

# Aspirin Desensitization in Aspirin-Exacerbated Respiratory Disease: Consideration of a New Oral Challenge Protocol

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In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Chen et al<sup>1</sup> from the University of Texas Southwestern Medical Center (SW) present their new oral aspirin challenge (OAC) protocol, which decreases the time to achieve aspirin desensitization in patients with aspirin-exacerbated respiratory disease (AERD). Because 5%-7% of all asthmatics and 15% of severe asthmatics have AERD,<sup>2</sup> this represents a substantial number of patients who should be undergoing aspirin desensitization and daily treatment with aspirin.

In patients with AERD, ingestion of full therapeutic doses of aspirin, or any non-steroidal anti-inflammatory drugs (NSAID) that inhibits COX-1, can induce such severe bronchospastic responses that intubation and mechanical ventilation are needed. Death from ingestion of full strength NSAIDs or parenteral injections of ketorolac has occurred, even inside hospitals. These observations are the genesis of reluctance on the part of some allergists to perform OACs, especially in their outpatient offices. And yet the facts are that 3 different initiating doses of aspirin, in the same patient with AERD, can be counted on to have profoundly different effects: 40.5 mg usually induces no reaction at all; 60 mg usually induces rhinorrhea, nasal congestion, and mild wheezing; while 650 mg may induce anywhere from mild to severe bronchospasm. Therefore, the safety of OACs is linked to the starting dose of aspirin, intervals between escalating doses, and accumulated doses over the time of the procedure.

Between 1979 and 1999, 3-day OACs, with intervals of 3 hours between doses, were standard.<sup>3</sup> This protocol was time consuming but safe because the 3-hour intervals were the outer boundaries of induced respiratory reactions and therefore eliminated adding the next aspirin dose just before a reaction was about to begin. Fortunately, 2 CystLTR<sub>1</sub> blocking drugs, montelukast and zafirlukast, were released into the US market in 1999. Pretreatment of patients with AERD with either inhibitor completely eliminated the bronchospastic component of the respiratory reactions in 50% of the OACs,<sup>4</sup> and in the other 50% of patients, the severity of the bronchial reactions was significantly diminished.<sup>5</sup> By withholding antihistamines, naso-ocular

reactions were not blocked, proving the diagnosis of AERD.<sup>4</sup> Thus, after montelukast pretreatment became standard, the intense respiratory reactions to aspirin (ASA) occasionally seen at Scripps Clinic in the 1980s and 1990s became unusual and the 3-hour wait between aspirin doses was no longer the only safety factor.

In 2005, we devised a protocol to shorten the time required to achieve aspirin desensitization. This goal was enhanced by the discovery<sup>6</sup> that intranasal ketorolac induced local reactions in the nasal mucosa, which sometimes desensitized the entire respiratory tract. A modified ketorolac OAC was then tested and eventually published in 2010.<sup>7</sup> This protocol involves a first morning of 30-minute escalating doses of nasal ketorolac, which frequently induces nasal reactions and desensitization by itself, followed by 2 doses of 60 mg of aspirin at a 90-minute interval. In this protocol, aspirin desensitization is usually achieved during the first day, but doses of 150 and 325 mg of aspirin are administered in the morning of the second day to prove completion of desensitization before discharge and treatment with daily aspirin.

The SW protocol by Chen et al<sup>1</sup> has a number of positive aspects: first, the doses of aspirin can be created with a pill cutter (40.5, 81, 120, 162, and finally 325 mg); second, doses are given orally; third, doses are given every hour during the morning, which reserves the afternoon for treating whatever reactions were generated. Additional doses, up to 325 mg, were frequently administered the next morning, with discharge during the second day. Table I compares this new protocol with the 2 Scripps protocols described above.<sup>7</sup> In the new SW protocol, 9 of 57 patients finished the protocol in 1 day because their challenges were negative, and 14 (29%) of the remaining 48 patients completed desensitization on day 1. The remaining 34 (71%) of the 48 patients continued challenges into the second day. For the 48 SW patients with AERD versus 82 ketorolac/OAC patients with AERD, the mean elapsed times from the first challenge on day 1 to completion (325 mg ASA without reaction) were 1.6 versus 1.9 days.

Potential concerns in the SW protocol are related to dosing, intervals, and safety. The first matter is the selection of patients, who, to be eligible, were required to remember a historical less than 60-minute elapsed time from NSAID ingestion to the onset of asthma. A patient's recall of the timing of an event, especially a distant event, seems to be potentially inaccurate to us. Furthermore, if this new protocol is advertised as a 1-day event, patient memory bias may shift to the required less than 60-minute historical interval to be eligible for a preferred shorter protocol.

In a large study at Scripps,<sup>8</sup> involving 420 patients, two-thirds were pretreated with montelukast and all underwent every 3-hour advancing doses of aspirin. In this study, 299 (71%) of the 420 patients experienced naso-ocular reactions with minimal or no bronchospasm and the remaining 121 (29%) experienced bronchospasm with FEV1 declining by 21% or greater. The

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**TABLE 1.** A comparison of the University of Texas Southwestern (SW) protocol with Scripps ketorolac and 3-d oral aspirin challenge (OAC) protocols\*

Respiratory reactions and timing	SW <sup>1</sup> (N = 48)	Modified ketorolac <sup>7</sup> (N = 82)	3-d OAC <sup>7</sup> (N = 92)
Naso-ocular reactions	30 (62%)	54 (65%)	35 (38%)
Bronchial reactions	36 (75%)	26 (32%)	35 (38%)
Laryngeal reactions	0 (0%)	6 (7%)	17 (19%)
Cutaneous reactions	4 (6%)	5 (6%)	9 (10%)
Gastrointestinal reactions	6 (13%)	10 (12%)	30 (33%)
Number of patients desensitized in 1 d	23 – 9 = 14 (29%) <sup>†</sup>	0 (0%)	0 (0%)
Number of patients desensitized in 2 d	47 (98%)	68 (83%)	18 (38%)
Achieving desensitization in days (mean)	1.6	1.9	2.6

\*All patients with AERD were pretreated with montelukast. Antihistamines were withheld. Standard inhaled steroids, with or without long-acting bronchodilators, were continued if this treatment was already underway.

<sup>†</sup>Nine patients underwent negative challenges and were therefore subtracted from the 57 patients who started the study, leaving an n = 48 of identified patients with AERD. Thus, 23 patients finished on day 1, including 9 patients who did not have AERD and 14 of 48 patients with AERD.

mean provoking dose was 61 mg of aspirin for the naso-ocular reactors and 68 mg for the bronchospasm reactors. For both groups, 75% of the patients reacted to either the initial 45 mg or the second dose of 60 mg, and the mean elapsed time to the onset of reaction was 1.7 hours (102 minutes). In the SW protocol, we assume that 75% of the reactions occurred after accumulated doses of 40 + 80 = 120 mg of aspirin, because the second dose was given 40 minutes before the mean elapse time in the Scripps study of 1.7 hours. Therefore, the minimal provoking dose may actually be 120 mg, which might account for the 75% bronchospastic reaction rate in the SW protocol. With only 48 patients in the SW study, the number studied may be insufficient to eliminate outlying severe reactors. In our ketorolac study of 82 patients,<sup>7</sup> after a negative ketorolac challenge in the morning, 1 patient experienced severe bronchospasm after a 1 PM dose of 60 mg of aspirin. This patient reacted an hour and 15 minutes after the 60 mg aspirin dose. In the SW protocol, she would have previously received 40.5 mg an hour before the 60 mg and then received another 120 mg of aspirin after 1 hour, potentially causing her to receive 220 mg of aspirin that could have generated an even larger bronchospastic reaction.

Another interesting difference between ketorolac/OAC and the SW protocol is the absence of any laryngeal reactions in the SW protocol group. We define laryngeal reactions as throat tightness, change in voice, or cutoff inspiratory loop of the flow volume curve with rapid and successful correction after inhaled racemic epinephrine. These reactions occurred in both of the Scripps protocols as shown in Table 1, including the 3-day oral challenge protocol. Finally, it was curious that 728 mg of aspirin, taken over 4 hours, produced gastrointestinal reactions in only 6 (13%) of the 48 patients in the SW protocol. We would have expected more gastrointestinal reactions, because the incidence was 30 (33%) of 92 patients in our 3-day

protocol and only 10 (12%) of 82 using our ketorolac/OAC protocol.

As the reader looks at Table 1 in this editorial, some advantages and disadvantages of the 3 protocols are available for comparison. Certainly, the 3-day protocol should be relegated to history or used as a part of an occasional investigative study. The other 2 protocols are similar enough (mean complete time 1.6 vs 1.9 days) that individual convenience, side effects, and safety considerations (such as the certainty of the less than 1-hour latency of the prior historical reaction) should be considered by the allergist in choosing which protocol to use to desensitize a patient with suspected AERD.

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