

Selection of aspirin dosages for aspirin desensitization treatment in patients with aspirin-exacerbated respiratory disease

Jennifer Y. Lee, MD,^a Ronald A. Simon, MD,^b and Donald D. Stevenson, MD^c

La Jolla, Calif

Background: Aspirin desensitization followed by daily aspirin therapy is effective add-on treatment for patients with aspirin-exacerbated respiratory disease. Prior studies used 650 mg of aspirin twice daily, but studies at lower dosages were inconclusive.

Objective: We sought to determine the optimal daily dosage of aspirin treatment.

Methods: We studied 137 patients who had undergone successful aspirin desensitization and randomized them into 2 groups, 650 mg twice daily versus 325 mg twice daily. After 1 month, patients either increased or decreased their dosage based on their symptom control and continued that dosage for the remainder of the year.

Results: Patients taking either 650 mg twice daily or 325 mg twice daily showed significant improvements in number of sinus infections, sinus operations, and hospitalizations for asthma (all $P < .0001$). Anosmia, nasal/sinus symptoms, and asthma symptoms also improved in both groups (all $P < .03$). Systemic corticosteroid dosages decreased by 3- and 4-fold in the 325 mg twice daily and 650 mg twice daily groups, respectively. Of the 137 patients, 32 had adverse effects from or discontinued aspirin therapy: 14 (44%) of 32 from the group randomized to taking 650 mg twice daily and 18 (56%) of 32 from the group randomized to 325 mg twice daily. The most common adverse effect was dyspepsia.

Conclusion: Both dosages were efficacious, and side effects occurred in both groups at similar frequencies. Some patients initially taking 325 mg twice daily required an increase to 650 mg twice daily for optimal symptom control.

Clinical implications: We recommend that patients begin daily aspirin therapy with 650 mg twice daily and subsequently decrease to the lowest effective dosage (usually 325 mg twice daily). (J Allergy Clin Immunol 2007;119:157-64.)

Key words: Aspirin, nonsteroidal anti-inflammatory drugs, aspirin-exacerbated respiratory disease, aspirin desensitization, leukotriene receptor antagonist, 5-lipoxygenase inhibitor

Aspirin-exacerbated respiratory disease (AERD) is an aggressive inflammatory disease of the upper and lower respiratory mucosa.¹ Patients with AERD can have mild or intermittent asthma but more typically have moderate-to-severe asthma. If they have moderate or severe asthma, most require full doses of inhaled corticosteroids, cysteinyl leukotriene receptor antagonists,² and sometimes the addition of a 5-lipoxygenase inhibitor.³ In addition, daily systemic corticosteroid therapy is also required in about a third of patients, at an average dosage of 10.3 mg of prednisone per day.⁴ In addition to lower airway inflammation, patients with AERD also have significant upper respiratory tract inflammation, leading to chronic hyperplastic eosinophilic sinusitis,⁵ nasal polyposis, and recurring infectious sinusitis. In all patients with AERD, aspirin and cross-reacting nonsteroidal anti-inflammatory drugs (NSAIDs) provoke acute respiratory reactions.

Aspirin desensitization, followed by daily aspirin therapy, is an effective treatment for patients with AERD in whom conventional therapy has failed, particularly those patients with recurrent nasal polyps or those dependent on systemic corticosteroids.⁶ Five published studies have shown that the majority of patients with AERD experience improvement in their chronic respiratory symptoms after aspirin desensitization treatment.⁷⁻¹¹ In addition to symptomatic relief, the same studies showed that patients with AERD receiving daily aspirin therapy were also able to significantly decrease their doses of systemic corticosteroids or even discontinue this drug.

A lingering question from these studies, however, concerns the optimal dosage of daily aspirin after aspirin desensitization. In terms of clinical efficacy, all of the above studies used a dosage of 650 mg twice daily. However, in a 2003 study by Berges-Gimeno et al,¹¹ after the first year of aspirin treatment, half of the patients with AERD decreased aspirin dosages to 325 to 975 mg/d and

From ^athe Division of Allergy, Asthma and Immunology, Scripps Clinic; ^bthe Division of Allergy, Asthma and Immunology, Scripps Clinic and the Scripps Research Institute; and ^cthe Division of Allergy, Asthma and Immunology, Department of Medicine, Scripps Clinic and the Scripps Research Institute.

Supported by a Skaggs Institutional Grant and a Novartis Grant.

Disclosure of potential conflict of interest: J. Y. Lee is employed by Scripps Health. R. A. Simon is employed by Scripps Clinic and is on the speakers' bureau for Merck, Critical Therapeutics, GlaxoSmithKline, Schering Plough, Novartis, Pfizer, and Sandoz-Aventis. D. D. Stevenson has received grant support from Skaggs Institutional Grant and Novartis; is employed by Scripps; and is on the speakers' bureau for Merck and Critical Therapeutics.

Received for publication June 14, 2006; revised September 5, 2006; accepted for publication September 8, 2006.

Available online November 14, 2006.

Reprint requests: Donald D. Stevenson, MD, Scripps Clinic and The Scripps Research Institute, 10666 North Torrey Pines Rd, La Jolla, CA 92037.
E-mail: Stevenson.donald@scrippshealth.org.

0091-6749/\$32.00

© 2007 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2006.09.011

Abbreviations used

AERD: Aspirin-exacerbated respiratory disease
 GCRC: General Clinical Research Center
 LTRA: Leukotriene receptor antagonist
 NSAID: Nonsteroidal anti-inflammatory drug

continued to enjoy the same efficacy during the subsequent 1 to 4 additional years of aspirin treatment. In that same study, 14% of the patients dropped out in the first year because of side effects, with epigastric pain responsible for the majority of the side effects. Intuitively, because some patients with epigastric pain can continue aspirin treatment if their dosage is reduced to less than 650 mg twice daily, a compelling reason to begin aspirin treatment with a lower dosage might be to reduce dose-related adverse effects.

The objective of this current study was to determine the optimal daily dosage of aspirin after aspirin desensitization, 325 mg twice daily versus 650 mg twice daily, taking into consideration both clinical efficacy and adverse effects of long-term treatment with daily aspirin.

METHODS

Patients

Patients were recruited who had nasal polyps, chronic sinusitis, asthma, and a history of at least one asthma attack after ingesting aspirin or one of the NSAIDs. Between 2003 and 2005, all patients admitted to the General Clinical Research Center (GCRC) underwent standard single-blind oral aspirin challenges.¹² One hundred thirty-seven patients experienced respiratory reactions to aspirin during single-blind standard oral aspirin challenges¹² and therefore were given diagnoses of AERD and were eligible to participate in this study. Any patients who had negative oral aspirin challenge results were excluded from this study.

Study design

This study was approved by the Scripps Human Subjects Committee and the GCRC Advisory Committee. The study consisted of randomizing patients into 2 treatment groups based on the next-to-last number of their medical record number. If the number was even, they were instructed to leave the GCRC while taking 325 mg of aspirin (buffered with antacid) twice daily. If the next-to-last number was odd, they were instructed to take 650 mg of aspirin twice daily. All 137 patients agreed to participate.

Specific instructions for each of the 2 groups

Group 1. The group taking 325 mg of aspirin twice daily was instructed to consult with their referring physician and, using the following guidelines, make a decision about changing or not changing the dosage of aspirin after 1 month of treatment. If the patients were asymptomatic, they were instructed to continue the same dosage of 325 mg of aspirin twice daily. If the patients continued to have nasal congestion, loss of smell, or both, they were instructed to increase aspirin dosages up to 650 mg twice daily. If the patients were asymptomatic and taking daily prednisone, with the help of their referring physician, they were instructed to reduce prednisone. If, as prednisone was reduced, nasal congestion or loss of smell returned,

they were instructed to increase aspirin dosages up to a maximum dosage of 650 mg twice daily. If the patients experienced side effects (gastritis, urticaria or angioedema, tinnitus, bleeding, or excessive bruising), they were instructed to receive treatment from their doctor for the condition and attempt to continue 325 mg of aspirin twice daily or, if side effects were uncontrollable, to decrease the dosage or abandon aspirin treatment. In essence, our starting group of patients taking 325 mg of aspirin twice daily evolved into 4 groups: those who continued 325 mg of aspirin twice daily, those who increased their dosages of aspirin to 975 mg (2 patients) and the remainder to 650 mg twice daily, those who decreased their aspirin dosages to 325 mg or less because of side effects, and those who discontinued aspirin because of side effects or for other reasons.

Group 2. The group assigned to taking 650 mg of aspirin twice daily was instructed to consult with their referring physician at the end of 1 month in a similar manner. However, their instructions were the opposite. If they were asymptomatic, they were instructed to reduce their aspirin dosage to 325 mg twice daily. However, if after reducing their dosages of aspirin, nasal congestion or hyposmia returned, they were instructed to increase their aspirin dosages back up to 650 mg twice daily and continue that dosage for the next year. If the patients were taking daily prednisone, they were instructed to reduce the dosage under the direction of their referring physician. As above, if side effects occurred, treatment of the side effects and reduction or discontinuation of aspirin was recommended. Group 2 evolved into 4 groups: those who continued 650 mg of aspirin twice daily, those who reduced the dosage of aspirin to 325 mg twice daily because they were doing well, those who decreased aspirin doses between 81 mg and 975 mg because of side effects, and those who discontinued aspirin because of side effects or for other reasons.

Instructions for both groups. There were no recommendations to reduce nasal or inhaled corticosteroids or leukotriene receptor antagonists (LTRAs). With or without the blessing of their referring physicians, some patients reduced topical corticosteroids, particularly nasal corticosteroids, during the course of the study. None of the patients were taking zileuton because it was not on the market during the time frame of this study. Eighty-four percent of the patients were taking montelukast or zafirlukast at the time of discharge from the GCRC. During the year of follow-up, a small number of patients who were not taking LTRAs at baseline were started on LTRAs by their referring physicians. This consisted of 2 patients in the 325 mg twice daily group and 4 patients in the 650 mg twice daily group. The remaining patients continued the same LTRA throughout the study. Patients who had superimposed respiratory infections with exacerbations of infectious sinusitis and asthma received bursts of prednisone or methylprednisolone and antibiotics from their referring physicians as they had in the past.

Follow-up collection and analysis of data

The GCRC nurses called the patients once a month, but the data were annualized to 1 year. During these telephone conversations, the nurses recorded symptom scores, clinical events, doses of aspirin and other medications that the patients were taking at that time, and any side effects or reasons for changing or discontinuing their aspirin dosages. The nurses did not recommend changes in the aspirin dosages unless the patients were experiencing side effects (particularly abdominal pain or hives). All patients were encouraged to receive their medical care from their referring physicians. The nurses were instructed to emphasize that they were not the patients' "telephone doctors" but were calling to find out what was happening between the patient and their referring physician so that this study could go forward. Patient cooperation was high, possibly because most of the telephone calls were made in the evening by the nurses who were on the night shift.

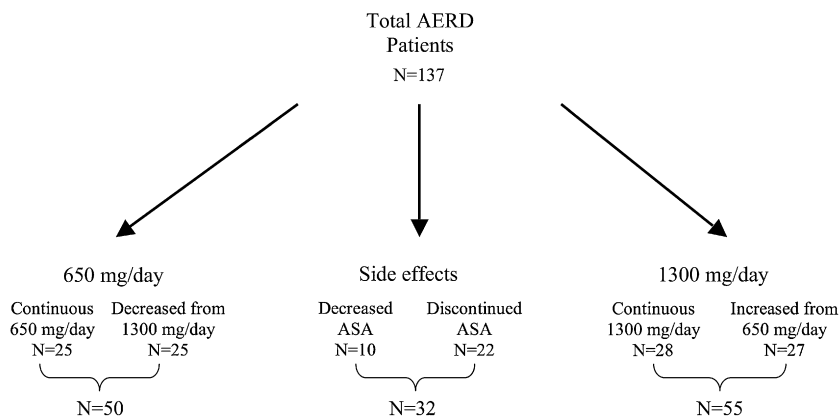


FIG 1. Subgrouping of patients based on final dosage of aspirin (ASA).

The following objective and subjective clinical end points were elicited and recorded.

Number of sinus infections. Sinus infection was defined as change to purulent nasal discharge requiring antibiotics and usually bursts of systemic corticosteroids as treatment. We recorded the number of sinus infections in the year before and after aspirin desensitization.

Number of sinus surgical procedures. Surgical interventions to resect polypoid tissue and debride infected sinuses were recorded before desensitization and during the year after starting aspirin desensitization treatment. The number of surgical procedures per year before desensitization (number of interventions divided by the numbers of years of disease before desensitization) and the number of surgical procedures in the year after desensitization were recorded.

Global assessment of rhinitis/sinusitis and asthma scores. Subjective scores for general assessment of rhinitis/sinusitis and asthma were as follows: 1, terrible; 2, poor; 3, fair; 4, good; and 5, excellent. From these subjective scores, patients rated the state of their asthma and rhinitis/sinusitis before the desensitization and a year later.

Smell scores. Subjective sense of smell scores were as follows: 0, no sense of smell at any time; 1, intermittent partial sense of smell; 2, intermittent complete sense of smell; 3, partial sense of smell the majority of the time; 4, complete sense of smell the majority of the time; and 5, perfect and continuous sense of smell. We scored the sense of smell in the previous year and the year after aspirin desensitization treatment.

Hospital admissions for asthma. The number of hospital admissions for asthma per year before desensitization and during aspirin treatment was compiled.

Topical corticosteroids for nasal insufflations. We recorded the number of patients who were taking nasal corticosteroids at baseline and after a year of their aspirin treatment. For comparison and statistical analyses, dosages in micrograms per day for those taking nasal corticosteroids were recorded before and after aspirin treatment.

Topical corticosteroids for bronchial inhalation. The same treatment of data that was described for nasal corticosteroids was used for inhaled corticosteroids.

Systemic corticosteroids. For the patients taking methylprednisolone, doses were converted to prednisone equivalents at a ratio of 4:5. In the patients who were taking prednisone on alternate days, we calculated the daily dose equivalent using half of the every-other-day dose. There were 29 (21%) of 137 patients taking daily prednisone at the time of entry into the study. Of the remaining 108 patients, 9 were not taking any systemic steroids before or after treatment with aspirin,

and 99 were taking bursts of prednisone. The numbers of bursts of prednisone per year were also calculated for the same time points. Although somewhat arbitrary, we reasoned that a burst of prednisone involved the consumption of approximately 350 mg of prednisone during the month of the burst (12 divided into 350 mg = 29 mg/mo). If this dose were spread out to the whole year, this would average 1 mg of prednisone per day. Therefore our calculations for change in doses of prednisone during the year after institution of aspirin treatment were based on the above calculations. For example, if a patient needed 5 bursts of prednisone during the baseline year, they were assigned the equivalent of 5 mg/d at baseline, and if the number of bursts decreased to 2 bursts per year, then they were assigned 2 mg/d.

LTRAs. We recorded the number and type of LTRAs at discharge from the GCRC and those taken over the next year of aspirin treatment. Because almost all the patients continued the same dose of LTRA throughout the study, with only 6 (4%) of 137 patients receiving new treatment with an LTRA during the follow-up year, we did not include LTRA treatment as a variable.

Individual responses to aspirin treatment

Analysis of individual responses to aspirin treatment were made in groups receiving 325 mg of aspirin twice daily and 650 mg of aspirin twice daily and the group who decreased or discontinued treatment. If symptoms improved or were the same after therapy, an affirmative response was recorded.

Statistical analyses

A nonparametric Wilcoxon signed-rank test was used to analyze changes in markers of clinical disease at baseline compared with 1 year of aspirin therapy. The parametric statistics paired *t* test was used to analyze the changes in medications. The McNemar 2-sided test was used to determine whether there were any changes in drug use when comparing baseline with 1 year of aspirin treatment. The Fisher 2-sided exact test was used to compare the frequencies of response to aspirin desensitization in the subgroups.

RESULTS

As shown in Fig 1, a total of 137 patients were included in our study. Fifty of 137 patients took 325 mg of aspirin twice daily either the entire year or beginning after the first

TABLE I. Changes in markers of clinical disease and daily corticosteroid use in patients taking 325 mg of aspirin twice daily continuously ($n = 25$) and those who decreased the dosage of aspirin from 650 mg twice daily to 325 mg twice daily at 1 month and continued this dosage for the remainder of the year ($n = 25$)

Clinical markers	Baseline (median [range])	1 y (median [range])	<i>P</i> value*
No. of sinus infection/y	5.5 (0-12)	2.8 (0-12)	<.0001
No. of sinus polyp operations/y	0.36 (0-2)	0.10 (0-1)	<.0001
No. of hospitalizations for asthma/y	0.15 (0-1.3)	0.02 (0-1)	<.0001
Nasal sinus scores	2.2 (0-3)	3.6 (0-3)	<.0001
Smell scores	0.7 (0-4)	2.4 (0-5)	<.0001
Asthma scores	3.8 (0-4)	4.1 (0-4)	<.03
Daily corticosteroid use	Baseline (mean [SEM])	1 y (mean [SEM])	<i>P</i> value†
Intranasal corticosteroid ($\mu\text{g}/\text{d}$)	183.6 (19.5)	113.2 (14.0)	<.0005
Inhaled corticosteroid ($\mu\text{g}/\text{d}$)	533.2 (51.3)	484.6 (67.0)	<.37
Systemic corticosteroid (mg/d)	3.9 (0.5)	1.3 (0.2)	<.0001

*Wilcoxon signed-rank statistic; 2-sided *P* values were reported.†Values were obtained with the paired *t* test.**TABLE II.** Changes in markers of clinical disease and daily corticosteroid use in patients taking 650 mg of aspirin twice daily continuously ($n = 28$) and those who increased the dosage of aspirin from 325 mg twice daily to 650 mg twice daily at 1 month and continued this dosage for the remainder of the year ($n = 27$)

Clinical markers	Baseline (median [range])	1 y (median [range])	<i>P</i> value*
No. of sinus infections/y	5.4 (0-12)	2.3 (0-12)	<.0001
No. of sinus polyp operations/y	0.31 (0-1.2)	0.09 (0-1)	<.0001
No. of hospitalizations for asthma/y	0.16 (0-1.3)	0.00 (0-0)	<.0001
Nasal sinus scores	2.3 (0-4)	3.5 (0-4)	<.0001
Smell scores	0.5 (0-4)	2.2 (0-5)	<.0001
Asthma scores	3.7 (0-4)	4.2 (0-4)	<.001
Daily corticosteroid use	Baseline (mean [SEM])	1 y (mean [SEM])	<i>P</i> value†
Intranasal corticosteroid ($\mu\text{g}/\text{d}$)	182.3 (22.7)	122.5 (15.8)	<.01
Inhaled corticosteroid ($\mu\text{g}/\text{d}$)	626.9 (62.9)	530.9 (51.3)	<.08
Systemic corticosteroid (mg/d)	4.0 (0.4)	1.1 (0.2)	<.0001

*Wilcoxon signed-rank statistic; 2-sided *P* values were reported.†Values were obtained with the paired *t* test.

month of evaluation: one half of the patients ($n = 25$) started with an initial dosage of 325 mg twice daily and continued this for the duration of the study. The other half ($n = 25$) started with an initial dosage of 650 mg twice daily and subsequently decreased to 325 mg twice daily, as instructed, because of good symptom control. In group 2, 55 (40%) of 137 patients took a dosage of 650 mg twice daily: 28 (51%) of 55 patients began the study at 650 mg twice daily and continued at this dosage, and 27 (49%) of 55 patients increased their dosage at the 1-month time point, as instructed, from 325 mg twice daily because of inadequate symptom control. In the third group 32 (23%) of 137 patients either discontinued ($n = 22$) or decreased ($n = 10$) their dosage of aspirin to less than 325 mg twice daily because of the adverse effects of aspirin.

For patients taking a dosage of 325 mg twice daily (Table I), they showed highly significant ($P < .0001$) improvement in clinical markers at 1 year. Factors, such as the number of sinus infections, number of sinus polyp operations, and number of hospitalizations for asthma per year, were all improved or the same. In addition, this

group of patients also experienced significant reductions in nasal ($P < .0001$) and asthma ($P < .03$) symptoms, as well as improvement in sense of smell ($P < .0001$). Daily corticosteroid use was calculated at baseline and at 1 year after initiating aspirin therapy. Systemic corticosteroid dosage decreased by 3-fold (3.9 mg/d to 1.3 mg/d). Intranasal corticosteroid doses also decreased significantly ($P < .0005$), although doses of inhaled corticosteroids did not change ($P < .37$).

Patients taking 1300 mg of aspirin per day experienced similar improvement among all clinical markers as the group taking 325 mg twice daily after 1 year of aspirin therapy (Table II). Again, both systemic and intranasal corticosteroid use decreased significantly.

Of the 137 patients, 32 (23%) had adverse effects from or discontinued aspirin therapy for the reasons cited in Fig 2, 18 (56%) of 32 from the group randomized to 325 mg twice daily and 14 (44%) of 32 from the group randomized to taking 650 mg twice daily. Ten (31%) of 32 patients had side effects from aspirin necessitating a decrease in their daily dosage: 975 mg/d for 1 patient,

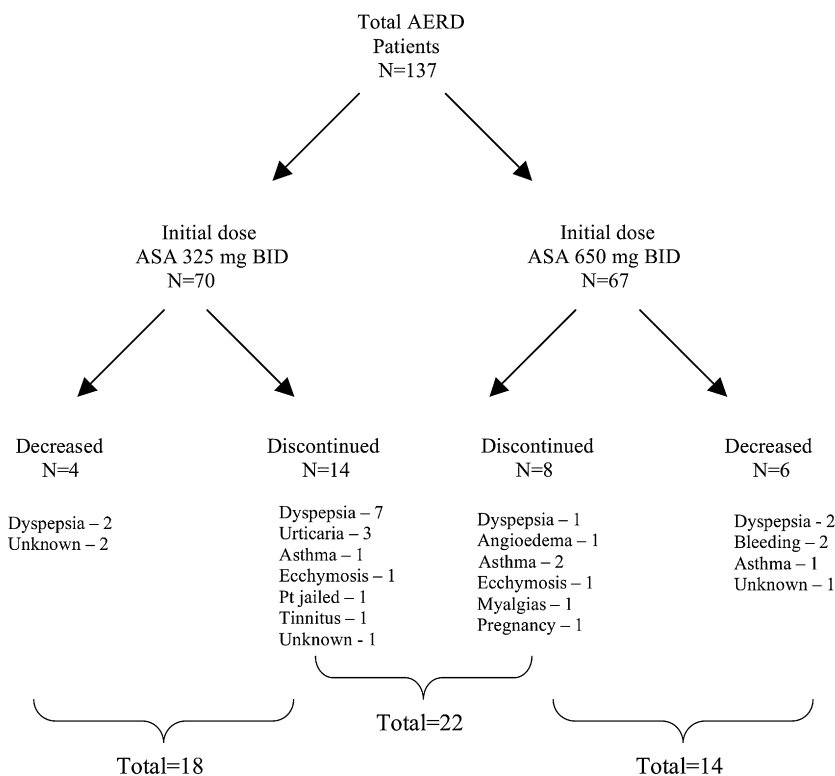


FIG 2. Pattern of discontinuation of aspirin (ASA). BID, Twice daily.

325 mg/d for 6 patients, 162 mg/d for 2 patients, and 81 mg/d for 1 patient. A total of 22 patients discontinued daily aspirin therapy by the end of 1 year: two thirds (14/22) were patients who had been randomized to 325 mg twice daily, and one third (8/22) were patients who had been randomized to 650 mg twice daily.

Dyspepsia was the most common adverse effect leading to aspirin dosage reduction (4 patients) or discontinuation of aspirin treatment (8 patients; total = 12/32 [38%]), followed by bleeding/ecchymosis (4/32 [13%]) and urticaria/angioedema (4/32 [13%]). Asthma attacks unrelated to daily aspirin therapy occurred in 4 (13%) of 32 patients. Other less common reasons for either discontinuation or reduction in aspirin dosages but related to aspirin effects included tinnitus and pregnancy (aspirin contraindicated). Other reasons unrelated to aspirin effects included incarceration in jail and inability to obtain aspirin, asthma flares during viral urinary tract infections, myalgias, and reasons not stated. Unfortunately, some of these patients dropped out of contact, and therefore a true 1-year assessment could not be obtained. Therefore based on the time of drop out, we extrapolated the follow-up data for a year. This was unfortunate because most of the symptom data were obtained at the time of aspirin treatment, and the effects of not taking aspirin treatment over the remainder of the year could not be obtained. Nevertheless, with reduction in dosages of aspirin (particularly in the largest subset of patients with gastritis), the continued requirement for systemic corticosteroids was apparent (Table III).

Analysis was performed at 1 year on the subgroup of patients (n = 32) who either decreased or discontinued aspirin therapy. Some clinical markers showed improvement, such as a decrease in number of sinus infections ($P < .0001$) and number of sinus operations ($P < .0026$) per year, but the number of hospitalization for asthma per year did not significantly decrease. Similarly, nasal sinus and smell scores showed improvement ($P < .0026$ and $P \leq .001$, respectively), but asthma scores did not significantly change. Of particular note, daily systemic corticosteroid use did not decrease in this group, in contrast to the 3-fold decrease seen in both the 325 mg twice daily and 650 mg twice daily groups.

Individual responses to aspirin therapy were analyzed (Table IV) among the groups taking 325 mg twice daily (n = 50) and 650 mg twice daily (n = 55) and the group who either decreased or discontinued aspirin treatment (n = 32). An affirmative response was recorded if the symptoms were the same (if already under good control at baseline) or improved compared to symptoms at baseline. The percentage of patients who derived symptomatic benefit was most impressive in the 325 mg twice daily and 650 mg twice daily groups. Ninety-two percent and 96% of patients from the 325 mg twice daily and 650 mg twice daily group, respectively, stated that their asthma symptoms were the same or improved in comparison with only 75% of patients in the group who either decreased or discontinued aspirin therapy. Improvement in nasal symptoms was also significantly less in the group who

TABLE III. Changes in markers of clinical disease and daily corticosteroid use in patients who discontinued (n = 22) or reduced (n = 10) aspirin dosages because of side effects

Clinical markers	Baseline (median [range])	1 y (median [range])	P value*
No. of sinus infections/y	4.5 (0-11)	1.9 (0-12)	<.0001
No. of sinus polyp operations/y	0.25 (0-1)	0.13 (0-1)	<.0026
No. of hospitalizations for asthma/y	0.06 (0-0.56)	0.03 (0-1)	<.10
Nasal sinus scores	2.4 (0-3)	3.2 (0-4)	<.0026
Smell scores	1.0 (0-4)	2.7 (0-5)	<.001
Asthma scores	3.5 (0-4)	3.9 (0-3)	<.06
Daily corticosteroid use	Baseline (mean [SEM])	1 y (mean [SEM])	P value†
Intranasal corticosteroid (μg/d)	168.7 (26.3)	115.3 (20.6)	<.0014
Inhaled corticosteroid (μg/d)	620.6 (64.6)	511.2 (59.0)	<.022
Systemic corticosteroid (mg/d)	3.9 (1.0)	2.9 (0.6)	<.1

*Wilcoxon signed-rank statistic: 2-sided P values were reported.

†Values were obtained with the paired t test.

TABLE IV. Comparison of individual responses to aspirin treatment in the groups that received 325 mg of aspirin twice daily and 650 mg of aspirin twice daily and the group who decreased or discontinued aspirin treatment

	D/C or decreased aspirin (n = 32)	325 mg of aspirin twice daily (n = 50)	650 mg of aspirin twice daily (n = 55)	P value*
Nasal symptom scores	20 (62%)	46 (92%)	45 (82%)	.005
Sense of smell scores	21 (66%)	39 (78%)	37 (67%)	.37
Asthma symptom scores	24 (75%)	46 (92%)	53 (96%)	.008

Yes is improved or the same.

D/C, Discontinued.

*Fisher exact test.

decreased or discontinued aspirin therapy (62%) compared with the 325 mg twice daily (92%) and 650 mg twice daily (82%) groups. Sense of smell was the most difficult symptom to improve among all 3 groups of patients.

DISCUSSION

Aspirin desensitization, followed by daily aspirin therapy, is an effective treatment modality for the majority of patients with AERD. Although patients with AERD can be successfully desensitized and their desensitization maintained with as little as 81 mg of aspirin per day, larger dosages of daily aspirin have been needed to improve their clinical courses. Previous work has shown that most patients with AERD begin to have a return of nasal congestion when their daily aspirin dosage decreases to less than 325 mg twice daily.⁸

In one of the first studies on aspirin desensitization, Stevenson et al⁸ attempted to discern whether a dose-response relationship existed with aspirin. A higher percentage of responders (69%) in the study were from the

group taking 650 mg twice daily compared with the group taking 325 mg twice daily (60%) or 325 mg once daily (57%). Although there appeared to be a trend, the study was small (25 patients), and results did not reach statistical significance. In 1996, 65 patients underwent aspirin desensitization and initiated daily aspirin therapy at 650 mg twice daily.¹⁰ Ten (15%) patients, under the direction of their physicians, were able to slowly reduce their aspirin dosages without reappearance of nasal congestion. The final maintenance dosage of aspirin ranged from 325 mg daily to 650 mg 3 times daily, with a mean daily dosage of 1214 mg/d.

In a study by Berges-Gimeno et al,¹¹ which analyzed 172 patients with AERD for up to 5 years, all patients were treated with 650 mg of aspirin twice daily for the first year, except for 6 patients who decreased their aspirin dosages to 325 mg twice daily because of epigastric pain at the higher dosage. Significant reductions in sinus infections, sinus surgeries, and systemic corticosteroids (all $P < .0001$) were seen, as well as improvements in both sinus and asthma symptoms scores. The percentage of patients who had a good or excellent response was highest (87%) in the 126 patients who completed at least 1 year of treatment with 650 mg of aspirin twice daily (except for the above 6 patients with epigastric pain). Randomly, half of the 110 patients, who had responded well during the first year of aspirin therapy and were taking 650 mg of aspirin twice daily, were encouraged to decrease their aspirin dosage. Of these 55 patients, 49 (89%) of 55 or 49 (45%) of 110 accepted this invitation and reduced their aspirin dosages to between 325 and 975 mg/d. Interestingly, none of these patients experienced deterioration in their clinical course or a requirement for more corticosteroids during the remainder of the 3 to 4 years of their participation in this study.

In our present study, patients randomized to either 325 mg twice daily or 650 mg twice daily adjusted their dosage of aspirin at 1 month based on symptom control. Twenty-five (48%) of 52 patients who began therapy at 325 mg twice daily experienced benefit at this dosage,

whereas 27 (52%) of 52 patients required an increase in dosage to 650 mg twice daily because of inadequate symptom control. Similarly, 28 (53%) of 53 patients who began the study at 650 mg twice daily continued at this dosage for the remainder of the year, whereas 25 (47%) of 53 patients decreased their dosage to 325 mg twice daily because of good symptomatic relief. Based on these results (see Tables I and II), it appears that after aspirin desensitization is completed, there is a fairly equivalent likelihood of benefiting from either 325 mg of aspirin twice daily or 650 mg of aspirin twice daily.

All patients taking a final dosage of 325 mg twice daily and 650 mg twice daily were analyzed for changes in clinical disease markers (Tables I and II). Both groups clearly had a significant reduction in number of sinus infections, sinus surgeries, and hospitalization for asthma per year, as well as an improvement in nasal/sinus symptom, asthma symptom, and smell scores. Furthermore, both groups were able to significantly decrease their daily systemic corticosteroid dosage by 3-fold (325 mg twice daily) to 4-fold (650 mg twice daily). In summary, dosages of 325 mg twice daily and 650 mg twice daily were both associated with significant improvements in clinical markers of disease and, furthermore, did so to a similar degree.

Although clinical efficacy is a vital component in determining the optimal dosage of daily aspirin therapy, the ability of patients to take the drug without side effects is equally important. Adverse effects to chronic aspirin and NSAID therapy are not unusual, the most common being gastrointestinal adverse effects.¹³ Although reports vary, at least 10% to 20% of patients taking regular dosages of aspirin or NSAIDs experience dyspepsia, and the prevalence can be as high as 50%.¹⁴ This is in contrast to more serious gastrointestinal complications, such as peptic ulcers, which occur on the order of 7.3 to 13 per 1000 patients per year.¹⁴ Although most evidence points to a dose relationship for serious gastrointestinal complications from aspirin, the relationship between dyspepsia (the most common reason for discontinuing aspirin therapy in aspirin desensitization studies) and aspirin dosage is not entirely clear.

In a large randomized controlled trial of aspirin therapy for prevention of myocardial infarction,¹³ healthy British physicians were randomized to receive either 500 mg of aspirin once daily or no treatment. Of the 3429 doctors taking aspirin, 17% had to discontinue the drug because of dyspepsia. In another large secondary prevention trial with smaller dosages of daily aspirin,¹⁵ subjects took either 324 mg of aspirin or placebo. Dyspepsia was reported in 37.0% of subjects in the aspirin group, but an even higher percentage (39.2%) of dyspepsia was reported in the placebo group.

Although these studies do not give us confidence that daily aspirin is necessarily responsible for all dyspepsia in patients taking daily aspirin (with placebo also being associated with dyspepsia), there is general agreement that aspirin has the capacity to cause gastric mucosal inflammation and epigastric pain in at least some patients. In our current study 12 (9%) of 137 of the patients had dyspepsia,

but abdominal pain was severe enough to warrant discontinuing aspirin in 8 patients. This percentage is at the low end of the above trials for prophylaxis of coronary disease^{13,15} but in line with our prior studies, in which approximately 10% of the patients with AERD had dyspepsia while taking 650 mg of aspirin twice daily.^{10,11}

In aspirin desensitization trials patients require relatively higher dosages of aspirin than in trials for cardioprophylaxis. Previous aspirin desensitization studies have all involved treatment with 650 mg of aspirin twice daily,⁹⁻¹¹ and except for the small 1984 study,⁸ none have stratified daily dosages of aspirin with the incidence of adverse effects. Thus it has not been clear as to whether there exists a correlation between dose and side effects.

In this study patients were randomized to take 325 mg of aspirin twice daily or 650 mg of aspirin twice daily. We did not find any relationship between higher dosages of aspirin with a higher incidence of adverse effects. In fact, quite the opposite occurred. In the 650 mg twice daily group, 4 (6%) of 67 discontinued therapy because of intolerable side effects clearly caused by aspirin, whereas 13 (18.6%) of 70 discontinued therapy in the 325 mg twice daily group. Furthermore, contrary to expectation, dyspepsia occurred with less frequency in the 650 mg twice daily group versus the 325 mg twice daily group (3/67 [4.5%] vs 9/70 [12.9%], respectively). There might be a trend toward a higher incidence of serious side effects of aspirin therapy in the 650 mg twice daily group (bleeding, 2; angioedema, 1) versus the 325 mg twice daily group (0), but the low incidence in each group prevents any definitive conclusion.

In conclusion, our current study demonstrates that both 325 mg of aspirin twice daily and 650 mg of aspirin twice daily are fairly equivalent in terms of clinical efficacy for treating symptoms and preventing complications of AERD, although a subgroup of patients might require the higher dosage for optimal symptom control. Furthermore, from the standpoint of the most prevalent side effect of aspirin-induced dyspepsia, patients tolerated 650 mg twice daily of aspirin as well, if not better, than those patients taking 325 mg twice daily of aspirin. Therefore our current recommendations are that patients with AERD, after completing aspirin desensitization, should be started on 650 mg of aspirin twice daily. After 1 month, if the patient has experienced improvement in his or her symptoms, particularly nasal patency and sense of smell, they might attempt to decrease their dosage of aspirin gradually to the lowest effective dosage (usually 325 mg twice daily) to minimize any potential complications of aspirin.

REFERENCES

1. Szczeklik ASD. Aspirin-induced asthma: advances in pathogenesis, diagnosis and management. *J Allergy Clin Immunol* 2003;111:913-21.
2. Dahlen S, Malstrom K, Nizankowska E, Dahlen B, Kuna P, Kowalski M, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist. A randomised, double blind, placebo controlled trial. *Am J Respir Crit Care Med* 2002;165:9-14.
3. Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlun M, et al. Benefits from adding the 5-lipoxygenase inhibitor

- zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998;157:1187-94.
4. Berges-Gimeno M, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2002;89:474-8.
 5. Borish L. Sinusitis and asthma: entering the realm of evidence-based medicine. *J Allergy Clin Immunol* 2002;109:606-7.
 6. Stevenson DD. Aspirin desensitization in patients with AERD. *Clin Rev Allergy Immunol* 2003;24:159-67.
 7. Chiu JT. Improvement in aspirin-sensitive asthmatic subjects after rapid aspirin desensitization and aspirin maintenance (ADAM) treatment. *J Allergy Clin Immunol* 1983;71:560-7.
 8. Stevenson DD, Pleskow WW, Simon RA, Mathison DA, Lumry WR, Schatz M, et al. Aspirin-sensitive rhinosinusitis asthma: a double-blind cross-over study of treatment with aspirin. *J Allergy Clin Immunol* 1984;73:500-7.
 9. Sweet JA, Stevenson DD, Simon RA, Mathison DA. Long term effects of aspirin desensitization treatment for aspirin sensitive rhinosinusitis asthma. *J Allergy Clin Immunol* 1990;86:59-65.
 10. Stevenson DD, Hankammer MA, Mathison DA, Christensen SC, Simon RA. Long term ASA desensitization-treatment of aspirin sensitive asthmatic patients: clinical outcome studies. *J Allergy Clin Immunol* 1996; 98:751-8.
 11. Berges-Gimeno M, Simon RA, Stevenson DD. Treatment with aspirin desensitization in patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol* 2003;111:180-6.
 12. Stevenson DD. Oral challenge: aspirin, NSAID, tartrazine, and sulfites. *N Engl Res Allergy Proc* 1984;5:111-6.
 13. Peto R, Gray R, Collins R, Wheatly K, Hennekens C, Jamrozik K, et al. Randomized trial of prophylactic daily aspirin in British male doctors. *BMJ* 1988;296:313-6.
 14. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs. *N Engl J Med* 1999;340:661-9.
 15. Lewis HD, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE, et al. Protective effect of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration cooperative study. *N Engl J Med* 1983;309: 396-403.

ON THE MOVE?

Send us your new address at least six weeks ahead

Don't miss a single issue of the journal! To ensure prompt service when you change your address, please photocopy and complete the form below.

Please send your change of address notification at least six weeks before your move to ensure continued service. We regret we cannot guarantee replacement of issues missed due to late notification.

JOURNAL TITLE:

Fill in the title of the journal here. _____

OLD ADDRESS:

Affix the address label from a recent issue of the journal here.

NEW ADDRESS:

Clearly print your new address here.

Name _____

Address _____

City/State/ZIP _____

COPY AND MAIL THIS FORM TO:

Elsevier Periodicals Customer Service
6277 Sea Harbor Dr
Orlando, FL 32887-4800

OR FAX TO:

800-225-6030
Outside the U.S.:
407-363-9661

OR PHONE:

800-654-2452
Outside the U.S.:
407-345-4000

OR E-MAIL:

elspcs@elsevier.com