An Open Label Study to Establish Dosing Recommendations for Nabumetone in Juvenile Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Once-a-day dosing with nabumetone has been shown to be effective in adults with rheumatoid arthritis. We establish dosing recommendations for nabumetone in children and adolescents with juvenile rheumatoid arthritis (JRA).

Methods. An open label, multicenter study was conducted in children with JRA aged 2–16 years, weighing > 14 kg, and requiring nonsteroidal antiinflammatory drugs (NSAID) for control of symptoms. NSAID were discontinued one day prior to study initiation to minimize disease flare. Patients received nabumetone 30 mg/kg once daily (as a tablet or a slurry) for 12 weeks. Efficacy assessment evaluations were performed at Weeks 1, 3, 6, and 12, based on the mean change from baseline at the study endpoint for 6 standard rheumatology variables. An overall assessment of efficacy was determined based on the percentage of patients who did not experience a flare, using the 6 rheumatology variables. Since this was an open label study, only descriptive statistics were obtained for efficacy variables. Routine safety assessments were completed for all patients.

Results. In total, 99 patients with JRA were enrolled and 89 completed the study; mean age was 9.2 years. The proportion of nabumetone treated patients with no flare in disease activity during the nabumetone treatment period was 92/99 (93%). Improvement was noted in each efficacy assessment, although statistical evaluations were not performed. The adverse event profile was similar to that reported for nabumetone in adults with RA.

Conclusion. Nabumetone 30 mg/kg/day (up to 2000 mg/day) demonstrated a safe profile with no loss of efficacy compared to previous treatment in children with JRA. The dose can be administered by suspending tablets in warm water to create a slurry. (J Rheumatol 2003;30:829–31)

Key Indexing Terms:
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Juvenile rheumatoid arthritis (JRA) is the most common form of childhood arthritis[1]. While the safety and efficacy of nabumetone in adult RA has been well established[2], use of nabumetone in JRA has only been studied in patients > 5 years of age who were intolerant to nonsteroidal antiinflammatory drugs (NSAID)[3]. Safety issues in children taking chronic NSAID are similar to those in adults, with the primary concern being gastrointestinal toxicity. In adults, nabumetone has been shown to have an excellent safety profile, including a low incidence of serious gastrointestinal events[4].

Nabumetone offers advantages for treating children because of a once-a-day dosing regimen and the ability to administer as a slurry. Nabumetone is well absorbed after oral administration and undergoes hepatic first-pass metabolism to form the major metabolite, 6-methoxy-2-naphthylacetic acid (6-MNA)[5]. Because of 6-MNA's long half-life, nabumetone can be given as a single daily dose of up to 2000 mg in adults. For children who are unable or unwilling to swallow tablets, nabumetone can be administered as a slurry by mixing the tablet in warm water. In this way, individualized doses can be administered to provide effective symptom control, regardless of age. Our purpose was to establish dosing recommendations for nabumetone in children with JRA.

MATERIALS AND METHODS

Design. This was an open label multicenter clinical trial conducted at 17 centers throughout the United States to establish dosing recommendations for nabumetone in children and adolescents with JRA, and to evaluate the safety and efficacy of nabumetone in patients with JRA. Following screening procedures, NSAID were discontinued one day prior to study initiation. All patients received nabumetone (roughly 30 mg/kg) once daily for 12 weeks, provided as 500 or 750 mg tablets (Relafen®, SmithKline Beecham Pharmaceuticals, Collegeville, PA, USA). For children unable to

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swallow a tablet, nabumetone was made into a slurry by placing the tablet into a 10 ml oral syringe with the plunger removed, mixing with 5–10 ml warm water, and administering the suspension into the side of the child's mouth. A rheumatology evaluation was performed at baseline and at Weeks 1, 3, 6, and 12. This study was conducted in accord with Good Clinical Practices and the Declaration of Helsinki as amended in 1996. The study was approved by each investigator's research ethics committee and informed consent was signed by the parent or the child if of an appropriate age. The study was carried out between December 1999 and December 2000.

Patients. Study participants included otherwise healthy male and female patients who were between the ages of 2 and 16 years, with a body weight of ≥ 14 kg. All patients were diagnosed with systemic, polyarticular, or pauciarticular JRA, as defined by the American College of Rheumatology (ACR) guidelines[6], and currently taking NSAID for control of JRA symptoms. Patients could continue with other antirheumatic medications during the study, as long as the dose remained stable throughout the study and had remained stable during the 3 months prior to study start. Acetaminophen and short-acting opiates were permitted during the study. A history of hypersensitivity to aspirin or other NSAID was cause for exclusion from the study. Treatment with beta-blockers, coumadin anticoagulants, probenecid, trimethoprim, sulfonamides, or procainamide was prohibited during the study and for 7 days prior to the start of the study (these drugs were excluded so as not to interfere with pharmacokinetic analyses). Intravenous or intraarticular corticosteroids were prohibited during the study and for 3 months prior to study start.

Assessments. Efficacy evaluations were based on change from baseline of 6 standard rheumatology variables and an overall measure of the percentage of patients who did not experience flare. The 6 standard variables included physician global assessment using a 10 cm visual analog scale (VAS), parent global assessment using a 10 cm VAS, number of active joints (active joint defined by the ACR[6,7]), number of joints with limitation of motion (LOM), functional ability assessed by the Children's Health Assessment Questionnaire (CHAQ)[8] on a scale of 0–3, and C-reactive protein (CRP; Quest Diagnostics, Collegeville, PA, USA). In addition, pain was measured as part of the CHAQ using a 15 cm VAS (with the value multiplied by 0.2). Change from baseline was measured for each variable. Since there was no NSAID washout period, children were not expected to experience a flare of disease symptoms prior to initiation of study drug. Thus, the primary efficacy evaluation was based on a continued response, or lack of flare. The percentage of patients who did not experience a flare of disease activity during the treatment period was determined. Flare was defined as worsening from baseline by ≥ 30% in ≥ 3 efficacy variables, with improvement by ≥ 30% in ≤ 1 variable and ≥ 2 active joints. This definition was modified from a similar definition[9], except that CRP was used instead of erythrocyte sedimentation rate as a measure of inflammatory activity that could be performed at a central laboratory.

About 100 eligible patients with JRA aged 2–16 years (with at least 23 between the ages of 6 and 12 years) were entered into the study to provide 70 evaluable patients. A 30% early withdrawal rate was anticipated. Since this was an open label study, no statistical analysis on efficacy measures was performed.

Routine safety evaluation included assessment of adverse events, a physical examination, measurement of vital signs, and routine clinical laboratory testing.

RESULTS

A total of 99 patients with JRA were enrolled and 89 patients completed the study. Table 1 summarizes patient and disease characteristics.

Efficacy. The proportion of JRA patients with no flare in disease activity during the nabumetone treatment period was 92/99 (93%). Control of symptoms, as expressed by the percentage of patients with no flare, was maintained in each age group (Figure 1). Improvement was noted in each efficacy outcome measurement. The mean (± SD) changes from baseline to endpoint for each efficacy variable are shown in Table 2. The percentage improvement for each efficacy variable is also shown.

Safety. The adverse event profile was consistent with data from studies in adult patients with RA. The proportion of patients reporting at least one adverse event characterized as

Table 1. Patient and disease characteristics.

Characteristic	JRA Population, n = 99
Sex, n (%)	
Female	79 (79.8)
Male	20 (20.2)
Age at enrollment, n (%), yrs	
2–5	18 (18.2)
6–12	58 (58.6)
13–16	23 (23.2)
Mean ± SD	9.2 ± 3.7
Range	2–16
Race, n (%)	
White	74 (74.7)
Black	8 (8.1)
Oriental	2 (2.0)
Other	15 (15.2)
Weight, kg	
Mean ± SD	38.62 ± 22.12
Range	12.7–120
JRA subtype, n (%)	
Polyarticular	44 (44.4)
Pauciarticular	46 (46.5)
Systemic	9 (9.1)
Disease duration, yrs	
Mean ± SD	3.2 ± 3.1
Range	0–14.1

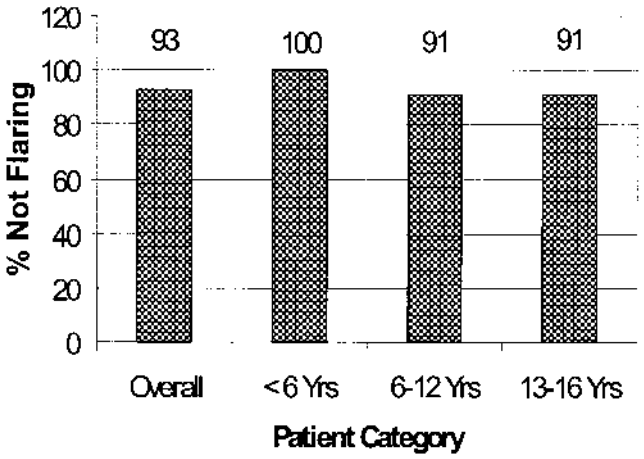

Figure 1. Percentage of patients with JRA, overall and by age group, without flare of disease activity during the nabumetone treatment period. Flare was defined as worsening from baseline by ≥ 30% in ≥ 3 efficacy variables, with improvement ≥ 30% in ≤ 1 variable and ≥ 2 active joints.

Table 2. Rheumatology evaluations.

Efficacy Assessment	Baseline Mean	Endpoint Mean	Mean Change ± SD	Improvement, %
No. of active joints	5.92	3.74	–2.01 ± 4.17	36.8
No. of joints with limitation of motion	1.56	0.77	–0.76 ± 2.61	50.3
Physician global, 0–10 cm VAS	2.54	1.43	–1.11 ± 2.05	43.5
Parent global, 0–10 cm VAS	2.54	1.75	–0.80 ± 2.10	31.2
CHAQ disability index, 0–3	0.51	0.35	–0.15 ± 0.39	30.5
CRP, 0–0.79 mg/dl	0.005	0.002	–0.0026 ± 0.0106	56.5
Pain, 0–15 cm VAS	0.82	0.52	–0.28 ± 0.62	36.5

CHAQ: Children's Health Assessment Questionnaire; CRP: C-reactive protein, VAS: visual analog scale.

probably related to study medication was 18%. Abdominal pain (5%), dyspepsia (4%), and headache (2%) were the most frequently reported adverse events of probable relationship to study medication. No clinically important changes were noted in vital signs or laboratory tests. Three patients withdrew from the study due to adverse events. None were considered serious and all 3 were due to exacerbation of arthritis symptoms. Seven other patients withdrew from the study, 2 for lack of efficacy, 4 lost to followup, and one withdrew at his own request.

DISCUSSION

Our results indicate that nabumetone dosed at approximately 30 mg/kg/day (up to 2000 mg/day) was safe in patients with JRA and provided control of the signs and symptoms of JRA. The dose could be administered by suspending tablets in a warm water slurry.

Nabumetone is well absorbed after oral administration and undergoes hepatic first-pass metabolism to form the major metabolite, 6-MNA[5]. Because of 6-MNA's long half-life, nabumetone can be given as a single daily dose of up to 2000 mg in adults.

Because patients did not undergo NSAID washout and did not experience flare at baseline in this study, true improvement from baseline could not be ascertained. However, the high percentage of patients who did not experience a flare of disease activity during the treatment period indicated that control of disease symptoms was maintained with nabumetone compared to their previous NSAID. A high degree of symptom control was maintained for patients in each age category. The adverse event profile was consistent with data from studies in adult patients with RA. In combination, the safety and efficacy profile observed in this study suggests that the dose of nabumetone used in patients with JRA was appropriate to maintain efficacy control with no additional toxicity.

For children who are unable to swallow tablets, nabumetone can be administered as a slurry in warm water. In this way, a dose of 30 mg/kg/day can be administered to provide effective symptom control to children of all ages.

In summary, the safety and efficacy data from this study suggest that nabumetone has an acceptable benefit to risk profile for use in patients with JRA dosed at 30 mg/kg/day up to 2000 mg/day. Nabumetone's daily dosing regimen and the potential to administer as a slurry may provide advantages for treatment of children with JRA compared to other NSAID requiring twice daily administration.

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