Asthma Causes

Asthma is a multifactorial disease whose management requires attention ranging from avoidance of allergens, stress reduction and diet control to appropriate drug use in emergencies. It says something about our culture that its incidence is increasing daily.  

The physiologic basis involves many peptide mediators (cytokines, chemokines and others) and the leukotrienes (LT’s), lipid metabolites of the pro-inflammatory 5-lipoxygenase (5-LO) enzyme. 

Until relatively recently only drugs prescribed for controlling immediate respiratory symptoms were FDA approved, such as bronchodilators like beta 2 agonists, anticholinergics, steroids or xanthines, etc.

5-Lipoxygenase and Leukotrienes in Asthma

The 5-LO enzyme works on the arachidonate substrate to produce the “misery” of the leukotrienes. These potent pro-inflammatory eicosanoids are in turn abundantly involved in over 35 chronic conditions including: asthma, allergies, colitis, arthritis, gastric disorders (promote ulcer formation, stimulate acid secretion, etc), scleroderma, psoriasis, atopic dermatitis, neurological diseases, and so on. 

Leukotrienes are synthesized following either chemical or physical stimulations, as f.ex. antigen-antibody reactions, cold temperature, etc. They lead to chronic inflammation, increased mucus production, airway hyper-responsiveness and bronchoconstriction. It is thus understandable why inhibition of 5-LO and its leukotrienes is so important in asthma, the other above mentioned conditions, and various other allergic illnesses such as allergic rhinitis and chronic urticaria. 

The LTs involvement in severe asthma, especially in aspirin induced asthma (AIA) and exercise induced asthma (EIA), is becoming well established. 5-LO inhibition has been demonstrated to significantly increase forced expiratory volume and morning and evening peak expiratory flow rate. Because inhibition of the 5-LO pathway is so highly effective in both AIA and EIA the use of LT antagonists has been recommended as meritng first line therapy status in both disorders. Patients with severe asthma and frequent asthma exacerbations may also be good candidates since there is a common association between neutrophil predominance and pronounced airway remodeling. (An additional highly significant advantage to 5-LO inhibition is that it fills the gap in anti-inflammatory coverage of inhaled glucocorticoids.)

Synthetic leukotriene inhibitors of various kinds are the first new class of asthma medications approved by the FDA in decades. They are either of the leukotriene receptor antagonist variety (Singulair®) or of the leukotriene synthesis inhibitor kind (Ziflo). In general they have been proven to be effective both as stand alone items as well as in combination with other modalities. They are prescribed mostly in persistent asthma but also in allergic rhinitis, urticaria and other allergic conditions. For exercise induced asthma they are as effective as long acting beta 2-agonist bronchodilators. 

Interestingly they have also been shown to have significant benefit in the prevention of viral induced asthma exacerbations in children.

An astonishing one third of all prescriptions written for the long term therapy of persistent asthma are for synthetic leukotriene inhibitors. This is a whopping market of several billion dollars a year even though lately concerns over significant side effects have emerged. One of the more popular ones, Zileuton®, warns of possible hepatotoxicity and requires monitoring liver enzymes before initiation of treatment, once a month for three months and every two to three months thereafter. Another one, Singular®, has been investigated recently by the FDA for a link to increased suicidal behavior. This comes on top of causing anxiousness, tremors and depressions in some users. Nevertheless, the persistent high use attests to...
the desire of the consumers to have medications that are administered more easily than inhalers and to be able to avoid the inevitable side effects of long term steroid use.

5-Lipoxygenase and other Respiratory Illnesses

Leukotrienes appear to be involved in a number of other major pathologies. Pulmonary damage in cystic fibrosis is mediated largely by leukotrienes. A reduction in pro-inflammatory mediators was deemed to substantially lessen the damaging tissue inflammation. RSV infection causes significant morbidity both in the adult but especially in the pediatric population. By the age of three most children have been infected at least once. The typical symptoms of runny nose, copious mucous discharge, cough, progression to wheezing and potential respiratory distress can lead to hospitalization in 1-2% of all cases. The illness can last for weeks and can exacerbate asthma. The mechanism for viral damage is not well understood and no specific therapy is indicated. Interestingly, however, the LT’s discharged from mast cells are significantly increased in the inflammatory discharge and a potential role for 5-LO inhibition is thus given. Leukotriene antagonists have been shown to be involved in COPD, interstitial lung disease, allergic and fungal disease, nasal polyposis, paranasal sinus disease and more. Pneumococcal otitis media is associated with the production of high levels of LT’s. The presumptive mechanism seems to be that the pneumococcus bacteria activates the 5-LO pathway by up-regulating the expression of the PLA2 and 5-LO genes. This in turn may stimulate the production of proteins leading to the formation of fluid in the middle ear. Rhinovirus infections can cause cough, wheezing and bronchial hyper-responsiveness in otherwise normal individuals. Bronchial aspirates in these patients demonstrated marked inflammation characterized by markedly enhanced expression of 5-LO pathway proteins.

Trials of 5-LO inhibitors in allergic rhinitis and sinusitis showed that 72% of participants had a positive response of symptom reduction and 50% experienced reduction of nasal polyps.

The natural inhibition of 5-LO and LT’s by AKBA

Sadly, the availability of a potent natural inhibitor of the 5-lipoxygenase (5-LO) enzyme, and its leukotriene metabolites, is little known. The premier natural 5-LO inhibitor is AKBA, acetyl-11-keto-beta-boswellia acid, the most active extractive component of the gum resin of frankincense, Boswellia serrata. Boswellia as such has been known for centuries to be a potent anti-inflammatory agent. Studies have proven its efficacy not only in asthma, allergies and environmental sensitivities but also in arthritis, colitis and various forms of cancers. (Of particular interest also are the newer findings regarding the anti-neoplastic properties of AKBA in prostate, pancreas, bladder and breast cancers). AKBA was found to specifically inhibit production of LTB4 in a dose dependent manner and with a very low IC50 of 1.5 μM. AKBA was proven to have a three times more potent inhibition of LT’s synthesis then the unpurified boswellic acids.

Significantly, AKBA exerts its anti-inflammatory effects by a multitude of mechanisms in addition to the non-redox inhibition of the 5-LO. Some examples are: impairing leukocyte infiltration; nearly complete suppression of the complement pathway; inhibition of mast cell degranulation, NFkB pathway, matrix metalloproteinases and adhesion receptors, IL-2 and IL-1β; human leukocyte elastase, matrix metalloproteinases and adhesion receptors, IL-2 and II and the activity of P-glycoprotein in leukemia cell lines; suppression of macrophage NO production thus lessening the risk of anaphylaxis and suppression of TNFα induction as well as suppression of the P-selectin up-regulation; and more.

Nutritional Support with AKBA in Asthma and Allergic Conditions

AKBA reduced passive paw anaphylaxis reaction and mast cell degranulation as shown in animal studies. A human, clinical, double blinded, placebo controlled study was done on forty patients with chronic asthma. They were given 300 mg three times daily (of a low standardization) boswellia extract for 6 weeks. 70% of patients showed improvement by the lowering of attack frequency, lowered eosinophilic counts, disappearance of dyspnea and rhonchi, and an increase in pulmonary function, such as increase of FEV1 and FVC. In the control group only 27% of patients showed improvement. In a second study 42 patients were divided into control and treatment groups and received, in the treated group, 2g/day of a boswellia extract, std. to approx. 1% (1) AKBA. Even with the extremely low AKBA dosage there was a statistically significant lowering of attacks/week; lowering of nightly attacks; increased mean value of FEV1 and lowering of mean blood eosinophilic counts as well as reduced levels of serum leukotrienes (LT C4, D4, and E4). This correlates well with the previous study which also showed reduced eosinophil counts and reduced ESR in the treated group. As the authors point out there is thus a definitive advantage to using this broader 5-LO and LT synthesis
inhibitor, rather then a leukotriene receptor antagonist, since a higher upstream inhibition also bars the formation of LTB4 and Cyst-LT’s. Cyst-LT’s are known to be up to 1,000 more potent bronchoconstricters than histamines. It clearly serves to elucidate the rationale behind the applicability of AKBA in a wide array of respiratory illnesses and other inflammatory diseases.

Dosage and Administration:

The success of boswellia extracts is all the more surprising since only poorly standardized products have been available on the general market. The component AKBA is recognized as the active anti-inflammatory principle in the boswellia and yet by far most of the formulas have only 1-3% AKBA concentration.

Better standardized AKBA can have a considerably enhanced efficacy by allowing that the necessary effective plasma levels be reached. For most adults the start up dosage is 50-60 mg three times daily of a 90% std. boswellia, ideally given at 8 hour intervals should be adequate for most patients. These calculations are based among others on the latest pharmacokinetic studies on AKBA.31 Giving AKBA with a fat containing meal will further improve absorption.32

Safety and Toxicology:

AKBA has practically no side effects. Isolated cases of headache have been noted with daily dosages in excess of several hundred mgs. There have not been any reports of the intestinal distress seen with unstandardized boswellia preparations.

Conclusion

There is convincing evidence that the inhibition of the 5-LO enzyme and the inhibition of the leukotriene synthesis play a major role in the therapy of asthma and allergic diseases. LT antagonists are currently prescribed as desirable adjunct or stand alone medications in the control of persistent respiratory airway disease. However, serious potential side effects and costs are a constant concern.

AKBA is presented here as an excellent natural alternative through its suppression of the 5-LO enzyme and its leukotriene metabolites.

References


22. Syrovets T, Gschwend JE, Büchele B, et al. Inhibition of IkB kinase activity by acetyl-boswellic acids promotes apoptosis in


*These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure, or prevent any disease.*