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Lidocaine -An Old Drug for New Indication

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ABSTRACT
Lidocaine, a known local anaesthetic agent has been demonstrated to possess significant efficacy in managing asthma due to its anti inflammatory and direct spasmolytic actions. Various clinical studies have been conducted to assess the role of Lidocaine in asthma management with convincing results showing reduction in steroid dose or discontinuation of steroid therapy associated with improvement in quality of life, marking this old drug as a novel efficacious, fast and safe addition in armamentarium of anti asthma drugs. Inhaled Lidocaine when given alone causes biphasic effect on bronchi with initial bronchoconstriction followed by bronchodilatation. Treatment with combination inhalers, containing Lidocaine and a long-acting β_2- agonist seems the safer and more reliable alternative to minimise adverse effects of initial reflex bronchoconstriction caused by inhaled Lidocaine. This review elucidates the available evidence on efficacy and safety of inhaled Lidocaine after analyzing various clinical studies. Searches of pubmed, Cochrane database, Medscape, Google and clinicaltrial.org were made for terms like Lidocaine and bronchial asthma.

Keywords: Lidocaine, bronchial asthma, bronchial hyper responsiveness.

INTRODUCTION

Bronchial asthma, a chronic inflammatory disease of respiratory tract is characterised by reversible bronchial hyper responsiveness and episodic airway obstruction. [1] Asthma is a major cause of morbidity and mortality among each age group. Globally, a rising trend is being witnessed in asthma prevalence resulting in enhanced healthcare costs and huge economic burden despite advancement in diagnostic techniques and therapeutics. Proliferation of allergens, increase in sensitisation, and rising environmental factors like passive smoking are the major factors associated with increased prevalence of asthma. [2]

Pathophysiology of asthma includes chronic inflammation as the major underlying mechanism. On exposure of allergen, mast cells and T Helper 2(TH2) cells are stimulated leading to release of vasoactive amines, prostaglandins, leukotriene, lymphokines, interleukins, tissue necrosis factor, granulocyte monocyte colony stimulating factor, endothelins, and nitric oxide. These inflammatory mediators are responsible for bronchoconstriction, plasma exudation, activation of neural mechanisms and mucus secretion. Eosinophils thought to be beneficial in past for asthma patients have been demonstrated to possess damaging action on airways as eosinophils infiltration develops airway hyper-responsiveness and epithelial cell damage due to release of oxygen dependent free radicals. [3] Besides conventional bronchodilator and corticosteroid therapy, drugs hindering eosinophilic recruitment, migration, activation and survival have the potential in therapeutics of asthma.

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Current status of asthma management

Management of asthma primarily aims at suppressing inflammation and hence decrease in airway hyper responsiveness and obstruction. Conventional management of asthma include relievers and controllers. Inhaled short acting β_2-agonists (Salbutamol, Fenoterol and Terbutaline) are the primary medications recommended for relieving the symptoms of acute attack of asthma. Theophylline and Anticholinergics agents (Ipratropium bromide, Tiotropium bromide) possess secondary place in asthma management. Controller drugs include inhaled glucocorticoids (Budesonide Beclomethasone, Fluticasone propionate), inhaled long acting β_2 agonists (Formeterol, Salmeterol) and leukotriene antagonists (Monteleukast, Pranleukast) along with cromones (Sodium chromoglycate and Nedocromil sodium) and anti IgE antibody (omalizumab). [4-6]

None of the existing treatments for asthma is curative, and symptoms return soon after treatment is stopped. Also their use is associated with adverse effects. Use of short acting β_2 agonists is associated with common adverse effects like tachycardia, palpitations, fine tremors and agitation. Long acting substitutes exhibit tolerance to their action if repeatedly used. Cromones activity is brief, so they must be given four times daily leading to decrease in patient

compliance. [5] Monteleukast therapy leads to headache and abdominal symptoms as common side effects. [6] Although Theophylline is inexpensive, monitoring its plasma concentrations is both expensive and inconvenient because rise in plasma concentration above 25mg/dl can lead to seizures. [5]

Inhaled steroids remain the most potent and consistently effective therapy for mild, moderate and severe asthma. Chronic use of inhaled steroids associated with oral thrush and hoarseness of voice whereas use of oral steroids in severe asthma leads to severe systemic adverse effects like truncal obesity, hypertension, glaucoma, glucose intolerance, acceleration of cataract formation, bone mineral loss, psychological effects, adrenal suppression and growth suppression in children. [7] Hence safety issues with steroid use demands for a novel substitute which is equally efficacious and safe too. The quest for searching new remedies for steroid dependent asthma has been going on since few years. Application of molecular and cell biology and the discovery of new targeted pharmacological therapies has remarkably refined the asthma management over the last few years. [5] But unfortunately no new drug has been able to achieve significant therapeutic success and to date no satisfactory substitute for systemic oral corticosteroid therapy for asthma has been developed, identified or received regulatory approval. In wake of fact that topical Lidocaine, a well known local anaesthetic, is a useful drug option to reduce airway reactivity prior to bronchoscopy as demonstrated in studies, it has also been recommended as an aerosol for intractable cough and asthmatic tussive attacks. [8-9] Research demonstrating role of topical Lidocaine in management of asthma has given satisfactory results showing its promising role in asthma, marking this old drug as a novel efficacious, fast and safe addition in armamentarium of anti asthma drugs. [10]

LIDOCAINE

Lidocaine is an amide derivative which is commonly used as local anaesthetic and antiarrhythmic drug. Off the label use of Lidocaine in bronchial asthma has grabbed attention in recent past for the treatment of corticosteroid dependent asthma. It not only possesses corticosteroid sparing effects but also substantially improves the clinical outcome. It acts by attenuating and blocking the afferent and efferent nerve conduction of autonomic nerve fibres and reflexes such as cough and bronchial reflex. [11] Attenuation of bronchial hyper responsiveness has been explained by blockade of neurogenic reflexes in lungs and neural blockade of vagal reflex pathways. [12] Both anti inflammatory and spasmolytic action of lignocaine are found to be associated with role of lignocaine in bronchial asthma. [4] Mechanism behind its anti inflammatory role in bronchial asthma has been demonstrated to be inhibition of the function of inflammatory cells like mast cells, TH2 cells, macrophages, neutrophils and eosinophils. *In-vitro* studies suggest that after diffusion through membrane, it blocks the ability of cytokines such as interleukin-5 (IL-5) to prolong the survival of eosinophils in concentration and time dependent manner resulting in eosinophils apoptosis 24 hours after exposure. [4, 13] Blockade of potassium channels is another mechanism by which apoptosis of eosinophils has been found to be enhanced. [14] Lidocaine possesses synergistic effect with corticosteroids as degree of inhibition of eosinophilic survival is more with sum of corticosteroids and Lidocaine as compared to Lidocaine alone. [13] It boosts the therapeutic effectiveness of corticosteroids in asthma, sparing their use thus promising its substantial role in steroid dependent asthma. [4, 13]

Reduction in bronchial hyper responsiveness has also been attributed to direct relaxant effect of Lidocaine on respiratory smooth muscles. [4, 15-17] Spasmolytic effect of Lignocaine is produced due to blockade of calcium channels resulting in decrease in calcium influx and release from stores. [4]

Safety profile of inhaled Lidocaine

Safe dose range of nebulised Lidocaine is 100-200 mg /dose with maximum tolerated dose of 600mg. [18] Side effect profile of inhaled Lignocaine is minimal. It is advised to avoid eating or drinking one hour before and two hour after lidocaine inhalation otherwise numbness of mouth and throat can occur. [13] Toxicity of Lignocaine occurs at plasma concentration of >5 mg/l which is a matter of serious concern as it cause tremors, hallucinations and even cardiac arrest. It is imperative to use Lidocaine in safe dose range weighing the risk benefit ratio and closely monitoring early signs of toxicity keeping in mind its serious toxicity. Caution is recommended for use of Lidocaine in hepatic disease as reduced elimination of the drug again predisposes to toxicity. [18]

Bimodal action of inhaled Lidocaine

Inhaled Lidocaine has been demonstrated to possess bimodal action as it causes initial airway irritation leading to reflex bronchoconstriction in 10% of patients showing decreased airflow in first 10 minutes followed by bronchodilatation. [13] Initial bronchoconstriction component is independent of histamine responsiveness and clinical severity of asthma. [19] Hence it is recommended to give first treatment under observation. [13] Pre-treatment with inhaled β_2 agonist and use of <2mg/kg dose of 4% Lidocaine are recommended for prevention of preceded mild bronchoconstriction. [11, 13, 20-21] Pre-treatment with aerosolized atropine has also been shown to revert reflex initial bronchoconstriction in a study. [20] An animal study has also demonstrated beneficial effect of intravenous bolus injection of Lidocaine in prevention of inhaled Lidocaine induced bronchoconstriction. [22] Though beneficial in asthma, Lidocaine alone is not preferred to be given to asthma patients. To combat bronchoconstrictor effects, use of inhaled Lidocaine and inhaled β_2 agonist together is the safe and more reliable option [23] (Table 1).

Clinical trials assessing the efficacy of Lidocaine in asthma

Various clinical studies have been conducted to assess the role of Lidocaine in asthma management and the results were convincing in favour of Lidocaine use in corticosteroid dependent asthma in all age groups. Use of Lidocaine resulted in reduction in steroid dose or discontinuation of steroid therapy in statistically significant proportion of patient population [24-26] associated with improvement in quality of life due to minimisation of steroidal adverse effects. [27] Chong, et al demonstrated statistically significant improvement in cough severity score in COPD patients with intractable cough, though its efficacy was found be similar to bronchodilator therapy. [28] Results of a single study demonstrated no significant improvement in pulmonary function and FEV1 after 12 weeks as compared to placebo. Also study results showed no corticosteroid sparing effects after 20 weeks. [29] Another study showed statistically significant difference in FEV1 and Peak Expiratory Flow (PEF) at 30 min after inhalation irrespective of sensitivity to

Table 1: Studies demonstrating initial bronchoconstrictor effect of Lidocaine and its prevention

Study	Study details	Study results
Fish, *et al* [20]	N=8 asthmatic patients • Inhaled 2cm^3 of Lidocaine (4%). • Pre-treatment with either aerosolized isoproterenol, or aerosolized atropine or intramuscular atropine	• Lidocaine alone- 23.4 +/- (SE) 4.8% fall in FEV1 64.1 +/-(SE)3.8% fall in SGaw ($p < 0.001$). • Reversal seen with aerosolized atropine and isoproterenol.
Bulut, *et al* [22]	Dogs • Pre-treatment with either intravenous or aerosol Lidocaine followed by histamine aerosol challenge. On separate days • Pre-treatment with intravenous Lidocaine, followed by aerosol Lidocaine at similar doses.	• Histamine alone- Decrease in the airway area by 32 +/- 3%. • Intravenous and inhaled Lidocaine- Significant inhibition of histamine-induced bronchoconstriction with no significant difference between two routes. • Inhaled Lidocaine at dose inhibiting histamine bronchoconstriction-decrease in baseline airway area by 27 +/- 3% ($P < 0.01$), • Intravenous Lidocaine prevented Lidocaine aerosol-induced bronchoconstriction • With the combination of intravenous and aerosol Lidocaine - Significant dilatation of the airways by 20 +/- 5% ($P < 0.01$) compared with control.
Harrison, *et al* [23]	N=20 patients with mild to moderate asthma Single doses of inhaled • Lignocaine 40 and • Lignocaine 160 mg • Saline	• Initial fall in (forced expiratory volume in one second)FEV1[mean maximum change] Saline / Lignocaine 40 /160 mg 0.13/ 0.19 / 0.231 respectively ($P = 0.2$). • No fall in FEV1 following Salbutamol pre-treatment

Table 2: Clinical studies demonstrating role of Lignocaine in bronchial asthma

Study	Study design	Patient details	Treatment details	Study results
Hunt, *et al*, 1996[25]	Open label study	N=20 Patients with severe asthma on corticosteroid(CS) therapy	Lidocaine inhalation 40-160mg q.i.d	Discontinuation of CS-13 patients Decrease in dose of CS -4 patients No apparent response - 3 patients
Decco, *et al* 1999[24]	Open label Paediatric study	N=6 Asthma patients on Oral Corticosteroid (OCS) therapy	• Nebulised Lidocaine 0.8-2.5 mg/kg/day t.i.d or q.i.d for mean duration of 11.2 months[7-16 months]	5 out of 6 children discontinued OCS in mean time of 3.4 months[1-7 months]
Groeben, *et al* 1999[12]	Randomised Placebo controlled Double blind	N=15 volunteers showing a decrease in FEV1 greater than 20% of baseline (PC20) in response to histamine inhalation.	On 3 different days volunteers given pre-treatment with either 1. Inhalational Lidocaine 2. Intravenous Lidocaine 3. Placebo Blood samples drawn for lidocaine plasma concentration	Baseline PC20 was 6.4± 1.1 mg/ ml Inhaled Lidocaine versus intravenous lidocaine • Increase in PC20 [mg/ml] 14.8±3.5 versus14.2±2.5 ($p< 0.0007$). • Peak plasma lidocaine concentrations at the end of challenges were 0.7±0.1 mg/ml Versus 2.2± 0.1mg/ml • Initial decrease of FEV1 greater than 5% following lidocaine inhalation in 7 subjects
Hunt, *et al* 2004[26]	Randomised Placebo controlled Double blind study	N=50[25/25] Mild/moderate asthma on Inhaled Corticosteroids(ICS) b.d for 2 months	1. Lidocaine 4% 100mg q.i.d 2. Placebo [normal saline] q.i.d For 8 weeks	Dose of ICS decreased by half in each week for 3 weeks and then ICS stopped.
de Paz, *et al* 2005[27]	Case report	Female patient with Steroid dependent asthma for 15 years having adverse drug reactions with steroids.	• Lidocaine nebulised -Initial dose 2%solution t.d.s Maximum dose -80mg	Reduction in steroid adverse effects Improvement in quality of life
Chong, *et al* 2005[28]	Prospective Randomised Double blind Comparison study	N=127 COPD patients with intractable cough	1. 4 ml Nebulised lidocaine 1mg/kg[n=62] 2. 4ml Nebulised bronchodilator [n=65]	Cough severity score Before treatment versus after treatment • Lidocaine group-8/3[$p<0.01$] • Bronchodilator group-8/3[$p<0.01$] No statistically significant difference between two groups[$p=0.44$]
Adamzik, *et al* 2007[31]	Randomised Placebo controlled Double blind study	N=30 Patients with asthma [on regular treatment till the day of surgery] undergoing intubation anaesthetised with etomidate, fentanyl and rocuronium.	1. 1% Lidocaine 2mg/kg intravenous for 5 minutes then 3 mg/kg/hr for ten minutes 2. Placebo-normal saline	Lidocaine group -Decrease in airway resistance by 26% Placebo group -increase in airway resistance by 38% [$P<0.004$]
Abuan, *et al* 2010[29]	Randomised Placebo controlled Double blind study	Study 1--- N=154 Patients with mild/moderate asthma not on OCS Study 2---- N=114	Lidocaine solution 40 mg twice daily inhaled • Study 1- 12 weeks study • Study 2-	Study1- No improvement in asthma symptoms scores, FEV1 ,morning and evening peak expiratory flow, proportions of patients with asthma instability, quality of life score as compared to placebo after 12

		Patients with severe asthma on OCS since 6 months	20 weeks study	weeks Study 2-No corticosteroid sparing effects after 20 weeks
Zuming, *et al* 2011[30]	Randomised Placebo controlled Double blind study	N=36 Patients of bronchial asthma on regular treatment Steroid Resistant Asthma [SRA] A1/A2-9/9 Steroid Sensitive Asthma [SSA] B1/B2-9/9	A1-Nebulise normal saline A2-Nebulised Lidocaine B1- Nebulise normal saline B2- Nebulised Lidocaine	Statistically significant difference in FEV1 and PEF at 30 min after inhalation irrespective of steroid sensitivity. Lidocaine group/normal saline • FEV1 69.00±3.52 Versus 74.22±3.28 (P<0.05) • PEF 60.66±4.15 versus 65.16±4.50(P<0.05)

corticosteroids in Lidocaine group as compared to normal saline [30] (Table 2). Despite one study results not witnessing any significant improvement in asthma patients and no corticosteroid sparing effect, Lidocaine seems an efficacious and safe steroid substitute because majority of data supports the use of Lidocaine in patients of asthma on corticosteroid therapy.

In conclusion, keeping in mind the fact that long term use of steroids is associated with serious adverse effects and there is lack of any such treatment strategy possessing steroid sparing effects, lidocaine seems a novel promising agent for it's off the label use in steroid dependent asthma. Inhaled lidocaine through its anti inflammatory and direct smooth muscle relaxant action possesses a substantial role in the treatment of steroid dependent asthma. Because lidocaine toxicity is a concern, it is important to carefully weigh the risk and benefit for each patient. Treatment with combination inhalers, containing lidocaine and a long-acting β2- agonist, may turn out to be the safer and more reliable alternative to minimise adverse effects of initial reflex bronchoconstriction caused by inhaled Lidocaine.

REFERENCES

1. Bara, Ozier A, Lara TD, Marthan R, Berger RP. Pathophysiology of bronchial smooth muscle remodelling in asthma. Eur Respir J 2010; 36:1174-84.
2. Neri M, Spanevello A. Chronic bronchial asthma from challenge to treatment: epidemiology and social impact. Thorax 2000; 55(Suppl 2):S57-S58.
3. Barnes PJ. Pathophysiology of asthma. Br J Clin Pharmacol 1996;42:3-10
4. Siqueira RA, Costa JCS, Cordeiro RSB, Serra MF,e Silva PMR, Martins MA. Local anaesthetic medication for the treatment of asthma. Mem Inst Oswaldo Cruz, Rio de Janeiro 2005; 100:161-65.
5. Barnes PJ. New drugs for asthma. Nat Rev Drug Discov 2004; 3: 831-44.
6. Ukena D, Fishman L, Niebling WB. Bronchial Asthma: Diagnosis and Long-Term Treatment in Adults. Dtsch Arztebl Int 2008; 105(21): 385-94.
7. Schimmer BP, Parker KL. Goodman and Gilmann's: The Pharmacological Basis of Therapeutics, Ed 12, New York, 2011, pp.1103-28.
8. Trochtenberg S. Nebulized lidocaine in the treatment of refractory cough. Chest 1994 May; 105(5):1592-3.
9. Sanders RV, Kirkpatrick MB. Prolonged suppression of cough after inhalation of lidocaine in a patient with sarcoid. JAMA 1984; 252(17):2456-7.
10. Ashburn TT, Thor KB .Drug Repositioning: Identifying and Developing New Uses for Existing Drugs. Nature Reviews2004; 3:673-83.
11. Burburan SM, Xisto DG, Rocco PRM. Anaesthetic management in asthma. Minerva Anestesiol 2007; 73:357-65.
12. Groeben H, Silvanus MT, Beste M, Peters J. Both intravenous and inhaled lidocaine attenuate reflex bronchoconstriction but at different plasma concentrations. Am J Respir Crit Care Med 1999; 159:530-35.
13. Zucker M. Nebulized Lidocaine: An Option for Severe Asthma. Respiratory Reviews.com. 2002; 7:4.
14. Bankers-Fulbright JL, Kephart GM, Loegering DA, Bradford AL, Okada S, Kita H, et al. Sulfonylureas inhibit cytokine-induced eosinophil survival and activation. J Immunol1998; 160:5546-53.
15. Kai T, Nishimura J, Kobayashi S, Takahashi S, Yoshitake J, McAlpine LG, *et al*. Lidocaine-induced bronchoconstriction in asthmatic patients. Relation to histamine airway responsiveness and effect of preservative. Chest 1989; 96:1012-15.
16. Okumura F, Denborough MA. Effects of anaesthetics on guinea pig tracheal smooth muscle. Br J Anaesth 1980; 52:199- 204.
17. Downes H, Loehning RW. Local anesthetic contracture and relaxation of airway smooth muscle. Anesthesiology 1977; 47:430-6.
18. Shirk MB, Donahue KR, Shirvani J. Unlabeled Uses of Nebulized Medications. Am J Health Syst Pharm 2006; 63(18):1704-16.
19. McAlpine LG, Thomson NC. Lidocaine-induced bronchoconstriction in asthmatic patients. Relation to histamine airway responsiveness and effect of preservative. Chest 1989; 96:1012-15.
20. Fish JE, Peterman VI. Effects of inhaled lidocaine on airway function in asthmatic subjects. Respiration 1979; 37:201-7.
21. Groeben H, Silvanus MT, Beste M, Peters J. Combined lidocaine and salbutamol inhalation for airway anesthesia markedly protects against reflex bronchoconstriction. Chest 2000; 118:509-15.
22. Bulut Y, Hirshman CA, Brown RH. Prevention of lidocaine aerosol-induced bronchoconstriction with intravenous lidocaine. Anesthesiology 1996; 85: 853-9.
23. Harrison TW, Tattersfield AE. Effect of single doses of inhaled lignocaine on FEV1 and bronchial reactivity in asthma. Respir Med 1998; 92:1359-63.
24. Decco ML, Neeno TA, Hunt LW, O'Connell EJ, Yunginger JW,Sachs MI. Nebulized lidocaine in the treatment of severe asthma in children: a pilot study. Ann Allergy Asthma Immunol1999; 82:29-32.
25. Hunt LW, Swedlund HA, Gleich GJ. Effect of nebulized lidocaine on severe glucocorticoid-dependent asthma. Mayo Clin Proc 1996; 71:361-8.
26. Hunt LW, Frigas E, Butterfield JH, Kita H, Blomgren J, Dunnette SL, et al. Treatment of asthma with nebulized lidocaine: a randomized, placebo-controlled study.J Allergy Clin Immunol 2004; 113:853-9.
27. de Paz AS, Rodriguez MM, Fernandez PB, Santaolalla MM, Herrera MI, Perez PA. Treatment with nebulized lidocaine in steroid-dependent asthma]. Allergol Immunopathol 2005; 33(4):231-4.
28. Chong CF, Chen CC, PMa H, Wu YC, Chen YC, Wang TL. Comparison of lidocaine and bronchodilator inhalation treatments for cough suppression in patients with chronic obstructive pulmonary disease. Emerg Med J 2005; 22:429–32.
29. Abuan T, Yeager M, Montgomery AB. Inhaled Lidocaine for the Treatment of Asthma: Lack of Efficacy in Two Double-Blind, Randomized, Placebo-Controlled Clinical Studies Journal of Aerosol Medicine and Pulmonary Drug Delivery 2010, 23(6): 381-8.
30. Zu-ming Lv, Li Chen, Jie Tang. Nebulized lidocaine inhalation in the treatment of patients with acute asthma. World J Emerg Med 2011; 2(1):30-2.
31. Adamzik M, Groeben H, Farahani R, Lehmann N, Peters J. Intravenous Lidocaine After Tracheal Intubation Mitigates Bronchoconstriction in Patients with Asthma. Anesth Analg 2007; 104:168-72.