

# Nebulised Adrenaline in Chronic Obstructive Pulmonary Disease and Asthma –A Review

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## ABSTRACT

Obstructive lung disease, namely Chronic Obstructive Pulmonary Disease and Asthma, are the most frequent causes of respiratory ill health, covering all ages. Acute breathlessness is a common emergency problem that is typically treated with bronchodilators and anti-inflammatory drugs. Nebulized selective, short acting  $\beta_2$  agonist such as salbutamol is the bronchodilators of choice in most cases. Other important treatments in moderate -to-severe cases include systemic and inhaled corticosteroids and in severe cases, addition of anticholinergics such as Ipratropium bromide, intravenous administration of theophylline and magnesium sulfate. Despite aggressive management, some patients do not respond adequately to these treatments. Therapeutic management options in these patients are limited to interventions such as adrenaline and non-invasive and mechanical ventilation or both. Adrenaline, also known as Epinephrine has earned the title of “the doctor’s friend”. Adrenaline have beneficial effects in acute breathlessness in addition to its direct beta-adrenoceptor mediated bronchodilation, such as alpha  $\alpha_1$ -receptor mediated reduction in microvascular leakage and oedema, and inhibition of bronchoconstrictor neural pathways. Nebulised adrenaline offers a number of advantages over pure  $\beta_2$  agonist like salbutamol that ensure its efficacy with fewer side effects. However, close monitoring of patient’s condition is necessary when adrenaline is nebulised especially in patient suffering from arrhythmia, hypertension or other cardiac problems. This article reviews current evidence regarding safe use of nebulised adrenaline in the management of acute breathlessness.

**Keywords:** Asthma, Chronic Obstructive Pulmonary Disease, adrenaline.

## INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are common obstructive airway diseases characterized by various degrees of airflow limitation, inflammation, and tissue remodeling. Bronchial asthma, an allergic disease that develops in childhood, is physiologically characterized by reversible airflow obstruction. It has an episodic course with a generally favorable prognosis, as it responds well to anti-inflammatory treatment.<sup>1</sup> In contrast, COPD is typically caused by tobacco smoke or deficiency of  $\alpha_1$  antitrypsin, develops in mid-life or later, and is characterized by incompletely reversible airflow limitation that results in a progressive decline in lung function leading to premature death.<sup>2</sup> Death rates from COPD have been rising steadily over the last

decade and, according to estimates of the World Health Organization (WHO), by 2020 COPD shall become the third most frequent cause of death, following coronary and cerebrovascular disease.<sup>3</sup>

Nebulised  $\beta_2$ -adrenergic agonists have become the drugs of choice for the first-line treatment of asthma and chronic obstructive pulmonary disease.<sup>4</sup>  $\beta_2$  agonists have attributed to the rapid onset of a vigorous bronchodilator effect associated with a large therapeutic index allowing the use of high doses of drugs without side effects.<sup>5</sup> These drugs were developed to avoid the cardiac toxicity associated with less selective adrenergic agents while retaining a potent relaxant effect on airway smooth muscle  $\beta_2$  receptors.<sup>6</sup> In this instance, nebulized

salbutamol is the most recommended  $\beta_2$  agonist.<sup>5</sup>

Adrenaline (epinephrine) is a potent stimulant of both  $\alpha$ - and  $\beta$ -adrenergic receptors. In addition to its widespread use in cardiopulmonary resuscitation, it is effective in the emergency management of acute breathlessness.<sup>7</sup> Nebulized epinephrine has been widely used for more than 40 years, after the first report of its effectiveness in 1971. Initial studies published in the 1970s and early 1980s suggested that epinephrine might be more effective when nebulized via intermittent positive pressure breathing (IPPB) than by nebulization alone. The use of IPPB has now fallen out of favour and it is no longer routinely used.<sup>8</sup>

Even though adrenaline was introduced into the treatment of asthma and COPD in the early century, it was rapidly superseded by selective  $\beta_2$  agonists, particularly because of its  $\alpha$  and  $\beta_1$  side effects which are mostly related to the intravenous route of administration. Accordingly, nebulisation of adrenaline might eliminate its adverse effects.<sup>5</sup> Clinical benefits of adrenaline in acute airway obstruction treatment results from reduction in respiratory secretions and respiratory mucosa edema ( $\alpha$ -adrenergic effects) and relaxation of airway smooth muscle and inhibition of the inflammatory process ( $\beta$ -adrenergic effects).<sup>7</sup>

$\beta_2$  adrenergic bronchodilators have mucosal and pulmonary vasodilator effects. The former increase mucosal absorption rates with resultant direct tachycardic effects, by virtue of the residual inherent  $\beta_1$  adrenergic activity effects. The latter enhance ventilation-perfusion mismatching which results in hypoxia and hypoxia induced tachyarrhythmia. Airway obstruction increases work of breathing and precipitates hypoxia; both are associated with tachycardia. The vasoconstrictive and bronchodilatory effects of adrenaline reduce the inflammatory airway obstruction, regulate the ventilation-pulmonary perfusion ratio and, thus improve hypoxemia, which is an important cause of tachycardia and arrhythmia.<sup>9,10</sup> It is therefore not surprising that in clinical studies, drugs such as salbutamol, with minimal residual  $\beta_1$  adrenergic activity, have more potential to cause tachycardia than adrenaline, which in spite of its potent  $\beta_1$  adrenergic activity might reduce heart rate.<sup>11</sup>

The pharmacological action of Adrenaline results from the temporary occupancy of only a fraction of the total receptor population to exert its maximum effect or intrinsic activity. In

contrast, the intrinsic efficacy of salbutamol is only 5% of that of adrenaline. Stated otherwise, epinephrine will activate 20 times more  $\beta_2$  adrenoceptors than salbutamol when both drugs occupy the same number of receptors.<sup>12</sup> Nebulised adrenaline offers a number of advantages over pure  $\beta_2$  agonist like salbutamol that ensure its efficacy with fewer side effects: adrenergic vasoconstrictor action that can decongest the mucosa, limit its own absorption, and regulate pulmonary blood flow, with little effect on ventilation-perfusion matching;  $\beta_2$  adrenergic bronchial muscle relaxant effect;  $\beta_2$  adrenergic action to suppress release of chemical mediators; physiological antihistamine effect that can reverse histamine effects, such as oedema; and it reduces catarrhal secretions.<sup>11</sup> However, these advantages may be hampered, at least theoretically, by a bronchoconstrictor effect due to the  $\alpha$  agonist properties of adrenaline and hence need for more frequent administration of drug according to its shorter half-life.<sup>12</sup>

The effect of adrenergic agonists in asthma depends on their net effect on microvascular leakage, mucosal oedema, vascular clearance of spasmogens, inhibition of cholinergic neurotransmission, and airway smooth muscle contractility. Adrenaline, by virtue of its alpha effects on the vasculature and cholinergic neurotransmission, may have additional useful properties in asthma compared with selective beta agonists such as salbutamol.<sup>6</sup>

Differences in the vascular effects of drugs may be very important in determining their effects on airway function. Non-selective adrenergic agents, through alpha-mediated vasoconstriction, might be expected to have a different effect on the bronchial and pulmonary vasculature than  $\beta$  agonists. In an animal model of asthma microvascular leakage induced by platelet activating factor was inhibited by adrenaline, while the selective  $\beta_2$  agonist salbutamol had no effect.<sup>13</sup> In acute asthma it has been shown that, whereas salbutamol produces a small fall in Pao<sub>2</sub>, due to bronchial arteriolar dilatation and consequent redistribution of pulmonary blood to poorly ventilated areas, adrenaline produced a small but consistent rise in Pao<sub>2</sub>, suggesting an improvement in the ventilation/perfusion relationship due to vasoconstriction.<sup>14</sup>

In infants and young children with acute asthma and wheezing, bronchial smooth muscle spasm is not as prominent as in older children, and mucosal oedema and secretion may dominate

the pathophysiology. Hence, inhaled  $\beta_2$  agonists may be less efficient. Nebulized adrenaline has a rapid but short acting effect on mucosal oedema and may be of value as initial treatment in severely obstructed older children, before administration of inhaled  $\beta_2$  agonists.<sup>15</sup>

Adrenaline is most frequently presented as a clear solution in a concentration of 1:1000 (1ml ampoule) or 1:10000 (10ml mini-jet for resuscitation). Both these formulations contain 1mg of adrenaline. Racemic adrenaline is a mixture of dextro (D) - and Levo (L) -rotatory isomers of adrenaline, where L-adrenaline is the active form. Racemic mixture is less active and may have fewer cardiovascular side effects when nebulised.<sup>16</sup> Side effects relate directly to the exaggerated effects of adrenaline, most commonly owing to over dosage or in appropriate use. Potential side effects, such as palpitations, tremor, tachycardia, hypertension, arrhythmia, cerebral hemorrhage, acute pulmonary edema and pallor are the main concerns about the use of adrenaline.<sup>7</sup>

The recommended dose of racemic adrenaline as bronchodilator is 0.5ml of 1:1000 (1mg/ml) solution diluted with 3-5ml of normal saline administer over 15 minutes every 3 to 4 hours as needed. All the anticipated effects of systemic adrenaline may occur when nebulised, so the patient should be carefully monitored in a high care environment. There are no absolute contraindications to the use of adrenaline, but extreme caution should be shown whenever it is used owing to its profound effect on the cardiovascular system. Particular care must be taken when using it in patients suffering from arrhythmia, hypertension or ischemic heart disease since these conditions may be acutely exacerbated. Caution should also be shown in patients with concurrent use or within 2 weeks of monoamine oxidase inhibitors since adrenaline is a substrate of COMT.<sup>16</sup>

## CONCLUSION

This review suggest that nebulised adrenaline is as effective as a nebulised beta -agonist and is without significant side effects. Nebulization with adrenaline is a safe therapy and potentially an important alternative option for acute inflammatory airway obstruction who have not responded adequately to maximal  $\beta_2$ -agonist therapy.

## REFERENCES

1. Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. The

- Journal of Steroid Biochemistry and Molecular Biology. 2010; 120: 76-85.
2. So Ri Kim and Yang Keun Rhee. Overlap between Asthma and COPD: where the two diseases converge. Allergy, Asthma and Immunology Research. 2010; 2(4): 209-14.
3. Caterina Anecchino, Elisa Rossi, Caterina Fanizza, Marisa De Rosa, Gianni Tognoni, et al. Prevalence of chronic obstructive pulmonary disease and pattern of comorbidities in a general population. International Journal of COPD. 2007; 2(4): 567-74
4. Kenneth J Broadley.  $\beta$ -Adrenoceptor responses of the airways: For better or worse?. European Journal of Pharmacology. 2006; 533 (1-3): 15-27.
5. Abroug F, Nouira S, Bchir A, Boujaria R, Elatrous S and Bouchoucha S. A controlled trial of nebulised salbutamol and adrenaline in acute severe asthma. Intensive care medicine. 1995; 21(1): 18-23.
6. David R Baldwin, Ziali Sivardeen, Ian D Pavord and Alan J Knox. Comparison of the effects of salbutamol and adrenaline on airway smooth muscle contractility in vitro and on bronchial reactivity in vivo. Thorax 1994; 49: 1103-1108.
7. Zhang L and Sanguetsche LS. The safety of nebulization with 3 to 5 ml of adrenaline (1:1000) in children: an evidence based review. Journal of Pediatrics. 2005; 81: 193-7.
8. Bjornson C, Russell K, Vandermeer B, Klassen TP and Johnson DW. Nebulized epinephrine for croup in children (Review).The Cochrane Collaboration. The Cochrane Library. 2013;10.
9. Bertrand P, Aranibar H, Castro E, et al. Efficacy of nebulised epinephrine versus salbutamol in hospitalized infants with bronchiolitis. Pediatric Pulmonology. 2001; 31: 284-8.
10. Menon K, Sutcliffe T and Klassen TP. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. Journal of Pediatrics. 1995; 126: 1004-7.
11. A Abul-Ainine and D Luyt. Short term effects of adrenaline in bronchiolitis:a randomised controlled trial. Archives of Disease in Childhood. 2002; 86: 276-279.
12. Gustavo J Rodrigo, Luis J Nannini. Comparison between nebulized adrenaline and  $\beta_2$  agonists for the treatment of acute asthma. A meta-analysis of randomized

- trials. American Journal of Emergency Medicine. 2006; 24: 217–22.
13. Boschetto P, Roberts NM, Rogers DF and Barnes PJ. Effect of anti-asthma drugs on microvascular leakage in guinea-pig airways. American Review of Respiratory Disease. 1989;139: 416-21.
  14. Coupe MO, Guly U, Brown E and Barnes PJ. Nebulised adrenaline in acute severe asthma; comparison with salbutamol. European Journal of Respiratory Diseases. 1987; 71: 227-32.
  15. Oymar K and Thomas Halvorsen. Emergency presentation and management of acute severe asthma in children. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2009; 17: 17-40.
  16. John Kinnear. Adrenaline (Epinephrine). Anaesthesia tutorial of the week. June 2011.