, AHN is complicated by PHN (i.e. persistence of pain for more than three months after the rash has disappeared). Approximately 50% of patients experience pain for longer than a year.

Administering an antiviral agent within 72 hours and early medication for ANP decreases the incidence of PHN, which is often difficult to manage.

Systemic treatment should be offered as soon as possible. The systemic agents recommended for AHN is the same as for ANP, namely a TCA, gabapentin or pregabalin, and an opioid (oxycodone or morphine). Lidocaine 5% should be offered. Aspirin in ointment or cream may be tried.

A single application of a capsaicin 8% patch provides pain relief for up to 12 weeks and does not have any systemic adverse effects. Application of the patch causes pain or discomfort for approximately 6 hours, but is well tolerated. Patients with more pain before the application of the patch experience less capsaicin-related discomfort than patients with less pain. Adverse effects are limited to transient local erythema and treatment-related discomfort.