

Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema

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Background: Acetylsalicylic acid (ASA), commonly known as aspirin, is indicated in the treatment of coronary artery disease (CAD). Many patients are denied treatment with ASA because of a history of ASA or nonsteroidal anti-inflammatory drug (NSAID)-induced urticaria or angioedema.

Objective: We sought to develop a safe and practical protocol to allow the administration of ASA to patients with a history of ASA- or NSAID-induced urticaria-angioedema.

Methods: Eleven subjects with a history of ASA- or NSAID-induced urticaria-angioedema were challenged-desensitized by oral protocols based on rapidly escalating doses of ASA. Most had CAD, one had a history of pulmonary embolism, and one had refractory chronic sinusitis and asthma. Starting doses ranged from 0.1 to 10 mg and were administered at intervals of 10 to 30 minutes. Dosing was individualized for each patient but followed this general sequence (in milligrams): 0.1, 0.3, 1, 3, 10, 20, 40, 81, 162, 325.

Results: Nine patients tolerated the procedure without adverse effects and continued taking ASA for periods ranging from 1 to 24 months, without development of urticaria or angioedema. A patient who had a history of chronic idiopathic urticaria in addition to aspirin-induced urticaria had chest tightness during the protocol. Another patient who had continuing urticaria and angioedema associated with antithyroid antibodies developed angioedema several hours after completing the protocol.

Conclusion: In patients with historical ASA- or NSAID-induced urticaria-angioedema reactions but who did not have urticaria and angioedema independent of ASA/NSAID, rapid oral challenge-desensitization to ASA was performed safely and permitted patients with CAD and other diseases to receive treatment with ASA. (*J Allergy Clin Immunol* 2000;105:997-1001.)

Key words: Aspirin, acetylsalicylic acid, nonsteroidal anti-inflammatory drug, urticaria, angioedema, desensitization, coronary artery disease

Acetylsalicylic acid (ASA), commonly known as aspirin, acetylates and irreversibly inhibits cyclo-oxyge-

Abbreviations used

ASA: Acetylsalicylic acid

CAD: Coronary artery disease

COX: Cyclo-oxygenase

HSA: Human serum albumin

LT: Leukotriene

MI: Myocardial infarction

NSAID: Nonsteroidal anti-inflammatory drug

nase (COX).¹⁻⁵ COX, also known as PGH synthase, exists in at least 2 isoforms, COX-1 and COX-2. ASA inhibits both COX-1 and COX-2, although in some assays it exerts greater inhibition of COX-1.¹⁻⁴ Because of its ability to interfere with platelet aggregation by platelet COX inhibition, ASA has been extensively studied for the prevention of thrombosis.⁶ ASA is effective in the primary and secondary prevention of myocardial infarction (MI) and reduces the risk of death or non-fatal MI in patients with unstable angina and non-Q wave MI.⁷ Treatment with ASA helps to prevent immediate reocclusion after coronary angioplasty.⁸ Many patients are denied treatment with ASA because of a history of ASA- or nonsteroidal anti-inflammatory drug (NSAID)-induced urticaria or angioedema. A safe and practical protocol for challenge-desensitization may allow the administration of ASA to such patients.

Whether ASA desensitization can be accomplished and maintained in subjects who have had urticaria or angioedema reactions to ASA is controversial. Stevenson and Simon⁹ found that desensitization to ASA was frequently achieved in subjects with ASA-induced asthma and rhinosinusitis but was difficult to achieve and maintain in subjects with ASA-induced urticaria or angioedema. In contrast, Grzelewska-Rzymowska et al¹⁰ and Asad et al¹¹ described the successful oral challenge-desensitization to ASA in patients with a history of ASA-induced urticaria or angioedema. Their treatment protocols involved dosing intervals of 2 to 24 hours, which would require many days to complete the entire desensitization procedure and hence would be impractical for patients with unstable coronary artery disease (CAD) who require rapid stent placement. We attempted to devise a procedure that would allow patients with CAD to begin ASA therapy safely within a few hours.

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TABLE I. Characteristics of the patients

No. of patients	11
Age (y)	34-84
Sex	
Male	8
Female	3
Prior adverse reactions to ASA or NSAID	
Angioedema	4*
Urticaria	3
Angioedema and urticaria	4

*One patient had angioedema, shortness of breath, and hypotension on ingestion of ibuprofen.

METHODS

Subjects

Eleven patients with a history of aspirin- or NSAID-induced urticaria or angioedema, or both, were seen at Massachusetts General Hospital (Table I). One patient had ibuprofen-induced angioedema associated with nasal congestion and sinus pressure; he also had ASA-induced sinus pressure and nasal congestion. One patient had ibuprofen-induced angioedema, shortness of breath, and hypotension. Nine had CAD, one had a history of pulmonary embolism, and one had concurrent chronic sinusitis and asthma.

Challenge-desensitization

Ten patients were pretreated with loratidine, cetirizine, hydroxyzine, or diphenhydramine. The choice of antihistamine was based on availability and the patient's previous tolerance. One patient also received prednisone, 60 mg, the night before and the morning of the challenge-desensitization because her reaction to aspirin had occurred recently and because she was clinically fragile. One patient was not pretreated. The suspension of ASA was prepared by dispersing a chewable ASA tablet, 81 mg, in 81 mL of tap water; dilutions of the suspension were prepared in water. Oral challenge-desensitization was performed with a starting dose of 0.1 to 10 mg; doses were increased every 10 to 30 minutes (Table II). After completion of the challenge, 2 patients were continued on antihistamine daily while receiving ASA.

RESULTS

History of reaction to ASA/NSAID, indication for treatment with ASA, and results of challenge-desensitization with ASA are shown below for first 7 patients.

Patient 1 was a 55-year-old white man with CAD. He had had 2 inferior MIs. Thereafter he was started on ASA daily. After he had taken ASA for 2 to 3 days, angioedema of the lips developed, which resolved within 24 hours of stopping the drug. A year later, he took Percodan (oxycodone 5 mg and ASA 325 mg) for 2 days. On the second day of treatment, angioedema of the lips developed. After Percodan was stopped, the angioedema resolved. The patient did not have a history of chronic urticaria-angioedema or atopic disease. Ten months later he required placement of a coronary artery stent. He was pretreated with loratidine, 10 mg, given 1 hour before the challenge-desensitization was started. He tolerated the procedure (Table II) and was maintained on ASA, 325 mg, and loratidine, 10 mg, daily. On follow-up after 6 months, he continued to tolerate ASA without adverse reaction.

Patient 2 was a 54-year-old white man with seasonal allergic rhinitis and a 10-year history of multiple episodes of ASA-induced urticaria and mild facial angioedema. He had recently taken ibuprofen without adverse reactions. He was seen for a non-Q wave MI. It was considered essential that he be treated with ASA. He was pretreated with hydroxyzine, 25 mg, the night before and the morning of the challenge-desensitization (Table II). He tolerated the procedure without development of either urticaria or angioedema. Seventeen months later he continued to tolerate ASA, 325 mg, daily.

Patient 3 was an 84-year-old white woman with CAD and carcinoma of the colon. She had urticaria after taking ASA; the urticaria resolved within a day without treatment. Several years earlier she had tolerated ibuprofen without difficulty. There was no history of chronic urticaria or atopic disorder. Three months after the episode of ASA-induced urticaria, she required placement of a coronary artery stent. She was pretreated with prednisone, 60 mg, the night before and on the morning of the challenge-desensitization. Pretreatment was given in an attempt to prevent any adverse reaction in this patient with severe CAD. She received loratidine, 10 mg, 1 hour before challenge. She tolerated the procedure (Table II) without urticaria or angioedema and was maintained on ASA, 325 mg, and loratidine, 10 mg, daily for 1 month. Months after stopping ASA therapy, she died of metastatic colon carcinoma.

Patient 4 was a 52-year-old white man with CAD who was admitted with an acute MI. He underwent percutaneous transluminal coronary angioplasty and was thereafter started on ticlopidine, diltiazem, and ReoPro (abciximab). He also received ASA. Two days later he had a sensation of "sore throat" on the right side and difficulty coordinating his tongue movement. The following morning his tongue felt large and he had difficulty swallowing pills. On examination, his tongue size was increased. He was treated with diphenhydramine, methylprednisolone, and cimetidine. He did not have a history of urticaria or atopic disorder. Three days after angioedema developed, the patient underwent challenge-desensitization with ASA and tolerated the procedure without difficulties (Table II). On follow-up 24 months later he continued to take ASA, 325 mg, daily without urticaria or angioedema.

Patient 5 was an 84-year-old white woman with hypertension and a history of pulmonary embolism 5 years earlier. She had initially received warfarin sodium but later fell and had a large ecchymosis. Subsequently, her primary care physician placed her on ASA 81 mg daily, which she continued for 5 years without recurrence of pulmonary embolism. She had taken lisinopril for 1 year. Four days after naproxen was started for musculoskeletal pain, pruritus of the hands and massive swelling of the tongue developed. The patient was unable to speak or swallow liquids. In the emergency department she received diphenhydramine; it is uncertain whether she also received epinephrine. After 1 hour her tongue gradually returned to its normal size and she was discharged.

TABLE II. ASA dose schedules

Patient No.		Dose (mg)*								
1	0.1	0.3	1	3	10	30	40	81	162	243
2	0.1	0.3	1	3	10	20	40	81		
3	0.1	0.3	1	3	10	30	40	81	162	
4	0.1			3	10	20	40	81	162	
5					10	20	40	81	162	
6	0.1	0.3	1	3	10	20	40	81	162	325
7†			1	3	10					
8-11	0.1	0.3	1	3	10	20	40	81	162	325
P‡	0.1	0.3	1	3	10	20	40	81	(162)§	(325)§

*Dose administered every 10 to 20 minutes for all subjects except for patients 5 and 7 (every 20-30 minutes).

†Patient had chest tightness within a few minutes after taking 10-mg dose, relieved by albuterol metered-dose inhaler.

‡P = protocol to be used for future patients; doses to be administered at intervals of 15 to 20 minutes.

§Numbers in parentheses represent optional doses that may be administered depending on dose of ASA that patient is expected to take long term.

on diphenhydramine. Aspirin and naproxen were discontinued, but the patient was maintained on lisinopril for 2 months. She was then referred to Massachusetts General Hospital Allergy Associates; after consultation, lisinopril was discontinued. Because the patient required prophylaxis against deep vein thrombosis, she was challenge-desensitized with ASA (as shown in Table II) 2 months after angioedema developed. She tolerated the procedure without adverse reactions. Four months later she continued to take ASA, 81 mg, without adverse effects. She did not have a previous history of chronic urticaria-angioedema or atopic disorder.

Patient 6 was a 49-year-old white man with a 12-year history of episodic swelling of the lips and scattered urticaria; he took ASA or ibuprofen intermittently. He had chronic sinusitis and despite sinus surgery continued to require frequent treatment with antibiotics. He also had moderate persistent asthma. Skin test was previously positive to many aeroallergens. Two years earlier he had swelling of the lips, increased sinus pressure, and nasal congestion after taking ibuprofen. One year ago he had increased sinus pressure and nasal congestion after taking aspirin. Subsequently, he avoided ASA and NSAIDs with only one major episode of urticaria and angioedema during the ensuing 12 months. Previously he had had 1 to 2 episodes per month, suggesting that many of these episodes were induced by ASA or ibuprofen. In an attempt to improve the chronic sinusitis, the patient successfully underwent rapid oral challenge-desensitization with ASA (Table II). During the procedure he had a transient increase in nasal congestion and a mild sensation of lip fullness without observable swelling. These symptoms resolved without treatment. Pulmonary function improved slightly during the protocol. He tolerated ASA for 3 months without development of angioedema or urticaria.

Patient 7 was a 64-year-old white woman with chronic idiopathic urticaria who, on several occasions, had urticaria after taking ASA. The last episode had occurred 24 years earlier. Recently, she had taken naproxen, ibuprofen, and oxaprozin without adverse reaction. She

also had a history of asthmatic bronchitis. She was admitted for unstable angina and was considered to require treatment with ASA. On the morning of the challenge she was pretreated with loratidine 10 mg. She was given 1 mg, 3 mg, and 10 mg of ASA 20 to 30 minutes apart (Table II). A few minutes after the third dose chest tightness without wheezing, hypotension, or urticaria developed. The electrocardiogram was unchanged. The patient's symptoms subsided after treatment with inhaled albuterol. She was not rechallenged with ASA. She underwent angioplasty and was placed on ticlopidine for 4 weeks and subsequently was maintained on clopidogrel.

Subsequent to submission of the original manuscript, we performed the challenge-desensitization protocol in an additional 4 patients with history of ASA- or NSAID-induced urticaria or angioedema. Three of the patients tolerated the protocol uneventfully. A fourth subject had a delayed onset of angioedema. He was a 67-year-old white man who had had angioplasty and stent placement 2 years earlier. He did not have a history of atopic disease. He had generalized urticaria that persisted for several months and was accompanied by angioedema of the lip and infraorbital region on 2 occasions. He had been receiving ASA, 81 mg orally daily, simvastatin, and metoprolol since the angioplasty. These medications were stopped; simvastatin and metoprolol were subsequently restarted. Laboratory workup was significant for the presence of antithyroid antibodies and a borderline elevated thyroid-stimulating hormone level. The patient was started on L-thyroxine 0.05 mg daily. The urticaria and angioedema improved, but the patient still continued to have minor outbreaks up to the ASA challenge-desensitization. The patient was taking cetirizine and ranitidine at the time of the challenge-desensitization. He received a total of 653 mg of ASA (the highest single dose was 325 mg) over 3 hours in accordance with the protocol. He tolerated the challenge without incident but then developed lip and throat swelling several hours after the protocol was completed. The swelling resolved without treatment. The patient was given clopidogrel in place of ASA.

DISCUSSION

Despite strong evidence that ASA decreases mortality in CAD, this treatment is withheld in some patients because of a history of ASA- or NSAID-induced urticaria-angioedema. Our study suggests that a rapid, graded, oral challenge-desensitization to ASA can be safely performed in patients with a history of ASA- or NSAID-induced urticaria-angioedema, provided that they do not have chronic urticaria-angioedema independent of the intake of ASA/NSAIDs. The two patients who failed had urticaria and angioedema that occurred in the absence of ASA/NSAIDs. Among the subjects successfully desensitized, only patient 6 had recurrent urticaria and angioedema that persisted despite the discontinuation of treatment with ASA/NSAIDs. This observation suggested that subjects who have continuing urticaria and angioedema independent of ASA/NSAIDs are more likely to fail the challenge-desensitization. Additional measures, such as pretreatment with a leukotriene antagonist, longer interval between doses, or stopping at a lower dose during the first day of challenge-desensitization may make it possible to desensitize such patients.

The published protocols for aspirin desensitization administer doses of ASA every 2 to 24 hours.¹⁰⁻¹² The long duration between doses may ensure that a given dose is tolerated before advancing to the higher dose. However, the entire procedure then requires several days to weeks to complete. The long interval required for desensitization is impractical for subjects with unstable CAD. Our purpose was to devise a rapid but safe protocol to allow the administration of ASA to patients who require it. We modeled the current protocol on the successful rapid intravenous desensitization protocol that we had developed for vancomycin¹³ and that we had used for rapid desensitization to β -lactam antibiotics. By starting with an initial dose of 0.1 mg and increasing the dose of aspirin (3- to 3.3-fold in the early steps and 2-fold in later steps) at 10- to 30-minute intervals, we were able to complete the challenge-desensitization procedure within a few hours. Although one of the patients (patient 5) tolerated a larger starting dose, the other patient (patient 7) who was started at a higher dose had chest tightness after 2 additional doses. Because some patients may be exquisitely sensitive to ASA, we chose 0.1 mg as the standard starting dose to provide an extra margin of safety. This dose is 300-fold lower than the starting dose of 30 mg described by Stevenson.¹² By use of short dosing intervals and lowering the starting dose from 30 mg to 0.1 mg added only 40 to 60 minutes to the procedure. The multiple steps permit smaller increments to be made, thereby enhancing the safety. The role of antihistamine pretreatment is uncertain. Given the historic efficacy of antihistamines in modulating urticaria and angioedema and their low toxicity, we elected to include their usage in the majority of the patients. The continuation of antihistamine after completion of the challenge-desensitization was discretionary because the majority of the subjects continued to tolerate ASA without further antihistamine treatment.

In our study the occurrence of adverse reactions to ASA or NSAIDs was based on patient history. We did not confirm ASA sensitivity by ASA challenge because most of our patients were admitted to the hospital with CAD, and we could not justify placing them at risk by inducing a reaction. It is quite possible that some of these subjects may have lost the sensitivity to ASA or NSAID and would have tolerated the full dose without dose escalation at the time of the challenge-desensitization. Several of the patients, however, had reactions in the recent past and were therefore likely to still be sensitive. Patients 1, 2, and 3 had definite histories of urticaria or angioedema after ingestion of ASA. Patient 4 had received diltiazem, abciximab, and ticlopidine in addition to ASA before his adverse reaction. Urticaria or angioedema occurs in fewer than 1% of patients receiving diltiazem or abciximab. Although 5% of patients receiving ticlopidine had nonspecific and urticarial rashes, angioedema had been rarely reported.^{14,15} Therefore ASA is considered the agent most likely to have caused the angioedema in patient 4. In patient 5, it was uncertain whether ASA, naproxen, lisinopril, or their interaction had caused the initial angioedema. This patient subsequently tolerated lisinopril for 2 months, suggesting that lisinopril was unlikely to be the sole culprit in this case, although it may have been a contributing factor to reactions induced by ASA or naproxen. Patient 6 had urticaria and angioedema and increased sinus pressure and nasal congestion on ingestion of ibuprofen and ASA.

Hypersensitivity to ASA and nonpyrazoline NSAIDs predominantly manifests as respiratory or cutaneous reactions.^{16,17} A small subgroup of patients have both the respiratory and cutaneous reactions.^{16,17} Current evidence suggests that ASA- and NSAID-induced exacerbation of asthma and rhinosinusitis is related to the inhibition by these drugs of the COX enzyme.^{5,9,18} This inhibition results in decreased PG, in particular PGE₂, and increased leukotriene (LT) production. Subjects with ASA- and NSAID-induced respiratory disease appear to have larger amounts of LTC₄ synthase and greater numbers of eosinophils and mast cells in their respiratory tract than do ASA-tolerant asthmatic and healthy subjects.^{19,20} These individuals are also more sensitive to the bronchoconstricting effects of LTE₄.²¹ In addition, the COX-1 enzyme in their monocytes was found to be more sensitive to inhibition by ASA.²²

The mechanism underlying ASA- and NSAID-induced angioedema and urticaria is less well defined. Stevenson and Simon⁹ suggest that different mechanisms maybe involved in subgroups of subjects with ASA- and NSAID-induced urticaria or angioedema. Subjects who have chronic urticaria or angioedema exacerbated by ASA and NSAID are believed to be sensitive to inhibition of the COX enzyme. Subjects who have urticaria or angioedema after ingestion of one, but not other, inhibitors belonging to the ASA and NSAID family and who do not have chronic urticaria are suggested to have drug-specific IgE antibodies as the underlying mechanism. However, evidence supporting the existence of

drug-specific IgE antibodies to ASA or NSAID is limited. Blanca et al²³ examined the serum of 17 subjects with urticaria, angioedema, or anaphylactic shock on ASA intake. Only one of the 17 subjects had an elevated level of IgE binding to an ASA-human serum albumin (HSA) conjugate used as substrate in a radioallergosorbent assay. This subject also had markedly elevated total IgE and the decline in IgE binding to ASA-HSA paralleled the decline in total IgE, raising the possibility that ASA-HSA binding may not have been specific. Zhu et al²⁴ studied 28 subjects who had asthma, rhinoconjunctivitis, urticaria, or angioedema induced by ASA. These investigators found increased binding of IgE to ASA metabolites used as substrates in a radioallergosorbent assay in 26 of these subjects. Their study is flawed, however, in that the control subjects, but not the ASA-sensitive subjects, were given large doses of ASA up to the time of testing. This treatment would lead to generation of ASA metabolite in vivo and may have reduced the amount of ASA metabolite-binding substance in the circulation. The ASA metabolite generated in vivo may also have competed in vitro for binding to the ASA metabolite-conjugated disk.

An alternative explanation for apparent single-agent sensitivity may be provided by pharmacologic considerations. Although ASA and NSAIDs are often linked together as a group, their pharmacologic potencies and relative effect on various enzymes can vary dramatically. There is a greater than 3 log difference between the strongest and weakest of these agents in COX-1 inhibition.^{1,3} The relative inhibition of COX-2 versus COX-1 enzymes varies over 2 logs among ASA and the various NSAIDs.¹⁻⁴ These agents may also have differential effects on non-COX enzymes. Thus differences in enzyme inhibition can provide a pharmacologic basis for the sensitivity of some individuals to a particular (or a few), but not all, agents that can inhibit COX.

In summary, our results demonstrated that most patients with ASA-induced urticaria or angioedema may be successfully and safely challenged-desensitized with use of a rapid oral protocol. Subjects who have a history of urticaria and angioedema in the absence of ASA-NSAIDs may require additional measures to bring about an ASA-tolerant state.

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