

Intravenous Ibuprofen For Desensitization In Aspirin Exacerbated Respiratory Disease: 2 Case Reports

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Abstract

Ibuprofen is in a category of non-steroidal anti-inflammatory drugs that has nearly complete cross-reactivity with aspirin in terms of ability to provoke symptoms in patients with aspirin exacerbated respiratory disease (AERD) (1,2). While the most widely used desensitization protocols utilize aspirin, these protocols typically involve serial increments of oral aspirin administration over several hours (1,2). Aspirin absorption itself can vary even with the use of rapid release aspirin, with time to peak blood levels ranging from 18 minutes to 2 hours (3). This absorption time could potentially be eliminated if intravenous administration were used, and thus could potentially enable a more rapid desensitization procedure in AERD patients.

The contrasting clinical courses of 2 patients desensitized with intravenous ibuprofen are described and the outcomes are discussed in terms of implications for managing AERD patients.

CASE 1:

A 43 year old African American female presented to the office in April 2013 after a reaction to aspirin. She had a history of severe asthma and was using twice daily inhaled fluticasone propionate/salmeterol in a 500/50 microgram combination formulation, montelukast 10 mg/day, albuterol metered dose inhaler and tiotropium 18 mcg inhaled per day. She had been on multiple courses of systemic prednisone but not in the prior month. She had a history of 3 prior sinus operations which included polypectomies, the most recent of which was in February 2013. Since the sinus operation she had recurrent frontal headaches. She reported having been intubated after taking ibuprofen in 2009, which she developed respiratory distress almost immediately after

ingestion. Two days prior to presentation, she had developed pruritus, lip swelling, rash and coughing several hours after ingesting an 81 mg aspirin tablet. She claimed penicillin, egg and shrimp allergy.

On physical examination, she had end inspiratory wheezing, no nasal polyps and a body mass index of 30.9 kg/m². The skin had many less than 1 mm erythematous macules (fig 1). Laboratory tests 3 weeks prior to presentation included a complete blood count which showed an absolute increase in eosinophils (800/uL), elevated specific IgE to egg white, dust mite, and Kentucky Bluegrass, and normal histamine release with lysine acetylsalicylate. The total IgE was 470 IU/mL. No specific IgE to shrimp or penicillin was identified. One month prior, the patient had office spirometry which showed a post-bronchodilator FEV₁ of 1.74L, which was noted to be 73% predicted. The patient was treated with fluticasone propionate nasal spray 100 ug/nostril/day and cetirizine with improved headache and skin symptoms. In the beginning of May the patient underwent ketorolac nasal challenge with 1.2 mg, 5.2 mg, and 7.8 mg doses separated by 1 hour intervals. She left the office 1 hour after the last nasal spray dose. 30 minutes after leaving the office, she developed asthma and took oral prednisone with resolution of symptoms by the following day.

Eight days later, the patient was admitted to the hospital for NSAID desensitization. She had been treated with oral prednisone during the prior 5 days and took 20 mg that morning. The patient had an expiratory peak flow rate of 350 L/min, before the desensitization was started. The first NSAID dose was given in the mid-morning as aqueous ibuprofen 12 mg diluted in 50 ml saline administered intravenously over 10 minutes. The next dose was administered as 24 mg diluted and administered similarly. 2

hours later the patient began to cough and had a decline in expiratory peak flow to 200 L/min. She was treated with 40 mg sodium methylprednisolone and albuterol/ipratropium nebulizations. 5.5 hours after the provoking ibuprofen administration, the patient was administered another 24 mg dose intravenously with no symptoms provoked. The next day in the mid-morning the patient received a 50 mg intravenous dose, which was followed shortly thereafter by itching and rash development. A serum tryptase drawn at that time was normal. The patient was treated with continued parenteral corticosteroid as well as parenteral anti-histaminic medication. By the afternoon, the patient had received a 200 mg intravenous dose, immediately after which time she had peak expiratory flow rate was 310 L/min and noted facial warmth and left foot itching only. Two hours later, however the patient developed dyspnea and the peak expiratory peak flow rate dropped to 100 L/min with a corresponding decrease in saO₂ to 93%. She also continued to have itching. The patient was treated again with multiple albuterol nebulizer inhalations, and continued parenteral methylprednisolone/antihistamines with improvement in peak flow and saO₂. The following morning the patient's peak expiratory flow rate had risen to 350 and no itching. She was then given a 100 mg oral dose of ibuprofen that morning with no subsequent reactions. She was discharged home with instruction to take 100 mg ibuprofen three times a day.

The patient returned 1 week later just after completing a course of oral prednisone. She was also taking ibuprofen orally 200 mg twice daily. Despite cetirizine and famotidine daily administration, the patient reported continued rash which were mostly spots (figure 1) on her arms and face and claimed she was getting some facial/lip swelling. Another brief course of prednisone was administered. On 6/18/13 the patient received her first subcutaneous injection of omalizumab 375 mg. On 7/2/13 the patient returned for her 2nd omalizumab injection and had not taken any oral prednisone for 3 weeks prior. She had no recurrence of pruritus or rash over that time period. The FEV₁ at that time was 2.25 L which was within normal range. In August 2013, she noted worsened asthma and increased frontal headaches. She also had complaints of arm pain. Some polypoid tissue was noted. The FEV₁ was 1.51L. The patient refused oral prednisone treatment. Topical nasal and pulmonary medications were continued. In September 2013 the patient returned continuing daily ibuprofen daily and but had missed her omalizumab injections. Polypoid nasal tissue was still noted. The FEV₁ was 1.78 L.

In October 2013 the patient inadvertently stopped ibuprofen for over weeks. The FEV₁ then was 1.51 L. The patient reported cold related rash, appearing similar to the rash she had previously. The patient was given oral prednisone 40 mg/day and told return for repeat ibuprofen desensitization in 1 week. With a pre-desensitization FEV₁ of 2.05 L (91% predicted) before administration, outpatient desensitization was attempted on 10/28/13. A bronchospastic reaction occurred with 50 mg intravenous ibuprofen, which resolved after repeated albuterol nebulizer inhalations and parenteral sodium methylprednisolone. The patient was then discharged on ibuprofen 50 mg take twice daily. The patient reported cough shortly after taking each 50 mg dose but continued taking ibuprofen. The rash had resolved while taking the ibuprofen in this manner. Repeat outpatient desensitization was attempted on 11/21/13 using oral ibuprofen 50 mg. The pre-procedure FEV₁ was 1.8L. After a total of 100 mg take orally (50 mg for 2 doses taken 1 hour apart), the patient had severe respiratory distress (about 2 hours after the initial 50 mg ibuprofen ingestion) with hypoxemia development while on nasal oxygen. The patient required a one day hospitalization for stabilization but improved with parenteral corticosteroid, epinephrine and antihistamines combined with repeated albuterol nebulization treatments. The patient was discharged and instructed to stop ibuprofen altogether. Omalizumab treatment was resumed and oral prednisone was prescribed with alternate day dosing of 20 mg. With continued omalizumab and inhaled corticosteroid, long acting bronchodilator and anticholinergic inhalations, the patient was able to discontinue prednisone at the beginning of January 2014. Her FEV₁ on 1/23/14 was 2.48 L.

In March 2014, the patient was treated in an emergency department for cough and discolored sputum. She also reported that her nasal symptoms had increased. She was treated with a course of prednisone and amoxicillin/clavulanate. While on 40 mg/day prednisone for 4 days, her FEV₁ was 1.62 L. The patient underwent aspirin desensitization on March 31, 2014. Patient underwent serial administrations with ketorolac 7.56 mg (intranasal), then after 90 minutes, 40 mg ASA which resulted in bronchoconstriction, body itching and nasal obstruction 90 minutes after aspirin ingestion. After rescue treatments with diphenhydramine/famotidine, bronchodilator nebulizer treatments, nasal phenylephrine and intravenous methylprednisone (125 mg) and the patient recovered and tolerated a repeat 40 mg aspirin administration with no subsequent bronchospasm or nasal reaction. The following

day, the patient was administered 81, 162 and 324 mg of aspirin at 90 minute intervals without any reactions. She then took 324 mg aspirin twice daily and continued regular omalizumab treatments. Her FEV1 on 4/29/14 off corticosteroids was 2.14 L.

Figure 1



CASE 2:

A 39 year old African American male presented to the office on 10/7/13 with a history of allergic reactions to non-steroidal anti-inflammatory drugs including ibuprofen. He claims that he developed projectile vomiting, diarrhea, SOB and sweating within 30 minutes of ingesting NSAIDs. He never had urticaria or angioedema with the drug allergic reactions. His reactions usually occur within 30 minutes of ingestion. He had 3 sinus surgeries involving polypectomies, with the last sinus operation being 1 year prior. He was told that his nasal polyps had returned since the last surgery. He had asthma since the age of 9, and was once hospitalized for asthma after NSAID ingestion when he was in college. He was using twice daily inhaled fluticasone propionate/salmeterol in a 500/50 microgram combination formulation, and albuterol metered dose inhaler. He was receiving allergen immunotherapy with tree/grass/dog/roach

and dust and had been receiving this for 3 years. He also claimed anosmia for 3-4 years except when on oral steroids which he not taken for about 1 year. He also had a history of tinnitus, amoxicillin allergy and knee pain. His physical examination revealed bilateral nasal polyps and his body mass index was 33.15 kg/m². The FEV1 was 2.2L(55% predicted) and the FEV1/FVC ratio was 71%. There was mild peripheral blood eosinophilia, 705/mcL and the total IgE was 1774 IU/mL. There was no increase in specific IgE or IgG antibodies to aspergillus species. Basophil histamine release through specific antibody to ibuprofen was detected, 4.1 ng/mL (Viracorp-IBT Laboratories, normal <0.8 ng/mL). No specific antibody related release was found for lysine-acetylsalicylate.

After a week's treatment with prednisone 40 mg/day, the FEV1 rose 2.34L(58% predicted). The following week, the patient underwent serial nasal sprays with ketorolac at 1.5, 4.5, and 7.5 mg at 1 hour intervals. After the last spray, the patient developed wheezing accompanied by oxygen saturation decline, sweating, marked bilateral conjunctival erythema, a sensation of epigastric warmth and hunger sensation. He was treated with parenteral hydrocortisone, multiple inhalations of bronchodilators and discharged home on a short tapering course of oral corticosteroids. On November 4, 2013, the patient was admitted to the hospital for inpatient desensitization. He had been taking prednisone 20 mg/day for 3 days. The FEV1 at the time was 3.1L. The patient received 12 mg, 25 mg, 50 mg, 100 mg and 200 mg intravenous doses over 24 hours without any reactions with 2-3 hour or more intervals between doses.

He was discharged on oral ibuprofen 200 mg twice daily and resumed his allergen immunotherapy treatments without any complaints or complications. In December the patient complained that his nasal polyps had return despite taking ibuprofen and mometasone nasal spray. He was changed from Motrin 200 mg twice to Aspirin 650 mg twice daily in January 2014 with no clinical reactions. He was treated for an asthma exacerbation at the end of January with a brief course of prednisone and started on budesonide sinus instillations. On 2/11/14, the patient's home peak flow was measured to be 300 L/min, which was 62% of his personal best reading. On 4/17/14 patient reported that he was doing well, could smell, and did not have obstruction from his polyps, with peak flow reading ranging from 320 to 350 L/min.

DISCUSSION

These 2 cases demonstrate that intravenous ibuprofen can be used for AERD desensitization in a similar manner to that used with oral aspirin. The first case had bronchospastic reactions approximately 2 hours after the 24 mg and 200 mg parenteral doses, which is similar to the time course usually described with aspirin ingestion. This patient had an urticarial like rash which resolved without antihistaminic therapy, several days after continued ibuprofen maintenance therapy, suggesting a different time effect for ibuprofen desensitization on respiratory and cutaneous disease co-existing in the same patient. Interestingly the rash recurred when the patient stopped ibuprofen, suggesting that maintenance desensitization had suppressed the cutaneous disease. NSAID desensitization literature mostly originates from large centers using aspirin desensitization protocols(1,2). To our knowledge, systematic head to head comparisons between aspirin and other NSAIDs have not been performed. The first case demonstrated in her November visit, that low dose NSAID is not protective of higher doses, as the patient had a bronchospastic reaction to the total daily dose(100 mg) that she had tolerated, but given at a much shorter time interval. This implies that the peak drug concentration is critical provoking a reaction, not the cumulative dose in a given day. This patient also had a relatively mild respiratory reaction, when she underwent ketorolac/aspirin desensitization, while on regular omalizumab treatment. This suggests that omalizumab may ameliorate the degree of respiratory reactivity in AERD.

Both of these patients underwent ketorolac intranasal challenge(4) and both had bronchospastic reactions. It is of interest that the second patient reacted to ketorolac 1 week prior to ibuprofen desensitization, and had no reactions to the latter protocol. This strongly suggests that the patient had become tolerant to NSAIDs after the ketorolac and that the patient was still tolerant 1 week after the ketorolac reaction. This prolonged period of tolerance(7 days) after a rather low topical dose was unexpected. The author is not aware of refractory periods of greater than 6 days in literature reports(5). The mean aspirin reaction refractory period is typically reported as being 3-4 days(5). The total ketorolac dose administered intra-nasally was 13.5 mg, which compares to the usual intravenous analgesic dose of 30-60 mg. These data suggest that desensitization protocols employing ketorolac challenge as the initial step can have benefits by inducing high NSAID dose tolerance with relatively milder respiratory reactions.

Although it has been purported that aspirin has never been caused anaphylaxis(2), increased tryptase levels are observed in aspirin reactions both in respiratory secretions and in serum(6,7). The second patient did have demonstrable histamine release(8) when control basophils were sensitized with the patient's serum and exposed to ibuprofen and not to lysine-acetylsalicylate. This suggests that specific IgE was present to ibuprofen. In contrast the clinical reaction that this patient had was more consistent with the typical AERD reactions including conjunctival erythema and bronchospasm. No urticarial, hypotension or angioedema was observed. Specific basophil activation has been reported for ibuprofen sensitivity patients but only in patients who had cutaneous not respiratory reactions to aspirin/NSAIDs.

It has been stated that AERD patients who are desensitized and tolerate 325 mg, can increase their doses as outpatients to 650 mg(1,2). Desensitizations maintained at high NSAID doses have been shown to have greater success rates in controlling AERD(1,2). This observation has not been described for ibuprofen. Maintenance therapy with non-aspirin NSAIDs for anti-inflammatory and anti-analgesic benefits has dosing advantages over aspirin. It is thus conceivable that certain patients with coexisting AERD and inflammatory joint disease would benefit more with treatment with non-aspirin NSAIDs such as ibuprofen. The observations in these 2 patients may be useful in promoting the description of experience of non-aspirin NSAID desensitization in the future.

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