

Aspirin Desensitization Treatment for the Management of Aspirin-Exacerbated Respiratory Disease

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Received: November 19, 2015 Revised: January 28, 2016

Accepted: February 1, 2016

Published online: March 18, 2016

ABSTRACT

Aspirin-exacerbated respiratory disease (AERD) is a clinical syndrome characterized by nasal polyps, chronic hypertrophic eosinophilic sinusitis, asthma, and sensitivity to cyclooxygenase-1 (COX-1) inhibitors. The treatment of asthma and chronic rhinosinusitis in AERD is difficult, since those patients usually suffer from severe steroid dependent asthma and frequent recurrence of nasal polyps despite combined medical and surgical treatment. Aspirin desensitization (AD) can be considered as an additional treatment option in selected patients with AERD. Aspirin doses ranging from 100 to 1,300 mg/day were reported to be effective for this purpose.

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Key words: Aspirin; Asthma; Chronic Rhinosinusitis; Desensitization

Comert S, Karakaya G, Kalyoncu AF. Aspirin Desensitization Treatment for the Management of Aspirin-Exacerbated Respiratory Disease. *Journal of Respiratory Research* 2016; 2(1): 24-27 Available from: URL: <http://www.ghrnet.org/index.php/jrr/article/view/1482>

GENERAL ASPECTS OF AERD

Aspirin-exacerbated respiratory disease (AERD) affects 0.3-0.9% of the general population, but the prevalence increases to 10-20% in asthmatics and 30-40% in asthmatics with nasal polyposis^[1]. The syndrome typically starts in the young adulthood with persistent rhinitis which is difficult to treat and may lead to loss of smell in 55% of patients. Usually two years after the onset of rhinitis, first symptoms of asthma with aspirin intolerance develop^[2]. The syndrome is more common among females (female/male ratio: 3/2 to 2.3/1). There is no racial or ethnic predilection for acquiring AERD. Family histories are reported to be 1% and 6% in two large series from US and Europe^[2,3].

Treatment of asthma in the context of AERD can be difficult. It was previously reported that 80% of analgesic-induced-asthma patients were treated with relatively high doses of inhaled corticosteroids (800-2,000 µg) and 51% required daily oral corticosteroid treatment equivalent to 8 mg of prednisone. Various side effects of steroids were observed in the patients, including obesity, osteoporosis, and hypertension^[2]. Another problem associated with the management of AERD is post-surgical regrowth of nasal polyps. The nasal polyps recurrence rate ranges between 24% and 80% following different types of surgery^[4-7]; on average, reoperation for nasal polyps is required every 3 years^[8].

Concerning the pathogenesis of AERD, many defects in overstimulation of inflammation or underproduction of counter measures, especially in the eicosanoid family can be observed. Excessive synthesis of Leukotriene (LT) C4 due to a genetic polymorphism of the LTC4 synthase promoter region^[9], increased expression of cysteinyl LT1 receptors^[10], undersynthesis of Prostaglandin (PG) E2 or its E receptors (EP2 or EP3)^[11-13] are all mechanisms accused in the pathogenesis of AERD.

The major goals of the control of AERD are prevention of nasal polyp formation, secondary sinusitis, and exacerbation of asthma using treatment strategies that target reducing inflammation in both

the upper and the lower airways. High doses of topical steroids (nasal/inhaled) are usually needed; however, inflammation in some patients with AERD cannot be controlled by topical corticosteroids alone, and frequent bursts or continuous treatment with systemic corticosteroids can be required^[3]. Both 5-lipoxygenase inhibitors and cysteinyl-LT1 receptor antagonists have been shown to help the management of AERD patients in double-blind, placebo-controlled treatment trials^[14,15].

Aspirin desensitization (AD) followed by daily aspirin is an effective treatment option for patients with AERD who have not benefited from conventional therapy. AD is recommended for patients with AERD who: (1) have moderate-severe asthma, intractable nasal congestion, or both, and have failed to respond to topical corticosteroids, LT receptor antagonists, and 5-lipoxygenase inhibitors; (2) develop multiple nasal polyps; (3) require systemic corticosteroids for control of AERD; (4) require aspirin for other conditions, such as coronary artery disease^[16]. Patients can readily receive other non-steroidal anti-inflammatory drugs after undergoing AD, and this can be considered another advantage of AD treatment. In our clinical practice, we consider AERD patients for AD if they present with chronic rhinosinusitis with or without nasal polypsis requiring repeated surgery (usually after the second operation) and/or moderate-severe asthma failing to respond to standard medical therapy.

The mechanism of AD in patients with AERD is not clear. A creation of a state of tolerance due to depletion of mast cell mediators, cyclooxygenase inhibition by aspirin, reduction in airway responsiveness to LTE4 because of downregulation of cysteinyl-LT receptors, diminished production of cysteinyl-LTs from monocytes are all suggested mechanisms^[17].

Before deciding to put a patient on AD treatment, a definite diagnosis of aspirin sensitivity should be confirmed with aspirin provocation testing, the details of which are explained elsewhere^[18]. Thereafter if the patient carries one of the above mentioned criteria, AD is achieved by administration of increasing oral doses of aspirin over a period of 2-5 days until the target dose is achieved^[16,19,20]. Some examples of AD protocols are provided in Table 1.

Both aspirin provocation testing and AD procedure carry the risk of development of severe asthma attacks or anaphylaxis. Therefore they should be carried out only in specialized allergy clinics under close medical supervision.

CLINICAL TRIALS OF AD

Many studies have shown that AD followed by daily aspirin treatment was associated with an improved clinical course in patients with AERD^[8, 19-32]. A wide of aspirin dosages (100-1,300 mg/day) were used for the purpose of AD in these studies. There was varying degree of clinical benefit obtained from AD in different studies; some showing benefit for only control of upper airway disease^[8,20-22] and some for both upper and lower airway disease^[19,23-32]. To our knowledge, in only one study, which was carried out on 10 aspirin sensitive asthma patients by using 500 mg aspirin, AD was found ineffective as measured as an improvement on pulmonary function tests and reduced need for systemic corticosteroids^[33]. However that study was

hampered by small sample size, lack of compensation for seasonal or intercurrent provoking factors, low doses of aspirin, lack of upward adjustment of aspirin doses during the study, lack of monitoring of any clinical parameters other than pulmonary function values, and lack of study-protocol clarity for lowering systemic corticosteroid doses.

Some AD trials have shown benefit only for the upper airway disease^[8,20,22]. In the study by Sweet *et al*^[8], 35 patients with AERD were continuously treated with a mean dose of 1300 mg/day aspirin and followed-up for 46 months, 30 patients were treated with a mean dose of 1300 mg/day aspirin for 25 months and then followed-up for 32 months, and 42 patients acted as controls and were followed-up for 102 months. There was an improvement in all parameters except nasal steroid use in the continuous treatment group. There was an improvement in all parameters except inhaled and nasal steroid use, but return to baseline after stopping aspirin treatment in the discontinued group. There was a higher frequency of improvement in treatment group as compared to controls in all parameters except chest symptoms and nasal steroid use.

Other studies support the findings of this study. Comert *et al* treated 29 AERD patients with 300 mg/day aspirin for a period of 1 year, and in 18 patients the treatment was continued for a period of 3 years. The annual rates of use of systemic corticosteroid regimens, episodes of sinusitis, and surgery decreased significantly both at 1 year and 3 years of treatment. Significant improvement was also observed in the nasal congestion and sense of smell scores at 1 year and the postnasal drainage score at 3 years. The asthma symptom scores, pulmonary function tests and hospitalizations for asthma did not show significant improvements both at 1 year and at 3 years of follow-up^[20].

The lack of efficiency for the improvement of lower airway disease in the study by Comert *et al* could have been attributed to a relatively lower dose of aspirin used, however, in the study by Stevenson *et al*^[21], in which aspirin doses of 325 mg/day, 1300 mg/day and 2600 mg/day were used, again the nasal symptoms improved and nasal beclomethasone use reduced with aspirin treatment, but no changes in asthma symptoms, pulmonary functions and antiasthmatic medications were observed. Furthermore, no significant difference between three doses of aspirin with regard to percentage of patients showing improvement was also seen in that study. The authors explained this finding of lack of efficiency of a combined treatment approach consisting of sphenoidectomy followed by AD, for control of lower airway symptoms, by presence of other asthmogenic pathways unaffected by the sinobronchial reflexes or aspirin^[21].

Other studies have shown the efficiency of AD treatment for control of both upper and lower airway disease^[19,23-32]. In the study by Stevenson *et al*^[23], 65 AERD patients were treated with a mean aspirin dose of 1,214 mg/day for a mean duration of 3.1 years. There was a reduction in annual numbers of sinus infections, hospitalizations for asthma, sinus, and polyp operations, doses of nasal steroids, use of systemic steroids, and improvement in olfaction. However emergency department visits and use of inhaled steroids did not show significant change. The study by Gosepath *et al*^[24] was unique in that it used the lowest aspirin dose among all clinical trials of AD and showed efficiency in control of both upper and lower airway symptoms. In that study 30 patients were treated with 100 mg/day for a period of 1 year and normalization of in vitro eicosanoid levels, lower rate

Table 1 Examples for different protocols of aspirin desensitization.

| Protocol | Incremental doses of aspirin | Commercial aspirin tablets | Maintenance dose |
|------------------------------|---|----------------------------|------------------|
| Scripps Clinic (16) | 20,25, 40.5, 60.75, 81, 101.25, 162.5, 325,650 mg | 81 and 325 mg | 650-1300 mg/day |
| University of Łódź (19) | 20,40,80,100, 150, 300, 600 mg | 80, 100 and 300 mg | 600-1200 mg/day |
| University of Hacettepe (20) | 25,50,75,100,250 mg | 100 and 300 mg | 300 mg/day |

of recurrence of nasal polyps, reduction in the number of purulent sinusitis episodes, marked improvement in pulmonary function, nasal airflow and sense of smell were observed^[24]. In another study by Berges-Gimeno *et al* the beneficial effects of AD started as early as 4 weeks of treatment assessed by the improvement of nasal and asthma symptom scores, olfactory scores and reduced need of systemic corticosteroids^[25].

The two largest prospective clinical trials on the efficiency of AD were performed by Berges-Gimeno *et al* which consisted of 172 patients, and Lee *et al* which consisted of 137 patients^[26,27]. In the first study, 126 out of 172 patients took aspirin for at least 1 year. The starting dose of aspirin was 1,300 mg/day and the mean dose was 1138 mg/day. The patients were followed-up for 1-6 years during which a reduction in the number of sinus infections, short courses of systemic steroids, doses of nasal, inhaled and systemic steroids, improvement in smell, nasal, and asthma symptom scores, reduction in the annual number of sinus operations, hospitalizations and emergency department visits for asthma were observed^[26]. In the study by Lee *et al*^[27] 137 patients were followed-up for 1 year. The starting dose of aspirin was 650 mg/day or 1,300 mg/day and dose adjustments were performed after 1 month of treatment. There were significant reductions in annual number of sinus infections, sinus polyp operations, hospitalizations for asthma, doses of inhaled and systemic steroids, improvement in nasal, smell and asthma symptoms in both groups receiving different aspirin doses. No significant change in inhaled steroid doses was observed^[26].

The study by Rozsasi *et al*^[28] aimed to compare the efficiency of 100 mg/day and 300 mg/day of aspirin for 1 year and then the long term efficiency of 300 mg/day of aspirin. There was a reduction in nasal polyp recurrence rate and asthma medications, and improvement in nasal patency, sense of smell, and pulmonary functions in 300 mg/day group. No change in asthma scores in both, and no improvement in all other parameters was observed in the 100 mg/day group. Recurrence rate of nasal polyps decreased, asthma and sinusitis scores improved with 300 mg/day aspirin after 2.3 years of median follow-up^[28].

One recent clinical study evaluated the efficiency of AD treatment in both AERD and aspirin-tolerant-asthma patients, as to investigate if the beneficial effects of aspirin might be attributable to its potent anti-inflammatory properties. Twelve patients with AERD and 6 patients with aspirin-tolerant-asthma were randomly assigned to receive 624 mg/day of aspirin, and 8 patients with AERD and 8 patients with aspirin-tolerant-asthma received placebo. Only the subjects with AERD treated with AD reported improvements in smell and peak nasal inspiratory flow and reductions in nasal and asthma symptoms, indicating that the beneficial effects of AD in patients with AERD is not related with the anti-inflammatory properties of aspirin^[29].

The most important concern with long term AD treatment is the risk of development of gastrointestinal side effects of aspirin. These side effects can be avoided by choosing the lowest effective dose of aspirin that will help to control of symptoms in patients with AERD. Lower rates of gastrointestinal side effects are reported in studies in which 300 mg/day aspirin is used^[20] rather than the higher doses of aspirin such as 1,300 mg/day^[8] and 1214 mg/day^[23].

AERD IN THE PEDIATRIC POPULATION

Number of the studies about analgesic intolerance and AERD among pediatric population is limited. In a large epidemiological survey by Kalyoncu *et al*, the prevalence of self reported drug intolerance was %5.6 in boys and 7.4% in girls among 4639 Turkish university

students age ranging between 15-24 years^[34]. In another study by Ergan Arsava *et al*, 50 (6.8%) among 729 patients with a diagnosis of analgesic intolerance had onset in childhood and among those 40% had asthma. The diagnosis was asthma was established during childhood in 24% of patients. Interestingly, analgesic intolerance and rhinitis preceded the onset of asthma by approximately five years^[35]. This finding was different than the chronology of events reported in the literature for adult onset AERD^[2]. The authors concluded that this disparity in the chronology of events could represent a difference in the underlying pathophysiology of adult and childhood onset AERD.

In pediatric population, AERD has much more favorable clinical characteristics and course than in adulthood. The asthma component is milder and the occurrence of intractable chronic upper airway disease is rare compared to adults. Therefore the experience with AD treatment in children is limited^[36].

CONCLUSION

AD should be considered as add-on treatment in patients with uncontrolled upper and lower respiratory symptoms, patients requiring multiple polypectomies and/or sinus operations, patients requiring unacceptably high intermittent or chronic systemic corticosteroids, and patients requiring aspirin for treatment of other conditions. When used to help management of AERD, doses 100-1,300 mg/day are found effective in clinical trials, thus an optimum dose of choice remains to be determined in future well designed placebo controlled studies.

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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