Gas exchange response to intravenous aminophylline in patients with a severe exacerbation of asthma

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Gas exchange response to intravenous aminophylline in patients with a severe exacerbation of asthma. J.M. Montserrat, J.A. Barberà, C. Viegas, J. Roca, R. Rodríguez-Roisin. ©ERS Journals Ltd 1995.

ABSTRACT: In patients with acute exacerbations of asthma, the intravenous administration of bronchodilators, such as salbutamol, entails the potential risk of worsening pulmonary gas exchange, despite an amelioration of airflow obstruction. The present study was designed to investigate the effect of intravenous aminophylline on pulmonary gas exchange in patients hospitalized with a severe exacerbation of asthma.

We studied 12 patients (aged 41 ± 13 yrs) admitted to the hospital because of an exacerbation of asthma. The study was of a randomized, double-blind, placebo-controlled design. Six patients were treated with intravenous aminophylline and six received placebo, in addition to standard treatment with inhaled salbutamol and intravenous corticosteroids. Forced spirometry, respiratory gas exchange, ventilation-perfusion relationships assessed with the multiple inert gas elimination technique, and systemic haemodynamics were measured at baseline and 60 min after treatment started.

In the aminophylline-treated group, mean theophylline plasma levels increased to 15.2 ± 3.6 $\mu\text{g}\cdot\text{ml}^{-1}$, forced expiratory volume (FEV_1) increased by $17 \pm 12\%$, and forced vital capacity (FVC) by $16 \pm 10\%$. The mean changes in FEV_1 and FVC in the aminophylline-treated group were significantly higher than in the placebo-treated group. Likewise, minute ventilation increased by $23 \pm 14\%$ and arterial carbon dioxide tension (Paco_2) decreased by 0.4 ± 0.3 kPa (3 ± 2 mmHg) during aminophylline infusion. No significant changes in arterial oxygen tension (Pao_2) or in ventilation-perfusion distributions were shown in aminophylline-treated patients. In contrast, a moderate worsening in ventilation-perfusion relationships developed in placebo-treated patients, as assessed by an increase of the dispersion of blood flow distribution ($\log_{\text{SD}} Q$, from 1.18 ± 0.26 to 1.25 ± 0.28 , these changes in pulmonary gas exchange were not significantly different between the groups.

We conclude that intravenous aminophylline, given at therapeutic plasma levels in severe exacerbations of asthma, produces a moderate increase in airflow rates without disturbing pulmonary gas exchange.

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The use of intravenous theophylline in the treatment of severe exacerbations of asthma has been a subject of controversy for many years [1, 2]. Nevertheless, the Panel of the International Asthma Management Project and the National Heart, Lung and Blood Institute [3], as well as the British Thoracic Society [4], recommend the use of theophylline in patients who need hospital admission because of an acute exacerbation of the disease. Furthermore, in view of the potential anti-inflammatory effect of theophylline [5], a reappraisal of its role in asthma management has recently been proposed [6, 7].

The intravenous administration of bronchodilators in patients with acute exacerbations of asthma entails the potential risk of worsening pulmonary gas exchange, despite the improvement in airflow rates [8]. The increase

in cardiac output and/or the release of hypoxic vasoconstriction, that most bronchodilators can produce when given at high doses, are likely to account for a further worsening of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality [9]. Aminophylline may increase cardiac output [10], reduce pulmonary artery pressure [11] and, in some cases, decrease arterial oxygen tension (Pao_2) [12]. Accordingly, the potential detrimental effect of aminophylline on pulmonary gas exchange should be considered before treating patients with acute exacerbations of asthma with this drug, especially those cases with more critical hypoxaemia.

In a previous study, we have shown that intravenously administered aminophylline moderately increased flow rates and did not modify pulmonary gas exchange in a group of patients with chronic obstructive pulmonary

disease (COPD) recovering from an acute exacerbation [13]. However, hypoxic vasoconstriction was ablated whilst breathing 100% oxygen, as assessed by a further $\dot{V}_A/\dot{Q}$ worsening.

Taking into account this background, the present study was designed to evaluate the acute effect of intravenous aminophylline on pulmonary gas exchange, specifically assessing the $\dot{V}_A/\dot{Q}$ ratio distributions, in a group of patients hospitalized with acute severe asthma, by using a placebo-controlled, double-blind design.

Methods

Subjects

Twelve nonsmoking patients (9 females and 3 males), aged 21–62 yrs, admitted to the hospital because of a severe exacerbation of asthma were studied. Main anthropometric and baseline functional data are shown in table 1. All patients fulfilled the criteria for the diagnosis of asthma [3] and had failed to respond to standard bronchodilator therapy, being hospitalized as judged by attending physicians in the emergency room. Patients received standard treatment with inhaled salbutamol (either aerosolized at a dose of 400 μg ·6 h^{-1} or nebulized at a dose of 2.5 g ·6 h^{-1}), intravenous

corticosteroids (40–60 mg ·6 h^{-1}), and supplemental oxygen if needed, as decided by the housestaff of the ward.

The study was performed between 24–72 h (mean 51 ± 17 h) after admission. At the time of the study, all patients had symptoms, predominantly shortness of breath and wheezing. All the patients were afebrile, and no evidence of atelectasis or consolidation was shown on the chest radiograph.

The study was approved by the Research Committee on Human Investigations of the Hospital Clinic, and written informed consent was obtained from each participant, after the purpose and risk of the investigation was explained and understood.

Procedures

Triplicate measurements of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were performed (Datospir 2002, Sibel, Spain) according to the recommendations of the European Respiratory Society [14]. Predicted equations were those of our own laboratory [15].

Blood samples were collected anaerobically through a small Teflon catheter (Seldicath 3F, Plastimed, France) inserted into the radial artery. Arterial pH, Pao_2 , and

Table 1. – Individual anthropometric and lung function data at baseline on entry to the study

Pat. No.	Sex	Age	Weight	Height	Theophylline* plasma level	FVC	FEV ₁	Pao ₂	Paco ₂	A-aPO ₂	Logsd	Logsd
		yrs	kg	cm	µg·ml ⁻¹	% pred	% pred	mmHg (kPa)	mmHg (kPa)	mmHg (kPa)	Q	V
Aminophylline Group												
1	F	48	68	157	14.9	50	46	72 (9.6)	35 (4.7)	34 (4.5)	1.31	0.61
2	F	62	77	151	10.2	18	17	51 (6.8)	47 (6.3)	39 (5.2)	1.41	0.90
3	F	50	50	150	19.6	57	48	63 (8.4)	31 (4.1)	47 (6.3)	1.33	1.12
4	F	50	100	164	16.8	57	54	64 (8.5)	37 (4.9)	39 (5.2)	1.39	0.75
5	F	21	55	155	12.0	88	73	77 (10.3)	31 (4.1)	35 (4.7)	1.09	0.74
6	F	52	89	168	17.8	40	28	56 (7.5)	42 (5.6)	42 (5.6)	1.00	1.23
Mean		47	73	158	15.2	52	44	64 (8.5)	37 (4.9)	39 (5.2)	1.25	0.89
SD		13	19	7	3.6	23	20	10 (1.3)	6 (0.8)	5 (0.7)	0.17	0.24
Placebo Group												
7	M	27	71	173	1.6	78	40	83 (11.1)	37 (4.9)	21 (2.8)	1.04	1.09
8	F	28	50	158	<0.5	44	42	58 (7.7)	32 (4.3)	52 (6.9)	1.69	0.81
9	M	41	72	169	<0.5	61	32	67 (8.9)	36 (4.8)	38 (5.1)	1.13	1.05
10	M	57	54	146	<0.5	64	38	78 (10.4)	33 (4.4)	30 (4.0)	0.95	0.85
11	F	37	78	158	<0.5	62	45	67 (8.9)	38 (5.1)	36 (4.8)	1.17	0.76
12	F	24	46	159	<0.5	51	26	62 (8.3)	37 (4.9)	47 (6.3)	1.09	1.20
Mean		36	62	161		60	37	69 (9.2)	35 (4.7)	37 (4.9)	1.18	0.96
SD		12	13	10		12	7	10 (1.3)	2 (0.3)	11 (1.5)	0.26	1.18

*: theophylline levels obtained by the blinded intravenous treatment during the study. Pat: patient; M: male; F: female; % pred: percentage of predicted value; FVC: forced vital capacity; FEV_1 : forced expiratory volume in one second; Pao_2 : arterial oxygen tension; Paco_2 : arterial carbon dioxide tension; A-a PO_2 : alveolar-arterial oxygen gradient; Logsd Q: log standard deviation of blood flow distribution; Logsd V: log standard deviation of ventilation distribution.

arterial carbon dioxide tension (P_{aCO_2}) were analysed in duplicate using standard electrodes (IL 1302, Instrumentation Laboratories, Milano, Italy). Haemoglobin concentration was measured with a co-oximeter (IL 482, Instrumentation Laboratories, Milano, Italy). A central venous catheter was used to inject indocyanine green dye to measure the cardiac output by the dye dilution method (Waters Instruments Inc., Rochester, NY, USA) and for the drug infusion.

A low dead space, low resistance, nonrebreathing valve (model 1500, Hans Rudolph Instruments, Kansas City, MO, USA) connected to a heated metal mixing chamber was used to collect mixed expired gas. Respiratory rate and minute ventilation were measured using a calibrated Wright respirometer (Respirometer MK8, BOC-Medical, Essex, UK). Oxygen uptake and CO_2 production were computed from mixed expired O_2 and CO_2 concentrations measured by mass spectrometry (Multigas MS2, Ohmeda BOC, UK). The alveolar-arterial oxygen gradient ($A-aP_{O_2}$) was calculated according to the standard alveolar gas equation, using the measured respiratory exchange ratio.

Ventilation-perfusion distributions were estimated by using the multiple inert gas elimination technique [16]. A full description of the technique as it is performed in our laboratory has been published previously [17]. The position of both perfusion and ventilation distributions was described by the $\dot{V}_A/\dot{Q}$ ratio at their mean, and their dispersion about the mean by the second moment on a log scale ($\log_{SD} Q$ and $\log_{SD} V$, respectively). The normal 95% confidence interval for $\log_{SD}$ is 0.3–0.6 [18]. The index $DISP R-E^*$, the root mean square difference among measured retentions and excretions of the inert gases corrected for the dead space, was also used as an overall descriptor of $\dot{V}_A/\dot{Q}$ mismatch (normal values ≤ 3.0) [19]. Shunt was defined as the fraction of cardiac output perfusing units with $\dot{V}_A/\dot{Q}$ ratios < 0.005 , and dead space as the ventilation to lung units with $\dot{V}_A/\dot{Q} > 100$.

Plasma levels of theophylline were measured by fluorescence polarized immunoassay.

Measurements

All studies were performed at the same time of the day (between 10 a.m. and 12 noon), with individuals breathing room air and seated in an armchair. Theophylline preparations and β_2 -agonists were withdrawn 24 and 12 h before the study, respectively. Other drugs, such as corticosteroids, as well as oxygen therapy, were kept unmodified. Once the patients were stable and the inert gas solution had been infused for more than 45 min, baseline measurements were performed. Subsequently, a loading dose of aminophylline (6 mg·kg⁻¹ body weight in 50 ml of 5% dextrose in water (D/W)) or placebo was administered over 20 min, followed by a maintenance infusion at a rate of 0.9 mg·kg⁻¹·h. Patients received aminophylline or placebo randomly, and both drugs were supplied in coded ampoules of identical

appearance. Sixty minutes after the infusion of aminophylline or placebo had started, all the measurements were repeated again. All patients completed the study without side-effects. Inhaled salbutamol (three puffs) was administered to all patients at the end of the study.

Data analysis

Data are expressed as mean $\pm$ SD. Differences between aminophylline- and placebo-treated patients at baseline were analysed using the Mann-Whitney test for two independent samples. The effect of treatment within each group was assessed by using the Wilcoxon test for two related samples. Differences between aminophylline and placebo effects were further analysed by comparing the changes from baseline in the two groups using the Mann-Whitney test. Differences were considered statistically significant whenever the value of p was lower than 0.05.

Results

Although no significant differences in age, time since admission, serum theophylline concentration, and baseline spirometric and gas exchange measurements were noticed between the two groups, aminophylline-treated patients were slightly older and showed lower spirometric values (table 1). Nevertheless, baseline gas exchange data were very similar in the two groups. At baseline, taken together, these patients with an acute exacerbation of asthma showed severe airway obstruction, moderate hypoxaemia, and severe $\dot{V}_A/\dot{Q}$ mismatch.

The $\dot{V}_A/\dot{Q}$ ratio distributions were moderately to severely abnormal in all subjects, following a pattern similar to that originally described, by our research group, in patients with acute severe asthma [8, 20, 21]. The distribution of pulmonary blood flow was broader than normal, and five patients exhibited a bimodal blood flow distribution profile with distinct low $\dot{V}_A/\dot{Q}$ regions. Mean perfusion to units with low $\dot{V}_A/\dot{Q}$ ratio (< 0.1), excluding shunt, was $9.8 \pm 8.5\%$ of pulmonary blood flow. Mean shunt of the whole population was small ($1.5 \pm 2.4\%$ of cardiac output) and dead space ($26.4 \pm 10.6\%$ of ventilation) was within normal limits in most cases. At baseline, the two groups were similar with respect to minute ventilation, breathing frequency, cardiac output, heart rate, and oxygen uptake (table 2).

Effects of aminophylline on spirometric measurements

Mean plasma levels of theophylline in the aminophylline-treated group increased to $15.2 \pm 3.6 \mu\text{g}\cdot\text{ml}^{-1}$, whereas they were negligible in placebo-treated patients (table 1). In aminophylline-treated patients, the mean percentage increases in FEV_1 and FVC were 17 ± 12 and $16 \pm 10\%$ respectively ($p < 0.05$ each) (table 2 and fig. 1). However, the FEV_1/FVC ratio remained unchanged after treatment, indicating that the change in FEV_1 , during

Table 2. – Spirometric, haemodynamic and gas exchange responses to placebo (n=6) and aminophylline (n=6)

	Placebo Group		Aminophylline Group	
	Baseline	Treatment	Baseline	Treatment
FEV ₁ l	1.19 (0.35)	1.19 (0.28)	1.24 (0.67)	1.43 (0.70) ^{#†}
FVC l	2.44 (0.96)	2.32 (0.77)	1.84 (0.92)	2.12 (0.95) ^{#†}
$\dot{V}_E$ l·min ⁻¹	7.8 (1.6)	8.2 (2.0)	7.8 (1.2)	9.5 (0.9) [#]
fR (min ⁻¹)	15 (5)	15 (4)	18 (6)	20 (4)
$\dot{Q}_T$ l·min ⁻¹	6.7 (1.4)	6.5 (1.4)	5.9 (1.9)	6.7 (1.6)
HR beats·min ⁻¹	97 (15)	89 (9)	81 (12)	91 (16) [†]
$\dot{V}_{O_2}$ ml·min ⁻¹	209 (17)	204 (41)	213 (70)	241 (65)
PaO ₂ mmHg	69 (10)	70 (8)	64 (10)	68 (11)
kPa	9.2 (1.3)	9.3 (1.1)	8.5 (1.3)	9.1 (1.5)
Paco ₂ mmHg	35 (2)	35 (1)	37 (6)	34 (6) ^{#†}
kPa	4.7 (0.3)	4.7 (0.1)	4.9 (0.8)	4.5 (0.8)
A-aPO ₂ mmHg	37 (11)	38 (10)	39 (5)	40 (4)
kPa	4.9 (1.5)	5.1 (1.3)	5.2 (0.7)	5.3 (0.5)
Shunt % $\dot{Q}_T$	2.3 (3.2)	2.5 (4.0)	0.8 (1.2)	2.3 (2.5)
$\bar{Q}$	0.48 (0.14)	0.48 (0.16)	0.55 (0.22)	0.67 (0.24)
LogSD Q	1.18 (0.26)	1.25 (0.28) [#]	1.25 (0.17)	1.22 (0.29)
$\bar{V}$	1.64 (0.53)	1.76 (0.46)	1.63 (0.34)	1.72 (0.30)
LogSD V	0.96 (0.18)	0.98 (0.17)	0.89 (0.24)	0.80 (0.13)
Dead space ml·breath ⁻¹	122 (56)	144 (39)	124 (27)	128 (41)
DISP R-E*	15.7 (3.0)	17.0 (2.4)	13.9 (4.9)	12.8 (3.5)

Data are presented as mean (SD). #: p<0.05, compared with baseline in each group (Wilcoxon test); †: p<0.05, compared with the change after treatment in the placebo group (Mann-Whitney test). $\dot{V}_E$: minute ventilation; $\dot{Q}_T$: cardiac output; HR: heart rate; $\dot{V}_{O_2}$: oxygen uptake; $\bar{Q}$: mean position of blood flow distribution; $\bar{V}$: mean position of ventilation distribution; DISP R-E*: root mean square difference among measured retentions and excretions of the inert gas corrected for the dead space. For further abbreviations see legend to table 1.

Fig. 1. – Effect of: a) aminophylline; and b) placebo on forced expiratory volume in one second (FEV₁) and ventilation-perfusion relationships. Individual values of (FEV₁) and the dispersion of blood flow distribution (logSD Q) before and after initiating aminophylline (—●—) or placebo (—○—) infusion. The mean values are indicated by diamonds at the sides of each panel. NS: nonsignificant.

aminophylline infusion was essentially due to the increase in FVC. Both changes in FEV₁ and FVC in aminophylline-treated patients were significantly higher (p<0.05 and p<0.01, respectively) than in placebo-treated patients (2±12 and -4±8%, respectively).

Minute ventilation increased by 23±14% (p<0.05) during aminophylline infusion (table 2), but no significant

difference from the change observed in the placebo-treated group (6±17%) could be established. No significant changes in breathing frequency and tidal volume after treatment were noticed in the two groups.

Effects of aminophylline on pulmonary gas exchange

During aminophylline infusion PaO₂ did not change, whereas Paco₂ decreased slightly (-0.4±0.3 kPa (-3±2 mmHg)) but significantly (p<0.05). The change in Paco₂ in aminophylline-treated patients was significantly different from that in the placebo-treated patients (p<0.05), whose Paco₂ remained unchanged (table 2).

No changes in the position, the dispersion, or the pattern of $\dot{V}_A/\dot{Q}$ distributions were observed in the aminophylline-treated group. The overall index of $\dot{V}_A/\dot{Q}$ mismatch (DISP R-E*), as well as the amount of shunt, perfusion to low $\dot{V}_A/\dot{Q}$ units (from 13±10% to 9±7% of cardiac output), and dead space remained essentially unchanged during aminophylline infusion (table 2). By contrast, in the placebo-treated group a moderate $\dot{V}_A/\dot{Q}$ worsening was noticed. The dispersion of blood flow distribution (logSD Q) increased slightly (by 6±5% from baseline) but significantly (p<0.05) after treatment (table 2 and fig. 1). Nevertheless, when comparing the mean change in the two groups, no significant differences could be established.

In patients receiving aminophylline, a minor increase in heart rate took place, as compared with patients receiving placebo (p<0.05) (table 2). By contrast, aminophylline treatment did not modify either cardiac output (p=0.22) or oxygen uptake (p=0.17).

Discussion

The present study shows that, in severe exacerbations of asthma, intravenous aminophylline moderately improves airflow rates without having detrimental effects on pulmonary gas exchange.

Theophylline administration is currently considered in patients with an acute exacerbation of asthma needing hospital admission [3, 4]. Although the bronchodilator effect of the drug is moderate when compared with other bronchodilators such as short-acting beta-agonists [8], there is some evidence that adding aminophylline to the standard treatment with beta-agonists and corticosteroids improves the outcome of patients with acute severe asthma [22, 23].

Despite the low number of subjects in each group, the results of the present study confirm that intravenous aminophylline has an acute bronchodilator effect in patients with a severe exacerbation of asthma already receiving intense corticosteroid therapy for more than 24 h. However, the bronchodilator effect of aminophylline can be considered moderate, accounting for only a 17% improvement in FEV_1 , when compared with the 44% increase in FEV_1 produced by inhaled salbutamol in similar patients [8]. The improvement in FEV_1 was parallel to that in FVC, probably reflecting the fact that the bronchodilator effect of intravenous aminophylline was preferentially exerted in peripheral airways and resulted in a decrease of air-trapping. The improvement in airflow rates was accompanied by a significant increase in minute ventilation and a moderate decrease in $Paco_2$. It is difficult to establish whether the latter changes resulted from the decrease in airway resistance or from a direct effect of aminophylline on respiratory muscles. Despite the improvement in ventilatory mechanics, no difference in dead space was noticed after aminophylline infusion.

The intravenous administration of aminophylline did not produce any significant change in $\dot{V}_A/\dot{Q}$ ratio distributions. In contrast, in the placebo-treated group a moderate worsening of $\dot{V}_A/\dot{Q}$ relationships took place, probably as a consequence of the time-course of the study and the lack of an adequate bronchodilator treatment throughout it. A potential detrimental effect of aminophylline on pulmonary gas exchange has been suggested previously [12]. The mechanism proposed was the release of hypoxic pulmonary vasoconstriction by the drug resulting in the deterioration of $\dot{V}_A/\dot{Q}$ relationships. Experimental studies attempting to test this hypothesis have reached different conclusions. Whereas the hypothesis was corroborated by HALES and KAZEMI [24] and BISGARD and WILL [25], BENUMOF and TROUSDALE [26] reached the opposite conclusion. Studies performed in dogs suggest that the release of hypoxic vasoconstriction by aminophylline takes place only at high plasma concentrations, above the conventional therapeutic range [27]. Clinical studies assessing the effect of aminophylline both on PaO_2 and $A-aPo_2$ have also reported conflicting results [12, 28, 29]. In a previous study conducted in patients with COPD recovering from an acute exacerbation, we also found no significant changes in $\dot{V}_A/\dot{Q}$ ratio distributions after the infusion of intravenous aminophylline [13]. Therefore,

our results support the notion that intravenous aminophylline, given at therapeutic levels, does not produce any significant deterioration of pulmonary gas exchange in patients with acute exacerbations of obstructive airway diseases, such as asthma and COPD.

The absence of effect of aminophylline on pulmonary gas exchange could not be attributed to inadequate blood levels of the drug or to a lack of reactivity of the pulmonary vessels, since patients with acute severe asthma exhibit a significant worsening of $\dot{V}_A/\dot{Q}$ relationships when breathing 100% O_2 , indicating a conspicuous vascular response to hypoxia [8, 30]. Moreover, in a previous study in patients with COPD, we showed that, whereas aminophylline exerted no effect on pulmonary gas exchange, 100% oxygen breathing elicited a significant vascular response [13].

The lack of effect of intravenous aminophylline on gas exchange in patients with acute severe asthma contrasts with the effects produced by salbutamol when given intravenously [8], or when using inhaled drugs, such as isoproterenol, with less selective beta₂-adrenergic activity [9]. Our group reported that the intravenous administration of salbutamol resulted in a substantial deterioration of $\dot{V}_A/\dot{Q}$ relationships, despite a significant improvement in airflow rates [8]. In contrast, the inhaled administration of the drug exerted no effect on gas exchange and improved airflow rates to a similar degree. The deleterious effect of intravenous salbutamol was ascribed to an increase both in cardiac output and in oxygen uptake induced by the drug, that took place despite the selective beta₂-adrenergic activity of the drug [8]. Aminophylline also has effects on cardiac output and oxygen uptake [10, 11], two extrapulmonary factors that could potentially modulate pulmonary gas exchange [31]. Nevertheless, in the present study we did not find any significant change in such measurements during aminophylline administration.

The absence of improvement in $\dot{V}_A/\dot{Q}$ relationships in aminophylline-treated patients, whereas airflow rates increased, reinforces the view that gas exchange and spirometric indices are dissociated in patients with severe exacerbations of asthma [20, 21]. Accordingly, spirometry would reflect the behaviour of large and middle-sized airways, whereas gas exchange would be affected predominantly by the narrowing and occlusion of small bronchioles.

In summary, our results show that intravenous administration of aminophylline in acute severe asthma moderately improves airflow rates, without having any detrimental effect on $\dot{V}_A/\dot{Q}$ relationships. Accordingly, it seems reasonable to anticipate that the combined therapy of an inhaled short acting beta₂-agonist and aminophylline in patients with severe exacerbations of asthma needing hospital admission, as has been recently been proposed by consensus guidelines [3, 4], will result in optimal bronchodilation without further disturbing pulmonary gas exchange.

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