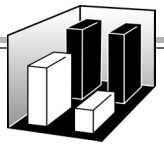
CLINICAL TRIALS REPORT



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Double-blind Placebo-controlled Trial of Pleconaril in Infants with Enteroviral Meningitis

Abzug MJ, Cloud G, Bradley J, *et al.*: **Double blind placebo-controlled trial of pleconaril in infants with enteroviral meningitis.** *Pediatr Infect Dis J* 2003, **22:**335–340.

Rating: •Of importance.

Introduction: Enteroviruses account for most cases of viral meningitis in patients with a proven etiology, and enteroviral meningitis has a high incidence in infants. Most infants who develop enteroviral meningitis respond well to treatment, although approximately 9% to 10% may develop neurologic complications including complex seizures, increased intracranial pressure, and decreased consciousness. Pleconaril is an experimental antiviral agent that has in vitro activity against the enteroviruses. Previous studies of the efficacy of pleconaril in children and adults with enteroviral meningitis have demonstrated a reduction in symptom intensity and duration. However, this agent has not been extensively studied in infants, the group with the highest incidence of enteroviral disease.

Aims: The aims of this study were to determine the multidose pharmacokinetics, safety, and virologic efficacy of pleconaril in infants with enteroviral meningitis.

Methods: Infants aged 12 months or younger with suspected enteroviral meningitis were eligible for enrollment. Patients were required to have cerebrospinal fluid (CSF) pleocytosis, positive CSF polymerase chain reaction (PCR) for enterovirus, or a positive CSF viral culture for a nonpolio enterovirus; confirmation of enterovirus infection was not required for study entry. Patients were randomized 2:1 in a double-blind manner to receive pleconaril 5 mg/kg per dose orally three times daily or placebo for 7 days. Clinical assessments were made at study entry, before hospital discharge, and at follow-up visits on days 4, 7, and 14, and by telephone contact on days 10 and 28. Plasma specimens for pharmacokinetic determinations were obtained immediately before and 2 hours after a dose of study drug on day 2 and before study drug administration on day 7. Viral cultures and PCR were obtained on day 1 on swabs of the throat, rectum and conjunctivae, serum or nonheparinized plasma, and CSF. Swabs of the throat and rectum, and serum or plasma, were obtained for viral culture and PCR during therapy.

Results: Of the 22 patients enrolled, 21 were evaluable—12 received pleconaril and nine received placebo. Of the 21 evaluable patients, all but one had proven, probable, or possible enteroviral infection of the central nervous system (CNS). The baseline characteristics of the pleconaril and placebo groups were similar. Among the pleconaril-treated patients, 26 of 29 peak and trough pleconaril concentrations exceeded the 90% inhibitory concentrations for enteroviruses, although a median 3.5-fold drug accumulation occurred between days 2 and 7. No significant differences in duration of positivity by viral culture, or in PCR, hospitalization, or symptoms were detected between the patients who received pleconaril or placebo. Although pleconaril was well-tolerated, twice as many adverse events occurred per patient in the pleconaril group.

Discussion: The trial determined that the dose of pleconaril studied attained sufficient plasma concentrations and was well-tolerated, but viral and clinical efficacy were not found in the infants enrolled in this small study. The study confirmed the typically short and benign course associated with enteroviral meningitis (symptoms ≤ 3–4 days), which may have affected the ability to attain sufficient enrollment and likely hindered demonstration of clinical efficacy. Furthermore, the relatively low yield of mucosal viral cultures and the short period of shedding of virus that could be cultivated was another difficulty. Although pleconaril may have a role in enteroviral meningitis in infancy, the typically short duration of symptoms and viral shedding in this study make it challenging to prove the efficacy of this agent.

Editor's comments

Viruses are the major cause of the aseptic meningitis syndrome, with enteroviruses accounting for 80% to 85% of all cases in which a pathogen is identified [1]. Estimates from the US Centers for Disease Control and Prevention indicate that 30,000 to 75,000 cases of enteroviral meningitis occur annually in the United States [2], although these figures are most likely an underestimation of the true incidence. Infants and children are most susceptible to enteroviral infection because there is absence of previous exposure and immunity. Clinical manifestations of enteroviral meningitis include headache (which is often severe), photophobia,

vomiting, anorexia, rash, diarrhea, cough, and myalgias [3,4]; the duration of enteroviral meningitis is usually less than 1 week. Treatment for enteroviral meningitis is supportive, although pleconaril represents a new investigational agent for the treatment of enteroviral infections [5]. Pleconaril is a novel compound that integrates into the hydrophobic pocket of picornaviruses (including the enteroviruses) and prevents viral replication by inhibiting viral uncoating and blocking viral attachment to host cell receptors. It is orally bioavailable and attains CNS concentrations four times higher than those achieved in serum. Recently, pleconaril has been shown to have beneficial effects on the clinical, virologic, laboratory, and radiologic parameters in patients with severe enteroviral infections [6] and has been shown to produce a reduction in symptom intensity and duration in children and adults with enteroviral meningitis [7].

In this double-blind, placebo-controlled study by Abzug *et al.*, oral administration of pleconaril resulted in sufficient plasma drug concentrations and was generally well-tolerated, but was not associated with improvement in symptoms, symptom duration, or viral efficacy. The lack of efficacy may have been the result of the small numbers of patients enrolled in this trial and the low level of culture positivity from mucosal sites. Although a larger study may show the efficacy of pleconaril in enteroviral meningitis in infancy, the short duration of symptoms and generally benign outcome of this illness suggests that specific antiviral treatment is not necessary in most cases. In addition, the authors noted that the trial was prematurely terminated, not only because of the low rate of accrual, but also because of the pharmaceutical sponsor's decision not to pursue an enteroviral meningitis indication for pleconaril. Once licensed for use, pleconaril may be considered for patients with more serious enteroviral infections, including chronic enteroviral meningoencephalitis in agammaglobulinemia and enteroviral neonatal sepsis. Because the study also demonstrated evidence of drug accumulation between days 2 and 7 of administration, careful surveillance for adverse events is necessary, especially for infants who are treated with pleconaril.

Reducing Intracranial Pressure may Increase Survival among Patients with Bacterial Meningitis

Lindvall P, Ahlm C, Ericsson M, *et al.*: **Reducing intracranial pressure may increase survival among patients with bacterial meningitis.** *Clin Infect Dis* 2004, **38:**384–390.

Rating: •Of importance.

Introduction: Bacterial meningitis continues to have a high mortality rate despite the availability of effective antimicrobial therapy, corticosteroids, and improvements in intensive care. One of the most important causes of death in patients with bacterial meningitis is increased intracranial pressure (ICP), which may cause brainstem herniation and cessation of intracranial circulation.

Aims: The aims of this study were to determine whether a model used for reduction of ICP in patients with post-traumatic brain edema is effective in reducing ICP and mortality in patients with bacterial meningitis.

Methods: Data from patients admitted to the neurointensive care unit at Umea University Hospital in Sweden from 1995 to 2001 were assessed. All patients with a Reaction Level Scale of 3 or more (Glasgow Coma Scale score ≤ 8) were considered for implantation of an ICP monitoring device. Elevated ICP was defined as 15 mm Hg or more. All enrolled patients were provided with full intensive care support (including ventilatory support and sedation). In addition to antimicrobial therapy and corticosteroids, all patients with Glasgow Coma Scale scores of 8 or less were treated with ICP-reducing therapy aimed to keep the ICP at less than 20 mm Hg.

Results: From January 1995 through December 2001, 18 patients were referred for severe bacterial meningitis. After arrival in the intensive care unit (ICU), an ICP-measuring device was placed in the brain parenchyma of 14 patients and was measured through a ventriculostomy in one patient. Thirteen of these patients were treated according to the ICP-targeted concept; the other two patients did not receive treatment because they were considered desolate cases. Nine of the 15 patients had intracranial hypertension measured directly after implantation of the ICP-monitoring device; during care in the ICU, 14 of the 15 patients developed intracranial hypertension (an ICP ≥ 15 mm Hg). Ten of the 15 patients survived and were discharged from the ICU; the mean duration of treatment was 8.4 days in patients who survived, compared with 3 days in patients who died. The mean ICP measured directly after device implantation was significantly higher in patients who died. In the patients who survived, the mean ICP was gradually reduced, following a linear trend, during the first 3 days of ICP-reducing therapy.

Discussion: The patients with bacterial meningitis in this study represented a risk population expected to have a high case-fatality rate; these patients were comatose at the time of referral, and 60% had a Glasgow Coma Scale score less