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Early administration of two intravenous bolus of aminophylline added to the standard treatment of children with acute asthma ☆

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Summary
Objectives: Evaluate the efficacy of adding two intravenous bolus of aminophylline to the standard treatment of acute asthma episode in children admitted to the pediatric emergency room (PER).
Methods: Between March 2001 and February 2002, 60 children (2–5 years old), admitted to the PER at Hospital de Clínicas de Porto Alegre (Brazil), due to an episode of acute asthma, refractory to conventional therapy (an oral dose of steroids and at least three doses of inhaled albuterol, associated or not with oxygen) were enrolled in a randomized, double blind, placebo controlled clinical trial. The randomization was performed in blocks of 10 patients, who received a "bronchodilator solution" (either saline or aminophylline), in two doses: on arrival at the PER and again 6 h later. The intervention group received aminophylline 5 mg/kg/dose diluted in normal saline (NS) solution up to a 20 mL volume, while the placebo group received plain NS, both in an infusion rate of 1 cc/min. The main outcomes were total length of hospital stay, length of supplemental oxygen use, number of bronchodilator nebulizations and/or aerosol inhalations performed and patient destination. The groups were compared using the Students *t*-test, Mann–Whitney test and Chi-Square test, accepting $p<0.05$ as significant.
Results: Comparing the main outcomes, we did not find differences between the placebo and aminophylline groups: 29.0 ± 14.7 versus 26.2 ± 13.4 beta-agonist nebulizations per patient ($p=0.46$); 2.4 ± 10.6 versus 5.6 ± 14.2 aerosol inhalations per patient ($p=0.32$); 24.7 ± 30.0 versus 26.0 ± 25.2 h for oxygen supplement ($p=0.86$); 43.2 ± 30.0 versus

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43.6 ± 23.7 h for length of hospital stay ($p = 0.95$). We also did not find differences between the two groups related to the blood pressure, heart rate, respiratory rate and oxygen saturation.
Conclusion: In children aged 2–5 years admitted to a PER with asthma, two intravenous doses of 5 mg/kg of aminophylline given 6 h apart did not change the length of stay in hospital, the number of nebulizations given or the duration of oxygen therapy required. We are unable to tell whether there would be benefit with higher doses of aminophylline designed to give levels in the usual therapeutic range.

Introduction

Methylxanthines have been used for treating bronchial asthma for over 50 years.[1] Theophylline and the soluble salt, aminophylline, have multiple potential beneficial actions in asthma, e.g.: bronchial muscle relaxation, improvement in diaphragm contractility, anti-inflammatory effect, diuretic function and increase in mucociliary activity.[2]

For a long time, aminophylline was considered as a first line drug for the treatment of acute asthma. In the last 20 years, some studies failed for demonstrating any additional benefit of this drug in the pediatric population, when corticosteroids and beta-agonist therapy are properly used. Nowadays aminophylline is considered as a second line drug for acute asthma treatment.[3–7]

In spite of the above-mentioned studies, aminophylline is still being considered as a therapeutic option in some centers. Recently, aminophylline was considered by the UK pediatricians working in the general wards as a first line agent for emergency respiratory disease.[8] We speculate that in spite of the guidelines, there is no consensus among pediatricians related to the aminophylline indications in pediatric patients. It seems to be more significant for those children with asthma attack under 5 years old.[9]

The aim of this study was to evaluate the efficacy of early administration of two IV bolus of aminophylline added to the conventional treatment in children (2–5 years old) with acute asthma admitted to the pediatric emergency room (PER).

Patients and methods

Between March 2001 and February 2002, all 2–5 year old children with a diagnosis of acute asthma admitted to the PER at Hospital de Clínicas de Porto Alegre (HCPA) were invited to participate in the study.

The inclusion criteria were the presence of an acute asthma episode refractory to an oral dose of corticosteroids (prednisolone or prednisone 1 mg/kg) and three consecutive nebulizations with albuterol (150 μg/kg/dose), or three consecutives inhalations of metered-dose albuterol (50 μg/kg/dose) over an 1-h period, associated or not with supplemental oxygen (nasal catheter or mask) to maintain hemoglobin saturation above 90%.

Patients who needed immediate tracheal intubation, had known allergy to methylxanthines, had used such medication in the previous hours, had a history of difficult to control convulsive seizures in the last week, had a seizure episode at the time of admission, were excluded. To avoid drug interactions, patients who were in current use of erythromycin, cimetidine, phenytoin, phenobarbital, carbamazepine or rifampicin were also excluded.

The study was previously approved by the Committee of Research and Ethics in Health at Hospital de Clínicas de Porto Alegre (HCPA, Brazil). One of the parents of all included children in the study should sign the informed consent.

The diagnosis of refractory asthma and the indication for admission to the pediatric emergency unit was exclusively decided by discretion of the attending physicians. The researchers had no influence on this decision neither on the prescriptions.

The patients were allocated in two treatment groups. Randomization was generated in blocks of 10 patients (5 in each group). The intervention group (group I) received two doses of IV aminophylline (5 mg/kg—at 6 h of interval) diluted in saline solution (up to 20 cc) and the placebo group (group II) received two infusions (at 6 h of interval) of normal saline (NS) solution (20 cc). The placebo solution (NS solution) and aminophylline infusion had the same color and volume (20 mL) infused at a rate of 1 cc/h over 20 min and it was impossible to discriminate them by direct inspection alone.

The head nurse of the PER was responsible for disclosing the codes and preparing the solutions according to the sequence of randomization. This nurse was not involved with the patient care. The serum levels of aminophylline were measured in 17% of patients from both groups. Thus, from the 41st to the 50th patient, blood sample was collected 1 h after the first dose of the solution infusion.

The attending physician in charge at the PER evaluated clinically all patients included in the study. Clinical data (heart rate, respiratory rate, hemoglobin oxygen saturation and blood pressure) were recorded 15 min before and after the first dose and the second dose, and also 1, 12 and 24 h after the second dose of the bronchodilator solution. The patients were followed until the hospital discharge searching for length of oxygen supply, number of inhaled albuterol, length of hospital stay and internal transferences (ward or PICU admission).

The protocol for initial asthma treatment at emergency department is based on three inhaled doses of beta agonists every 20 min, systemic steroids and oxygen supply. Inhalation with beta agonist could be delivered by: (a) nebulization with face mask, at oxygen (8 L/min) and albuterol (150 μg/kg till maximum of 5 mg) diluted in NS (3 mL);

(b) For those children who were regular users of MDI at home, they were treated with MDI plus spacer (albuterol 50 μg/kg up to a maximum of 1000 μg or 10 puffs). Inhaled albuterol at every 20 min is maintained over 1–4 h depending on the severity of the crisis and on the response of the patient. After this period the interval could be enlarged (every hour) for those patients who showed good response. For those children not responding after 4 h of inhaled albuterol, intravenous albuterol infusion or PICU admission is considered. The researchers were not involved with these decisions that were at the discretion of the staff members of the PER.

The main outcomes considered were length of supplemental oxygen, number of bronchodilator nebulizations or aerosol puffs, length of stay in the PER (in h). The criteria adopted by the staff members of the PER for defining modifications in the treatment are based on: arterial saturation of oxygen and signs of respiratory distress (respiratory rate and retractions). Discharge was just considered for those children without any respiratory distress, on inhaled albuterol not more frequently than every 3 h of interval and without oxygen supply. The staff members defined the destination of the patient (hospital discharge, transfer to the pediatric ward or to the ICU) which was also considered as a main outcome.

To calculate the sample size, we defined a minimum difference of 20% in the length of oxygen use (h), establishing $\alpha = 0.05$ and $\beta = 0.10$, to detect an effect size (mean/standard deviation difference) greater than or equal to 0.90 (moderate magnitude). Taking these characteristics into account and considering similar studies in medical literature, the estimated sample size was 30 patients per group.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 9.0 for windows, SPSS Inc., Chicago, IL, USA).

The continuous variables means were compared using the Student's *t*-test. For those variables without normal distribution, Mann–Whitney test was used. Categorical variables were compared through the Chi-Square test (using the Yates correction), or the Exact Fisher test. We defined a value of $p < 0.05$ as significant.

Results

Between March 2001 and February 2002, 60 patients were included in the study. There were no losses or refusal by the family members. Although children in both groups were more often enrolled during Autumn and Winter (47/60; 78.3%), this difference was not significant ($p = 0.34$).

No significant differences were observed between the two groups at the entry of the study in terms of general characteristics (Table 1), except for the time after onset of current attack at admission, which was shorter in the aminophylline group (15.0±9.3 versus 22.0±19.5 days; $p = 0.04$).

Half of the patients included in the study received at least one nebulization before being admitted to the PER and 23.3% received an oral dose of steroids at home.

Physical examination findings at the time of study enrollment were not different between the two treatment groups (Table 2).

Table 1 General characteristics of the population.

Characteristics	Aminophylline Group I ($n = 30$)	Placebo Group II ($n = 30$)	Total ($n = 60$)	*p*
Age (years)				
Median (interquartile interval; 25–75%)	3.1 (2.4–3.8)	2.9(2.4–4.4)		0.63†
Male (%)	12 (40)	9 (30)	21(35)	0.59‡
First episode of wheezing (months)				
Median (interquartile interval; 25–75%)	12 (6.3–22.5)	12 (7.0–20.5)		0.85†
Frequency of hospital admissions (%)				
EOR	19 (63.3)	14 (46.7)	33 (55)	0.29‡
Ward	11 (36.7)	17 (56.7)	28 (46.7)	0.19‡
PICU	4 (13.3)	3 (10)	7 (11.7)	1.00‡
Time of onset of current crisis (h)				
Median (interquartile interval; 25–75%)	13.5 (8.3–18.8)	17.5 (10–22.3)		0.43†
Use of medication at home in the last 24 h (%)				
Inhaled β-2 adrenergic	11 (36.7)	19 (63)	30 (50)	0.07‡
Oral β-2 adrenergic	3 (10)	3 (10)	6 (10)	1.00‡
Oral corticosteroids	8 (26.7)	6 (20)	14 (23.3)	0.76‡
Exposure to smoking at home: patients (%)	17 (56.7)	17 (56.7)	34 (56.7)	1.00‡

SD, standard deviation; EOR, emergency observation room; PICU, pediatric intensive care unit.
*Student's *t*-test for independent samples.
†Mann–Whitney test.
‡Chi-Square test or Exact Fisher test.

Table 2 Physical examination of the patients at the time of inclusion in the study.

Characteristics	Aminophylline Group I ($n = 30$)	Placebo Group II ($n = 30$)	p
Dyspnea			
Absent	0	0	0.61
Moderate *n* (%)	29 (96.7)	27 (90)	
Severe *n* (%)	1 (3.3)	3 (10)	
Level of consciousness			
Normal *n* (%)	28 (93.3)	22 (73.3)	
Normal-excited *n* (%)	2 (6.7)	8 (26.7)	0.83
Excited-depressed	0	0	
Use of accessory muscles			
Mild	0	0	
Moderate *n* (%)	26 (86.7)	26 (86.7)	1.00
Severe *n* (%)	4 (13.3)	4 (13.3)	
Auscultation of the lungs			
Wheezing at the end of expiration *n* (%)	2 (6.7)	4 (13.3)	
Ins/expiratory wheezing *n* (%)	27 (90)	22 (73.4)	0.22
Inaudible vesicular murmur *n* (%)	1 (3.3)	4 (13.3)	

Table 3 Interventions and outcomes observed in the aminophylline and placebo groups.

Characteristics	Aminophylline Group I ($n = 30$)	Placebo Group II ($n = 30$)	p
Number of nebulizations, per patient*	24.5 (19–36)	23.0 (16–36)	0.46†
Number of sprays, per patient*	30 (14–57)	28 (14–53)	0.64‡
Length of oxygen use during the period in hospital (h)*	17.5 (6–26)	19.4 (12–31)	0.39‡
Length of hospital stay (h*)	30.8 (24–55)	40.0 (26–55)	0.48‡
Intravenous salbutamol *n* (%)	1 (3.3)	3 (10)	0.61§
Destination			
Discharged from EOR *n* (%)	25 (83.3)	21 (70)	
Admission to ward *n* (%)	5 (16.7)	8 (26.7)	0.36§
Admission to PICU *n* (%)	0	1 (3.3)	

*Median (interquartile interval; 25–75%).
†Student's *t*-test for independent samples.
‡Mann–Whitney test.
§Chi-Square test or Exact Fisher test.

The mean serum level of aminophylline in the intervention group was $7.37 \pm 1.39\,\mu g/mL$, whereas in the placebo group was $0.38 \pm 0.11\,\mu g/cc$ ($p < 0.01$).

No significant differences were found between the groups related to the main outcomes (Table 3). Concerning to supplemental oxygen, we observed that 5 patients (16.7%) in group II did not use it, 12 (40%) needed it for at least 24 h by extra nasal catheter and four (13.3%) for longer than 48 h. On the other hand, in the intervention group seven (23.3%) did not need it, 14(46.7%) used it for a period of at least 24 h and 4 (13.3%) used it for a period of over 48 h, without any significant difference in any of these parameters.

We did not find any statistical difference between both groups related to the physiologic signs (Table 4) evaluated in the "*pre*", "*post*" and "1 h *later*" moments for the IV bolus infusions (groups I and II).

Discussion

In this study we could not demonstrate any beneficial effect when two IV loading doses of aminophylline were added to the standard treatment for acute asthma in children less than 5 years old admitted to the emergency department in consequence of refractory crisis. We did not observe any significant difference between the two groups related to the length of stay in the observation room, the length of oxygen use, the number of beta agonist nebulizations and/or the

Table 4 Physiologic variables of patients with acute severe asthma pre, post and 1 h after IV bolus infusions.

Variables	Aminophylline Group I ($n = 30$)	Placebo Group II ($n = 30$)	p
Heart rate			
Pre	146.47 ± 12.29	145.40 ± 16.26	0.78
Post	146.43 ± 15.10	140.27 ± 16.89	0.14
1 h after	141.03 ± 17.46	142.57 ± 18.95	0.75
Respiratory rate			
Pre	46.17 ± 9.84	42.80 ± 10.37	0.20
Post	45.23 ± 8.26	42.90 ± 11.05	0.36
1 h after	43.37 ± 8.83	41.03 ± 8.51	0.30
Systolic blood pressure			
Pre	105.17 ± 14.88	107.33 ± 17.21	0.30
Post	110.67 ± 21.16	106.33 ± 14.97	0.18
1 h after	106.00 ± 19.40	106.67 ± 16.47	0.44
Diastolic blood pressure			
Pre	64.00 ± 10.03	62.83 ± 8.87	0.32
Post	66.00 ± 14.29	62.50 ± 9.17	0.13
1 h after	63.67 ± 11.59	62.67 ± 9.07	0.35
Hemoglobin saturation			
Pre	94.30 ± 1.86	94.60 ± 3.11	0.65
Post	95.33 ± 1.79	95.53 ± 1.70	0.66
1 h after	95.27 ± 2.32	95.47 ± 2.29	0.74

Data presented as mean ± standard deviation. HR, heart rate; RR, respiratory rate; BP, blood pressure; Hb, hemoglobin. Pre = 15 min before IV bolus infusion; post = 15 min after IV bolus infusion

MDI puffs administered the destination of these patients (admission to the ward or to the PICU and/or discharge from PER). These findings are in accordance with other previous studies enrolling older children.[10–12]

Some systematic reviews evaluating the use of aminophylline compared to placebo in children with acute asthma attack, demonstrated an improvement in lung function tests in the intervention group.[13] However, as in our study, the length of hospital stay and the number of nebulizations performed with beta agonists were not reduced.[13] On the other hand, there are few studies that were able for demonstrating better outcomes when aminophylline was added to the standard treatment in children with acute asthma.[14–16]

These intriguing and controversial results involving aminophylline in children with acute asthma could be explained by different criteria inclusion and/or methodological aspects.

In spite of these controversy results related to aminophylline in asthma, this drug is still used at some centers.[8] Recently, it was demonstrated that aminophylline was available in over 90% of the general pediatrician's wards in United Kingdom. The pediatric staff working in these units elected aminophylline as one of the six most useful drugs for caring children in emergency situations.[8] This position is in opposition to the current opinion and international guidelines for asthma treatment in children.[3,6]

Conversely, Kelly, evaluating 38 emergency departments in Australia, observed that aminophylline was administered just to 6 of 1340 acute asthma crisis.[17] It should be remarked that five of these six patients had severe asthma attack. Based on our results and on other studies it seems reasonable that children with acute mild to moderate asthma have no benefits in adding aminophylline to the standard treatment. It could be reserved for those children candidates to PICU admission and/or submitted to the mechanical ventilation, where some benefits could be expected with this drug.[15,18]

Until this moment there were few studies evaluating the effect of IV bolus of aminophylline in children with acute asthma less than 5 years old. Our results demonstrated that these young group has the same response that is observed in older children when receiving the drug in a constant infusion.[11,14,15]

This study may have some bias. Our definition for refractory acute asthma attack was based only on the lack of response to the initial treatment, without an objective quantification. Nevertheless, this is an intrinsic restriction related to the age of the study subjects. The adopted criteria (lack of response to three consecutive nebulizations associated to a systemic steroid and the need of admission to the PER) reflect the real scenario at the most of pediatric emergency department, which is based on clinical response.

As observed in an studies [15,19] the majority of our patients would be classified as having mild to moderate acute asthma (see Table 2). In spite of being young children, this group with less severe asthma crisis demonstrated the same response observed in older children to the beta-agonist treatment.

For obtaining the maximal bronchodilator effect an aminophylline serum level between 10 and 20 μg/mL is recommended. However, considering the risk for side effects some authors have proposed aminophylline serum levels between 5 and 15 mg/L which could have an acceptable

bronchodilator effect with lower toxic risk.[20] In our study the average serum level of aminophylline ($7.37 \pm 1.39\,\mu g/mL$) measured 1 h after the first IB bolus infusion in 17% of the intervention group was included in this range.

However, the aim of our study was not to obtain a dose–response curve for aminophylline infusion. We intended to evaluate the effect of two IV loading doses of aminophylline added to the conventional treatment for acute asthma in children. For acute refractory asthma attack, aminophylline or beta2-agonist could be administered in a continuous infusion after a loading dose.[3,6] Nevertheless some studies have demonstrated that an early IV loading dose of salbutamol added to the conventional treatment for acute asthma in children admitted to the emergency room was able to decrease the length of stay, the number of nebulizations and the length of oxygen supply.[21,22] We speculate that in such peculiar group the same effect could be achieved after two bolus of aminophylline infusion. Two intravenous doses of 5 mg/kg of aminophylline given 6 h apart did not demonstrate any benefit when added to the conventional treatment for acute asthma in children aged 2–5 years admitted to a PER. We are unable to tell whether there would be benefit with higher doses of aminophylline designed to give levels in the usual therapeutic range.

References

1. Hermann G, Aynesworth MB. Successful treatment of persistent extreme dyspnea "Status Asthmaticus". *J Lab Clin Med* 1937; **23**:135–48.
2. Nichols D. Emergency management of status asthmaticus in children. *Pediatr Ann* 1996;**25**:394–400.
3. Werner HA. Status asthmaticus in children. A review. *Chest* 2001;**119**:1913–29.
4. Fanta CH, Rossing TH, McFadden ER. Treatment of acute asthma. Is combination therapy with sympathomimetics and methylxantines indicated? *Am J Med* 1986;**80**:5–10.
5. Littenberg B. Aminophylline treatment in severe, acute asthma. *JAMA* 1988;**259**:1678–84.
6. NHLBI/WHO. Global strategy for asthma management and prevention. In: Lefant C., editor. *Global initiative for asthma*. Bethesda: National Institute of Health, National Heart, Lung and Blood Institute; 2002 (updated 2005).
7. South M. Second line treatment for severe acute childhood asthma. *Thorax* 2003;**58**:284–5.
8. Perkin MR, Wey EQ. Emergency drug availability an general paediatric units. *Resuscitation* 2004;**62**:243–7.
9. Goodman D, Littenberg B, O'Connor GT, Brooks JG. Theophylline in acute childhood asthma: a meta-analysis of its efficacy. *Pediatr Pulmonol* 1996;**21**:211–8.
10. DiGiulio GA, Kercsmar CM, Krug SE, Alpert SE, Marx CM. Hospital treatment of asthma: lack of benefit from theophylline given in addition to nebulized albuterol and intravenously administered corticosteroid. *J Pediatr* 1993;**122**:464–9.
11. Carter E, Cruz M, Chesrown S, Shieh G, Reilly K, Hendeles L. Efficacy of intravenously administered theophylline in children hospitalized with severe asthma. *J Pediatr* 1993;**122**:470–6.
12. Strauss RE, Wertheim DL, Bonagura VR, Valacer DJ. Aminophylline therapy does not improve outcome and increases adverse effects in children hospitalized with acute asthmatic exacerbations. *Pediatrics* 1994;**93**:205–10.
13. Mitra A, Bassler D, Goodman K, Lasserson TJ, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. *Cochrane Database Syst Rev* 2005(2):CD001276.
14. Roberts G, Newsom D, Gomez K, Raffles A, Saglani S, Begent J, et al. Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomised controlled trial. *Thorax* 2003;**58**:306–10.
15. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. *Arch Dis Child* 1998;**79**:405–10.
16. Ream R, Loftis LL, Albers GM, Becker BA, Lynch RE, Mink RB. Efficacy of IV theophylline in children with severe status asthmaticus. *Chest* 2001;**119**:1480–8.
17. Kelly AM, Powell C, Kerr D. Snapshot of acute asthma: treatment and outcome of patients with acute asthma treated in Australian emergency departments. *Intern Med J* 2003;**33**: 401–13.
18. Sarnaik AP, Daphtary KM, Meert KL, Lieh-Lai MW, Heidemann SM. Pressure-controlled ventilation in children with severe status asthmaticus. *Pediatr Crit Care Med* 2004;**5**:133–6.
19. Powell CVE, Raftos J, Kerr D, Rosengarten P, Kelly AM. Asthma in emergency departments: combined adult and paediatric versus paediatric only centres. *J Paediatr Child Health* 2004; **40**:433–7.
20. Barnes PJ, Pauwels R. Theophylline in the management of asthma: time for reappraisal? *Eur Respir J* 1994;**7**:579–91.
21. Browne GJ, Penna AS, Phung X, Soo M. Randomised trial of intravenous salbutamol in early management of acute severe asthma in children. *Lancet* 1997;**349**:301–5.
22. Browne GJ, Lam LT. Single-dose intravenous salbutamol bolus for managing children with severe acute asthma in the emergency department: reanalysis of data. *Pediatr Crit Care Med* 2002;**3**:117–23.