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Hot topic in geriatric medicine

Herpes zoster-related pain in aged individuals: How to manage it safely

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ABSTRACT

Varicella-Zoster virus, an exclusively human herpes virus is responsible for chickenpox and herpes zoster. After the primary infection, the virus becomes permanently latent in the dorsal-root sensory ganglias and may be reactivated several decades later causing a vesicular dermatomal rash, traditionally metameric. Old adults can present severe pain during the acute phase, and late complications, such as postherpetic neuralgia that can be trying and crippling. Initiated within the first 72 hours of the rash, antivirals accelerate rash healing, reducing both rash and acute pain severity as well as avoiding the onset of other complications. The combination of antivirals and corticosteroids may further alleviate short-term zoster pain, increasing the risk of serious adverse effects, especially among older adults. Recently, some therapeutic recommendations focused on analgesic treatments (NSAIDs, opioid agonists, antidepressive drugs, calcium channel α2-δ ligands, corticosteroids and even antiviral agents) were published. However, their applications in old, frail, comorbid and often polymedicated patients have to be consciously pondered and are sometimes contraindicated (as tricyclic antidepressants). Specific recommendations for the therapeutic management of acute and post herpes zoster-related neuralgias, in older adults are proposed.

1. Introduction

When shingles occurs, both acute herpes zoster neuralgia (AHN) and post herpes zoster neuralgia (PHN) severely impair quality of life, and interfere with activities of daily living. Antiviral therapy initiated within the first 72 hours of rash, reduces the severity of rash, and severity AHN as well as the risk of PHN [1]. However, as none of the available antiviral agents completely alleviates AHN and prevent PHN, adjunctive analgesic therapy is more often required.

Due to the impairment of cellular immune responses to Varicella-Zoster virus (VZV) incurred by ageing, the risk of developing herpes zoster (HZ) increases markedly with age. The sharpest increase occurs between 50 and 60 years of age and continues on an upward trend, with a lifetime risk upper to 50% for those reaching their eighth decade [2]. Similarly, aged patient are more likely to develop pain where shingles occurs. Close to 75% of older patients have prodromal pain in the dermatome(s) where the rash will appear, and 90% have acute pain during the acute phase [3,4]. This pain can last for weeks, months, or even years [3]. A review of PHN risk factors in 821 patients with recent HZ demonstrated that patients aged over 50 years had a 15-fold higher prevalence of PHN at 30 days and 27-fold higher at 60 days than younger patients [5].

Pain is one of the most challenging complications of HZ to manage. Some therapeutic recommendations focusing on analgesic treatments were published (non steroidal anti-inflammatory drugs [NSAIDs], opioid agonists, antidepressant drugs, calcium channel α2-δ ligands, corticosteroids and antiviral agents). However, their application in old, frail, comorbid and often polymedicated patients have to be carefully considered as their use may be contraindicated (for example tricyclic antidepressants [TCAs]) [6–8]. As a physician, you play a key role in reducing the burden of shingles in this population by rapidly identifying and treating HZ, and a safe management of the more debilitating complication: pain (AHN and PHN). The prescribing recommendations presented here give adequate consideration to the particular frailties, potential comorbidities and polypharmacy likely to be encountered in the old patient population.

2. Acute herpes zoster neuralgia

Acute herpes zoster neuralgia (AHN) is produced by the inflammation associated with movement of viral sensory nerves

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to skin and damage to nerve structure. It is defined as pain that occurs within 30 days after rash onset [9]. In HZ-related acute pain management, it is important to recognize that pain changes over time and can become more severe as the acute infection progresses [6]. A stepwise clinical and pharmacological management of AHN is presented in Table 1. The first step is a careful pain assessment with the description of location, duration, intensity, quality of pain and the overall burden of pain [10]. Randomized placebo-controlled trials of oral analgesic treatments for HZ-acute pain have yet to be published. Beyond the effect achieved by antiviral therapy alone, oral corticosteroids do not contribute significantly to the reduction of prolonged pain [6]. Furthermore, they are associated with an increased risk of secondary bacterial skin infections and visceral and cutaneous disseminations [1,11].

The choice of analgesic treatment depends on the patient's pain severity and underlying conditions. It is important to prescribe these medications so as to achieve a constant level of analgesia rather than to use as-needed at the point where pain becomes unmanageable. Patients with mild to moderate pain may be managed with NSAIDs alone or in combination with weak opioid analgesics, or with acetaminophen. In frail older patients, with multiple-system diseases, caution should be exercised in the prescription of NSAIDs because their use is associated with a high rate of gastrointestinal, cardiovascular and renal adverse-effects [12]. In patients with moderate to severe pain, opioid analgesics are recommended. The advised approach is to begin treatment with a short-acting medication: controlled-release oxycodone has been demonstrated to be effective, compared to placebo, for the management of steady pain, paroxysmal spontaneous pain, and allodynia in PHN in a randomised study [13]. Tramadol, a weak opioid agonist but also a serotonin and noradrenalin reuptake inhibitor, seems to be effective in patients with neuralgia, but has never been studied in pain-related HZ [14,15]. These two opioids are often difficult to introduce in elderly people with polypharmacy because of potential drug interactions. Probably all short-acting opioid analgesics can be used alone or in combination with acetaminophen to treat acute pain in the elderly, if emergent side effects are carefully monitored. Once an effective dosage is determined, treatment can be switched to a long-acting medication. Short-acting opioids may be continued as required for exacerbations of pain, in combination with the long-acting opioid [6]. During the subacute phase, in the event of no or inadequate relief of severe pain with an optimum dose of opioid analgesics, the prompt addition of either (i) calcium channel $\alpha 2$-δ ligands (gabapentin or pregabalin) or (ii) a specific serotonin and noradrenalin reuptake inhibitor (SSNRI – duloxetine, venlafaxine) should be considered, although there are no published studies showing their efficacy in preventing PHN [6]. Despite the demonstrated efficacy of TCAs in relieving acute HZ-related pain, these agents are not recommended for use in elderly patients (contraindications, warnings, and precautions to this effect are found in product information within the packaging) [7]. Many conditions, such as cardiovascular complaints, and anticholinergic side effects of these drugs, render their use inappropriate [15,16].

Final dosages should be determined by adequate relief of pain or the development of unacceptable adverse effects that do not resolve within 1 or 2 days. A slow and cautious titration of these analgesics drugs is recommended to limit major adverse events. Guidelines for drug prescription in old adults are presented in Tables 2 and 3. For patients benefiting from appropriate viral treatment combined with oral analgesics, but without gaining effective pain relief, referral to a specialist pain service is recommended. After evaluation of the treatment, neural blockade or epidural analgesic administration can be proposed [17,18].

3. Post-herpes zoster neuralgia (PHN)

PHN, results from "central sensitisation" or cicatricial changes observed within the dorsal horn of the spinal cord upon resolution of acute process leading to the persistence of sensory symptoms (pain, numbness, dysesthesias [sensation in the absence of stimulus], allodynia, and/or pain precipitated by movement), in the affected dermatome for more than 30 days after the rash onset [9]. When PHN occurs, it persists for more than 6 months in 50 to 75% of the case [19].

Table 1
Stepwise clinical management of acute herpes zoster neuralgia.

Step 1
Assess the intensity of acute herpes zoster-related pain
Identify relevant comorbidities (such as cardiac, renal, or hepatic disease, depression, or gait instability)
That could be relieved or exacerbated by analgesic treatment
That may worsen or reactivate herpes zoster-related pain
Which indicate dosage adjustment or additional monitoring of therapy
Explain the diagnosis and treatment plan to the patient
Establish realistic therapeutic expectations in collaboration with the patient
Step 2
Initiate, within the initial 72 hours of rash, a treatment with an antiviral agent in combination with first line-analgesic medication
In mild to moderate pain, with acetaminophen alone or combined with weak opioid agonist analgesics (such as tramadol)
In moderate to severe pain, with strong opioid agonist analgesic
Begin treatment with short-acting medications, at a morphine-equivalent analgesic dosage of 2.5 mg, 4 times daily
Once an effective dosage is determined, switch to a long-acting medication
For patients with episodic exacerbations of pain, short-acting medication must be continued on an as-required basis
Step 3
Reassess pain frequently and evaluate impact on health-related quality of life
Where significant pain relief has been achieved (average pain reduced to $\leq 3/10$[a]) and side effects are tolerable, continue treatment
Where there is lack of adequate therapeutic response (average pain remains $\geq 4/10$[a] or $< 30\%$ reduction), at the highest recommended dose of opioid analgesic, particularly during the subacute phase, the prompt combination of one second-line additional treatments should be considered
A calcium channel $\alpha 2$-δ ligands: either gabapentin or pregabalin
An antidepressive drug: either duloxetine or venlaflaxine
Step 4
If trials of first-line medications alone or in combination with second line treatments fail
Refer the patient to a pain specialist or pain center
Evaluate eligibility for neural blockage or administration of epidural analgesics

[a] Range scores of the visual analogic scale using for assessment of pain: 0 = no pain; 10 = worst pain possible