GAVIN PUBLISHERS

Emergency Medicine Investigations

Larry B Mellick, et al. Emerg Med Inves 2016: G125.

DOI: 10.29011/2475-5605.000025

Editorial

"Kitchen Sink" versus "Out the Door" Asthma Management

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Citation: Mellick LB (2016) "Kitchen Sink" versus "Out the Door" Asthma Management. Emerg Med Inves 2016: G125. DOI: 10.29011/2475-5605.000025

Received Date: 14 December, 2016; **Accepted Date:** 14 December, 2016; **Published Date:** 20 December, 2016

Editorial:

It is not uncommon to see articles about treatment options for the crashing asthma patient. Typically, these publications discuss every therapeutic option available including the proverbial "kitchen sink" for managing severe asthma emergencies. Generally, "kitchen sink" recommendations include continuous albuterol nebulization, intravenous magnesium sulfate, intramuscular epinephrine or terbutaline, noninvasive (NIV) positive pressure ventilation, helium-oxygen administration and ultimately intubation and ventilation using ketamine. Nevertheless, there is another category of asthma management that is far less commonly discussed. Another very common clinical setting is the patient whose bronchospasm has improved but his or her disease process appears to be resistant to ongoing interventions and remains severe enough that discharge "out the door" is not a consideration.

The typical emergency department asthma protocols will use repeated albuterol treatments with at least two of those treatments combined with nebulized ipratropium bromide. Additionally, corticosteroids are administered either orally or intravenously. When these interventions fail most practitioners continue to treat the bronchospasm with additional doses of albuterol and ultimately continuous nebulization of β2 agonist. However, when these investigations have already not resolved the mild to moderate persistent bronchospasm, continuing to treat the patient with the same medication seems a little illogical. Nevertheless, most clinicians maintain a relatively limited number of therapeutic tools in their toolbox when it comes to the routine management of asthma. And consequently, at least in my experience, many patients are ultimately admitted to the hospital for ongoing treatment because other asthma treatment options are overlooked.

This editorial is a brief discussion of evidence for the potential effectiveness of five other potential asthma treatment options currently not commonly used by clinicians. The treatment options will be discussed in the order of their strength of evidence beginning with those with the strongest apparent evidence. It is the author's opinion that adding one or more of these therapeutic interventions to a clinician's therapeutic toolbox will result in fewer patients being admitted and more patients crossing the threshold of the emergency department door as they head for home.

Inhaled Corticosteroids

One of the best supported asthma management options is that of inhaled corticosteroids. The literature supporting this intervention is consistently positive and appears to support the use of inhaled steroids in addition to other systemic corticosteroids. In our shop we typically give one dose of oral dexamethasone (0.6 mg/kg) up to a maximum of 16 mg for asthma exacerbations that have been ongoing for one to two days and resistant to home management. My choice for an inhaled or nebulized corticosteroid is 0.5 mg of budesonide, but other options are also effective.

A published review article and a Cochrane review of the benefits of inhaled corticosteroids provide excellent supporting evidence for routinely adding this intervention to patients with recalcitrant bronchospasm [1,2]. The Cochrane review states the following: "This review found that inhaled corticosteroids used alone or in combination with systemic corticosteroids helped to relieve asthma."[1] The review article by Volovitz summarizes its findings as follows, "The current evidence base revealed encouraging results regarding the efficacy of the ICS budesonide in patients with wheeze and acute worsening of asthma" [2].

Intramuscular or Nebulized Epinephrine

Epinephrine has always worked for bronchospasm. Older clinicians remember well using subcutaneous epinephrine every twenty minutes as the standard management for asthma exacerbations. And, despite the tears caused by the painful injections, it worked. In truth, the literature is packed with papers that describe both injected and nebulized epinephrine as being non-inferior to older agents such as terbutaline oralbuterol. In other words, it works equally well to the bronchodilator medications that we currently use. It is just easier and less objectionable to nebulize medi-

cations rather than inject needles into adults and children. And, there is always some consideration for the known but minor side effects of epinephrine, a non-selective β2 agonist. Therefore, most clinicians reserve epinephrine, if they use it at all, for the patient presenting with severe and status asthma.

However, nebulized epinephrine probably works just as well as intramuscular epinephrine and possibly delivers a greater quantity of epinephrine with minimal side effects. Both regular epinephrine (5 mg maximum) and racemic epinephrine (11.25 mg maximum) can be nebulized in the treatment of asthma and croup. However, it seems to be much easier to use the current commercially supplied preparations of racemic epinephrine for nebulization. Again, there is good evidence for the effectiveness of nebulized racemic epinephrine in the treatment of asthma [3-7]. While it is probably no better than currently used bronchodilators, it is clearly a different option to consider when nebulized albuterol has not successfully resolved the bronchospasm.

Antihistamines

Asthma causes or triggers can be divided into allergic and non-allergic etiologies. It is reported that allergies trigger asthma attacks in 60 to 90% of children and 50% of adults [8]. Sensitization to mite and cockroach antigens commonly found in the environment has been shown to increase asthma morbidity [9]. While complicated, the bottom line is that IgE binds to high-affinity receptors on the surface of mast cells and basophiles leading to mast cell and basophil degranulation. Mast cell mediators, histamine, pro-inflammatory cytokines and proteases, are released leading to an early allergic response. Histamine is a known inflammatory mediator in the pathophysiology of asthma. Therefore, it would seem to make intuitive sense that antihistamines could play a role in the treatment of asthma. Evidence for benefit from first generation antihistamines in asthma is relatively limited. This may be due the fact that for many years the teaching was to avoid antihistamines because of possible drying and inspissation of airway secretions. However, research exists for second generation antihistamines and suggests benefit [10-12]. Clinical studies have shown mixed results, but no detrimental effects are noted and definite positive effects of antihistamines can be documented especially with the second generation antihistamines [11-14]. Consequently, despite the weaker but positive evidence and because histamine is a known factor in the pathophysiology of asthma, the addition of intravenous or oral antihistamines during and acute asthma event, seems both safe, reasonable disease mechanism based. And, it is possible that the benefit of antihistamines may be interdependent or synergistic with other anti-inflammatory interventions.

Ibuprofen and NSAIDS

Another and more controversial option is the use of ibuprofen in asthma. Ibuprofen is a non-selective inhibitor of the enzyme cyclooxygenase (COX) which is required for the synthesis of prostaglandins via the arachidonic acid pathway. This pathway is active in the pathogenesis of asthma [15]. (Figure 1) [16]

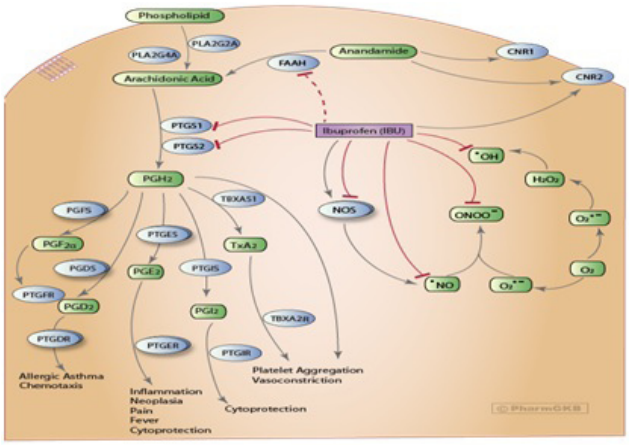

Figure 1: Ibuprofen pathways [16].

Ibuprofen as a therapeutic intervention for asthma is often immediately rejected because of concerns about exacerbating asthma in the context of aspirin sensitivity. However, literature analysis seems to indicate that the use of ibuprofen in the pediatric population does not exacerbate asthma morbidity [17,18]. In fact, one author states the following: "Given the infrequent occurrence of aspirin/NSAID sensitivity in children with asthma, it seems reasonable to allow the use of ibuprofen in this population unless there is a personal or family history of aspirin-induced asthma. In addition, the inflammatory pathogenesis of asthma, anti-inflammatory effect of ibuprofen, and evidence suggesting ibuprofen may reduce morbidity in children with asthma raises the intriguing possibility that ibuprofen might actually have therapeutic benefit for at least some children with asthma."[17] Lesko et al. stated that rather than supporting the hypothesis that ibuprofen increases asthma morbidity among children who are not known to be sensitive to aspirin or other nonsteroidal anti-inflammatory drugs, their study suggested that compared with acetaminophen, ibuprofen may reduce such risks [19]. Another study showed that single dose ibuprofen inhibits early and late asthmatic responses to allergen bronchoprovocation and recommended that ibuprofen be withheld for at least 24 h prior to investigations utilizing allergen broncho provocation [20]

In summary, while the evidence is limited, ibuprofen may actually decrease morbidity in asthma and based on its mechanism of action ibuprofen should theoretically decrease the inflammatory factors causing bronchospasm in asthma through its actions on the arachidonic acid pathway.

Nebulized $MgSO_4$

Other options potentially exist and one of these includes nebulized magnesium sulfate. What is fascinating about nebulized $MgSO_4$ is that the multiple systematic reviews and meta-analyses

have come to exactly opposite conclusions. The evidence for this intervention was reviewed in a 2012 Cochrane review and the final implications for practice statements were as follows: [21]

1. Treatment with nebulised $MgSO_4$ could be considered in addition to inhaled β_2-agonists and ipratropium bromide in combination as per most national guidelines in asthma exacerbations, particularly in those patients with more severe exacerbations. However this point, regarding severity, requires further investigation in clinical trials. More data are required especially in pediatric studies.

2. There is no evidence that nebulised $MgSO_4$ can be used as a substitute for inhaled β_2-agonists.

3. Nebulised MgSO4 appears to be effective and safe to administer to patients experiencing asthma exacerbations.

However, a 2013 systematic review and meta-analysis by Shan et al. reported that the use of nebulized magnesium sulfate appears to produce benefits just for adults and not children [22]. And then, a 2016 systematic review and meta-analysis by Su et al. came to the conclusion that while intravenous magnesium sulfate was an effective treatment in children, nebulized magnesium sulfate treatment showed no significant effect on respiratory function or hospital admission and further treatment [23]. And another 2016 meta-analysis of adult patients treated with nebulized magnesium sulfate stated that evidence to date suggests that nebulized $MgSO_4$ has no role in the management of adult patients with acute or stable asthma [24].

The bottom line is that while there are studies that conclude nebulized $MgSO_4$ alone or combined with salbutamol has a clinically significant bronchodilator effect in acute asthma and leads to clinical improvement, increase in PEFR, reduction in heart rate and reduction in respiratory rate, [25,26] other studies come to the exact opposite conclusion [27]. No studies, however, found that nebulized magnesium sulfate was harmful. Finally, the actual dosage of $MgSO_4$ nebulized may vary between the studies and could be a contributing factor to this variability in findings and conclusions.

Conclusion

For the clinician who finds himself or herself regularly frustrated with asthma patients improving but lingering at clinical asthma scores incompatible with discharging home, consider trying some of the other treatment modalities that have either been overlooked or put on the shelf because of our newer therapeutic tools for treating asthma. It is possible that more patients will have their bronchospasm successfully treated and be eligible for discharge after responding to these other "out-the-door" asthma management options.

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