

Original article

Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300 mg aspirin daily

Background: The daily dose of aspirin in desensitization in aspirin-sensitive asthmatics with nasal polyps is still a matter of debate.

Aims of the study: To compare two doses of aspirin during the first year of desensitization and to evaluate long-term effects on nasal/pulmonary symptoms.

Methods: Patients with positive aspirin provocation test were treated with either 100 or 300 mg aspirin daily.

Results: In all patients taking 100 mg aspirin ($n = 7$) recurrent nasal polyps were observed. No patient experienced reduction of asthma medication or improvement of pulmonary function. In the 300 mg group no recurrent nasal polyps were seen. Asthma medication could be reduced in three patients, pulmonary function was improved in five patients. Thirty-nine consecutively desensitized patients, taking 300 mg aspirin, showed significant improvement of olfaction and polyp-free nasal passages during the first year of therapy. After a median follow-up of 27 months no sinus revision surgery was necessary.

Conclusions: Aspirin desensitization followed by 300 mg aspirin daily is efficacious and results in polyp-free nasal airways, improvement of sense of smell, and reduction of the need for sinus revision surgery for recurrent nasal polyps.

Aspirin in a dose of 100 mg daily is not sufficient to effectively reduce nasal and bronchial or pulmonary symptoms and to prevent recurrent nasal polyps by at least the first 12 months of treatment.

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Intolerance to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is caused by an abnormal metabolic shift of arachidonic acid towards the lipoxygenase pathway and hyperproduction of cysteinyl-leukotrienes (cys-LTs). Inhibition of cyclo-oxygenase-1 (COX-1) enzyme is the most likely underlying pathogenic mechanism (1).

The aetiology of nasal polyps in aspirin-intolerant patients still remains unclear (2, 3). Patients with aspirin-exacerbated respiratory disease (AERD) and nasal polyps often need sinus surgery. The rate of polyp recurrences is higher than in patients tolerant to aspirin and NSAIDs (4, 5). Therefore, patients with AERD frequently undergo one or more sinus revision procedures (4, 6).

Aspirin desensitization, i.e. the induction of tolerance to aspirin by repeated ingestion of aspirin, has been carried out successfully in patients with AERD and now plays a major role in the management of patients with AERD (7–11). However, only a few prospective reports have been focusing on the effect of aspirin desensitization on the growth of nasal polyps and nasal function (such as sense of smell and nasal patency) (8, 9, 12). Moreover, the daily dose and preferable administration route of aspirin

in adaptive desensitization in AERD patients are a matter of debate. Significant improvement in symptoms of rhinosinusitis has been observed after oral administration of 1300 mg aspirin daily (8, 9, 12, 13), 650 mg aspirin daily (13), 600 mg aspirin daily (14, 15), 500 mg aspirin daily (6), 300 mg aspirin daily (9, 15–17) and 100 mg aspirin daily (15, 18). Endonasal administration of lysine-acetylsalicylic acid until a maximum dose of 2 mg has been reported to reduce the recurrence rate of nasal polyps (19), whereas in a recent report no clinical benefit of intranasal lysine-aspirin in a dose of 16 mg on nasal polyp growth and nasal symptoms was shown (20).

Taken together, daily oral administration has been the most advocated form of aspirin desensitization. Higher doses than 325 mg aspirin twice daily have been shown to be efficacious (13). Because of the high drop out rate when aspirin is administered in a dose of 500 mg or higher (9, 17), doses as low as possible are preferred. The aims of the present study were to compare two different doses of aspirin during the first year of aspirin desensitization in aspirin-sensitive asthmatics with nasal polyps and to evaluate long-term effects on nasal and pulmonary symptoms.

Methods

Patient selection

Patients with suspected AERD referred to the Department of Otorhinolaryngology – Head and Neck Surgery of the University Hospital of Ulm, Germany between August 2001 and 2006 volunteered in the study. The study aims were detailed to each participant and the patients signed consent forms complying with the Guidelines of the Institutional Review Board of the University of Ulm. Male and female patients between 18 and 70 years with a history of asthmatic responses to aspirin, recurrent chronic rhinosinusitis with nasal polyps (CRSNP⁺), and asthma were admitted to our clinic to undergo oral aspirin challenge. Patients unable to exclude aspirin intolerance with recurrent CRSNP⁺ and asthma, were also challenged. Patients with mental impairment or severe illness, cystic fibrosis, pregnancy or breast-feeding, immunosuppressive therapy, or less than 6 weeks since the last paranasal sinus surgery were not eligible. Before aspirin challenge, various parameters, including age, sex, duration of chronic rhinosinusitis and asthma, previous polypectomies and sinus procedures, and previous reactions to NSAIDs were registered. Clinical asthma and bronchial hyper-reactivity were defined according to the American Thoracic Society guidelines of reversible airway obstruction, as demonstrated either by methacholine challenge or inhaled β_2 -agonist bronchodilation (21).

Clinical investigations

Clinical investigations included complete blood counts, otorhinolaryngologic examination, flow/volume spirometry, and skin prick tests with inhalant allergens common in Central Europe as reported elsewhere (3).

Aspirin challenge

Oral, single-blind, placebo-controlled diagnostic aspirin challenges were performed in all patients as described by Stevenson and Nizankowska-Monilnicka (11, 16). Aspirin sensitivity was defined as a decrease of 20% or more in forced expiratory volume in 1 s (FEV₁) and/or naso-ocular reactions within 3 h after incremental oral aspirin challenges (9, 11, 16).

On day 1, single-blind control challenges were conducted beginning in the late morning. Baseline FEV₁ values were recorded before and at half-hourly intervals after administration of the placebo. In case of a negative response in FEV₁ control measurements, a single-blind oral challenge with 1000 mg paracetamol was performed. Escalating doses of aspirin, beginning with 30 mg and thereafter 60, 100, 150, 250 and 500 mg were administered at 3-h intervals. Flow/volume spirometry, respiratory responses, and patient's nasal and ocular symptoms at 30 min intervals were recorded by the patients in a diary and controlled by a physician. All challenges were performed on an intensive care unit. All patients received an intravenous catheter and continuous ECG monitoring.

Aspirin desensitization

Patients with a positive response received the threshold dose after recovery to normal FEV₁ values repeatedly at intervals of 3 h until no more positive responses were observed. Thereafter, increasing aspirin doses were given until the patients tolerated 500 mg aspirin without adverse reactions. After reaching a maintenance dose of 500 mg aspirin, patients with positive aspirin challenge were eligible for aspirin treatment.

Maintenance treatment

About 100 or 300 mg Aspirin protectTM (Bayer Vital, Leverkusen, Germany) were given and prescribed. After a 3-h interval and tolerance to aspirin, patients checked out and returned to the care of their referring physicians. After positive oral aspirin provocation and allocation to either 100 or 300 mg aspirin daily, the patients continued to take aspirin once daily. All patients were followed 6, 12 and 24 months after aspirin desensitization on a regular basis at our department. Polyp growth, sinusitis and asthmatic complaints, sense of smell, and general complaints were recorded.

Concomitant medication

Before aspirin challenge procedures were performed, oral, inhaled and nasal corticosteroids were withdrawn whenever possible. If regular treatment was necessary, the dose of oral corticosteroids did not exceed 10 mg of prednisolone or equivalent in any of the patients. After desensitization, chronic use of systemic and topical corticosteroids was not interrupted because of their effectiveness in treating AERD-sensitive patients with asthma. However, systemic corticosteroids were reduced to the lowest doses that would control the patient's asthma.

Assessments of clinical courses

Endoscopic appearance. Endoscopy scores were assessed according to Malm using rigid nasal endoscopy (22). Polyp extension was classified from zero (no polyps) to three (polyps occlude the entire nasal cavity) for each side. The values of both sides were added to obtain a final endoscopy score.

Active anterior rhinomanometry. Active anterior rhinomanometry (AAR) (Rhinomanometer 300, Atmos, Lenzkirch, Germany; trans-nasal reference pressure, 150 Pa) before and after nasal decongestion with xylometazoline was performed in all subjects according to current recommendations of the Committee Report on Standardization of Rhinomanometry (23). The results of rhinomanometry are presented as the sum of nasal airway resistances of both sides.

Smell test. The sniffin' sticks test of nasal chemosensory performance was based on penlike odor-dispensing devices (Burghart, Wedel, Germany) (24). In this study, patients were asked to identify 12 items using a forced choice paradigm. The results of this test are presented as the sum of identification measures for both sides simultaneously.

Severity of sinusitis and asthma. Clinical severity of sinusitis was assessed according to a modified validated quality of life questionnaire (25). Symptom severity was rated according to the following scale: 0 = none: symptoms absent; 1 = mild: symptoms present but not annoying; 2 = moderate: symptoms present and annoying; and 3 = severe: symptoms interfere with daily activities or sleep.

At the 6-, 12- and 24-month follow-up visit, flow/volume spirometry (FEV₁) was controlled and information on changes in asthma medication was obtained. Asthma was classified according to the Global Initiative for Asthma (GINA) (26, 27). The GINA recommendations for controller medications were used, to classify patients based on the asthma treatment they were taking: 0 = Step 1: no controller medication; 1 = Step 2: inhaled corticosteroids < 800 µg/day, or nedocromil, or theophylline without oral corticosteroids; 2 = Step 3: inhaled corticosteroids 800–2000 µg/day, without theophylline; 3 = Step 4: oral corticosteroids, or inhaled

corticosteroids >2000 µg/day, or 800–2000 µg/day inhaled corticosteroids plus theophylline.

In the pretreatment assessment of sinusitis and asthma, patients were asked to assess their symptoms during the first year after previous sinus surgery and not their symptoms during the last weeks after revision sinus surgery preceding the aspirin provocation test and aspirin desensitization.

Statistical analysis

Statistical analysis was performed on consultation with the Department of Biometry and Medical Documentation, University of Ulm. Data were tabulated and imported to a commercially available software program (WINSTAT®, Kalmia Inc., Cambridge, MA, USA and SYSTAT®, Richmond, CA, USA). The response rate, defined as a reduction of polyp score or increase of less than two points of the pretreatment endoscopy score, was the primary outcome variable. Absolute values of follow-up parameters at various evaluation times were calculated and shown. Results were presented as a median and range where appropriate. Inter- and intra-group comparisons were performed using nonparametric tests: Wilcoxon and Friedman's tests where appropriated. Significance was accepted at the 95% confidence level.

Results

Study-part one

Of 16 orally provoked patients, 14 patients were enrolled. Two of 16 patients had a negative reaction in oral provocation test and were not eligible. Fourteen patients who reacted positively in aspirin provocation test were alternately allocated to take 100 mg aspirin (100 group) or 300 mg aspirin (300 group) daily and were followed for at least 1 year. Clinical and demographic characteristics were similar in both treatment arms (Table 1). All 14 patients had at least one previous sinus surgery. There was no study withdrawal. Serious adverse events were not observed. No patient discontinued aspirin therapy because of gastrointestinal (GI) adverse events or lack of improvement of pulmonary function.

Endoscopic polyp score (primary outcome variable)

About 1½ year after start of the study, 14 patients had completed 1 year of aspirin treatment. After ½ year of aspirin desensitization, four patients of the 100 group

(57%; 95% CI, 18–90%) showed recurrent nasal polyps, whereas no patient of the 300 group (0%; 95% CI, 0–41%) showed recurrent polyposis. After 1 year of aspirin therapy, all patients of the 100 group (100%; 95% CI, 59–100%) had developed recurrent nasal polyps. No patient of the 300 group showed recurrent nasal polyps in endoscopic examination (0%; 95% CI, 0–41%).

Secondary outcome variables

Significant improvement in nasal patency, as measured by active anterior rhinomanometry before and after nasal decongestion with xylometazoline, was found in the 300 group, whereas a significant increase of nasal airway resistance was measured in the 100 group (Table 2). The 300 group showed significant improvement in the smell score. In the 300 group, the sinusitis score improved nonsignificantly after 1 year of aspirin therapy. No significant change in the asthma score was found in both study groups, whereas spirometric testing significantly improved in the 300 group. In the 300 group, asthma medication could be reduced in three of seven patients. All patients of the 100 group had significant nasal blockage of the nasal airways and needed revision surgery of the sinuses.

Study-part two

As a result of the first evaluation and critical interpretation of the clinical results after 1½ year of aspirin therapy of 14 patients, the prospective study comparing two aspirin dosages was not continued and all consecutively orally provoked and positively tested patients were administered 300 mg aspirin daily.

Until May 2006, 39 positively tested patients who had completed more than 1 year of aspirin therapy were followed-up (20 males and 19 females; 36 patients having bronchial asthma; 22 patients taking systemic corticosteroids; number of previous sinus surgeries, mean: 2 and range: 1–6).

Table 1. Demographic and clinical data of 14 patients (Study-part one)

Characteristic	100 group	300 group
Patients, <i>n</i>	7	7
Age, median	37 years (31–59)	45 years (33–66)
Sex, M/F	3/4	4/3
Bronchial asthma	7	7
Systemic corticosteroids	4	3
Number of previous sinus surgeries	2 (1–5)	2 (1–4)

100 group, taking 100 mg aspirin daily; 300 group, taking 300 mg aspirin daily; median and range.

Table 2. Clinical follow-up parameters (median changes, i.e. values after 1 year of aspirin therapy minus pretreatment values) in seven patients taking 100 mg aspirin daily and seven patients taking 300 mg aspirin daily (Study-part one)

Follow-up parameters	100 group	300 group
Rhinomanometry-ND	–134	182*
Rhinomanometry+ND	–92	312*
Smell score	1	–3*
Sinusitis score	0	1 n.s.
Asthma score	0	0 n.s.
Spirometry improved (no. of patients)	0	5*
Reduced asthma medication (no.)	0	3*
Need of revision sinus surgery (no.)	7	0*

100 group, taking 100 mg aspirin daily; 300 group, taking 300 mg aspirin daily; –ND, without nasal decongestion; +ND, after nasal decongestion; statistics, Fisher's exact test or Mann–Whitney test; **P* < 0.05; n.s., not significant.

Endoscopic polyp score (primary outcome variable)

After 2½ years of study, a second evaluation was performed. Clinical results of 19 patients were available (10 females, nine males; median age, 44 years; range, 25–60 years). Nasal polyposis significantly decreased in all patients, as verified by endoscopic examination (Fig. 1).

Secondary outcome variables

Nasal patency, as measured by active anterior rhinomanometry without and after application of xylometazoline, significantly increased after nasal decongestion. Before nasal decongestion, nasal patency showed a trend towards reduced nasal airway resistance (Fig. 2). In smell testing, a significant improvement of smell scores could be measured after 6 and 12 months of aspirin therapy, respectively (Fig. 3).

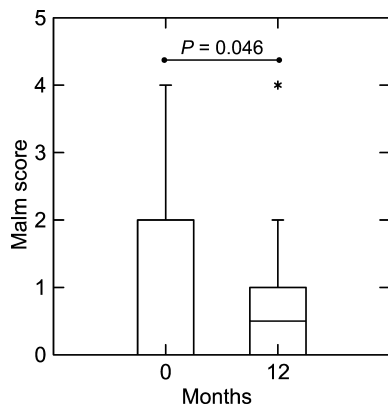


Figure 1. Endoscopic polyp score (line in box, median; box, interquartile range; whiskers, upper and lower extremes) before and after 12 months of oral treatment with 300 mg aspirin daily (Study-part two).

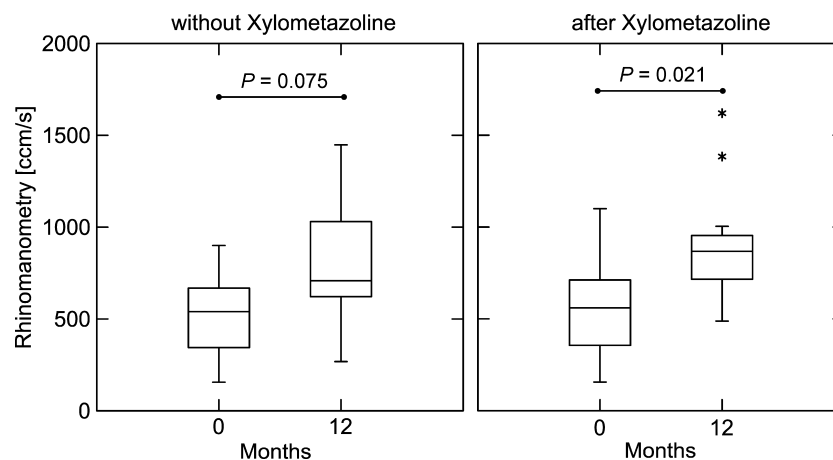


Figure 2. Nasal patency, detected by active anterior rhinomanometry, before and after nasal decongestion with xylometazoline (line in box, median; box, interquartile range; whiskers, upper and lower extremes) before and after 12 months of oral treatment with 300 mg aspirin daily (Study-part two).

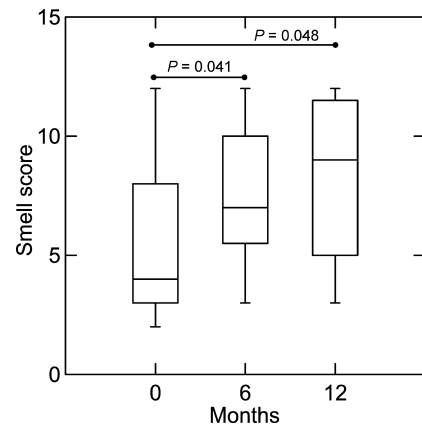


Figure 3. Nasal chemosensory testing using the Sniffin' Sticks test kit. The sum of identification (line in box, median; box, interquartile range; whiskers, upper and lower extremes) before, after 6 and 12 months of oral treatment with 300 mg aspirin daily is shown (Study-part two).

About 5 years after begin of the study, results of 39 patients who had taken aspirin of more than 1 year were available and could successfully be followed-up (median follow-up, 2.3 years; range, 1–4.5 years) by two investigators (A. R. and T. K.). Four patients had discontinued aspirin therapy after more than 1½ year because of GI intolerance (two patients) or lack of improvement of pulmonary function (one patient). One patient omitted aspirin for more than 1 week and was reluctant to restart. None of the remaining 35 study patients had needed revision surgery of the sinuses in the study period. At latest follow-up, the patients reported significant reduction of sinusitis complaints and improvement of asthma therapy (Table 3).

Table 3. Mean clinical follow-up results of sinusitis and asthma scores (in parentheses: median and range) in 35 patients more than 1 year after continuous aspirin therapy with 300 mg aspirin daily (Study-part two)

Follow-up parameters	Before therapy	At latest follow-up	P-value
Sinusitis score	0.8 (1; 0–2)	0.45 (0; 0–2)	0.001
Asthma score	1.28 (1; 0–3)	1.11 (1; 0–3)	0.01

Discussion

In the first part of this prospective study, patients who showed positive reactions in oral aspirin provocation test were treated with either 100 or 300 mg aspirin daily. Within 1 year of aspirin treatment after desensitization, all patients with 100 mg aspirin daily ($n = 7$) showed recurrent nasal polyps that needed sinus revision surgery. In no patient asthma medication could be reduced or pulmonary function was improved. In the patients who were treated with 300 mg aspirin daily ($n = 7$), no recurrent nasal polyps were observed during the same follow-up period. After recruitment time of 1½ years re-evaluation was performed. Statistical analysis of data showed significant differences in confidence intervals of polyp recurrence between both study groups. Therefore, the study was not continued and the consecutive patients who were tested positive were nonrandomly desensitized with 300 mg aspirin daily. In consecutively desensitized 39 patients, significant improvement of sense of smell and rhinomanometrically or endoscopically free nasal passages during the first year of aspirin desensitization treatment could be achieved. After a median follow-up of 27 months no revision surgery of the paranasal sinuses was necessary in any of the 39 patients.

We agree with others that a study on aspirin treatment after desensitization should ideally be performed in a prospective, double-blind, placebo-controlled design (16, 28). However, in a pilot study on aspirin desensitization at our department, each patient was willing to elect active treatment because of seriously suffering from asthma and recurrent nasal polyps. Further, in all patients of the pilot study preceding this clinical trial who were taking 100 mg aspirin daily, nasal polyps returned within several weeks after desensitization. Thus, an open study design for a treatment period of at least 1 year was chosen. Patients were alternately allocated to the two treatment arms after prior consultation by the Department of Biometry and Medical Documentation, University of Ulm. To assess outcome after desensitization, we used the endoscopic polyp score as primary outcome measure because it was successfully used in previous studies performed at our department (3, 29). We also included validated methods that have been successfully used in detecting nasal airway changes such as active anterior rhinomanometry and sniffin' sticks test of nasal chemosensory performance (23, 24).

An analysis of outcome measures for nasal polyp growth, nasal patency and sense of smell showed a

significant improvement of all parameters after 1 year of treatment with 300 mg aspirin daily. Whereas several authors have been reported on patients with AERD taking 300 mg aspirin daily, systematic evaluation after 1 year of treatment with 300 mg aspirin has not been reported yet (9, 15–17). Stevenson and others reported on even higher doses of aspirin daily. However, patients taking up to 1300 mg aspirin daily often develop GI complications, and therefore, discontinue aspirin therapy (9, 16). Recently, Lee et al. recommended that patients begin daily aspirin therapy with 650 mg twice daily and subsequently decrease to the lowest effective dosage (325 mg aspirin twice daily in their study) to reduce adverse effects (13). Although any patient taking aspirin can experience these side-effects, no patient taking 100 or 300 mg aspirin stopped this medication because of GI complications during the first year of aspirin treatment in our study. Only two of 39 patients taking 300 mg aspirin for more than 1 year discontinued aspirin therapy because of GI complaints.

In a recently published study, 30 patients with aspirin intolerance were treated following a desensitization protocol with a dose of oral aspirin of only 100 mg daily (18). Interestingly, only 12 of 30 patients had asthma. After 12 months of aspirin therapy in a dose of 100 mg, in only one patient was a progressive nasal disease found, whereas in 26 patients no polyp recurrence or marked improvement of nasal polyposis was observed. These results are in contrast to our observation of recurrent nasal polyps in all patients taking 100 mg aspirin daily after desensitization after 1 year of treatment.

In the above mentioned study, the patient characteristics of the study patients was not typical for AERD since only 40% of the patients studied were asthmatics. We also speculate that the study patients might not be tested accurately enough in oral aspirin challenge test because no placebo challenge prior to provocation with increasing doses of aspirin was performed. There is a certain probability that false-positive (spontaneous) bronchospasm during aspirin provocation occurred because no placebo challenge to eliminate this was performed (30). Therefore, there is a possibility that a certain number of patients without recurrence of nasal polyps that were tested false-positive were taking aspirin without having AERD.

The above mentioned study (18) was unblinded and uncontrolled and thus more susceptible to observer bias. Although the current study was also unblinded and uncontrolled, we believe that our study design was more suitable to compare different doses of aspirin because the 100 mg treated group could be considered as a placebo group that could maintain the desensitized state but not provide enough aspirin to block polyp re-formation.

Data of our study support the experience that aspirin desensitization followed by 300 mg aspirin daily is efficacious and results in polyp-free nasal airways, improvement of sense of smell, and reduction of the

need for revision surgery of the paranasal sinuses for recurrent nasal polyps. Aspirin in a dose of 100 mg daily is not a sufficient aspirin dose to effectively reduce nasal and bronchial or pulmonary symptoms and to prevent recurrent nasal polyps by at least the first 12 months of treatment.

The main limitation of our study is the small sample size of both groups and the open study design. To further obtain valid data on recurrence of nasal polyps and impact of aspirin treatment on pulmonary

symptoms, a large prospective randomized trial and multi-centre study would be necessary to demonstrate possible differences between 100 and 300 mg aspirin daily.

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