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Pharmacological Therapy in Sub-Acute Postherpetic Neuralgia Patients: A Case Report

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ABSTRACT

Introduction: Herpes zoster is caused by the reactivation of the varicella-zoster virus. Post-herpetic neuralgia (PHN) is pain due to a zoster that persists 1 month after vesicle development. Usually, the prognosis is good, but some patients continue to suffer from long-term pain. The goal of PHN therapy is to reduce pain and improve quality of life. Antiepileptic drugs and tricyclic antidepressants are the first choices. **Case presentation:** A 32-year-old man presented with complaints of left-sided headache radiating like electricity to the left eyelid for ± 6 weeks, sudden spikes of nails, numbness/cramping sensation, and pain when touched (allodynia), and hypoesthesia. His previous medical history was herpes zoster, and he received acyclovir and symptomatic therapy such as paracetamol, mefenamic acid, dexamethasone, and cetirizine. The patient presented with a 6-7/10 visual analog scale (VAS) and was diagnosed with subacute post-herpetic neuralgia. The patient received Lyrica (Pregabalin) 50 mg 2 times a day 1 tablet, amitriptyline 10 mg once a day 1 tablet, Ultracet (Tramadol 37.5 mg + paracetamol 375 mg) 3 times a day 1 tablet. After the 14th day, the patient's VAS was reduced to 2/10, but side effects occurred in the form of dry lips and frequent sleepiness, and continued treatment with only Amitriptyline 10 mg/day. **Conclusion:** Rapid therapy for PHN provides prevention of refractory pain, making it difficult to provide adequate therapy. Giving first-line therapy in subacute PHN using amitriptyline, pregabalin, and tramadol agents have a very good effect in overcoming pain in subacute PHN, but it is necessary to monitor the side effects that occur due to potentiation of these three drugs.

Keywords. amitriptyline, pregabalin, subacute post herpetic neuralgia, tramadol, visual analog scale.

Introduction

Herpes zoster (HZ) is caused by the reactivation of the varicella-zoster virus (VZV), which has previously caused chickenpox infection in childhood. The incidence of herpes zoster infection is dominated by older people with weakened immunity to the virus. The incidence of HZ in the United States is about 1 million a year, and 2%-3% of patients will be hospitalized. And annual funds are used from $1 million – $2 million, the incidence of HZ is about 2 patients in 1000 people. A meta-analysis study showed the incidence of post-herpetic neuralgia (PHN) reached 42 cases per 100,000 people per year. Usually, the prognosis is good, but some patients continue to suffer from long-term pain, leading to PHN, a persistent pain syndrome that is difficult to treat. Pain is an important sign of PHN, which can interfere with a person's activities to disrupt sleep and mood. Patients who experience severe pain even experience anxiety and depression, resulting in reduced quality of life (QoL) [1-3] There is no consensus on the definition of PHN, but it is generally defined as pain due to a zoster that persists 1 month after vesicle development.[3] The goals of PHN therapy are to reduce pain and increase QoL.[1-5] This study aims to present pharmacotherapy in post-herpetic neuralgia patients.

Case Presentation

A 32-year-old male patient complained of pain in the left head that radiates from the left head to the left eyelid area. Pain is like being stabbed by nails, sudden attacks of pain radiating like electricity, and feeling numb/tingling. Cramping is present if an attack occurs. It is very painful and feels intermittent. If touched, it feels very painful (allodynia). Hypoesthesia is present. This pain is felt for ± 6 weeks and is disturbing at work. History of previous illness diagnosed with herpes zoster (HZ), history of previous treatment with acyclovir tablets and ointment, nerve vitamins, anti-pain paracetamol 500 mg 3 times a day 1 tablet and mefenamic acid 500 mg 3 times a day 1 tablet, dexamethasone 0.5 mg 2 times 1 tablet a day, cetirizine 10 mg 2 times a day 1 tablet.

The patient looks moderately ill, has a height of 170 cm, and has a weight of 65 kg. Vital signs showed blood pressure 120/80 mmHg, pulse 75x/minute, breathing 18x/minute, temperature 36.8^{o}C, SpO_2 99%, and visual analog scale (VAS) 6-7/10. On local examination of the head region, it was found that pain in the left head radiated from the left head to the left eyelid area. The pain was like being pricked by a nail, radiated like electricity, a feeling of numbness/cramping was present, allodynia was present, and hypoesthesia was present.

Figure 1. Clinical photos of the patient.

The patient was diagnosed with acute sub-post-herpetic neuralgia and received therapy Lyrica (Pregabalin) 50 mg 2 times a day 1 tablet, Amitriptyline 10 mg once a day 1 tablet, Ultracet (Tramadol 37.5 mg + paracetamol 375 mg) 3 times a day 1 tablet. After receiving treatment for a week, there was a decrease in the pain scale in patients on the face with VAS from 6-7 to 2-3, and the pain attacks also decreased, but side effects occurred in the form of dry lips and frequent sleepiness, so Ultracet containing tramadol was stopped, and the dose of pregabalin was reduced. to 50 mg/day. The 14th day of treatment showed almost no pain, but numbness in the facial area was still felt with VAS decreased to 2/10, and current therapy was only Amitriptyline 10 mg/day.

Discussion

Post-herpetic neuralgia (PHN) is persistent chronic pain, most often occurring in elderly patients. According to a recent study, pain associated with herpes zoster is divided into 3 phases. Namely, acute herpetic neuralgia, which is pain felt during the onset of vesicles up to 30 days after healing, and subacute herpetic neuralgia, which is pain felt 30 days – 120 days after healing, while PHN is pain that persists 120 days after healing. The duration of PHN varies greatly. About 50% of pain will resolve on its own within 1 year.[3] The patient was diagnosed with subacute herpetic neuralgia because the pain had been felt for approximately 6 weeks.

PHN pain caused by HZV usually follows a typical dermatomal pattern of rash onset. Unilateral thoracic area and dermatome of the trigeminal nerve (mostly in the ophthalmic

branch), pain is felt as a sharp sensation or like an electric shock, like burning, along with patchy allodynia, hyperesthesia, and hypoesthesia.[2-7] In this patient, the lesion was acquired in the left ophthalmic dermatome, and the pain sensation was sharp, electric shock, allodynia, and hypoesthesia.

During primary infection, the varicella-zoster virus enters the base of the dorsal sensory ganglia. Then due to depression of cell-mediated immunity, the virus can activate and replicate and migrate to sensory nerves causing dermatomal pain distribution. Inflammation of the peripheral nerves causes demyelination, Wallerian degeneration, and fibrosis. This results in an excessive activity of unmyelinated primary afferents causing pain associated with NPH. Pain and hyperaesthesia in these patients are due to severe damage to large, myelinated nerve branches in the peripheral nerves as a result of the absence of inhibition of large myelinated nerves causing pain and atrophy of the spinal cord dorsal horn. There is also an increase in the activity of –αδρενεργιχ agonists and sympathetic nerves, which explains why peripheral nerve blocks cannot work effectively. Research has been carried out to describe post-herpetic neuralgia subtypes based on the type of neuronal damage so that an appropriate treatment protocol can be given.[3.8]

Based on the type of pain, PHN is divided into 3 groups, patients can experience more than 1 group, namely (1) constant pain without any stimulus (sometimes described as burning, stabbing, or throbbing), (2) intermittent pain without a stimulus (sometimes described as being stabbed with a sharp object, shooting or like an electric shock), and (3) pain that occurs is accompanied by a stimulus but the stimulus is misinterpreted (allodynia). Symptoms in this patient include pain.

Pharmacological therapy in cases of PHN, according to the recommendations of NeuPSIG for the first line recommended, is calcium channel modulators, namely gabapentin and pregabalin, which selectively bind to the α2δ subunit protein and inhibit neurotransmitter release, and tricyclic antidepressants, namely amitriptyline, nortriptyline, and desipramine (Table 1). [1,3-5]

Gabapentin reduces calcium influx into cells and reduces the production and release of the excitatory transmitter glutamate.[3-5] This drug is able to reduce 41-43% of pain in PHN patients. The initial dose of 300 mg/day and then increased to 3600 mg/day after 1 week can reduce pain.[5] Previous studies have shown that gabapentin 600 mg divided into 2 doses for 3 days and increased to 1200 mg/day for 4 days reduces daily pain levels and improves sleep, mood, and quality of life.[1,3,10,11]

Pregabalin exerts ion-gate modulating, pain-relieving, anti-convulsant, and anxiolytic effects, with a more rapid onset of action. It is known that this drug has succeeded in reducing 50% of pain in PHN patients. The initial dose is 100-150 mg/day in 2 divided doses, increased to 300 mg/day a week to 600 mg/day for 2-4 weeks if not effective.[5,9] Dosage is adjusted based on pain relief and renal function, with the most common side effects being drowsiness, dizziness, and peripheral edema.[1,3,5,9] In these patients, 50 mg of pregabalin was used 2 times 1 tablet to get fast results with small doses, but there were side effects such as somnolence and dizziness in the second week, so the dose was reduced to 50 mg per 24 hours.

A randomized study by David et al., 1997 showed that a minimal dose combination of amitriptyline and an antiviral helped patients to be pain-free for 6 months. The dose of this drug is started with a low dose of 10-25 mg in a single dose (before bedtime), then slowly titrated to reduce side effects, especially in elderly patients with cardiovascular disease.[1,3,5,8,11,13] In these patients, a single and minimal dose of amitriptyline 10 mg was administered at night. There are side effects in the form of sedation and dry lips in patients. This is due to the synergistic effect of taking tramadol together with pregabalin.

Based on a systematic review showed nortriptyline is effective in treating neuropathic pain. Even the combination with gabapentin further reduces the pain scale. The initial dose is 10-25 mg/day for 1 week, with a maintenance dose of 30-75 mg/day in divided or single doses at night. This drug is safer for elderly patients with minimal side effects such as cardiac, cognitive, constipation, and orthostatic hypotension.[5] A randomized controlled study showed that 67% of patients with amitriptyline rated good to very good, and 63% of patients with desipramine rated it moderate or better.

The second-line pharmacological therapy of PHN, capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) activates the transient receptor potential vanilloid 1 receptor (TRPV1)-expressing cutaneous nociceptors with the initial effect of producing a burning sensation and erythema, then skin nociceptors become less sensitive is called 'desensitization' which is reversible after a few weeks. There are several capsaicin preparations based on their concentration, namely capsaicin cream 8%, 0.075%, and 0.025%.[3] Based on controlled clinical trials, the effectiveness of 8% capsaicin application for 60 minutes in PHN patients was able to reduce pain for 12 weeks.[1,3]

Mechanisms of inhibition of the sodium pathway in the lesion area have been shown to show significant improvement in PHN patients with allodynia after administration of a 5% lidocaine patch, despite mild side effects, namely rash and erythema. A previous study found

the same level of analgesia between the administration of 5% lidocaine and pregabalin in PHN patients with minimal side effects. Due to its efficacy and safety, it is still the first-line treatment for neuropathic pain (Table 3). Another patch (EMLA) containing lidocaine and prilocaine may also be used.[1,3,5]

Several types of topical NSAIDs are topical aspirin, *Skin Coolants*, namely ethyl chloride (Chloroethane) and fluori-methane, and preparations containing menthol. Two randomized controlled trials by Benedittis G et al. showed excellent results in reducing pain, 93% and 87% in AHN patients and 65% and 82% in PHN patients, respectively. While skin collants aim to cool the blood vessels in the skin, they cannot provide long-term benefits.[3]

Tramadol is an opioid that acts to inhibit noradrenaline reuptake and serotonin release stimulation at the spinal level. It has been shown to be significant in reducing pain in PHN patients, at a dose of 100-400 mg/day or in divided doses of 50 mg every 4-6 hours.[1,5,11] In these patients, tramadol provides analgesia as well as side effects of sedation due to its potentiation with the use of amitriptyline and pregabalin. This is because tramadol and amitriptyline work synergistically with the reuptake of noradrenaline and serotonin.

Table 1. Drugs for the treatment of PHN.[3]

Medication	Dosage	Adverse effects
Antiepileptics		
Gabapentin	100 to 300 mg orally at bedtime; increase dosage by 100 to 300 mg every three days until dosage is 300 to 900 mg three times daily or response is adequate	Mild peripheral edema, cognitive impairment, somnolence, fatigue, dizziness, ataxia
Pregabalin	75 mg twice daily, increase to 150 mg bd daily within one week	Sleep disturbance, dizziness
Tricyclic antidepressants		
Amitriptyline Nortriptyline Imipramine Desipramine	10 to 25 mg orally at bedtime; increase dosage by 25 mg every two to four weeks until response is adequate, or to a maximum dosage of 150 mg per day	Sedation, dry mouth, constipation, sweating, xerostomia, confusion, dysrhythmias, weight gain, dizziness
Opioids		
Oxycodone ER Morphine SR Methadone Transdermal buprenorphine Transdermal fentanyl Tramadol	10-40 mg every 12 hours, as titrated 5-50 mg every 12 hours, titrate as required 2,5 mg -10 mg TDS 5-20 mcg/hour, changed every three days 25 mcg/hour-100 mcg/hour 50 mg/day, increased to a maximum 400 mg/day	Nausea, constipation, sedation, cognitive dysfunction, hormonal changes, skin irritation, vertigo
Topical agents		

Capsaicin cream 0. 025%	Applied to affected area three to five times daily	localized erythema and uncomfortable burning, stinging or itching
Capsaicin cream 0. 075%		
Capsaicin cream 8%	Single-application placed on the skin for 60 minutes after pretreatment with lidocaine cream; up to four patches may be applied at one time, and repeated as often as every three months	
5% lidocaine gel	Apply to affected area every four to twelve hours, as needed.	Lcalized skin irritation
Transdermal 5% lidocaine	One-to-three patches worn for 12-hours intervals	
Eutectic mixture of local anesthetics (2.5 % lignocaine, 2.5 % prilocaine)	Apply to affected every six to twelve hours, as needed	

For third-line therapy, the use of opioids is recommended in PHN patients with severe pain. The most common side effects of opioid analgesic therapy are constipation, sedation, the potential for abuse, and nausea. In elderly patients, cognitive and mobility impairments may occur.[1,3,5] The initial dose is 10 mg/day and increased 2 times a week to reach a maximum dose of 200 mg/day, while the target dose for intravenous administration is 0.3 mg/kg in 1 hour and a maximum of 25 mg. Studies with controlled morphine titrated to a maximum dose of 240 mg/day have been associated with decreased pain and sleep. PHN patients with severe pain experienced a significant reduction after morphine administration, but another study related to the combination with gabapentin was found to provide a better reduction in pain scores.[1,3,5] A systematic review of 254 PHN patients with severe pain who received oxycodone doses titrated slowly to 60-120 mg/day showed no conclusive effect. However, in a randomized study, oxycodone at a dose of 10 mg/12 hours and increased to 60 mg/day had a significant effect on PHN compared to placebo.[1,3,5]

Methadone is a synthetic opioid agonist with a potent NMDA receptor glutamate antagonist. A randomized controlled study showed that the effect of spontaneous pain intensity was not significant when measured using the VAS scale, whereas, on the verbal scale, there was a decrease in pain in the methadone group. The initial dose is 5 mg/day and is increased until the pain is gone. This drug is also good for patients with kidney failure because most of it is excreted through feces.[5]

Table 2. Combination therapy in neuropathic pain.[14]

Pregabalin/ gabapentin combined with:	**CDC rating of scientific evidence**	**RCTs testing the combination**	**Clinical practice experience concerning combinations**
TCAs	I + A	Gilron et al[10] Holbech et al[11]	Combination well documented. Most with peripheral NeP. Useful combination for patients who do not tolerate either drug in larger doses, as well as sedative effect from TCA to improve sleep disturbance
SNRIs	VII + B/C	Tesfaye et al[12] and Tannenberg et al[13]	Combination reasonably well documented. Used by some of the experts with good effect and fewer side effects than TCA
SSRIs	III + C	None	Insufficient evidence available. SSRIs not relevant in the treatment of NeP
Opioids[1]	1 + B	Gilron et al[16], Hanna et al[17], and Caraceni et al[18]	Good evidence to support combination therapy. Frequently used in daily clinical practice
Other antiepileptics[b] (Na+channel blockers)	C	None	Insufficient evidence available. Combination could work in theory due to different mechanisms of action. Limited clinical experience
Cutaneous patches	I + A/C	Casale et al[19], Meier et al[20] and Irving et al[21]	Mixed evidence and results for localized NeP. Patches add-on to oral therapy are used by some experts with good effect
Others	C	None	Insufficient evidence and clinical practice available

Although opioids are effective, intensive monitoring and the side effects associated with them lead to further research in favor of tramadol. Continuous use of tramadol in post-herpetic neuralgia resulting in the percentage of pain relief during the sixth week was found to be significantly higher in the tramadol group than in the placebo group.[3] In this patient, the combination therapy of pregabalin, amitriptyline, and tramadol gave a good analgesia effect, according to the evidence in Table 2. The side effects that occurred in the patient were dry lips and sedation.

Botulinum toxin A (BTX-A) plays an additional role as a promising therapeutic modality for PHN with its proven efficacy, safety, and tolerability. BTX-A blocks

acetylcholine by cleaving the 25 kDa synaptosomal-associated protein (SNAP25), which plays a role in the formation of the soluble N-ethylmaleimide-sensitive fusion protein attachment receptor complex (SNARE). Therefore, local peripheral injection of BTX-A may result in anti-nociceptive effects associated with inhibition of glutamate release, which participates in neurogenic inflammation. BTX-A can induce antitoxin antibodies which may limit long-term repeated use of the treatment. Use of botulinum toxin only in patients who are refractory to PHN.[1,5]

N-methyl-D-aspartate (NMDA) antagonist It works by inhibiting excitatory nociceptive interactions with NMDA receptors in the spinal dorsal horn (peripheral sensitization). This drug prevents the occurrence of allodynia, persistent pain, which acts like an opioid in central sensitivity. One of them is ketamine which is often used intravenously, which can reduce pain and even relieve pain in PHN, usually accompanied by side effects such as fatigue, dizziness, mood disorders, and hallucinations. However, in the study, oral ketamine gave significant results without any side effects.[3,8] In a double-blind RCT that compared intravenous lidocaine with normal saline, the results showed a reduction in PHN pain and allodynia in the lidocaine group compared to the saline group. Subcutaneous administration of lidocaine provides temporary pain relief in cases of severe pain.[3.8] The American Academy of Neurology recommends the level of evidence of therapeutic use for patients with post-herpetic neuralgia (Table 3).[3]

Table 3. Level of evidence on various therapies for PHN.[15]

Strong evidence supports • Tricyclic antidepressants (amitriptyline, nortriptyline, Desipramine, and maprotiline), gabapentin, opioids, and topical lidocaine patches are effective and should be used in the treatment of post-herpetic neuralgia. (Level A, classes I and II) • In countries where preservative-free intrathecal methylprednisolone is available, it may be considered in the treatment of post-herpetic neuralgia. (Level A, Classes I and II)
Good evidence supports • There is limited evidence to support nortriptyline over amitriptyline, because of fewer side effects, (Level B, Class II single study) and the data are insufficient to recommend one opioid over another. Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and Desipramine. • Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis or vincristine, lorazepam, vitamin E, and zimelidine are NOT of benefit. (Level A, Classes II)
Weak evidence supports

• Aspirin in cream is possibly effective in the relief of pain in patients with post-herpetic neuralgia. (Level C, Class II and III). The magnitude of the benefit of aspirin in cream is low, as is seen with capsaicin. (Level A, Class I and II)
There is insufficient evidence to support or refute • The effectiveness of carbamazepine, nicardipine, biperiden chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of Ganoderma lucidum, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of post-herpetic neuralgia. (Level U, Class II single study, and Class IV studies) • There is insufficient evidence at this time to make any recommendations on the long-term effects of these treatments.

Approximately 40-50% of patients experience pain so severe that it requires combination therapy. High-risk grouping (parents) and good initial therapy in herpes zoster will reduce the incidence of PHN. Nerve damage can be so severe that it must be prevented with antiviral therapy, TCAs, corticosteroids, and nerve blocks (table 4).[3]

Table 4. Prevention of PHN.[3]

Therapy	**Drug / Treatment**	**Evidence**
Antiviral agents (with symptom onset 72 hours)	Acyclovir Famciclovir Valacyclovir	A
TCA	Amitriptyline	B
Corticosteroids only in high-risk groups	Prednisolone	I
Nervus Block	Nervus block Repetitive paravertebral nerve block with local anesthetic +/- Steroid Block sympathetic (lumbar sympathetic, stellate ganglion block)	I

Conclusion

Rapid therapy for PHN prevents refractory pain, making it difficult to provide adequate therapy. Giving first-line therapy in subacute PHN using amitriptyline, pregabalin, and tramadol agents have a very good effect in overcoming pain in subacute PHN, but it is necessary to monitor the side effects that occur due to the potentiation of these three drugs.

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