Prevention and medical management of postherpetic neuralgia

Postherpetic neuralgia is the commonest complication of shingles, a debilitating disease common in daily clinical practice. Treatment of postherpetic neuralgia is often complicated, with numerous potential options. This review looks at the evidence in support of the more commonly used medical therapies for this challenging condition.

Varicella-zoster virus is a medium-sized dsDNA virus of the herpesvirus group. Primary infection (chicken pox) presents as a febrile illness associated with typical skin and respiratory tract features. During primary infection varicella-zoster virus from mucocutaneous lesions enters sensory nerve endings. From here it establishes latent infection in dorsal root ganglia that can later undergo reactivation, the clinical presentation being shingles.

Shingles is characterized by an erythematous, vesicular rash in a dermatomal distribution. It is common in the elderly and, although often considered a straightforward skin rash, has a significant associated morbidity, especially in the elderly. The most common and significant associated complication of shingles is the development of chronic neuropathic pain (postherpetic neuralgia). As with all neuropathic pains, the pain of postherpetic neuralgia is often challenging to treat, being relatively refractory to established front-line or standard analgesics.

This article will look more closely at the epidemiology of herpes zoster infection and subsequent postherpetic neuralgia in the elderly, and consider current medical therapeutic options for the prevention and treatment of postherpetic neuralgia. It is beyond the scope of this article to look at the role of complementary or alternative treatments, or the role of interventional procedures.

Epidemiology of shingles and postherpetic neuralgia

Shingles is common, having been estimated to affect over 1 million people in the USA each year (Watson et al, 1993). Epidemiological data suggest that the incidence of herpes zoster is 3.4 per 1000, and that the risk of developing postherpetic neuralgia 1 month after onset of the zoster rash is 6.5% in those under 55 years of age, rising to 11.7% in those aged 55 years or older (Opstelten et al, 2002). The incidence of postherpetic neuralgia in the elderly population is estimated as about 10% (Davis and King, 2003). Population studies from the UK suggest that the incidence of postherpetic neuralgia will account for about 200 000 cases at any one time (Bowsher, 1999), meaning that a good understanding of its presentation, complications and treatments is essential for GPs, general physicians, geriatricians, neurologists and pain specialists.

Increasing age has been identified as an independent risk factor for development of postherpetic neuralgia (Choo et al, 1997; Jung et al, 2004), with the risk of postherpetic neuralgia becoming marked in otherwise healthy people once they are aged over 50 years (Whitley et al, 1998). Postherpetic neuralgia has a significant negative impact on quality of life (Dworkin and Schmader, 2001).

Preventing postherpetic neuralgia

The adage that 'prevention is better than cure' is particularly relevant to patients with conditions for which safe, well-tolerated and effective treatment is limited (e.g. postherpetic neuralgia). It is with this in mind that a number of approaches have been tried in order to reduce the number of patients developing postherpetic neuralgia. Some of these are discussed in the following section.

Antiviral therapy

In the UK acyclovir, valaciclovir and famciclovir are licensed for use in acute herpes zoster infection. Meta-analyses have shown that oral acyclovir (800 mg five times per day) significantly shortens the duration of acute pain associated with shingles and the numbers developing postherpetic neuralgia compared to placebo (Wood et al, 1996; Jackson et al, 1997). Valaciclovir is effective in both reducing acute pain and preventing postherpetic neuralgia (Beutner et al, 1995). There is no trial evidence showing the efficacy of famciclovir in reducing the incidence of postherpetic neuralgia. The nucleoside analogue brivudin (not licensed in the UK) is also effective in reducing the incidence of postherpetic neuralgia (Wassilew, 2005).

Corticosteroids

Steroids are potent anti-inflammatory agents and their use in shingles has been suggested as a means of reducing the incidence of postherpetic neuralgia. Two studies (Wood et al, 1994; Whitley et al, 1996) have shown no benefit of prescribed courses of oral steroids given concurrently with antivirals, with the former of these highlighting an increased frequency of adverse events in those treated with steroids. Single epidural administration of steroids is also ineffective at preventing development of postherpetic neuralgia (van Wijck et al, 2006).

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Despite the largely negative data attached to the use of corticosteroids it has been suggested that earlier return to premorbid function and decreased use of analgesics can be promoted by the use of steroids (Whitley et al, 1995), but at present widespread prescription of steroids to reduce the incidence of postherpetic neuralgia is not recommended.

Vaccination

Vaccination of adults against varicella-zoster virus could be a useful method of reducing both shingles and postherpetic neuralgia. Live attenuated varicella vaccine protects against varicella and its complications (Gershon, 2001), and Oxman et al (2005) showed the efficacy of vaccination in a large, double-blind, randomized, placebo-controlled trial of over 38 000 subjects. This study achieved a large (66.5%) reduction in those in the intervention group who developed shingles then developing postherpetic neuralgia. Although not yet widespread, vaccination against varicella-zoster virus has huge implications for future management of shingles and its major complication.

Pharmacological treatment options

As with other neuropathic pain conditions various analgesics (both standard and adjuvant) have been trialled for successful treatment of postherpetic neuralgia. Formulations tried include parenteral, oral and topical therapies as well as interventional and surgical methods. It is beyond the scope of this article to look at all options, and this article will concentrate on the medical approaches and some of the newer treatments being tried.

Anticonvulsants

Patients with wide-ranging neuropathic pain conditions (including postherpetic neuralgia) have been treated with anticonvulsants for many years, often on a background of anecdotal reports and a limited evidence base. More recently, there have been attempts to study the effects of anticonvulsants more systematically, as outlined below.

Gabapentin is a newer anticonvulsant and has been established as an effective treatment of postherpetic neuralgia in randomized, placebo-controlled trials (Rowbotham et al, 1998; Rice and Maton, 2001). These studies demonstrated improvements in pain relief alongside other quality of life measures, and although side effects were more common in the treatment group there was no significant difference in the rates of withdrawal from active treatment or placebo. Largely on the basis of these findings gabapentin is one of the first-line therapies in the management of postherpetic neuralgia, with an extensive review concluding that 'gabapentin appears to be effective and well tolerated for short-term treatment of postherpetic neuralgia' (Singh and Kennedy, 2003). This review did raise the need for further trials to establish an evidence base for long-term treatment and optimal dose, and to allow direct comparison with other agents.

One of the major practical difficulties of using gabapentin is the need for gradual uptitration of dose to allow maximum clinical benefit without the associated development of side effects (commonly somnolence and dizziness). Such complex titration regimens are often impractical and confusing, especially for elderly or frail patients who may already be taking large numbers of medications.

Pregabalin, a structurally similar molecule to gabapentin, may alleviate some of these difficulties. Initial randomized controlled trials showed that pregabalin produced rapid significant benefits in pain reduction (Dworkin et al, 2003), an effect that, along with improved sleep and better quality of life, has been demonstrated in further studies (van Seventer et al, 2006).

Over the past 15 years there has been a large increase in the number of anticonvulsant medications on the market. Although at present they have not been extensively studied in the treatment of neuropathic pain or postherpetic neuralgia, it seems likely that they will receive some attention in this field in the future. One such newer anticonvulsant that does have a small body of supporting evidence for efficacy in postherpetic neuralgia is lamotrigine (Harbison et al, 1997).

Antidepressants

Antidepressants have been used as adjuvant analgesics for a variety of neuropathic pain conditions for many years. Until relatively recently the major class available for this was the tricyclic antidepressants, which although supported by a reasonable body of evidence, were often used sparingly because of their adverse side-effect profile (particularly of concern in elderly patients) and cardiotoxicity. There have been exciting developments in the use of antidepressants in postherpetic neuralgia, as discussed below.

Tricyclic antidepressants

Tricyclic antidepressants have a wide range of therapeutic targets including inhibition of reuptake of serotonin and noradrenaline, as well as calcium-channel blockade and interaction with histamine receptors. This wide-ranging activity is felt to contribute to their analgesic effect (and their wide side-effect profile). Meta-analyses have demonstrated the efficacy of tricyclic antidepressants for treatment of neuropathic pain conditions (McQuay et al, 1996; Collins et al, 2000) including postherpetic neuralgia, with their effect independent of the reduction of associated depression in studied populations (Max et al, 1992).

The most widely studied of the tricyclic antidepressants is amitriptyline which has data confirming its efficacy (Hempenstall et al, 2005). If side effects are a significant concern nortriptyline (an alternative tricyclic antidepressant) has similar efficacy to amitriptyline but is better tolerated (Watson et al, 1998).

Tricyclic antidepressants still have a major role in the treatment of postherpetic neuralgia. There will always be concerns about the wide range of side effects (confusion, dry mouth, sedation, urinary retention), but providing these are carefully monitored tricyclic antidepressants should not be dismissed entirely. Many of these side effects

can to some degree be limited by cautious prescribing, close observation and by the old adage of 'start low and go slow' (e.g. for amitriptyline start with 10 mg nightly and monitor response before careful up-titration).

Other antidepressants

Evidence supporting the use of other antidepressants for postherpetic neuralgia is more limited than that for tricyclic antidepressants. Selective serotonin-reuptake inhibitors are largely ineffective in management of chronic pain (McQuay et al, 1996), but there is some evidence for management of neuropathic pain in general with other antidepressants including venlafaxine (Sindrup et al, 2003), bupropiron (Semenchuk et al, 2001) and duloxetine (Wernicke et al, 2004). These trials tend to be small and do not specifically relate to postherpetic neuralgia.

Opioid analgesics

Neuropathic pain, of whatever aetiology, is commonly believed to be relatively unresponsive to 'traditional' analgesics such as non-steroidal anti-inflammatory drugs and opiates. As well as the perceived lack of efficacy of opiates there exists a significant (and relevant) concern regarding potential adverse events and side effects that has tended to promote avoidance of these drugs, especially in the elderly, unless 'all else fails'.

Although Rowbotham et al (1991) showed intravenous morphine to be effective in postherpetic neuralgia in small numbers of patients, this is of limited practical value because of the chronic nature of the pain and the need for outpatient treatment. More practical data were provided by Raja et al (2002). This double-blind, placebo-controlled, crossover trial involving 76 patients used morphine or methadone, and showed that opioids were superior to placebo for pain relief without significant cognitive side effects. The same study found that treatment with opioids was more acceptable than treatment with tricyclic antidepressants. Controlled-release oxycodone reduces pain, disability and allodynia compared with placebo in patients with postherpetic neuralgia (Watson and Babul, 1998).

Tramadol has numerous therapeutic targets similar to both antidepressants (i.e. inhibition of serotonin and noradrenaline reuptake) and opioids (its major metabolite is a μ-opioid agonist). It has demonstrable benefit in treating neuropathic pain (Harati et al, 1998), but does not have trial data specific to postherpetic neuralgia.

Opioids may well have a role in management of postherpetic neuralgia. Concerns regarding adverse events will always be present, but by following the principles of start low and go slow these problems may be avoided.

Topical treatments

Topical treatments can be useful in the management of postherpetic neuralgia. Cutaneous application allows drugs to act on peripheral sensory nerves, with resultant analgesic effect occurring without marked elevation of systemic drug levels (contrary to transdermal drug delivery systems) (Sawynok, 2005). This has the theoretical benefit of limiting potentially troublesome side effects and promoting compliance. The two most commonly prescribed topical treatments are capsaicin and lidocaine (lignocaine).

Capsaicin is the active ingredient in chilli peppers, and the therapeutic effect of its use topically has been recognized for many years. Its mechanisms of action are complex, and felt to be linked to its affinity for VR1 receptors (Sawynok, 2005). Open-label studies (Watson et al, 1988) showed topical capsaicin to be effective in the short term. Further trials confirmed this (Watson et al, 1993) and established longer term benefits (Peikert et al, 1991). The main side effect of topical capsaicin is burning pain at the application site which can lead to treatment withdrawal in up to one-third of cases (Watson et al, 1988). This, and the often slow onset of therapeutic effect, results in capsaicin's use as an adjuvant rather than first-line therapy.

Lidocaine (lignocaine) is a commonly used local anaesthetic. There is some evidence for its efficacy in treating the pain of postherpetic neuralgia when used intravenously (Rowbotham et al, 1991), but concerns regarding its cardiovascular toxicity have prevented its widespread systemic use. Topical applications are effective in the treatment of postherpetic neuralgia, with evidence for gel (Rowbotham et al, 1995) and patch (Galer et al, 1999) preparations. The latter trial also highlighted the limited systemic absorption of the active ingredient, meaning that there is no significant difference in side-effect profile compared to placebo. However, evidence for the use of topical lidocaine is based on small trials, and a systematic review concluded that there was 'insufficient evidence to recommend topical lidocaine as a first-line agent' (Khaliq et al, 2007).

Conclusions

Postherpetic neuralgia is a common and significant problem which seems likely to increase with increasing numbers of elderly patients. There are numerous therapeutic options that have been tried in postherpetic neuralgia with varying success. Prevention of postherpetic neuralgia is to some degree possible by the rapid use of antivirals such as aciclovir, or by the more widespread approach of vaccination, but as neither of these approaches are 100% effective, an understanding of relevant therapeutic options is clearly warranted. Good evidence exists for the use of tricyclic antidepressants, newer anticonvulsants (gabapentin and pregabalin) and opiates, as well as for topical agents.

It seems likely that effective treatment of this challenging condition will require a combination of pharmacological and other treatments. Further research into mechanisms of neuropathic pain transmission is needed, and further large scale placebo-controlled and direct comparison studies if we are to achieve robust guidelines and comprehensive treatment approaches. **BJHM**

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KEY POINTS

- Postherpetic neuralgia is a common debilitating condition that can be difficult to treat.
- The incidence and prevalence of shingles and postherpetic neuralgia increases in the elderly population.
- Early treatment of shingles with antiviral therapy may reduce the risks of developing long-term neuropathic pain.
- Newer anticonvulsants (e.g. gabapentin or pregabalin) are effective treatments, as are tricyclic antidepressants and opioids.
- Side effects of treatment are common, but can be limited by a 'start low and go slow' approach.
- Topical therapies provide a useful adjunct to systemic therapies.
- More research and trials are required to develop both knowledge and a more robust evidence base.