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Short communication

Unique clinical trial design: combination acyclovir plus prednisone therapy of localized zoster in the normal host

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The utilization of prednisone in combination with antiviral therapeutics for the management of localized herpes zoster has been debated for some time. The original rationale for utilization of prednisone dates back to small, underpowered clinical trials reported between the 1950's and 1980's, suggesting that the administration of prednisone has a significant anti-inflammatory effect and, therefore, reduced acute pain and its persistence. (Gelfand, 1954; Appleman, 1955; Sauer, 1955; Elliott, 1964; Eaglstein, 1970; Keczkes, 1980). Prednisone administration for three consecutive weeks significantly reduces acute pain as has been noted in two clinical trials (Esmann et al., 1987; Wood, 1994). Other explanations include a direct analgesic effect mediated by corticosteroids and independent of anti-inflammatory effects. The early beneficial effects of combination corticosteroid administration, however, were lost on long term follow-up in the assessment of both post-herpetic neuralgia as well as zoster-associated pain, as in both prior trials.

The National Institute of Allergy and Infectious Diseases (NAID) Collaborative Antiviral Study Group (CASG) performed a controlled clinical trial which utilized a 2 × 2 factorial design for the treatment of herpes zoster in individuals greater than 50 years of age with disease less than 72 h in duration. For this controlled clinical trial, patients were randomized to acyclovir plus a prednisone placebo, acyclovir plus prednisone, and acyclovir placebo plus prednisone, or an acyclovir and prednisone placebo. Dosage of acyclovir which was utilized in this study was 800 mg 5 times daily for 21 days. Prednisone was administered at a dosage of 60 mg once daily for the first week and tapered to 30 and 15 mg once daily for the second and third weeks. To our knowledge, this is the first clinical trial in infectious diseases which utilized a 2 × 2 factorial study design. The application of this methodologic approach to clinical trials allows direct assessment of acyclovir and prednisone main effects as well as evaluation of the combination therapeutics. The ability to employ placebo regimens in this trial further enhances the validity of the conclusions.

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The demographic characteristics of all patients entered into this clinical trial were similar for each of the randomization groups except for severity of pain at baseline. Subsequent statistical analyses were adjusted for extent of pain. On evaluation of acute neuritis there was accelerated resolution of disease in the combination treatment arm as compared to those individuals randomized to the placebo group. However, the effect of combination acyclovir plus prednisone did not remain statistically significant as compared to other randomization groups when assessed 6 months after the onset of disease.

Nevertheless, significant beneficial effects were achieved for acyclovir plus prednisone as compared to placebo group on return to normal activity, total cessation of analgesic use, and ability to sleep uninterrupted at night. For each of these parameters, there was significant resolution of acceleration in return to an acceptable lifestyle. No toxicities were encountered which would invalidate this regimen.

The NIAID CASG investigators concluded that the treatment of patients with such a regimen should be limited to healthy individuals greater than 50 years of age who do not suffer from diabetes melitis, hypertension, osteoporosis or other concomitant diseases which would invalidate the use of high dose corticolsteroids. Subsequent clinical trials, likely, will further define the value of corticosteroid therapy under such circumstances. Importantly, the utilization of novel trial designs, as was employed by the NIAID CASG, allows for the direct assessment of acyclovir and prednisone main effect as well as the evaluation of the combination therapeutics.

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