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.

Table 1. Clinical Description of Subjects

Age (years)	
Mean	7.9 (1.3 SD)
Range	5.3–9.8
Antibiotic Assigned ($n = 23$)	
Penicillin	11 (48%)
Azithromycin	12 (52%)
Gender ($n = 23$)	
Male	15 (65%)
Female	8 (35%)
Primary Psychiatric Diagnosis ($n = 23$)	
OCD only	9 (39%)
OCD and tic disorder	7 (30%)
Tic disorder and subclinical OCD	4 (17%)
Tic disorder only	3 (13%)

OCD, obsessive-compulsive disorder.

Results

Study Subjects

Between July 1999 and September 2002, 248 telephone screenings were conducted and 51 children were seen in the outpatient clinic for an in-person assessment. Thirty-three of these met criteria for study entry. Nine children either chose not to participate in the study ($n = 7$) or were excluded after the baseline evaluation ($n = 2$). Of the latter group, one subject was unable to tolerate the baseline blood draw and one subject was unable to swallow the study capsules. One subject dropped out of the study at month 3 when he became unable to tolerate monthly blood draws and was excluded from the analysis. Clinical data from the 23 subjects who completed the 12 month long study are summarized in Table 1. Of the 3 subjects with a tic disorder without obsessive-compulsive symptoms, 1 (33%) had another comorbid anxiety disorder (social phobia).

Psychiatric cormorbidity was common (Table 2) with 16/23 (70%) of the subjects having at least 1 comorbid diagnosis.

Streptococcal Infections

During the baseline year, there were 50 GAS infections microbiologically documented by positive throat culture or rapid GAS antigen test, 21 GAS infections in the group randomized to penicillin [1.9 (1.2)] and 29 GAS infections in the group randomized to azithromycin [2.4 (1.1)]. There were only 2 documented GAS infections during the study year (a 96% reduction from the previous year). One subject in the penicillin group and one subject in the azithromycin group each had a positive throat culture for GAS or rapid GAS antigen test [mean for each group .1 (.3)]. Thus the number of GAS infections was decreased significantly in both groups ($p < .01$ for both) during the study year (Table 3). Of note, there were no significant antistreptococcal antibody titer (ASO and anti-DNase B) elevations in any of the subjects during the study year including the 2 subjects who had documented GAS infections. Titers from these two subjects from the time of infection to 3 months after infection are summarized in Table 4. There were no significant differences between the two study groups.

Table 2. Comorbid Psychiatric Disorders

	$N = 23$	Percentage
Separation Anxiety Disorder	9	39%
Attention Deficit/Hyperactivity Disorder	6	26%
Major Depressive Disorder	5	22%
Oppositional Defiant Disorder	5	22%
Enuresis	4	17%
Simple Phobia	4	17%
Social Phobia	3	13%
Generalized Anxiety Disorder	2	9%
Panic Disorder	1	4%
Overanxious Disorder	1	4%
None	7	30%

Table 3. Summary of Streptococcal Infections and Neuropsychiatric Exacerbations

Streptococcal Infections[a]	Baseline Year	Study Year
Penicillin ($n = 11$)	1.9 (1.2 SD)	.1 (.3 SD)
Azithromycin ($n = 12$)	2.4 (1.1 SD)	.1 (.3 SD)
Neuropsychiatric Exacerbations[a]	**Baseline Year**	**Study Year**
Penicillin ($n = 11$)	2.1 (1.0 SD)	.5 (.5 SD)
Azithromycin ($n = 12$)	1.8 (.6 SD)	.9 (.5 SD)

[a] $p < .01$.

Neuropsychiatric Exacerbations

During the baseline year there were 44 neuropsychiatric symptom exacerbations. Of these 44 exacerbations, 34 occurred within 6 weeks of a documented GAS infection, and 10 were not associated with a GAS infection or a medication change. There were 23 neuropsychiatric symptom exacerbations in the group randomized to penicillin [2.1 (1.0)] and 21 neuropsychiatric symptom exacerbations in the group randomized to azithromycin [1.8 (.6)]. During the study year there were 17 neuropsychiatric symptom exacerbations (61% reduction from baseline year.) Of these 17 exacerbations, 2 occurred within 6 weeks of a documented GAS infection, 10 occurred within 6 weeks of a non-GAS infection, 1 within 6 weeks of a psychosocial stressor, 1 associated with a decrease in anti-obsessional medication, and 3 that were not associated with an infection, medication change, or psychosocial stressor. There were 6 neuropsychiatric symptom exacerbations in the group randomized to penicillin [.5 (.5)] and 11 neuropsychiatric symptom exacerbations in the group randomized to azithromycin [.9 (.5)]. Thus, the number of neuropsychiatric symptom exacerbations was decreased significantly in both groups ($p < .01$ for both) during the study year

Table 4. Antistreptococcal Antibody Titers

	At Infection	1 Month	2 Months	3 Months
Subject 11				
ASO	58	57	69	57
Anti-DNase B	480	680	960	680
Subject 23				
ASO	<40	<40	<40	<40
Anti-DNase B	167	241	227	240

Antistreptococcal antibody titers from time of GAS infection to 3 months after in the two subjects who had documented GAS infections during the study year.

ASO, antistreptolysin O titer; Anti-DNase B, anti-deoxyribonuclease B titer; GAS, group A beta-hemolytic streptococcus.

(Table 3). There were no significant differences between the two study groups.

Blinding and Compliance

Compliance was excellent in both treatment groups with 98.7% of all doses taken as prescribed over the 12 months of the study period. The mean number of missed doses or doses taken 8-12 hours late per month for all 23 subjects was .77 (.9 SD) doses out of 60 doses (median = .42 doses per month). In order for penicillin to be an effective prophylaxis against GAS it must be taken twice a day 12 hours apart. The mean number of missed study capsules or study capsules taken 8-12 hours late per month in the penicillin group was .75 (1.0 SD) out of 60 doses (median = .33), with 98.8% of all study capsules in the penicillin group taken as directed. Azithromycin can be taken once a week and still be effective prophylaxis against GAS, so that only a completely missed dose will affect its efficacy. The mean number of missed study capsules per month (including the 52 placebo capsules) in the azithromycin group was .52 (.6 SD) out of 60 doses (median = .37), with 99.1% of all study capsules in the azithromycin group taken as directed.

Discussion

Both the penicillin group and the azithromycin group demonstrated significant decreases in GAS infections during the study year, compared to the year prior to receiving antibiotic prophylaxis. The results indicate that both penicillin and azithromycin are effective in preventing GAS infections when taken as prescribed. There was only one GAS infection in each group over a 12-month observation period, which represents a 96% reduction in GAS infections during the year of antibiotic prophylaxis compared to the year prior when the subjects were not on antibiotic prophylaxis. Even if one takes a conservative estimate that 8% of the positive throat cultures during the baseline year represented colonization, rather than true infection ("carrier status") the results are still highly significant (Ginsburg et al 1985). Further, if the positive GAS culture and positive rapid streptococcal antigen test documented during the study year represented colonization, rather than a true infection, this would make the differences in infection rates observed in this investigation even more significant. However, it is worthy to note that both subjects had negative GAS throat cultures in the preceding months and subsequent months making it unlikely that they were "carriers." Of note the literature demonstrates blunting of titer elevation when antibiotic treatment is initiated promptly as was the case in these two infections (el Daher et al 1991; Rantz et al 1946).

The data indicate that both penicillin and azithromycin may be effective in preventing GAS triggered neuropsychiatric exacerbations in children in the PANDAS subgroup. There was a 61% overall reduction in neuropsychiatric symptom exacerbations during the year of antibiotic prophylaxis and a 94% reduction in GAS triggered neuropsychiatric symptom exacerbations. One of the limitations of this study is that the baseline year data were collected retrospectively through an in-person baseline interview and review of medical records. The data for the study year were also collected retrospectively, but were able to be confirmed through prospectively collected in person ratings. Although the retrospective collection of data for the baseline year is not ideal, it should have worked against our observed treatment effects, as recall bias results in under-reporting of symptoms, rather than over-reporting (Fendrich et al 1999; Jenkins et al 2002). The strong agreement between parental reports of GAS infections and documentation in the medical record provides evidence to suggest that parental recall during the baseline year was accurate. Additional support is provided by the agreement found between prospectively collected symptom ratings as validation of the end-of-study retrospective reports. The potential for reporting bias is not completely negated, however, as parents may have improved their observational skills during the study year. These limitations are being addressed in follow-up investigations, but do not negate the significance of the present findings.

In this study both penicillin and azithromycin prophylaxis were found to be effective in preventing GAS infections and decreasing neuropsychiatric symptom exacerbations among children in the PANDAS subgroup when compliance was assured. These results suggest that antibiotic prophylaxis may play a role in the management of children in the PANDAS subgroup, as well as provide support for the assertion that GAS plays an etiologic role in some children with tics and/or obsessive-compulsive disorder. However, the small sample size and lack of placebo control merit caution in the interpretation of these results. Further, a recent study suggesting azithromycin is not superior to placebo in preventing recurrent acute tonsillitis (Lildholdt et al 2003), as well as a number of reports of macrolide-resistant streptococci raise public health concerns about the decreasing utility of the macrolide antibiotics (Seppala et al 1997; Granizo et al 2000; Varaldo et al 1999; Martin et al 2002). Thus, azithromycin prophylaxis should not routinely be recommended for children with post-streptococcal neuropsychiatric disorders. The results of this study suggest that penicillin prophylaxis might be considered for children who meet all criteria for membership in the PANDAS subgroup and who have ongoing risk of GAS exposure.

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