

Local anaesthetic medication for the treatment of asthma

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It is presumed that drugs able to prevent bronchial spasm and/or inflammation may have therapeutic potential to control asthma symptoms. The local anaesthetic lidocaine has recently received increased attention as an alternative form of treatment for asthmatic patients. This paper reviews the major findings on the topic and summarizes the putative mechanisms underlying the airway effects of local anaesthetic agents. We think that lidocaine extends the spectrum of options in asthma therapy, probably by counteracting both spasmogenic and inflammatory stimuli in the bronchial airways. The possibility of development of new anti-asthma compounds based on the synthesis of lidocaine derivatives is also on the horizon.

Key words: local anaesthetic - lidocaine - inflammation - asthma

Asthma is a chronic inflammation of the lung airways caused by environmental factors in genetically predisposed individuals. Episodic airway obstruction and reversible bronchial hyperresponsiveness to non specific irritants are the major symptoms of the disease, whose prevalence has remarkably increased worldwide over the past two decades despite important advances in therapy (Busse & Rosenwasser 2003, Kay 2003, Barnes 2004). Among the potential reasons for causing the increase in asthma prevalence are changes in the environment due to improved hygiene (Umetsu et al. 2002), and lack of adherence to therapy by patients, as well as by physicians who do not always follow guidelines on the established anti-inflammatory therapy in asthma (Apter & Szeffler 2004, Barnes 2004). Most of asthmatic patients are atopic, i.e., they have a genetic predisposition to produce high levels of immunoglobulin (Ig) E against environmental antigens and to mount an allergic inflammatory response. Inflammation is indeed central in the pathogenesis of asthma. The antigen activates mast cells and T_H2 cells in the airways, which in turn release preformed and neosynthesized proinflammatory substances, including vasoactive amines, lipid mediators and interleukins 4, 5, 9 and 13, deeply implicated in the early and late phase reactions (Barnes 2004). An interesting aspect of the asthma pathogenesis is the strong T_H2 response in the airway mucosa resulting in accumulation of a large number of eosinophils in tissue locations (Umetsu et al. 2002). Experimental and clinical observations have linked eosinophil derivatives with asthma dysfunctions such as epithelial cell damage and airway hyperresponsiveness. Other pivotal pathological changes that appear to be associated with eosinophils include subepithelial fibrosis, increased airway smooth

muscle mass, angiogenesis and increased mucus production caused by goblet-cell and submucosal-gland hyperplasia (Busse & Rosenwasser 2003, Payne et al. 2003, Barnes 2004). Therefore it is presumed that drugs able to prevent recruitment and/or activation of mast cells, T_H2 cells and/or eosinophils may have therapeutic potential to control asthma.

Current treatment strategies

It is a clinical consensus that every patient with persistent asthma, regardless of disease severity, should use a daily controller medication (Redding & Stoloff 2004). The therapeutic arsenal for asthma is relatively ample, basically consisting of two classes of drugs: (i) the bronchodilators, including inhaled long-acting β_2 -agonists (salmeterol and formoterol), inhaled anticholinergics (ipratropium bromide and tiotropium bromide) and theophylline (slow-release theophylline and aminophylline); and (ii) the anti-inflammatory agents, including inhaled glucocorticosteroids (budesonide, fluticasone propionate, beclomethasone dipropionate and mometasone), anti-leukotrienes (montelukast, pranlukast and zafirlukast), cromones (sodium cromoglycate and nedocromil sodium) and anti-IgE (omalizumab). Inhaled glucocorticosteroids is by far the most effective treatment available for the control of mild, moderate and severe asthma (Barnes 2004). They inhibit the transcription of interleukins such as IL-4, IL-5, IL-13 and β chemokines, and it is likely that switching off these key interleukins strongly contributes to the glucocorticosteroid efficacy in controlling asthma (Caramori & Adcock 2003, Barnes 2004). However, concerns regarding its long-term administration and steroid-resistance have provided pivotal motivation for discovering new asthma therapies. Treatment with combination inhalers containing a glucocorticosteroid and a long-acting β_2 -agonist is becoming now the gold standard therapy for asthma. The β_2 -agonist acts by binding to specific receptors expressed along the surface of the bronchial smooth muscle cells. This agonist binding activates a complex intracellular cascade of events that elevates cyclic AMP levels, leading to decrease in intracellular cal-

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cium, smooth muscle relaxation and bronchodilation (Shore & Drazen 2003). Despite being the most effective way of opening the airways and providing relief in the event of a severe asthma attack, the use of β_2 -agonist as monotherapy is no longer recommended, since a number of studies have demonstrated that asthmatics who are chronically treated with bronchodilating β -agonists alone sometimes experience a worsening of their condition (Lazarus et al. 2001, Sears 2002, Ellis 2003).

Local anaesthetics and allergic inflammation

Local anaesthetics block voltage-gated sodium channels in peripheral nerves causing reversible inhibition of impulse transmission and blockade of neuronal function in a circumscribed area of the body (Tetzlaff 2000). Lidocaine is largely used in clinic as a short-acting local anaesthetic and antiarrhythmic agent (Tetzlaff 2000). Interestingly, lidocaine also inhibits the function of non-excitable cells, particularly inflammatory cells, such as neutrophils, eosinophils, macrophages, mast cells and T_H2 cells, raising the promising possibility of alternative clinical applications on the control of chronic inflammatory diseases, including asthma (Hunt et al. 1996, Ohnishi et al. 1996, Okada et al. 1998, Hollmann & Durieux 2000, Tanaka et al. 2002).

Ohnishi et al. (1996) incidentally discovered that concentrations of lidocaine as high as 10 mM could be detected in the bronchoalveolar lavage fluids recovered from asthma patients subjected to bronchoscopy under lidocaine topical anesthesia, and that such an effluent was a strong inhibitor of eosinophil viability *in vitro*. It was further demonstrated that lidocaine preferentially inhibited survival and activation of human eosinophils stimulated by cytokines, such as IL-5, IL-3 and GM-CSF, in a concentration dependent-manner ($IC_{50} \cong 110 \mu M$). Such an effect did not seem to be accounted for by the blockade of sodium channels and could not be explained by an action on either cytokine receptor expression or cytokine-induced protein tyrosine phosphorylation (Ohnishi et al. 1996, Okada et al. 1998). Of note, these effects were not due to nonspecific cytotoxicity either, since (i) lidocaine inhibited eosinophil survival by causing apoptosis rather than necrosis; (ii) the mechanism of cell death was clearly time-dependent, requiring at least 24 h of exposure to lidocaine; and (iii) eosinophil survival and superoxide production induced by IgG, PAF or PMA were not modified by lidocaine, indicating that this local anaesthetic was not a general inhibitor of eosinophils (Okada et al. 1998). Other local anaesthetic agents such as tetracaine, dibucaine, benoxinate, procaine and bupivacaine also inhibited IL-5-evoked eosinophil survival *in vitro* but their pro-apoptotic performance did not reflect their respective anaesthetic potencies (Okada et al. 1998). It is well established that lidocaine at high concentrations can also block K^+ channels (Illek et al. 1992, Yoneda et al. 1993, Olschewski et al. 1996). Therefore, Bankers-Fulbright and coworkers studied the effect of three classes of K^+ channel blockers and reported that the sulfonylureas including glyburide, tolbutamide, and glipizide (one class of K^+ channel blockers) were the only ones able to mimic the effect of lidocaine on the inhibition

of cytokine-mediated eosinophil survival and superoxide production *in vitro*. Similar functions of sulfonylureas and lidocaine suggested that these agents might be working through a similar mechanism – blockade of K^+ channel – in order to evoke apoptosis of eosinophils (Bankers-Fulbright et al. 1998).

Clinical findings with lidocaine treatment

Since eosinophils are expected to play a pivotal role in the pathogenesis of asthma, studies on the putative beneficial effect of nebulized lidocaine in adults and children with asthma have been carried out. Administration of nebulized lidocaine four times daily in 20 adult patients with severe asthma, who had side effects of exogenous hypercortisolism, allowed for the complete elimination of steroid treatment in 13 of 20 patients (Hunt et al. 1996). A pilot study involving six pediatric patients with severe asthma added support to the interpretation that nebulized lidocaine in doses of 40 to 100 mg (0.8 to 2.5 mg/kg/dose) four times daily had indeed steroid-sparing actions (Decco et al. 1999). The results indicated that during a mean of 11.2 months of therapy (range 7 to 16 months) 5 of the 6 patients completely discontinued their oral steroids within an average time of 3.4 months. Similar findings were also reported by Rosario and coworkers, while treating a 12-year-old severe steroid-dependent asthmatic with nebulized lidocaine (Rosario et al. 2000). The side effects observed in these patients were limited to transient oropharyngeal anaesthesia and bitter taste.

In a more recent evaluation, Hunt et al. (2004) reported the results of a placebo-controlled 8-week study in 50 adult subjects with mild-to-moderate asthma. The patients were randomized (25 receiving lidocaine and 25 receiving placebo) and their inhaled steroids were progressively withdrawn over 4 weeks. The analysis revealed a significant benefit for lidocaine treatment (4%, 100 mg) four times daily compared with placebo (saline), particularly concerning FEV_1 symptom scores, night-time awakening, β -agonist use, and blood eosinophils. There were no serious adverse effects in either group, but 15 subjects (9 receiving lidocaine and 6 receiving placebo) did not complete the full 8-week trial. Reasons for withdrawal included worsening asthma symptoms (4 receiving lidocaine and 6 receiving placebo) and treatment intolerance (4 receiving lidocaine). From the latter group, one had a cold feeling in the throat, one reported a feeling of claustrophobia, one had cough, one had wheezing after lidocaine, and only the last presented a 16% decrease in FEV_1 (Hunt et al. 2004). In line with previous studies, Harrison and Tattersfield (1998) reported that patients with mild-to-moderate asthma did not bronchoconstrict significantly more than to 0.9% NaCl (saline). However, the possibility that patients with more severe asthma might have more marked bronchoconstriction could not be discarded. It should be emphasized that at least five single-dose studies have demonstrated bronchoconstriction following lidocaine inhalation (Miller & Awe 1975, Weiss & Patwardhan 1977, Fish & Peterman 1979, McAlpine & Thomson 1989, Bulut et al. 1996), indicating that the putative use of lidocaine for the treatment of asthma should be investigated with caution.

Effects of lidocaine on the airways

The effects of lidocaine on the airways are heterogeneous and complex. It is well established that in patients with asthma, airway instrumentation such as endotracheal intubations can cause life-threatening bronchospasm (Caplan et al. 1990), and that lidocaine when administered either intravenously or as an aerosol significantly attenuates that sort of reflex bronchoconstriction (Groeben et al. 1999). Inhaled lidocaine can also diminish the response to an inhalational provocation with hyperosmolar saline solution (Makker & Holgate 1993), histamine (Groeben et al. 2000), water (Loehning et al. 1976) and under conditions of exercise-induced asthma (Enright et al. 1980). On the other hand, a number of studies has pointed out that aerosolization of lidocaine itself produces an initial bronchoconstriction in a significant proportion of patients with asthma and hyperirritable airways, as attested by reduction in FEV₁ and other respiratory parameters (Miller & Awe 1975, Weiss & Patwardhan 1977, Fish & Peterman 1979, McAlpine & Thomson 1989, Bulut et al. 1996). Bronchoconstriction following lidocaine inhalation was also assessed using high-resolution computed tomography in Basenji-Greyhound dogs with hyperreactive airways (Bulut et al. 1996). Analyzing airway caliber before and after the administration of lidocaine aerosol, a 27% decrease from baseline was observed. Intravenous administration of lidocaine did no cause airway changes but clearly prevented initial bronchoconstriction evoked by aerosolized lidocaine in these animals (Bulut et al. 1996). In asthmatics, bronchoconstriction caused by lidocaine aerosol was clearly reversed with aerosolized atropine, isoproterenol (Fish & Peterman 1979) or salbutamol (Harrison & Tattersfield 1998, Groeben et al. 2000). Moreover, combined lidocaine and salbutamol inhalation protected against histamine-evoked bronchoconstriction in mild asthmatics to a much greater extent than pretreatment with either drug alone (Groeben et al. 2000). These findings pointed out that in the case of using lidocaine for the control of asthma, the treatment should be accompanied by a β -adrenergic aerosol. The combined inhalation might prevent the putative irritant effects of lidocaine, and yield an improved bronchial hyperreactivity blockade due to the synergistic interaction of these substances (Harrison & Tattersfield 1998, Groeben et al. 2000).

Several mechanisms may explain the attenuation of bronchoconstriction by lidocaine but none of them has been definitively proven in vivo. Aerosolized lidocaine is theoretically capable of blocking neurogenic reflexes in the lung, and the neural blockade of vagal reflex pathways may indeed explain its ability to attenuate the response to different stimuli evoking bronchoconstriction (Enright et al. 1980, Makker & Holgate 1993, Groeben et al. 2000). Actually, the lidocaine protective effect occurs at plasma concentrations much lower than those required for intravenous lidocaine to impair airway bronchoconstriction, in line with the interpretation that this effect is accounted for by topical airway anaesthesia. If this is the case, the protective effect should be presumably independent of the local anaesthetic used. While trying to clarify this point, Groeben et al. (2001) tested three local

anaesthetics with distinct anaesthetic potencies (Groeben et al. 2001). They reported that inhaled lidocaine and ropivacaine significantly attenuated histamine-evoked bronchoconstriction whereas dyclonine, despite its longer lasting and more intense local anaesthesia, did not. In addition, inhaled dyclonine was by far the most irritant for the airways (Groeben et al. 2001). These findings were double-folded illustrative. First because they made clear that the protective effect of lidocaine on bronchospasm might indeed be dissociated from its local anaesthetic activity. Second because they raised the possibility that lung anaesthesia might indeed account for the airway irritant properties of this class of agents.

Lidocaine effects on bronchial hyperreactivity might also be accounted for by a direct relaxant effect on airway smooth muscle (Downes & Loehning 1977, Weiss et al. 1978, Okumura & Denborough 1980, Kai et al. 1993). Kai et al. (1993) reported that lidocaine had direct spasmolytic properties by inhibition of calcium influx and release of stored calcium. Accordingly, circulating concentrations of lidocaine of more than 100 μ M had marked airway relaxant effects (Kai et al. 1993).

Conclusion

There is renewed interest in lidocaine for treatment of atopic asthma. Inhaled lidocaine has glucocorticosteroid-sparing properties in atopic asthmatics as demonstrated by significant reduction in symptoms, bronchodilator use and blood eosinophilia. Lidocaine has marked effects in several settings beyond neuronal blockade, and some of these alternative actions may also be beneficial to asthma control. There is clear evidence for anti-inflammatory and spasmolytic properties. Inhibitory effects of lidocaine on eosinophil survival and activation, mast cell secretor function, as well as CD4⁺ T-cell proliferation and cytokine generation, seem to be most important. Lidocaine also significantly attenuates the response to direct stimulation of airway smooth fibers in a mechanism closely associated with blockade of calcium influx. On the other hand, inhalation of lidocaine initially evokes a significant decrease in FEV₁ in the majority of asthmatic volunteers, an effect sensitive to β_2 -agonist pretreatment. As in the case of glucocorticosteroid therapy, treatment with combination inhalers, containing lidocaine and a long-acting β_2 -agonist, may turn out to be the safer and more reliable alternative. In addition, since airway anaesthesia alone does not necessarily attenuate bronchial hyperreactivity, further research should be directed to (i) clarify the mode of action of lidocaine on both inflammation and airway obstruction and (ii) structure-activity studies, particularly concerning non anaesthetic lidocaine analogues.

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