Sympathomimetics in acute severe asthma: inhaled or parenteral, nebulizer or spacer?

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ABSTRACT: It is accepted today that all patients with acute asthma should be treated with a sympathomimetic, irrespective of previous therapy. This short review addresses the question of the optimal mode of administration of these drugs in acute severe asthma. Inhaled sympathomimetics are as effective as subcutaneous adrenaline, or intravenous salbutamol or terbutaline, and, as they produce fewer side-effects, are recommended as the best mode of administration. However, self-medication with a ready to use subcutaneous preparation may be indicated in those patients prone to very abrupt attacks. The conventional mode of inhalation therapy in acute asthma is nebulization, but equally effective bronchodilatation may be obtained with metered-dose inhalers combined with valved spacers. Tachypnoeic patients unable to perform a conventional inhalation manoeuvre can use one-way valve inhalation devices with repeated tidal breaths. Finally, sequential or even continuous inhalation techniques have recently been advocated, particularly in patients with impending respiratory failure.


Acute asthma remains a matter of consternation as it may be life-threatening even in young people. Sympathomimetics are considered as the first choice bronchodilators since the Boston group has demonstrated their superiority to intravenous (i.v.) aminophylline. In an early publication (1980) these investigators [1] reported in young asthmatics (under 45 yrs of age) presenting to the ward of a general hospital, a mean improvement in forced expiratory volume in one second (FEV₁) within one hour of 80-90% of the initial value after inhaled isoproterenol or subcutaneous adrenaline, to be compared with +25% after i.v. aminophylline despite the use of a loading dose as high as 5.6 mg·kg⁻¹ body weight. In a second step they showed that inhaled isoproterenol alone was as effective as combination therapy (inhaled isoproterenol plus i.v. aminophylline) even in those patients with the most severe baseline obstruction (FEV₁ < 0.8) as well as in those admitted to hospital with low (<10 µg·m⁻³) serum theophylline levels [2]. These results were further confirmed in a subsequent study [3], as well as by another group [4] using metaproterenol as the inhaled beta-mimetic. Moreover, the latter investigators demonstrated that i.v. aminophylline increased the frequency of side-effects (tremor, anxiety, palpitations) without additional benefit in terms of bronchodilatation.

Although the use of i.v. aminophylline is still recommended [5] in patients with insufficient response to first-line therapy it has recently been shown [6] that i.v. aminophylline given after a cumulative dose of 2.4 mg nebulized fenoterol produces a clinically significant (>0.2 l) additional improvement in FEV₁ in only a minority of patients (4 out of 18). Preliminary results with i.v. enprofylline, a new xanthine derivative more potent on a molar basis than theophylline, suggest that it may compare favourably with an inhaled sympathomimetic in the initial management of acute asthma [7], but this needs to be confirmed.

The Boston group has also shown that patients pretreated with sympathomimetics respond in the emergency room to a nebulized sympathomimetic as well as patients who have not used such drugs [8]. This evidence, that all the young adult patients with acute asthma may be successfully treated with sympathomimetics irrespective of their medication history, is very important as it had been speculated in the late Sixties that tachyphylaxis resulting from regular inhalation of sympathomimetics could exacerbate an episode of acute asthma by inducing resistance to catecholamines [9]. Since then, many pharmacological studies [10-12] have provided strong evidence that tachyphylaxis is not clinically relevant in asthma [13]. It is now accepted that when sympathomimetics delivered from a metered-dose inhaler (MDI) fail to provide relief to a patient with acute asthma, this failure should not be ascribed to pharmacological resistance, but in
some patients to an inadequate mode of administration and in others to severe inflammation of the airways. In the former patients, sympathomimetics do work when either an adequate mode of aerosol delivery or the parenteral route is used [8], while in the latter, steroid therapy is required to improve airway obstruction [14]. In summary the evidence is now that all patients with acute asthma should be treated with a beta-adrenergic agent, irrespective of previous therapy. The present short review addresses the question of the best mode of administration of these agents, aerosol versus parenteral, nebulizer versus metered-dose inhaler (MDI) plus spacer.

Route: aerosol or systemic?

Whereas several pharmacological studies have shown that in stable asthmatics the inhaled route provides the most effective bronchodilatation and the fewest side-effects [15], it has been questioned whether an inhaled drug would be able to reach its site of action in patients with severe airway obstruction.

Efficacy

Several groups have compared the efficacy of inhaled versus subcutaneous or intravenous sympathomimetics in acute asthma. Compared to subcutaneous adrenaline, inhaled isoproterenol or terbutaline was constantly found to be as effective [1, 16] or more effective [3, 17]. When i.v. salbutamol or terbutaline were administered, the results varied from a slight superiority of parenteral therapy [18, 19] to equal effectiveness of both regimens [20-22], or slight [23] or more marked [24] superiority of inhaled therapy. Compilations of method data available from five recent studies suggests these differences in results to be at least partly related to the inhaled to i.v. dose ratio (R) used and the mode of administration of i.v. therapy. A continuous i.v. infusion of rather high doses (R=5) favours superiority of i.v. therapy [19], single i.v. bolus of lower doses (R=10, 11.1 and 16.7) favours the equal effectiveness [20-22] or even (R=30) superiority of inhaled therapy [24].

Side-effects

a) Cardiovascular. In acute asthma studies, an increase in heart rate has often been reported after parenteral sympathomimetic therapy [17, 19, 21, 23] while baseline tachycardia is reduced after nebulized fenoterol [25], salbutamol [22, 26] or terbutaline [17, 21, 27]. Cardiac arrhythmias induced by beta-mimetics have only been reported in isolated instances [28] but prolonged electrocardiographic monitoring has rarely been performed. In a prospective study, severe arrhythmias during combined continuous i.v. infusion of terbutaline and aminophylline were found to involve a minority (24%) of patients and to resolve spontaneously in all cases [29]. Elevated serum CPK-MB levels that may indicate subclinical myocardial injury have been reported in children with acute severe asthma treated with i.v. isoproterenol [30].
b) Hypokalaemia. Sympathomimetic-induced hypokalaemia has been well documented with the parenteral route [31]. Haalboom et al. [32] have also observed in stable asthmatics a moderate though significant decrease in serum potassium level after inhalation of doses up to 1,200-2,400 μg (6-12 puffs) fenoterol over a short period of 90 min; this protocol was thought to mimic repeated inhalations such as patients with acute asthma self-administer. The clinical significance of these observations has to be evaluated in future prospective trials.

c) Hypoxaemia. It is a current concept that bronchodilators may aggravate ventilation-perfusion imbalance and exacerbate pre-existing hypoxaemia. However, in a group of 23 moderately hypoxaemic patients with acute asthma, the mean arterial oxygen tension (Pao2) remained unchanged after nebulized terbutaline and even improved after i.v. terbutaline (from 7.55 to 8.90 kPa); nevertheless, a clinically significant (0.67 and 1.33 kPa) decrease in Pao2, was seen in two individuals treated by inhalation [22]. Although the possibility of bronchodilator-induced hypoxaemia has probably been overemphasized, oxygen therapy may be recommended in all patients with severe acute asthma.

Adrenaline or beta2-mimetic?

From controlled studies comparing the efficacy and side-effects of parenteral versus inhaled sympathomimetics in acute asthma, we conclude that both routes of administration are effective but that a higher efficacy to side-effects ratio supports the use of the inhaled route as the first choice. If, however, the parenteral route is chosen, which drug should be used? In a recent study of 20 patients with acute asthma [33], 0.5 mg terbutaline and 0.5 mg adrenaline given subcutaneously produced equal bronchodilatation without serious side-effects. The subcutaneous route is well adapted for self-medication in those patients who are prone to very abrupt attacks of asthma and a high risk of ventilatory arrest [34, 35]. To be truly effective this acute administration requires "ready to use" preparations analogous to those marketed in some countries for therapy of anaphylactoid reactions.

If the inhaled route is chosen, it has been speculated that nebulized adrenaline might be better than a nebulized β2-selective agent, through a reduction in bronchial mucosal oedema via an α effect on bronchial arterioles. However, in a recent crossover study comparing 1 mg nebulized adrenaline with 2.5 mg nebulized salbutamol, both drugs were found to be equipotent, but the short duration of action of adrenaline with a return of lung function to baseline value within 30 min was found to be a strong disadvantage [26]. Thus, it seems reasonable to conclude that, as in stable asthmatics [36], only...
Long acting specific $\beta_2$-stimulants should be used for inhalation therapy in acute asthma.

**Dosage**

Doses of inhaled sympathomimetics used in acute asthma are largely empirical. Most investigators have used doses as high as 2.5-10 mg salbutamol or terbutaline given by nebulizer without reported serious side-effects. Mitchell et al. [25] performed a dose-response study in patients with acute asthma (as defined by an FEV$_1<$1.2 l) and found the dose required to obtain a maximum bronchodilatation with nebulized terbutaline to range from 1-3 mg (4-12 drops of the commercially available solution). There is obviously a need for further dose-response studies in patients with acute asthma.

**Inhaled sympathomimetics: mode of delivery?**

**Aerosol therapy in acute asthma: general concepts**

Modes of aerosol delivery available include inhalation from an MDI, nebulization and, for the last few years, inhalation from an MDI combined with a spacer. Spacers are inhalation devices fitted to the mouthpiece of a conventional MDI, including extension tubes, collapsible bags and cone- or pear-shaped devices with a one way valve [37].

Until recently MDIs were thought to be ineffective in acute asthma. This idea was supported by Rossano et al. [8] who showed that asthmatic out-patients deteriorating on sympathomimetics inhalation from MDIs may be successfully treated by sympathomimetics given by nebulization in the emergency room. There is now evidence that spacer-aided delivery may be as effective as nebulization in patients with acute asthma using either the Nebulhaler [27, 38, 39] or the Inspir Ease [40] device, with a terbutaline dose of 4 mg in adults [27], and of 1.25-2.5 mg [38] or 0.1 mg·kg$^{-1}$ [39] in children. This could be important. As patients with severe asthma treated during a hospital stay with a nebulizer often attribute their improved status to this particular administration [41, 42], there has subsequently been an increasing patient request for nebulization maintenance therapy at home. However, some concern has been expressed about the uncontrolled domiciliary use of nebulizers [43] and the potential short-term [28] and long-term [44] cardiac consequences from chronic use of moderate to high doses of sympathomimetics.

**Co-ordination problems, inhalation manoeuvre and deposition fraction**

Proper use of an MDI requires adequate “hand-mouth” (“actuation-inhalation”) co-ordination. Up to 50% of stable asthmatics have been found to be “bad co-ordinators” [45], a proportion that may even increase during acute exacerbations. Optimal use of an MDI also requires a slow, deep inspiration manoeuvre, followed by a ten second breath holding [46]; in these optimal conditions the fraction of the metered dose which reaches the respiratory tract may be increased up to 11.2% [47]. This figure compares favourably with the lung deposition obtained by nebulization which is also influenced by many technical factors and is often found to be around 10% [48, 49].

Spacers added to MDIs may enhance lung deposition through decreasing impaction in the oropharynx and decreasing the size of particles following evaporation of the solvent [37]. Deposition fractions around 15% have indeed been reported with the Nebulhaler [50] and Inspir Ease [47] devices. With these devices, which contain the spray momentarily before it is inhaled, the co-ordination between firing the MDI and inhaling is no longer required. However, a slow deep inspiration combined with breath holding remains necessary, which limits the use of spacers in patients with tachypnoea [51].

Recent studies [52, 53] in stable asthmatics suggest that valved spacers can be used with tidal breathing, the expired air being rejected into room air on each cycle. In children inhaling terbutaline from a Nebulhaler device, five normal breaths which are just sufficient to move the valve compared favourably in terms of bronchodilatation with two deep inspirations from residual volume, each held for 5 s [52]. In a crossover study in adults, 200 $\mu$g salbutamol inhaled with four breaths from an Aerobedhaler was as effective as 2.5 mg given by nebulizer. As the relative benefit of the two methods of administration was not influenced by the severity of baseline obstruction, it was concluded that spacers used with tidal breathing might be useful in the treatment of acute asthma [53].

**Comparative studies**

Traditionally, much higher doses are used via nebulizers than via MDIs. As lung deposition fraction is of the same order of magnitude, equal doses should be tested. In patients with stable asthma, studies comparing different modes of delivery in terms of bronchodilatation have shown either the MDI and nebulizer to be equipotent [36, 49], the MDI plus spacer and nebulizer to be equally effective but both better than the MDI alone [54], or the MDI plus spacer to be more effective than the nebulizer [55, 56].

In patients with acute asthma only two studies comparing spacer and nebulizer delivery were performed using equal doses in a crossover design [27, 39]. Terbutaline was used in both studies, at a dose of 4 mg in adults [27], 0.1 mg·kg$^{-1}$ in children [39], and bronchodilatation obtained with the MDI plus Nebulhaler was found to be equivalent [27] or even greater [39] than that obtained with the nebulizer. In two other studies [38, 40] patients with acute asthma were randomly allocated to either spacer or nebulizer delivery, which were found to be equally effective despite the use of higher doses with the nebulizer. In one study, asthmatic
children used a Nebuhaler device with repeated breaths for one minute to ensure complete intake of the metered dose actuated in the spacer, which was two-fold lower than the terbutaline dose given via the nebulizer [38]. The other investigation involved adults, metaproterenol and an Inspir Ease device with a nebulizer to spacer dose ratio as high as 7.5 [40]. In the paediatric studies [38, 39], it was concluded that the inability of some children to produce sufficient flow rates to trigger the valve was the only limitation to spacer delivery in acute asthma. Further studies comparing spacer and nebulizer delivery in patients with acute severe obstruction are required, but there is reasonable evidence that spacers have a place in the treatment of these patients, particularly if a tidal breath technique can be used; there is a need for manufacturers to investigate spacers with a lower threshold for valve triggering.

**Sequential or continuous inhalation therapy**

Finally, therapeutic regimens including sequential inhalations have recently been advocated. An initial dose of salbutamol by nebulizer followed by six consecutive doses at 20 min intervals may be used in children with severe acute asthma [57]. Newhouse and Dolovich [42] have recommended the use in the emergency room of four puffs of the sympathomimetic of choice via an MDI combined with a valved spacer, followed by one puff per minute until subjective, and if available objective, benefit is achieved, or side-effects such as tremor limit further drug administration. Similarly continuous nebulization has recently been proposed. In a preliminary study on children with acute asthma including 14 subjects with impending respiratory failure (mean arterial carbon dioxide tension (Paco₂) 5.90 kPa), continuous nebulization of 4 mg terbutaline per hour was effective in improving clinical asthma score and Paco₂ (mean 4.34 kPa after continuous nebulization), weaning from continuous nebulization being possible after 3–37 h [58].

**Conclusion**

From this short review of the use of beta-mimetic drugs in the treatment of acute asthma we conclude that in the vast majority of cases theinhaled route may be preferred to the parenteral one and also that conventional nebulization can be replaced by MDIs coupled to some kind of spacer.

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Les sympathicomimétiques en crise d'asthme aiguë: En inhalation ou systémique, nébulisation ou chambre d'expansion. A. Noseda, J.C. Yernault.

RÉSUMÉ: Il est actuellement bien établi que tout patient en crise d'asthme aiguë doit être traité par un sympathicomimétique, quel que soit le traitement reçu antérieurement. Cette revue aborde le problème du mode d'administration optimal de ce type de médication en cas de crise d'asthme sévère. Les sympathicomimétiques en inhalation, aussi efficaces que l'adrénaline sous-cutanée, le salbutamol ou la terbutaline intra-veineuse, sont recommandés comme le mode d'administration de premier choix, dans la mesure où leurs effets secondaires sont moindres. Toutefois, l'injection précoce d'un sympathicomimétique sous forme d'une préparation sous-cutanée prête à l'emploi peut être indiquée chez les patients à haut risque de crise survenue. Le mode d'inhalation habituel dans la crise d'asthme aiguë est la nébulisation, mais une bronchodilatation équivalente peut être obtenue en utilisant un aérosol doseur couplé à une chambre d'expansion munie d'une valve. Les patients tachypnéiques incapables d'exécuter une manœuvre classique peuvent inhaler le contenu d'une chambre d'expansion munie d'une valve uni-directionnelle à l'aide de plusieurs cycles respiratoires à volume courant. Enfin, des techniques d'inhalation séquentielle, voire continue, ont été proposées récemment, particulièrement pour les patients menacés d'insuffisance respiratoire aiguë. 