An older woman with herpes zoster

MARTINE O'NEILL BSc, MB BS, FANZCA, FFPMANZCA

The immediate management and investigation of an acute pain presentation in general practice is discussed in this article.

Elaine is 68 years old and has been your patient for several years. Her medical history is brief: a moderately elevated cholesterol level, which is treated with atorvastatin 20 mg daily, and also osteoarthritis for which she underwent a right-sided total knee replacement without complication. She and her husband are retired and walk 2 km most days. They attend your practice every year for vaccination against influenza. Today, Elaine presents with a rash on her back in the right midthoracic region, extending anteriorly to the underside of her breast. She is also experiencing pain in the same area. You are concerned she may have herpes zoster (HZ).

What further information do you need from Elaine?

Answer: A detailed pain history is required, including location, character, intensity, associated features and aggravating and relieving factors. The timing of symptom development in HZ, commonly known as shingles, is important; the prodrome phase usually commences several days before the appearance of the rash and may include pain, itch, hypoaesthesia or dysaesthesia. Zoster-associated pain is caused by haemorrhage and inflammation in the affected dorsal root ganglion and peripheral nerve.[1]

Elaine may describe both spontaneous and evoked symptoms in the neuroanatomical distribution of the affected nerve(s). She may have experienced systemic symptoms associated with varicella–zoster virus (VZV) reactivation, such as fever, chills, headache and malaise. Although Elaine is well known to you, revisiting her medical history and performing a physical examination (including detailed assessment of the rash) will confirm the diagnosis clinically and identify complications. Up to 20 vesicles may be detected outside the affected dermatome before disseminated HZ is defined.

To confirm the diagnosis, viral swabs of fluid from the vesicles can be sent for VZV nucleic acid testing by polymerase chain reaction (PCR); other methods such as culture and immunofluorescence testing are less sensitive. Nevertheless, if HZ is suspected clinically, treatment should not be delayed while awaiting confirmatory test results. Risk factors for immunosuppression need to be identified. Measurement of fasting blood glucose level will identify diabetes, and tests for renal and hepatic function will be useful for deciding on pharmacological treatment options. It will also be important to establish whether the pain and rash are causing Elaine any significant sleep disturbance or loss of daily functioning, and to explore what supports she has available to assist her if required.

Elaine reports the rash has been present for two days and was preceded by moderate to severe aching pain and itch in the same region for several days before that. Now the pain is constant and keeping her awake at night. The rash has the typical maculopapular appearance of HZ, with small vesicles developing, and is confined to the right T5 dermatome. Elaine has also been feeling mildly unwell. Her vital signs today are normal. You make a presumptive diagnosis of HZ and initiate treatment. You also send swabs of the lesions for VZV PCR testing, and order measurement of fasting blood glucose,

PAIN MANAGEMENT TODAY 2015; 2(2): 38-40

Dr O'Neill is a Pain Medicine Specialist and Consultant Anaesthetist at Royal North Shore Hospital and St Vincent's Hospital, Sydney, NSW.

urea, electrolytes and creatinine levels, a full blood count and liver function tests.

Elaine wants to know how she contracted the HZ virus and whether she could have done anything to prevent it.

Answer: In language appropriate to Elaine's prior knowledge, you explain that she has had a previous varicella infection (chickenpox) and that HZ is caused by reactivation of latent VZV in the neurons of cranial nerve ganglia, autonomic ganglia and dorsal root ganglia of peripheral nerves.[2] Primary VZV infection results in VZV-specific IgG and shorter-lasting IgM antibodies and memory T cells, which may be periodically boosted by community re-exposure to the virus.[3]

VZV-specific T cells maintain the latency of the virus in the ganglia and are crucial for protection against reactivation. With age and immunosenescence, T cell immunity wanes, leading to increased vulnerability to HZ. VZV-specific IgG antibodies persist but mainly protect against generalised varicella infection.[2] Provided the lesions are covered by clothing, the risk of transmission to Elaine's contacts is low (in contrast to highly infectious chickenpox).[4] There is a sharp rise in the incidence of HZ with age, with more than 65% of cases occurring after 50 years of age.[1] The lifetime risk is approximately 30%.

An adult VZV high-titre live attenuated vaccine is available in Australia and is recommended for immunocompetent patients aged 60 years and over. The Shingles Prevention Study, a double-blind randomised controlled trial, reported a significant decrease in the incidence of both HZ and postherpetic neuralgia (PHN) with use of this vaccine; however, a long-term persistence substudy showed declining vaccine efficacy over time.[5,6] An adjuvanted HZ subunit vaccine was shown in a recent phase 3 efficacy trial to reduce the risk of HZ by more than 97% and is a promising future preventive therapy.[7]

What are the pharmacotherapy options for acute HZ? What treatment will you commence today?

Answer: The primary goals of treatment of VZV reactivation are to limit the duration and severity of the acute attack, relieve symptoms such as pain and prevent complications.[1] Complications can include persistent pain, bacterial infection of the affected skin, vasculopathy, neurological sequelae such as meningoencephalitis, ocular disease and visceral involvement (e.g. pneumonia).[2]

To hasten resolution of the skin lesions and reduce the severity of acute pain associated with HZ, treatment with antiviral therapy is recommended, ideally within 72 hours of onset of the rash (Box). Early use of antiviral agents reduces the severity and duration of acute zoster-associated pain. Antiviral therapy also reduces the severity (but not the incidence) of PHN.[8]

The use of corticosteroids in combination with an antiviral agent has also been shown to reduce the severity of acute zoster-associated pain, and may improve quality of life in the short term, provided there is no contraindication to their use. The addition of a corticosteroid does not reduce the incidence of PHN.

Acute pain following HZ reactivation is often moderate to severe in intensity. Therefore, early and effective acute pain management is essential; it may also reduce the risk of progression to PHN. There is no consensus regarding the precise definition of PHN, but it is frequently defined as clinically significant pain lasting for more than three months from rash onset.[3] Some consider zoster-associated pain to be a continuum from onset to resolution, encompassing both acute phase pain and PHN. Options for management of pain associated with HZ are listed in the Box.

Pharmacological management of pain in HZ should follow a multimodal, stepwise approach appropriate for the individual's medical circumstances.[9] Regular doses of paracetamol and NSAIDs should be trialled in the first instance, and combined with weak opioids such as tramadol if analgesia is not adequate. Stronger opioids may be required. Any opioid trial should be instigated in accordance with published guidelines such as those of the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists (ANZCA).[10] Patients such as Elaine will need regular review to assess the efficacy of opioid therapy and the possible emergence of adverse events, which can be more profound in elderly patients. She will also need to use aperients routinely.

Pharmacotherapy options for patients with herpes zoster

Acute phase

- Antiviral therapy (e.g. famciclovir, valaciclovir)
- Corticosteroids
- Pain management options
  - Paracetamol
  - NSAIDs
  - Weak opioids (e.g. oral tramadol)
  - Stronger opioids (e.g. oral oxycodone ± naloxone, tapentadol, morphine)
  - Pregabalin, gabapentin
  - Tricyclic antidepressants (e.g. amitriptyline, nortriptyline)

Postherpetic neuralgia

- Pain management options
  - Capsaicin (0.025%, 0.075%)
  - Topical lignocaine patches 5%
  - Pregabalin, gabapentin
  - Tricyclic antidepressants (e.g. amitriptyline, nortriptyline)
  - Serotonin and noradrenaline reuptake inhibitors (SNRIs; e.g. duloxetine, desvenlafaxine)
  - Opioids (third-line in postherpetic neuralgia)

The gabapentinoids pregabalin and gabapentin are recommended as first-line agents for the treatment of established neuropathic pain, but gabapentin did not show superiority over placebo for the treatment of zoster-associated pain in a single randomised controlled trial (level II evidence).[11,12] The tricyclic antidepressant amitriptyline, commenced at a dose of 25 mg from the emergence of the rash and continued for 90 days, was shown to reduce the risk of PHN in a small randomised controlled trial (level II).[13] Tricyclic antidepressants for pain management (off-label use) are usually initiated at lower doses (e.g. 5 to 10 mg), with careful patient monitoring for side effects, particularly those related to the anticholinergic effects of this class of drug. Nortriptyline is often better tolerated in the elderly population.

If pain is not satisfactorily managed by simple analgesics or a trial of a single opioid plus an antineuropathic agent, or if complications of drug therapy are emerging then early

referral for an urgent appointment with a specialist pain management service is recommended for further treatment options.

You prescribe a course of oral famciclovir (valaciclovir is an alternative) for Elaine, and recommend regular doses of paracetamol (modified release) and ibuprofen. You also give her a script for tramadol controlled release 100 mg twice a day, and commence her on nortriptyline 5 mg at night. You follow her up regularly during the eruptive phase of the condition. The rash resolves completely after three weeks without complications, but the pain persists. Her blood test results are normal.

You increase the nortriptyline dose to 15 mg at night (without significant side effects), and Elaine continues to take paracetamol regularly. She trials various opioid preparations, including tramadol and oxycodone, but cannot tolerate the side effects of constipation and nausea.

Ten weeks after resolution of the rash, Elaine returns to report the pain in the area has not resolved and she is unable to wear a bra. The pain is a constant aching, with flares of shooting pain evoked by touch and cool wind. Despite attempting to 'carry on as usual and not bother anyone', the pain is significantly interfering with her daily activities and enjoyment of life. She can no longer play bowls, and she and her husband did not go on a planned holiday.

What concerns do you have about Elaine?

Answer: Elaine's pain has progressed to PHN, which is the most common complication of HZ. Risk factors for development of PHN include greater severity of symptoms during the acute phase (including prodrome, rash and pain) and older age.[14] Patients such as Elaine often have a combination of positive and negative sensory phenomena in addition to pain (e.g. hypoaesthesia, hyperalgesia and allodynia). Neuropathic pain conditions such as PHN have significant effects on health-related quality of life, including emotional and social functioning and mood. Sleep quality is often poor. The financial burden of health care to the individual and community are also significant.[14] A careful psychosocial history is essential to establish Elaine's pain-associated disability and possible deterioration in mood. Treatment of emerging depression or anxiety may be required.

What pharmacological treatments exist for PHN?

Answer: The goal of treatment of PHN is symptom control, but outcomes with currently available pharmacological agents are often far from ideal. Reductions in pain intensity are usually modest, and fewer than half of patients experience clinically significant analgesia.[1] Treatment may be required for years or for life, creating issues with respect to efficacy and adverse events, particularly in the older age group. Comorbid conditions must be carefully considered.

Randomised, placebo-controlled trials have shown the effectiveness of several oral and topical agents (Box). Topical treatment with capsaicin 0.025% or 0.075% is effective, with a number needed to treat (NNT) of around three; however, its use may be limited by the need to re-apply frequently and the local side effects of pain on application, erythema and rash. Topical lignocaine patches 5% are also effective, but skin irritation and cost may be barriers to their use.

Oral treatments that may be effective in reducing PHN pain intensity include tricyclic antidepressants (amitriptyline and nortriptyline). These agents are supported by high quality evidence and have a low NNT. They are first-line therapy for neuropathic pain, as outlined by the IASP Neuropathic Pain Special Interest Group (NeuPSIG).[11] Common adverse effects are related to their anticholinergic action, and they should be considered carefully in elderly people with end-organ dysfunction. Doses used for chronic pain are in the range 5 to 25 mg (as outlined above).

Other oral agents whose use in patients with PHN is supported by high quality evidence include pregabalin and gabapentin. As with the tricyclic antidepressants, starting doses should be low and titrated appropriately (e.g. 25 mg twice daily for pregabalin and 100 mg three times daily for gabapentin). Cognitive adverse effects are common, particularly sedation. Serotonin noradrenaline reuptake inhibitors (SNRIs) such as duloxetine and desvenlafaxine are also first-line treatments for neuropathic pain conditions (off-label use).[11] However, there are no randomised trials of their use in patients with PHN.

Because of the significant problems associated with long-term use of opioids, specialist pain medicine review is recommended for patients taking more than 40 mg of oral morphine equivalents daily and for those with problems related to their use. A useful guide to trialling opioids in patients with chronic noncancer pain is available from the Faculty of Pain Medicine, ANZCA (www.fpm.anzca.edu.au/resources/professional-documents/documents/4462_001.pdf), as well as a guide to opioid dose equivalence (www.fpm.anzca.edu.au/resources/professional-documents/OPIOID%20DOSE%20EQUIVALENCE.pdf).

What other treatment options need to be explored concurrently with a medication trial?

Answer: Early referral to a multidisciplinary pain management centre should be considered for any patient with PHN for comprehensive assessment and management of pain, functional limitation, pain-associated disability and mood disturbance. Failure to respond adequately to pharmacotherapy for neuropathic pain, the consideration of combination therapy and the need for pain self-management strategies and/or pain programs are indications for referral.

Additionally, the Agency for Clinical Innovation's Pain Management Network website is an invaluable resource for patients living with persistent pain (see www.aci.health.nsw.gov.au/chronic-pain).

Outcome: You refer Elaine to a multidisciplinary pain clinic. The ongoing management of her PHN includes topical and oral pharmacotherapy and participation in a pain management program. **PMT**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

An older woman with herpes zoster

MARTINE O'NEILL BSc, MB BS, FANZCA, FFPMANZCA

References

1. Haanpaa M, Rice ASC, Rowbotham MC. Treating herpes zoster and postherpetic neuralgia. Pain Clin Updates 2015; 23(4): 1-8.
2. Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology 2013; 81: 928-930.
3. Wrigley P, Cousins M. Postherpetic neuralgia: an update on management and prevention. Med Today 2008; 9(4): 36-44.
4. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. Mayo Clinic Proc 2009; 84: 274-280.
5. Oxman M, Levin MJ, Johnson GR, et al; Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005; 352: 2271-2284.
6. Morrison V, Johnson GR, Schmader KE, et al; Shingles Prevention Study Group. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis 2015; 60: 900-909.
7. Lal H, Cunningham AL, Godeaux O, et al; ZOE-50 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med 2015; 372: 2087-2096.
8. Chen N, Li Q, Yang J, Zhou M, Zhou D, He L. Antiviral treatment for preventing nerve pain after shingles (postherpetic neuralgia). Cochrane Database Syst Rev 2014; 2: CD006866.
9. Macintyre PE, Schug SA, Scott DA, Visser EJ, Walker SM; APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence. 3rd ed. Melbourne: FPM, ANZCA; 2010.
10. Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists. Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain. Melbourne: FPM, ANZCA; 2015. Available online at: http://www.fpm.anzca.edu.au/resources/professional-documents/documents/PM1%202010.pdf (accessed July 2015).
11. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015; 14: 162-173.
12. Dworkin RH, Barbano RL, Tyring SK, et al. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. Pain 2009; 142: 209-217.
13. Bowsher D. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. J Pain Symptom Manage 1997; 13: 327-331.
14. Johnson R, Rice ASC. Postherpetic neuralgia. N Engl J Med 2014; 371: 1526-1533.