Antibiotic Prophylaxis with Azithromycin or Penicillin for Childhood-Onset Neuropsychiatric Disorders

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Background: *The acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) describes a subgroup of children with obsessive-compulsive disorder and/or tic disorder that experience symptom exacerbations following streptococcal infections. We hypothesized that the prevention of streptococcal infections among children in the PANDAS subgroup would decrease neuropsychiatric symptom exacerbations.*

Methods: *Twenty-three subjects with PANDAS were enrolled in a double blind, randomized controlled trial. Antibiotic prophylaxis with penicillin or azithromycin was administered for 12 months. Rates of streptococcal infections and neuropsychiatric symptom exacerbations were compared between the study year and the baseline year prior to entry.*

Results: *Significant decreases in streptococcal infections during the study year were found with a mean of .1 (.3 SD) per subject, compared to the baseline year with 1.9 (1.2 SD) in the penicillin group and 2.4 (1.1 SD) in the azithromycin group [$p < .01$]. Significant decreases in neuropsychiatric exacerbations during the study year were also found with a mean of .5 (.5 SD) per subject in the penicillin group and .8 (.6 SD) in the azithromycin group, compared to the baseline year with 2.0 (.9 SD) in the penicillin group and 1.8 (.6 SD) in the azithromycin group [$p < .01$].*

Conclusions: *Penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and neuropsychiatric symptom exacerbations among children in the PANDAS subgroup.*

Key Words: Streptococcal, autoimmune, obsessive-compulsive disorder, tic disorder

The reduction of rheumatic fever (RF) recurrences by antibiotic prophylaxis against infections with group A beta-hemolytic streptococcus (GAS) was a key factor in determining that GAS played an etiologic role in RF. This was particularly true for Sydenham's chorea, in which laboratory evidence of an inciting GAS infection was often unobtainable (Stollerman 1975). Antibiotic prophylaxis not only prevented recrudescence, but also improved the long-term prognosis of RF sufferers by preventing additional scarring of the cardiac valves (Veasy 1995). Because of the known effectiveness of penicillin prophylaxis for rheumatic fever (Massell et al 1988), it was hypothesized that children with GAS-triggered episodes of obsessive-compulsive symptoms and tics (the PANDAS [pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections] subgroup) would have an improved outcome while maintained on antibiotic prophylaxis against GAS infections.

The effectiveness of oral penicillin prophylaxis has been the subject of investigation among patients with rheumatic fever. A study investigating the pharmacokinetics of oral penicillin V demonstrated suboptimal serum trough levels at doses currently used in prophylaxis against GAS infections (250 mg given orally twice a day) (Thamlikitkul et al 1992) In a previous trial of antibiotic prophylaxis conducted at the National Institute of Mental Health on children in the PANDAS subgroup, subjects were randomized to receive penicillin or placebo (Garvey et al 1999). Oral penicillin administration in this trial failed to provide adequate prophylaxis against GAS, as evidenced by the fact that 14 of the 35 GAS infections occurred during the penicillin phase. The current guidelines established by the American Heart Association for the prevention of rheumatic fever recommend the use of oral penicillin at 250mg taken twice a day, however, compliance is crucial as the short half-life of oral penicillin makes it difficult to maintain adequate trough levels without continual redosing (Dajani et al 1995). The prevalence and associated morbidity of GAS infections and their sequelae has resulted in the development of newer antibiotic regimens, which effectively target GAS while also maximizing pharmacokinetic profiles. Antibiotics from the macrolide class have demonstrated efficacy against GAS infections. One of the antibiotics from this class, azithromycin, has also been shown to provide effective prophylaxis against GAS infections at a dose of 500mg taken once a week (Gray et al 1998). Azithromycin has also been used in children as prophylaxis against otitis media, with high efficacy and low rates of adverse events (de Diego et al 2001).

We hypothesized that the prevention of GAS infections in the PANDAS subgroup would result in an overall reduction in neuropsychiatric symptom exacerbations and that 'break through' infections with GAS, as evidenced by a positive throat culture or a 4-fold dilution rise in anti-streptococcal antibody titers 4-6 weeks after the infection, would be associated with exacerbations of obsessive-compulsive and/or tic symptoms. Our objective was to determine if the failure to reduce neuropsychiatric symptoms among children in the PANDAS subgroup in the previous antibiotic trial was due to a lack of association between GAS infections and neuropsychiatric symptoms or the result of ineffective prophylaxis against GAS infections (through noncompliance, administration problems, or efficacy of penicillin prophylaxis against GAS). Based on the results of the previous study, we expected that penicillin would function as an "active placebo" and prevent only one-third to one-half of GAS infections. Azithromycin was expected to provide complete prophylaxis, and therefore was postulated to be superior to penicillin in its ability to prevent GAS-associated neuropsychiatric exacerbations. Subjects and their parents were informed of this expecta-

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tion during the consent process, and were prepared for the possibility that they might receive the less effective compound.

Methods and Materials

Subjects

Children with a history of a sudden onset or abrupt exacerbations of tic or obsessive-compulsive symptoms associated with GAS infection were recruited for this study from July 1999 through September 2002. Recruitment was achieved by advertisements placed in the newsletters of the Tourette's syndrome Association and the Obsessive Compulsive Foundation, direct mailings to child psychiatrists and pediatricians in the Washington D.C. metro area, and on the National Institute of Mental Health PANDAS web site. The study protocol and consent forms were approved by the National Institute of Mental Health institutional review board. Informed consent was obtained from the parents of each subject. Informed assent was obtained from all subjects over the age of 7. Children were eligible for entry into the study if they met the following criteria: 1) A tic disorder and/or obsessive-compulsive disorder (OCD) as defined in the Diagnostic and Statistical Manual of Mental Disorders-IV edition; 2) A history of a sudden onset of symptoms or an episodic course with abrupt symptom exacerbations interspersed with periods of partial or complete remission; 3) Onset of neuropsychiatric symptoms prior to puberty; and 4) Evidence of a temporal association between a preceding streptococcal infection and the onset or exacerbation of neuropsychiatric symptoms.

Study Design

Following baseline assessment, subjects were randomized in a double-blind fashion to receive either penicillin V-K 250 mg two times a day or azithromycin 250 mg two times a day on one day of the week and placebo capsules taken 2 times a day on the other 6 days. All subjects had a baseline throat culture prior to randomization; all of which were negative for GAS infection. Nonantibiotic treatments received prior to study entry were continued throughout the study and adjustments were permitted as needed during the course of treatment. At each monthly visit psychiatric medication or therapy changes were noted. Also recorded were any illnesses in the preceding month including the results of throat cultures that were taken and possible contacts with family members, friends, or classmates who had streptococcal infections. Adverse events were reported to the principle investigator.

Baseline Assessment

Children who met criteria for study entry underwent a baseline evaluation: history, physical and neurologic examination, psychologic testing, standardized symptom ratings, measurement of antistreptolysin O (ASO) and anti-deoxyribonuclease B (Anti-DNase B) titers, and throat culture for GAS. A semi-structured clinical interview and the Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (Kaufman et al 1997) were used to assign psychiatric diagnoses.

GAS Infection Assessment

GAS infection was defined by positive rapid antigen test, positive throat culture, or four-fold dilution rise in antistreptococcal antibody titers. GAS infections were documented by review of medical records for the baseline year data. Throat cultures and GAS antibody titers (ASO and DNaseB) were collected monthly and used to document GAS infections during the study year. The rating clinicians did not know these results during the study period, although active GAS infections, whether diagnosed at the National Institute of Mental Health (NIMH) or at an outside clinic, were reported to the principal investigator. Those subjects with evidence of GAS infection were taken off the study medication and treated with a 10-day treatment course of an antibiotic that was not in the penicillin or macrolide class. Upon completing the treatment course of antibiotics, the subject resumed study medication.

Neuropsychiatric Exacerbation Assessment

Parent and child reports obtained at the end of the baseline year and at completion of the study year were used to assign neuropsychiatric symptom severity ratings for each month of the preceding year. A rating of 0–2 was assigned for subclinical, 3–5 for mild, 6–8 for moderate, and 9 or 10 for severe symptoms. During the study year, systematic behavioral ratings were obtained monthly for tics and obsessive-compulsive symptoms with the Yale Global Tic Severity Scale (Walkup et al 1992; Leckman et al 1989) and the Children's Yale-Brown Obsessive Compulsive Scale (Scahill et al 1997; Goodman et al 1989a, 1989b). By the definition of the CY-BOCS scale a score of 0–7 is subclinical, 8–15 is mild, 16–23 is moderate, and 24–40 is severe. We defined the YGTSS for a score of 0–10 to be subclinical, 11–20 to be mild, 21–35 to be moderate, and above 36 to be severe. These prospectively collected ratings were used to validate the retrospectively assigned ratings for the study year. A neuropsychiatric symptom exacerbation was defined as an increase in neuropsychiatric symptoms from subclinical (0, 1, or 2) to clinically significant (3–10) or a 3 point or greater increase in neuropsychiatric symptoms lasting at least 2 weeks.

Blinding and Compliance

An attempt was made to control for the compliance issue that had arisen during the previous antibiotic prophylaxis trial. It was a requirement for study entry that the subjects be able to swallow the study capsules. Since the use of the liquid formulation of penicillin made it difficult to quantify missed doses and its bitter taste made it difficult to administer, this study used blinded identical capsules for both the penicillin and azithromycin doses. These capsules were packaged in blister packs labeled with the day of the week and am or pm designations. Parents returned the unused blister packs for pill counts each month and were also asked to report any missed doses on a monthly written form.

Analysis

The primary aim of this study was to determine whether prevention of GAS infections with prophylactic antibiotics would reduce the number of neuropsychiatric symptom exacerbations in children in the PANDAS subgroup. The primary outcome variable was the number of GAS infections and the secondary outcome variable was the number of neuropsychiatric exacerbations. Each of these variables was assessed for both the baseline year and the study year. The statistical analyses were done using the Number Cruncher Statistical System (NCSS Statistical Software, Kaysville, Utah) 2001 version. A paired *t*-test was used to compare both GAS infections and neuropsychiatric symptom exacerbations across the baseline year and the study year. All reported values are mean and standard deviation (SD) unless otherwise stated.