A controlled trial of nebulized salbutamol and adrenaline in acute severe asthma

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Abstract Objective: To compare efficacy and safety of nebulisation of adrenaline (2 mg over 10 min) and salbutamol (5 mg over 10 min) in acute severe asthma. Design: Prospective randomized and double blind study. Setting: Intensive care unit of a University teaching hospital. Patients and participants: 22 asthmatic patients presenting to the emergency room with acute severe asthma. Interventions: Patients were randomly assigned to receive either adrenaline (n = 11) or salbutamol (n = 11) via a nebulizer. Additional treatment comprised hydrocortisone hemisuccinate (100 mg) and supplemental oxygen (7 l/min). The efficacy and safety of both drugs were evaluated at 20 and 40 min. Results: A statistically significant increase in the Peak Expiratory Flow (PEF) was achieved at the 20th min in both groups (from 85+38 l/min to 120+45 l/min; p<0.001; and from 107+28 l/min to 145+19 l/min; p<0.001; in adrenaline group and salbutamol group respectively). With both drugs, PEF further increased at 40 min to a level that was statistically significant when compared to the 20 min evaluation. The magnitude of the absolute variation in PEF was similar with both drugs. Both drugs induced a significant decrease in heart rate, respiratory frequency and PaCO2 while the increase of PaO2/FIO2 ratio was not significant. The decrease of respiratory frequency at 40 min was more important with salbutamol (p = 0.03). No side effects were recorded in both groups. Conclusion: After a single dose, nebulized adrenaline (2 mg) proved as effective and safe as salbutamol (5 mg) in acute severe asthma.

Key words Acute severe asthma · Bronchodilators · \( \beta_2 \) agonists

Introduction

Nebulized \( \beta_2 \) agonists have become the drugs of choice for the primary treatment of acute severe asthma [1–3]. This has been 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 [4]. In this instance nebulized salbutamol is the most recommended \( \beta_2 \) agonist [3, 5].

Although introduced into the treatment of asthma early in the century [6], adrenaline was rapidly superseded by selective \( \beta_2 \) agonists, particularly because of its \( \alpha \) and \( \beta_1 \) side effects which are mostly related to the intravenous route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 [4]. It is now well demonstrated that nebulisation of \( \beta_2 \) agonists is more potent and is associated with less side effects than their systemic administration [3, 5]. Accordingly, nebulisation of adrenaline might eliminate its adverse effects. Nebulized adrenaline offers potential theoretical...
advantages when compared with a pure $\beta_2$ agonist like salbutamol: first it may act more rapidly than $\beta_2$ agonists; second it may increase bronchial caliber reducing bronchial mucosal oedema through its $\alpha$ agonist effects [4]. Additional beneficial effects of adrenaline in acute asthma could be expected from its antagonistic effect on the vagal bronchial tonus by inhibition of airway cholinergic neurotransmission [7, 8]. However, these advantages may be hampered, at least theoretically, by a bronchoconstrictor effect due to the $\alpha$ agonist properties of adrenaline and the need for more frequent administration of the drug according to its shorter half-life.

Previous studies reported the efficacy of nebulized adrenaline in the treatment of acute severe asthma [9–11]. These studies were either uncontrolled, or used low dosage with regard to usual recommendations. Therefore, comparison of the short term effects of the two types of treatment is needed.

The aim of this prospective controlled study was to compare the bronchodilator effects and safety of nebulized salbutamol and adrenaline at the dosages currently recommended in the treatment of acute severe asthma (5 and 2 mg respectively).

**Patients and methods**

All patients attending the emergency room during the 12-month study period (October 1990—September 1991) and fulfilling the entry criteria were enrolled. The study protocol was approved by the Ethics Committee of our institution.

**Patients**

Twenty two consecutive adult patients who attended the emergency room with a severe acute attack of asthma were enrolled into the study after verbal consent was obtained. All patients had asthma according to the definition of the American Thoracic Society [12].

Asthma attack was considered severe when it was unrelieved by an otherwise usually effective course of bronchodilator therapy with a peak expiratory flow (PEF) less than 150 l/min (as measured by a Wrights Peak Flow Meter, best value of 3 trials) and at least 3 of the following features: tachypnea with respiratory rate > 30 breaths/min; tachycardia > 100 beats/min; contraction of accessory respiratory muscles, in particular contraction of the sternocleidomastoids; a widened paradoxical pulse (> 20 mmHg). Hypoxemia, whether or not associated with hypercapnia was not considered as a criterion of enrollment. Pregnant women, patients with chronic cardiac disease or severe hypertension, patients who were taking $\beta_2$ blocking drugs and chronic smokers were excluded from the study.

**Protocol**

Shortly after a clinical evaluation in the emergency room, patients with severe acute asthma who were enrolled in the study were referred to the intensive care unit (ICU) before any administration of $\beta_2$ agonists. Upon admission to the ICU, all patients were given hydrocortisone hemisuccinate (100 mg, intravenously) and $O_2$ (7 l/min) via a nebulizer (Mini nebuliseur 40-115510; Peters, France). Cardiac rhythm was continuously monitored throughout the study with a digital storage type monitor.

Patients were then randomised, with a sealed envelope system, to receive either nebulisation of 2 mg of adrenaline [10] (Aguettant; solution of 1 mg/ml for intravenous injection, pH = 3.2; osmolarity = 300 mM/m) or 5 mg salbutamol (Ventoline, Glaxo, solution of 3 mg/ml for nebulisation) diluted respectively in 3 and 4 ml of 0.9% saline. Solutions were prepared by the pharmacist. Patients and investigators were unaware of the treatment assignment. Flow through the nebulizer was supplied by $O_2$ (7 l/min) via facial mask.

**Recording of effects**

The following variables were measured at baseline, 20 min and 40 min after the start of nebulisation: PEF (best value of 3 trials) expressed as absolute change [13]; respiratory rate; heart rate, systolic and diastolic blood pressure; presence and magnitude of pulsus paradoxus; arterial blood gases.

Safety of the nebulisation was assessed by the occurrence of arrhythmia, hypertensive crisis, angina, nausea, vomiting and tremor. The occurrence of such side effects and/or a worsening of ventilatory status requiring mechanical ventilation led to interrupt the study protocol.

**Statistics**

Data are reported as means ± standard deviation (SD). To assess the within groups effects of adrenaline and salbutamol, Wilcoxon’s paired test was used. Comparison between groups was based on the Mann-Whitney U test. A $p$ value $< 0.05$ was considered significant.

**Results**

Twenty two consecutive asthmatics (mean age: 33 ± 14 years; 10 men, 12 women) fulfilled the inclusion criteria and were enrolled in the study. Patients were randomly assigned to receive either adrenaline ($n = 11$) or salbutamol ($n = 11$). The main features of patients in both treatment groups are summarized in Tables 1 and 2. Both groups were similar with respect to the items analysed.

Mean changes in the magnitude of PEF (expressed as absolute change) in both groups are reported in Fig. 1. PEF increased from 85 ± 38 l/min to 120 ± 45 l/min ($p < 0.001$) with adrenaline and from 107 ± 28 l/min to 145 ± 19 l/min ($p < 0.001$) with salbutamol. A further increase in PEF was recorded with both drugs at the second evaluation time (40 min): from 120 ± 45 l/min to 150 ± 68 l/min ($p < 0.001$) and from 145 ± 19 to 168 ± 25 l/min ($p < 0.001$) respectively with adrenaline and salbutamol. Comparison of absolute increase of PEF between baseline and 20 min, and between baseline and 40 min assessments did not show any statistically significant difference between groups. Absolute variation between baseline and 20 min evaluation was 35 ± 26 l/min in adrenaline group and