Advances in the Nutritional Approach to

Asthma & Allergies

*The Natural Inhibition of the 5-Lipoxygenase and Leukotrienes: AKBA- A neglected opportunity to promote health **

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. [1]

The physiologic basis involves many peptide mediators (cytokines, chemokines and others) and the leukotrienes (LT's), lipid metabolites of the pro-inflammatory 5-lipoxigenase (5-LO) enzyme. [2]

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.[3] 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. [4]

Leukotrienes are synthesized following either chemical or physical stimulations, as f.ex. antigen-antibody reactions, cold temperature, etc.[5]
They lead to chronic inflammation, increased mucous 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. [6]

The LTs involvement in severe asthma, especially in aspirin induced asthma (AIA) and exercise induced asthma (EIA), is becoming well established. [7, 8] 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 meriting first line therapy status in both disorders.[9, 10] 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. [11] (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. [6]
Interestingly they have also been shown to have significant benefit in the prevention of viral induced asthma exacerbations in children. [12]

An astonishing one third of all prescriptions written for the long term therapy of persistent asthma are for synthetic leukotriene inhibitors. [6] 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, Singulair®, 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. [13]

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.[14]

Leukotriene antagonists have been shown to be involved in COPD, interstitial lung disease, allergic and fungal disease, nasal polyposis, paranasal sinus disease and more. [15]

Pneumoccocal otitis media is associated with the production of high levels of LT's. The presumptive mechanism seems to be that the pneumoccocus bacteria activates the 5-LO pathway by up-regulating the expression of the $_c$PLA2 and 5-LO genes. This in turn may stimulate the production of proteins leading to the formation of fluid in the middle ear. [16]

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. [17]

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. [18]

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.[19, 20]

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. [3] 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.[21] (Of particular interest also are the newer findings regarding the anti-neoplastic properties of AKBA in prostate, pancreas, bladder and breast cancers). [3, 22, 23]

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. [24]

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, NFκB pathway, matrix metalloproteinases and adhesion receptors, IL-2 and IL-1β, human leukocyte elastase, topoisomerase I 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. [25-28]

Nutritional Support with AKBA in Asthma and Allergic Conditions

AKBA reduced passive paw anaphylaxis reaction and mast cell degranulation as shown in animal studies.[25]

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 FEV 1 and FVC. In the control group only 27% of patients showed improvement. [29, 30]

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%(!) 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 FEV 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

1. Cloutier MM. Considerations in culturally directed asthma disease management programs. *Disease Management and Health Outcomes*. 2008;16(2):95-105.
2. Kostikas K, Koutsokera A, Papiris S, Gourgoulianis KI, Loukides S. Exhaled breath condensate in patients with asthma: Implications for application in clinical practice. *Clinical and Experimental Allergy*. 2008;38(4):557-565.
3. Whitehouse MW, Rainsford KD. Lipoxygenase inhibition: The neglected frontier for regulating chronic inflammation and pain. *Inflammopharmacology*. 2006;14(3-4):99-102.
4. Werz O. Inhibition of 5-lipoxygenase product synthesis by natural compounds of plant origin. *Planta Medica*. 2007;73(13):1331-1357.
5. Salvi SS, Krishna MT, Sampson AP, Holgate ST. The anti-inflammatory effects of leukotriene-modifying drugs and their use in asthma. *Chest*. 2001;119(5):1533-1546.
6. Scow DT, Luttermoser GK, Dickerson KS. Leukotriene inhibitors in the treatment of allergy and asthma. *American Family Physician*. 2007;75(1):65-70.
7. Rubin P, Mollison KW. Pharmacotherapy of diseases mediated by 5-lipoxygenase pathway eicosanoids. *Prostaglandins and Other Lipid Mediators*. 2007;83(3 SPEC. ISS.):188-197.
8. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *British Medical Journal*. 2004;328(7437):434-437.
9. Dahlén B, Nizankowska E, Szczeklik A, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *American Journal of Respiratory and Critical Care Medicine*. 1998;157(4 PART I):1187-1194.
10. Kuziemski K, Slominski JM. New directions in asthma therapy - the role of 5-lipoxygenase inhibitor and the antagonists of leukotriene receptors. *Medical Science Monitor*. 1998;4(3):564-567.
11. Sur S, Crotty TB, Kephart GM, et al. Sudden-onset fatal asthma: A distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? *American Review of Respiratory Disease*. 1993;148(3):713-719.
12. Bisgaard H, Zielen S, Garcia-Garcia ML, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *American Journal of Respiratory and Critical Care Medicine*. 2005;171(4):315-322.
13. Keicher U, Koletzko B, Reinhardt D. Omega-3 fatty acids suppress the enhanced production of 5-lipoxygenase products from polymorph neutrophil granulocytes in cystic fibrosis. *European Journal of Clinical Investigation*. 1995;25(12):915-919.
14. Dimova-Yaneva DN, Helms PJ. The role of leukotrienes and eosinophil cationic protein in acute respiratory syncytial virus bronchiolitis. *Folia medica*. 2003;45(3):5-11.
15. Riccioni G, Bucciarelli T, Mancini B, Di Ilio C, D'Orazio N. Antileukotriene drugs: Clinical application, effectiveness and safety. *Current Medicinal Chemistry*. 2007;14(18):1966-1977.
16. Lin J, Vambutas A, Haruta A, Paparella MM, Giebink GS, Kim Y. Pneumococcus activation of the 5-lipoxygenase pathway and production of glycoproteins in the middle ear of rats. *Journal of Infectious Diseases*. 1999;179(5):1145-1151.
17. Seymour ML, Gilby N, Bardin PG, et al. Rhinovirus infection increases 5-lipoxygenase and cyclooxygenase-2 in bronchial biopsy specimens from nonatopic subjects. *Journal of Infectious Diseases*. 2002;185(4):540-544.
18. Steinke JW, Borish L. Leukotriene receptors in rhinitis and sinusitis. *Current Allergy and Asthma Reports*. 2004;4(3):217-223.
19. Safayhi H, Sailer E-, Ammon HPT. Mechanism of 5-lipoxygenase inhibition by acetyl-11-keto-β-boswellic acid. *Molecular Pharmacology*. 1995;47(6):1212-1216.
20. Gupta I, Mahajan A, Gupta V. Salai guggal-boswellia serrata leukotriene antagonist & inhibitor: Clinical applications. *JK Science*. 2002;4(4):169-173.
21. Ammon HPT. Boswellic acids (compounds of francincense) as active principles for the treatment of chronic inflammatory diseases. *Wiener Medizinische Wochenschrift*. 2002;152(15-16):373-378.
22. Syrovets T, Gschwend JE, Büchele B, et al. Inhibition of IκB kinase activity by acetyl-boswellic acids promotes apoptosis in

androgen-independent PC-3 prostate cancer cells in vitro and in vivo. *Journal of Biological Chemistry*. 2005;280(7):6170-6180.
23. Zhao W, Entschladen F, Liu H, et al. Boswellic acid acetate induces differentiation and apoptosis in highly metastatic melanoma and fibrosarcoma cells. *Cancer Detection and Prevention*. 2003;27(1):67-75.
24. Wildfeuer A, Neu IS, Safayhi H, et al. Effects of boswellic acids extracted from a herbal medicine on the biosynthesis of leukotrienes and the course of experimental autoimmune encephalomyelitis. *Arzneimittel-Forschung/Drug Research*. 1998;48(6):668-674.
25. Poeckel D, Werz O. Boswellic acids: Biological actions and molecular targets. *Current Medicinal Chemistry*. 2006;13(28):3359-3369.
26. Gayathri B, Manjula N, Vinaykumar KS, Lakshmi BS, Balakrishnan A. Pure compound from boswellia serrata extract exhibits anti-inflammatory property in human PBMCs and mouse macrophages through inhibition of TNFα, IL-1β, NO and MAP kinases. *International Immunopharmacology*. 2007;7(4):473-482.
27. Takada Y, Ichikawa H, Badmaev V, Aggarwal BB. Acetyl-11-keto-β-boswellic acid potentiates apoptosis, inhibits invasion, and abolishes osteoclastogenesis by suppressing NF-κB and NF-κB-regulated gene expression. *Journal of Immunology*. 2006;176(5):3127-3140.
28. Knaus U, Wagner H. Effects of boswellic acid of boswellia serrata and other triterpenic acids on the complement system. *Phytomedicine*. 1996;3(1):77-81.
29. Gupta I, Gupta V, Parihar A, et al. Effects of boswellia serrata gum resin in patients with bronchial asthma: Results of a double-blind, placebo-controlled, 6-week clinical study. *European journal of medical research*. 1998;3(11):511-514.
30. Cuaz-Pérolin C, Billiet L, Baugé E, et al. Antiinflammatory and antiatherogenic effects of the NF-κB inhibitor acetyl-11-keto-β-boswellic acid in LPS-challenged ApoE-/- mice. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2008;28(2):272-277.
31. Sharma S, Thawani V, Hingorani L, Shrivastava M, Bhate VR, Khiyani R. Pharmacokinetics study of 11-keto β-boswellic acid. *Phytomedicine*. 2004;11(2-3):255-260.
32. Sterk V, Büchele B, Simmet T. Effect of food intake on the bioavailability of boswellic acids from a herbal preparation in healthy volunteers. *Planta Medica*. 2004;70(12):1155-1160.

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