MAJOR ARTICLE

Efficacy and Safety of Oral Pleconaril for Treatment of Colds Due to Picornaviruses in Adults: Results of 2 Double-Blind, Randomized, Placebo-Controlled Trials

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The novel capsid-binding antiviral pleconaril inhibits in vitro replication of most rhinoviruses and enteroviruses. Oral pleconaril treatment was studied in 2 parallel randomized, double-blind, placebo-controlled trials. Among 1363 picornavirus-infected participants (65%) in the studies combined, the median time to alleviation of illness was 1 day shorter for pleconaril recipients than for placebo recipients ($P < .001$). Cold symptom scores and frequency of picornavirus cultured from nasal mucus specimens were lower among pleconaril recipients by day 2 of treatment. No treatment effects were seen in those without picornavirus infection. Pleconaril was associated with a higher incidence of nausea (6% vs. 4%) and diarrhea (9% vs. 7%) and with small increases in mean serum cholesterol levels and platelet counts, compared with baseline measurements. A subsequent 6-week prophylaxis study found that pleconaril induces cytochrome P-450 3A enzymes, which metabolize a variety of drugs, including ethinyl estradiol. Early pleconaril treatment was well tolerated and significantly reduced the duration and severity of colds due to picornaviruses in adults.

The majority of common colds are due to picornaviruses, principally rhinoviruses (>100 serotypes) and, less often, enteroviruses (≥67 serotypes), which together cause ~50% of colds annually [1]. The incidence of colds due to picornaviruses increases to 60%–80% during peak months in the fall and spring in the Northern Hemisphere [1, 2]. No antiviral therapy of proven value for colds due to picornaviruses is currently available, and prior studies of investigational antivirals did not show therapeutic benefit for established colds [3, 4]. The pathogenesis of cold symptoms is not fully understood [5], and the importance of ongoing viral replication to symptom causation remains uncertain.

Pleconaril is a novel, orally absorbed viral capsid–function inhibitor that specifically inhibits the replication of ~90% of rhinoviruses and >99% of enteroviruses [6–8]. In experimentally induced human coxsackievirus A21 infections, oral pleconaril significantly reduced viral shedding and illness measures [9]. More recently, retrospective analysis of 2 phase II randomized, double-blind, placebo-controlled studies found that pleconaril treatment provided clinical

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benefit for colds due to picornaviruses in previously healthy adults [10]. Consequently, 2 large, randomized, double-blind, placebo-controlled, multicenter trials were conducted to evaluate the efficacy and safety of oral pleconaril for treatment of naturally occurring colds presumptively due to picornaviruses in adults.

METHODS

Participants. Participants in both studies were otherwise healthy adults (age, ⩽18 years) with self-diagnosed colds who were enrolled within 24 h after symptom onset. Participants had moderate to severe rhinorrhea and ⩾1 other respiratory symptom (nasal congestion, cough, or sore throat) that was rated moderate or greater in severity.

Subjects were excluded if they had fever (oral temperature, >37.8°C), if they had allergic rhinitis that had been treated within the previous 2 weeks, if they had received asthma treatment within the previous 2 months, or if they had chronic cough, any known immunodeficiency, or an underlying medical condition that would confound the study results. Pregnant or nursing women were excluded, and urine pregnancy tests were done at entry. Smokers were allowed.

The institutional review board of each participating site approved the protocol, and written informed consent was obtained from each participant at the time of enrollment into the study. Participants were compensated for participation.

Study design and drug administration. Two prospective, multicenter, randomized, double-blind trials of identical design were conducted from August through November 2000; each enrolled participants from geographically diverse areas of the United States (150 sites) and Canada (47 sites). Participants were randomized in a 1:1 ratio to receive either pleconaril at 400 mg (two 200-mg tablets; Picovir; ViroPharma) or matching placebo tablets 3 times per day for 5 days. To enhance oral absorption, participants were instructed to take the study medication within 15 min after a meal or snack. Randomization was stratified by the subject's preenrollment smoking status and preenrollment use of cold symptom–relief medication to ensure that these subjects were balanced between the treatment arms. Acetaminophen and dextromethorphan were provided for disabling symptoms, because these agents were unlikely to affect the prominent nasopharyngeal symptoms of colds. The concomitant use of prescription and other over-the-counter cold symptom–relief medications was not permitted.

Clinical monitoring. Participants were evaluated at enrollment and again on study days 3, 6 (end of treatment), and 18 (end of the study) for clinical assessment and obtainment of samples for laboratory testing. Study personnel contacted participants every other day by telephone until their cold had resolved or through day 18.

Participants recorded the severity of 6 individual cold symptoms (rhinorrhea, nasal congestion, sore throat, cough, malaise, and myalgia) in study diaries twice daily, grading each as "not present," "mild" (noticeable but not bothersome), "moderate" (bothersome), or "severe" (limiting usual activities), which were scored as 0, 1, 2, and 3, respectively, for data analysis. Once per day, subjects also recorded data on the number of facial tissues used, sleep disturbance, impairment of daily activity as a result of cold symptoms, and use of cold symptom–relief medications or other medications for any reason. Safety laboratory studies (hematological study, clinical chemistry, and urinalysis) and physical assessments were done at enrollment and on study day 6.

Virology assessments. Nasal mucus samples were obtained for virological studies at baseline and on study days 3 and 6. Subjects were asked to blow nasal mucus directly onto plastic wrap; mucus was induced, if necessary [11]. The sample was transferred into a tube containing viral transport medium (Starswab Multitrans Collection and Transport System; Starplex Scientific) and shipped for storage at −80°C until assayed.

The presence of picornavirus RNA in nasal mucus samples was identified using a real-time, quantitative RT-PCR assay (TaqMan; Applied Biosystems). The PCR primers and probe used in the TaqMan assay were derived from conserved sequences within the 5′ nontranslated region of sequenced human rhinovirus (HRV) genomes. The forward primer sequence was 5′-GTGAAGAGCC(G/C)C(A/G)TGTGCT-3′, corresponding to nucleotides 414–432 of HRV89. The reverse primer sequence was 5′-GCT(G/C)CAGGGTTAAGGTTAGCC-3′, corresponding to the reverse complement of nucleotides 461–481 of HRV89. The double-labeled fluorescent probe sequence was 5′-(FAM)-TGAGTCCTCCGGCCCCTGAATG-(TAMRA)-3′, corresponding to nucleotides 438–459 of HRV89. In this assay, the lower limit of detection for the virus (HRV1B) used to generate the standard curve was 10 pfu/mL, or 10,550 genome equivalents/mL (211 genome equivalents per reaction).

If all 3 samples obtained from a patient had negative or indeterminate results for this assay, the baseline sample was retested by a modification of an enzyme-linked oligosorbent RT-PCR assay, which detects all prototype rhinoviruses and culturable enteroviruses [12–15]. A patient was considered to be positive for picornavirus infection if nasal mucus specimens tested positive with either RT-PCR assay on any sampling day.

For subjects who had positive RT-PCR results, an aliquot of the baseline mucus sample (200 μL) was submitted for viral culture on monolayers of HeLa-I cells by a previously described technique [16]. If culture of the baseline sample yielded positive results, aliquots of samples obtained on days 3 and 6 were also cultured.

TaqMan assays were performed at ViroMed Biosafety Laboratories (St. Paul, Minnesota), enzyme-linked oligosorbent

Table 1. Disposition of subjects in 2 studies of efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses.

Variable	No. (%) of subjects			
	Study 843-043		Study 843-044	
	Placebo group	Pleconaril group	Placebo group	Pleconaril group
Randomized	526	526	524	520
Treated	526 (100)	526 (100)	524 (100)	520 (100)
Completed treatment	487 (93)	479 (91)	493 (94)	486 (93)
Did not complete treatment, reason				
Adverse event	15 (3)	17 (3)	13 (2)	19 (4)
Lost to follow-up	11 (2)	8 (2)	8 (2)	4 (1)
Noncompliance	5 (1)	11 (2)	1 (<1)	6 (1)
Subject request	7 (1)	6 (1)	6 (1)	3 (1)
Other	1 (<1)	5 (1)	3 (1)	2 (<1)
Total	39 (7)	47 (9)	31 (6)	34 (7)

RT-PCR assays were performed at ViroPharma Incorporated (Exton, Pennsylvania), and viral cultures were performed at the University of Virginia (Charlottesville) or the University of Rochester Medical Center (Rochester, New York). Study personnel at each laboratory were blinded to treatment and sample collection day.

Efficacy end points. The primary efficacy population included any randomized participant with ⩾1 nasal mucus sample that tested positive for picornavirus RNA on any sampling day by either quantitative or qualitative RT-PCR methods. The secondary efficacy population included all randomized participants. These participants are referred to as the intent-to-treat infected (ITT-I) and intent-to-treat (ITT) populations, respectively.

The primary end point was the time from initiation of therapy to alleviation of illness, defined as the number of days until complete resolution of rhinorrhea and the other 5 cold symptoms self-assessed as absent or mild for ⩾48 h without use of cold symptom–relief medication. Prospectively defined secondary end points were the time to subject-assessed "no cold," times to complete resolution of individual symptoms, total cold symptom severity scores, tissue counts, proportion of nights with disturbed sleep, duration of cold symptom–relief medication use, and frequency of viral shedding in nasal mucus. Other end points were the time to ⩾50% reduction in symptom score and changes in viral RNA levels over time.

Data analysis. The distribution of time to resolution of symptom scores was estimated by the Kaplan-Meier method [17], and the Wilcoxon-Gehan statistic [18] was used to test the difference in median resolution times between treatment groups. These analyses included stratification for smoking status and preenrollment use of cold symptom–relief medication. Combined analyses of both studies also included stratification by study. In these time-to-event analyses, subjects who discontinued the study were included up to the point of the last recorded observation. The distribution of time to ⩾50% reduction from baseline in total cold symptom severity score was analyzed in the same manner.

The treatment effect for change from baseline in daily total symptom severity score and total symptom severity score over the 18-day study was analyzed by analysis of covariance, with effects for treatment, study, smoking status, preenrollment use of cold symptom–relief medication, and baseline total symptom severity score. The last observation carried forward was used to impute missing individual symptom severity scores.

Treatment effect for presence of picornavirus by culture and percentage of subjects using cold medications was evaluated using Fisher's exact test. Analysis of variance was used to compare the treatment groups for reduction in virus levels (measured by PCR) from baseline to days 3 and 6, proportion of nights with sleep disturbance, and tissue use.

All study participants who received ⩾1 dose of study medication were included in the safety analysis. Adverse events that began or worsened at any time after receipt of the first dose of study drug through 5 days after the last dose were summarized. All analyses were done using SAS statistical software, version 6.12 (SAS Institute) [19], and a 2-sided test at the 5% level was used for all comparisons.

Sample size. Calculations indicated that enrollment of 1000 subjects in each study was required to detect a 25% relative difference between treatment groups in the proportion of picornavirus-infected subjects reaching the primary end point (or an estimated 2-day difference in median time) with 90% power (2-sided test at the 5% level of significance [20]).

RESULTS

Study population. The 2 studies randomized 2096 participants (1046 in the pleconaril group and 1050 in the placebo group); >90% of subjects completed treatment (table 1). The

Table 2. Demographic and clinical characteristics of picornavirus-infected subjects (intent-to-treat infected population) at baseline in 2 studies.

Characteristic	Study 843-043		Study 843-044	
	Placebo group (n = 326)	Pleconaril group (n = 337)	Placebo group (n = 356)	Pleconaril group (n = 344)
Age				
Median years (range)	35 (18–73)	33 (18–75)	35 (18–86)	33 (18–82)
Distribution, no. of patients				
18–44 years	244	257	261	259
45–64 years	73	74	82	74
⩾65 years	9	6	13	11
Female sex, no. (%) of patients	211 (65)	230 (68)	251 (71)	231 (67)
Smoker,[a] no. (%) of patients	88 (27)	107 (32)	96 (27)	97 (28)
Time from symptom onset to receipt of first dose, h				
Mean ± SD	18 ± 5	18 ± 5	18 ± 6	18 ± 6
Median	20	20	20	20
Total symptom score				
Mean ± SD	9.5 ± 2.6	9.5 ± 2.5	9.0 ± 2.5	9.2 ± 2.5
Median	9	9	9	9
Used cold medications before study, no. (%) of patients	99 (30)	107 (32)	119 (33)	120 (35)

[a] Current smokers or those who stopped smoking ⩽3 months before the start of study.

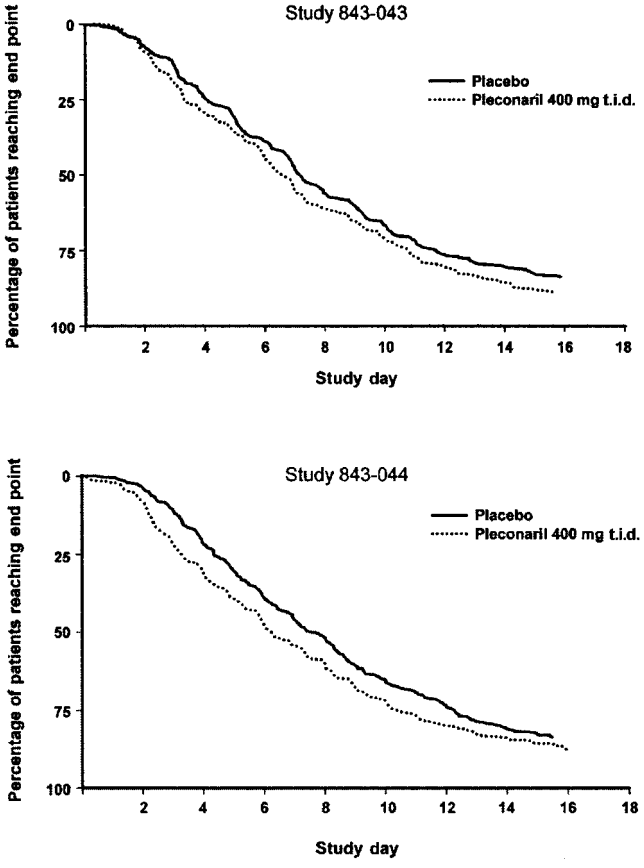


Figure 1. Kaplan-Meier analyses of time to alleviation of illness (primary efficacy end point) among picornavirus-infected subjects. Marks on the *x* axis represent end of study day.

most common reason that subjects did not complete treatment was an adverse event (3% of subjects each in the pleconaril and placebo groups). Overall, 65% of participants were infected with picornavirus, with a narrow range (62%–68%) across treatment groups in each study. The pleconaril and placebo groups were similar at baseline with regard to relevant demographic and illness characteristics (table 2). The mean age of the ITT-I population was 36 years, 69% were female, and 28% were smokers. The median time from symptom onset to receipt of the first dose of study drug was 20 h.

Illness resolution. Among the picornavirus-infected (ITT-I) population, the time to reach the primary end point of illness alleviation was significantly shorter among pleconaril-treated subjects than among placebo recipients in each study (figure 1). Overall, pleconaril-treated patients experienced a 1-day reduction in the median duration of illness, compared with placebo-treated subjects ($P < .001$; table 3). The treatment effect was similar for subjects who had positive results of viral cultures at baseline (combined median time to illness alleviation, 7.9 days for the placebo group and 6.8 days for the pleconaril group; $P = .002$) and for those with negative results of viral culture at baseline (7.0 days for the placebo group and 6.0 days for the pleconaril group; $P = .048$). No treatment effect was observed among participants without detectable picornavirus infection (table 3). In the ITT population, the magnitude of the treatment benefit was smaller than that observed among ITT-I subjects but favored pleconaril in both studies.

Among ITT-I subjects, the self-assessed times to "no cold" and to resolution of each individual cold symptom were reduced in pleconaril recipients (table 4). The total cold symptom

Table 3. Data on the primary efficacy end point (number of days to alleviation of illness) in 2 studies of oral pleconaril for treatment of colds due to picornaviruses.

Subject group, variable	Study 843-043			Study 843-044			Studies combined		
	Placebo group	Pleconaril group	*P*	Placebo group	Pleconaril group	*P*	Placebo group	Pleconaril group	*P*
Positive RT-PCR results (ITT-I population)									
No. of patents	326	337		356	344		682	681	
Time to event, days									
25th percentile	4.1	3.3		4.3	3.3		4.3	3.3	
Median	7.2	6.6	.037	7.7	6.2	.001	7.3	6.3	<.001
75th percentile	11.7	10.8		12.3	10.4		12.0	10.8	
Negative RT-PCR results									
No. of patients	200	189		168	176		368	365	
Time to event, days									
25th percentile	3.3	3.3		3.7	3.7		3.3	3.4	
Median	5.9	6.1	.639	5.9	6.0	.776	5.9	6.0	.591
75th percentile	10.1	10.9		13.8	11.3		11.4	11.3	
All randomized subjects (ITT population)									
No. of patients	526	526		524	520		1050	1046	
Time to event, days									
25th percentile	3.8	3.3		4.1	3.4		3.9	3.3	
Median	6.9	6.4	.201	7.1	6.2	.015	7.0	6.3	.009
75th percentile	11.2	10.8		12.3	10.9		11.9	10.8	

NOTE. Alleviation of illness is defined as the absence of rhinorrhea and presence of no or mild other cold symptoms for ⩾48 h without use of cold symptom–relief medication. ITT, intent-to-treat; ITT-I, intent-to-treat infected.

severity score was reduced by 19% over the duration of the study for pleconaril recipients (table 4), who also experienced significant reductions from baseline in symptom severity scores by day 2 of treatment, compared with placebo recipients (figure 2). A reduction in total symptom severity score of ⩾50% occurred earlier among pleconaril recipients than among placebo recipients (combined medians of 2.9 and 3.9 days, respectively; $P < .001$). Pleconaril treatment was associated with fewer tissues used for nose blowing (24% reduction), fewer nights of sleep disturbance (1 night reduction), and fewer days of cold symptom–relief medication use (table 4).

Analyses of the combined study results were conducted with

Table 4. Data for secondary end points used as efficacy measures in 2 studies of oral pleconaril for treatment of colds due to picornaviruses among picornavirus-infected subjects (intent-to-treat infected subjects).

End point	Study 843-043			Study 843-044			Studies combined		
	Placebo group (*n* = 326)	Pleconaril group (*n* = 337)	*P*	Placebo group (*n* = 356)	Pleconaril group (*n* = 344)	*P*	Placebo group (*n* = 682)	Pleconaril group (*n* = 681)	*P*
Time to subject-assessed "no cold" status, median days	6.8	6.0	.026	7.0	6.0	.048	6.9	6.0	.003
Time to complete resolution of specific symptoms, median days									
Rhinorrhea	6.9	6.0	.025	7.1	5.9	<.001	7.0	6.0	<.001
Nasal congestion	6.3	5.8	.005	6.4	6.0	.152	6.3	5.9	.003
Sore throat	3.8	2.8	<.001	3.8	3.0	.004	3.8	2.9	<.001
Cough	6.1	5.9	.087	6.8	5.4	.024	6.3	5.4	.005
Malaise	4.5	3.9	.022	4.1	3.8	.193	4.2	3.8	.011
Myalgia	3.8	2.8	<.001	3.9	2.9	.003	3.9	2.9	<.001
Total symptom severity score,[a] median	36.1	28.5	.006	34.4	29.0	<.001	35.4	28.8	<.001
Median no. of tissues used[a]	115.0	96.0	.198	131.5	91.0	<.001	122	93	<.001
Median no. of nights with sleep disturbance	3	2	<.001	3	2	.270	3	2	<.001
Median no. of days of cold medication use	1	0	.058	1	0	.028	1	0	.004

[a] During study period (i.e., days 1–18).

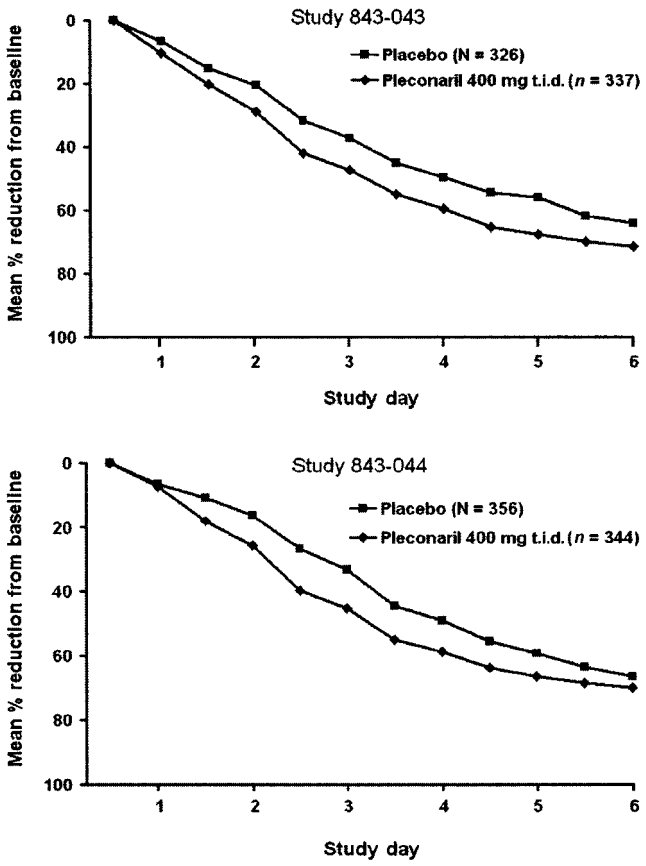


Figure 2. Change from baseline value in total cold symptom severity scores among picornavirus-infected subjects, days 1–6. Pleconaril recipients experienced significant ($P < .05$) reductions from baseline by day 2 of treatment in each study.

a Cox regression model to assess 2-way interaction effects between treatment and the variables age, sex, race, smoking status, and preenrollment cold medication use. The only interaction with significant impact on treatment effect was smoking status ($P = .013$). The time to reach the primary end point was shorter for pleconaril recipients than for placebo recipients among nonsmokers (6.0 vs. 7.3 days; $P < .001$), but it was not different among smokers (8.3 vs. 7.4 days; $P = .692$). However, additional analysis regarding effects of pleconaril for smokers is limited by the fact that smokers constituted only 28% of the study population.

Virologic analysis. Among subjects with detectable picornavirus RNA in baseline nasal mucus samples, 827 (65%) of 1263 subjects had positive results of viral cultures. Acid stability testing of 69 randomly selected isolates determined that 68 (99%) were acid-labile and presumed rhinoviruses, whereas 1 was acid-stable and a presumed enterovirus.

Among those who had positive results of culture at baseline, fewer pleconaril recipients had positive culture results on day 3 (range, day 2–4) than did placebo recipients (53% vs. 72%; $P < .001$; figure 3). Additional analysis of the subset of subjects who had samples obtained for culture on day 2 revealed that significantly fewer pleconaril recipients than placebo recipients had positive viral culture results (27 [60%] of 45 subjects vs. 49 [84%] of 58 subjects; $P = .007$).

Nasal mucus viral RNA levels decreased rapidly in both pleconaril and placebo treatment groups. Subjects in the pleconaril group showed a larger median percentage reduction from baseline in virus levels on study day 3, compared with subjects in the placebo group (97.7% vs. 90.3%; $P < .001$). By day 6 (range, day 5–9), the median percentage reduction in virus levels was >99% in both treatment groups.

Safety. Pleconaril was generally well tolerated. The most commonly reported adverse events were headache, diarrhea, and nausea (table 5); ⩾95% of adverse events were mild or moderate in severity. Four subjects receiving pleconaril and 2 receiving placebo reported a serious adverse event, none of which was considered by the investigators to be related to study drug except for 1 case of inadvertent overdose of pleconaril (with no adverse sequelae).

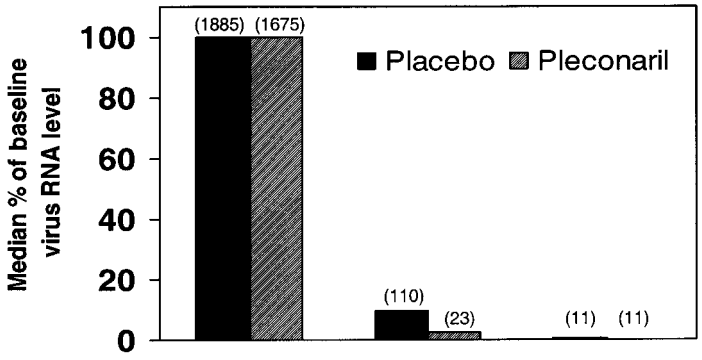
No differences were noted in vital signs or physical examination findings in either treatment group, and there were no clinically significant laboratory abnormalities (data not shown). The only laboratory findings associated with pleconaril use were small median increases from baseline values in the pleconaril group for nonfasting serum cholesterol levels (an increase of 5 mg/dL [or 3%], compared with a decrease of 4 mg/dL [or 2%] in placebo recipients; $P < .001$) and for platelet counts (an increase of 15×10^3 platelets/mm^3 [or 6%], compared with an increase of 7×10^3 platelets/mm^3 [or 3%] in placebo recipients; $P < .001$).

Table 5. Most common adverse events for all treated subjects in 2 studies of oral pleconaril for treatment of colds due to picornaviruses.

Adverse event	Placebo group (n = 1050)	Pleconaril group (n = 1046)
Headache	215 (20)	231 (22)
Diarrhea	73 (7)	93 (9)
Nausea	46 (4)	59 (6)
Bronchitis	28 (3)	27 (3)
Rhinitis	30 (3)	21 (2)
Sinusitis	22 (2)	28 (3)
Total[a]	575 (55)	575 (55)

NOTE. "Most common" is defined as incidence of ⩾3% in either treatment group.

[a] Total no. of subjects who experienced ⩾1 adverse event, regardless of its relationship to use of the study drug.



Percentage of subjects virus culture positive among those with positive cultures at baseline	Placebo	**72%** (282/394)	**51%** (196/387)
	Pleconaril	**53%** (202/380)	**44%** (165/375)
	P value	< .001	.070

Figure 3. Antiviral activity in studies 843-043 and 843-044 combined: change in viral RNA levels from baseline values, as determined using the RT-PCR TaqMan assay (Applied Biosystems; numbers in parentheses are median virus levels at each time point in relative plaque-forming units per milliliter derived from the HRV1B standard curve) and results of viral cultures for subjects with positive culture results at baseline.

DISCUSSION

These prospective, double-blind, placebo-controlled studies found that early pleconaril treatment significantly reduces the duration and severity of colds due to picornaviruses in adults; these findings establish pleconaril as the first antiviral to have proven therapeutic value for such illnesses. These results confirm and extend those of an earlier retrospective analysis of adults with colds due to picornaviruses, which found a 1.5-day reduction in the time to alleviation of illness in pleconaril recipients, compared with placebo recipients [10]. Pleconaril use was associated with significant reductions in symptom severity scores and the frequency of recovery of picornaviruses within 1 day after initiation of therapy. In addition, pleconaril therapy resulted in a significant reduction in the duration of each individual cold symptom monitored in the study, a finding consistent with the hypothesis that ongoing viral replication is an important contributor to the pathogenesis of cold symptoms.

The rapid decrease in viral RNA levels in both pleconaril and placebo groups illustrates the importance of early initiation of antiviral therapy. We also observed that substantial proportions of both placebo recipients and, less often, pleconaril recipients continued to have positive culture results on study day 6 or later, although at very low levels of viral RNA. This prolonged recovery of virus is consistent with earlier data from natural and experimentally induced rhinovirus infections [21, 22], but it raises the issue of emergence of drug-resistant variants. In the current studies, viruses with reduced susceptibility to pleconaril ($\geq$10-fold change from baseline value) were recovered during or after therapy from ~10% of patients who received pleconaril. However, subgroup analyses indicate that clinical benefit for these participants was as good as or better than that for pleconaril recipients with no reduction in virus susceptibility to the drug (unpublished data). Further phenotypic and genetic characterization of viruses from these and other pleconaril trials is ongoing, to determine relationships between in vitro susceptibility and clinical outcomes.

Pleconaril was shown to be safe and generally well tolerated. Compared with placebo, there were only small (2%) excess frequencies of headaches, nausea, and diarrhea in patients receiving pleconaril. The small increases from baseline in cholesterol levels and platelet counts are not clinically significant, an observation that was confirmed in a subsequent 6-week prophylaxis study (unpublished observations). In that study, an excess of mild or moderate menstrual disorders (most commonly breakthrough bleeding or spotting) was reported from women taking oral contraceptives and pleconaril. Subsequent investigations revealed that pleconaril induces hepatic cytochrome P-450 3A enzymes. Pleconaril reduced the area under the curve of plasma levels of ethinyl estradiol by 34% following single-dose administration (G. Rhodes, personal communication). Retrospective review of all randomized, placebo-controlled trials in which pleconaril was administered for 5–7 days revealed that menstrual irregularities were reported by 3.5% of 310 pleconaril-treated women who were using oral contraceptives and by none of 291 placebo-treated women. None of the menstrual irregularities led to discontinuation of treatment. Additional studies are ongoing to better characterize the magnitude and duration of cytochrome P-450 3A induction

and to determine the clinical significance for coadministration of pleconaril with other drugs metabolized by cytochrome P-450 3A.

One limitation of the current studies is that most participants were generally healthy young adults. Other studies have established that rhinoviruses can cause both upper and lower respiratory tract complications, including asthma exacerbations in both adults and children [23–25], acute exacerbations of chronic obstructive pulmonary disease [26], acute otitis media in children [27], and sinusitis in adults [13]. Others at risk for lower respiratory complications due to rhinovirus infection include patients with cystic fibrosis [28], elderly individuals [29], and immunocompromised persons [30]. The positive findings in the current trials indicate that studies of pleconaril should be extended to children, smokers, and those with underlying airway disease.

In summary, early pleconaril treatment of colds due to picornaviruses reduces the duration and severity of illness in adults. Pleconaril at this dosage was well tolerated, although additional data are needed to better characterize its potential for drug interactions.

PLECONARIL RESPIRATORY INFECTION STUDY GROUP

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