Development of resistance to beta-lactam antibiotics during therapy of Pseudomonas aeruginosa infections. Lancet i, 1466.


The chemotherapeutic approach to zoster

Zoster is a common disease. Population based cohort studies have shown incidence rates of 1.3-3.4 per thousand population per year (Hope-Simpson, 1965; Ragozzino et al., 1982). Hope-Simpson calculated that 50% of people reaching the age of 85 years will have suffered zoster and 1% will have had more than one attack. The incidence rises sharply with advancing years, possibly owing to a decline in cellular immunity, with post herpetic neuralgia (PHN), the major complication of zoster, being more common in the older group. Figures for PHN vary according to the population studied, but differences also occur between apparently similar groups studied by different workers. Pain persisting for more than six months after acute zoster has been reported as occurring in 45-6% of one cohort of 430 patients over the age of 60 years (de Moragas & Kierland, 1957). In contrast, in 164 patients over 60 years studied in Sheffield only 34 (21%) still had some pain at six months, and only eight (5%) of these had moderate or severe pain (personal observations).

Zoster is readily identified clinically once the rash appears and the astute physician may make the diagnosis before the onset of the rash, from the dermatomal distribution of pain which is characteristic in the prodromal illness. Many remedies have been used in zoster and there is much folklore surrounding the illness. Most, such as acupuncture, photodynamic inactivation, stellate ganglion block and amantadine have no proven efficacy; some, such as corticosteroids, remain controversial.

Antiviral therapy offers a logical approach to the treatment of the acute infection and the prevention of the PHN even though the pathogenesis of this condition has not been established. Histological changes may occur in the posterior root ganglion and peripheral nerve in some patients following zoster and it is a reasonable hypothesis that effective antiviral therapy early in the course of the acute illness will limit viral replication and hence may reduce inflammation and pain. Assessment of antiviral agents in zoster has been based on observations on the rash and the pain, on virus isolation during the acute illness, and on PHN. Adenine arabinoside, interferon and idoxuridine have all shown some effect in modifying the acute illness, although an effect on PHN has not been proven with any of these agents at the conventional dosages (Whitley et al., 1976; Merigan et al., 1978; Wildenhoff et al., 1981). All have the common disadvantage of toxicity.

Acyclovir has been established as an effective, well tolerated and non toxic oral therapy for the treatment and prophylaxis of herpes simplex infections. Varicella zoster virus (VZV) is less sensitive than herpes simplex virus by a factor of about ten. The steady state peak serum concentrations of acyclovir following intravenous doses of 5 mg and 10 mg/kg 8-hourly exceed the effective median dose (ED 50) of most strains of VZV. Serum concentrations are lower after oral administration of similar dosage as only 15-20% is absorbed. Nonetheless, the steady state peak and trough concentrations of 7.5 and 4.5 μmol/l, respectively, obtained with a dose of 800 mg 4-hourly exceed the ED 50 of the majority of strains of VZV (unpublished findings).

Studies of intravenous acyclovir (10 mg/kg, 8-hourly) in immunocompromised patients have shown benefit in decreasing cutaneous
and visceral complications and speeding local healing (Balfour et al., 1983). The situation in the immunocompetent patient, in whom the life threatening complications are uncommon, is less straightforward.

Initial studies in zoster, using intravenous acyclovir at doses of 10 mg/kg and 5 mg/kg 8-hourly, demonstrated a reduction in virus shedding with enhanced healing and a reduction in pain during the acute illness in patients entered within 72 h of the onset of the rash or within 96 h of the onset of the prodrome (Peterslund et al., 1981; Bean, Braun & Balfour, 1982). No effects were seen on the PHN though numbers in the studies were small. A placebo-controlled study with oral acyclovir, 400 mg five times daily for five days, showed a significant reduction in the number of days of new lesion formation (McKendrick et al., 1984), but the results were less good than those with intravenous therapy. A double-blind, randomized, placebo-controlled study in 205 patients given acyclovir 800 mg five times daily for seven days demonstrated reduction in severity of rash with treatment. When patients were stratified according to duration of rash before start of treatment, statistical significance was found only in the patient group entered within 48 h of onset (McKendrick et al., 1986). Pain was also significantly reduced during treatment but improvement was not sustained after the end of therapy. No significant differences were noted in the resolution of rash or pain scores in the sub-group of patients with ophthalmic zoster; a placebo controlled study on acute zoster using intravenous acyclovir (5 mg/kg 8-hourly for five days) did show a significant effect of treatment on some parameters of rash development though not on pain in patients with trigeminal involvement (McGill, MacDonald & Fall, 1983).

What about modification of PHN? Analysis of PHN data has shown no significant differences between the treatment and placebo groups (McKendrick, M. W., Wood, M. J. & McGill, J. I., 1988), although an American study using an equivalent dose of acyclovir by mouth for ten days indicated reduction in PHN at three months in the treated group (Huff, 1987). The differences between the results are difficult to explain and further studies are required. Whether the coincidential use of prednisolone with acyclovir will prove successful is yet to be determined but preliminary results of a Danish trial have shown no benefit (Esmann et al., 1987).

Is there any place for antiviral therapy for zoster in the immunocompetent patient? Those most likely to benefit are elderly patients in whom PHN is more common but it is essential in every case that treatment is started early, preferably within 24 h of the onset of the rash. There is no firm evidence that treatment started after 48 h is effective, and as yet no regimen can be recommended that will influence post herpetic neuralgia.

Acyclovir is the most useful antiviral agent in zoster and certainly reduces rash progression and pain. The decision to use an expensive agent in a self-limiting or non life-threatening disease can be difficult. If regimens are found that will reduce PHN the balance will move towards the regular use of such therapy.

M. W. McKENDRICK
Lodge Moor Hospital,
Redmires Road,
Sheffield S10 4LH, UK

References


