

## Short paper

## Effect of adding aminophylline infusion to nebulised salbutamol in severe acute asthma

B M Z Zainudin, O Ismail, Khalid Yusoff

**Abstract**

**Background** – The benefit of adding theophylline to  $\beta_2$  agonists in acute asthmatic attacks has been debated frequently.

**Methods** – In an open randomised study 25 patients with severe acute asthma who presented to the emergency department were treated with either a combined nebulised salbutamol (5 mg/dose) and aminophylline infusion (0.6–0.9 mg/kg/hour), or nebulised salbutamol alone.

**Results** – The responses to treatment as measured by peak expiratory flow (PEF) and the time taken to achieve maximum PEF were similar in both groups. Side effects were observed more commonly in patients receiving the combined treatment.

**Conclusions** – Nebulised salbutamol is equally efficacious in acute asthma when given alone or in combination with aminophylline.

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Theophylline has been used to treat bronchospasm for more than 50 years.<sup>1</sup> It has non-linear pharmacokinetics with a narrow therapeutic range.<sup>2</sup> A small rise in the dose can be associated with a large increase in the serum concentration which may lead to dangerous adverse effects including death.<sup>3</sup> Combined treatment with a nebulised  $\beta$  adrenergic agent and parenteral aminophylline, either as a bolus or an infusion, is widely used for the treatment of acute severe asthma, although the benefit is not clear and the potential deleterious side effects are real. We have studied the efficacy of, and cardiovascular responses to, combined aminophylline and nebulised salbutamol compared with nebulised salbutamol alone in patients with severe acute asthma.

**Methods**

Twenty five patients aged between 18 and 60 years who presented to the Accident and Emergency Department, General Hospital, Kuala Lumpur with a severe asthmatic attack were studied between June 1991 and January 1992 after their consent was obtained. They were randomised into two treatment groups: 11 in group A and 14 in group B. Ten of the 11 patients in group A and 13 of the 14 in group B were receiving oral theophylline as one of their

antiasthma medications. Five of the 25 patients (two in group A and three in group B) had been given an intravenous bolus of aminophylline 16–36 hours before the admission for their deteriorating symptoms of asthma. Patients in group A were treated with nebulised salbutamol, 5 mg in 3 ml normal saline inhaled via a mouthpiece from a hand held jet nebuliser (Peri-Gerat 37.0002, Paul Ritzau, Starnberg, Germany) at the beginning of the study, then hourly for three hours, three hourly for the next nine hours, four hourly for 12 hours, and reducing to six hourly the following day if the patient's condition improved. They also received aminophylline infusion in dextrose 5% at a rate of 0.6–0.9 mg/kg/hour for 48 hours. Patients in group B received nebulised salbutamol in the same way as group A but without the aminophylline infusion. In addition, all patients received intravenous hydrocortisone 100 mg six hourly in the first 24 hours; this was changed on the following day to oral prednisolone 30 mg daily for two days, then 20 mg daily for two days, followed by 10 mg daily for the next two days. Oxygen 45% was given via a Hudson mask to all patients at least for the first 24 hours.

The severity of the asthma was assessed at enrolment by clinical examination, and measurement of arterial blood gas tensions and peak expiratory flow rate (PEF). Measurement of PEF was repeated before each dose of nebulised salbutamol. Blood samples were taken on admission and at 5 and 20 hours for the measurement of theophylline concentrations using an enzyme mediated immunoassay technique (EMIT). Twelve lead electrocardiography was performed on admission and 24 hour Holter electrocardiography (Oxford Medilog 4000-II) was recorded on each patient. Symptoms for side effects were assessed at 1, 6, 12, and 24 hours. Responses to treatment between the two groups were assessed by comparing the mean values of PEF at 1, 3, 6, 12, 24, 36, and 48 hours and the time taken to achieve the maximum PEF using the unpaired Student's *t* test. The cardiovascular responses were assessed by comparing the mean maximal systolic blood pressure changes from baseline and heart rate at 1, 3, 6, 12, 24, 36, and 48 hours by the unpaired Student's *t* test. The occurrence of arrhythmias and side effects were compared with  $\chi^2$  tests. Statistical significance was taken at  $p < 0.05$ .

Respiratory and Cardiology Units, Department of Medicine, University Kebangsaan Malaysia, 50300 Kuala Lumpur, Malaysia  
B M Z Zainudin  
O Ismail  
K Yusoff

Reprint requests to:  
Associate Professor  
Dr B M Z Zainudin.

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## Results

The two groups were comparable in terms of age, sex, and severity of asthma at presentation as indicated by pulse rate, PEF and  $P_{aO_2}$ . The PEF values before each dose of nebulised salbutamol *v* time for each group are summarised in fig 1. No significant difference was noted between the groups at any time of measurement. The mean (SD) time to achieve the maximum PEF values were 81.8 (31.5) hours *v* 68.6 (25.9) hours for groups A and B respectively. The difference is not significant. The cardiovascular response in terms of heart rate is shown in fig 2. All patients had sinus tachycardia, particularly for the first six hours, which fell with the improvement in lung function. The heart rate was significantly faster in group A than group B at 12 and 36 hours, and a similar trend was present throughout the treatment period. Systolic blood pressure changes were similar between the two groups (13 (9) mm Hg for group A *v* 12 (13) mm Hg for group B). Fourteen episodes of cardiac arrhythmias were noted in group A (four atrial ectopics, eight ventricular ectopics, one bigeminy, one short run of ventricular tachycardia) and 16 in group B (seven atrial ectopics, nine ventricular ectopic, one short run ventricular tachycardia). These were not significantly different. Patients in group A experienced significantly more symptoms of side effects (seven tremor, seven palpitation, nine insomnia, three nausea) than those in group B (one palpitation, four insomnia). Serum theophylline levels at 0, five, and 20 hours were 5.7 (2.4) mg/l, 10.2 (2.5) mg/l, 14.0 (1.6) mg/l for group A, and 9.7 (2.6) mg/l, 7.4 (2.1) mg/l, 3.1 (1.7) mg/l for

group B. Most patients in group A had their concentration in the therapeutic range by five hours which lasted until 20 hours. Five patients, three from group A and two from group B, had relapses of asthma after initial improvement. All of them recovered with intensification of nebulised salbutamol. One patient in group B responded poorly to therapy in the first 15 hours and subsequently was treated with aminophylline infusion. Only her baseline data were included in the analysis.

## Discussion

An intravenous bolus of aminophylline has been shown to be either equally or less efficacious than parenteral or nebulised  $\beta$  adrenergic agonists in the treatment of acute severe asthma.<sup>4-5</sup> Studies comparing the combination of aminophylline with a  $\beta$  adrenergic agent compared with a  $\beta$  adrenergic alone are, however, conflicting, either in favour of the combination therapy<sup>6</sup> or showing no difference between the two regimens.<sup>7</sup> Our results also fail to detect any difference in therapeutic response between combined aminophylline with nebulised salbutamol and nebulised salbutamol alone. Although our study was not blind and involved a relatively small number of subjects, the results would not be expected to differ with a larger group of patients as no trend in favour of either treatment was observed. The lack of benefit of adding aminophylline to nebulised  $\beta$  agonists was also noted in a meta-analysis looking at the role of aminophylline in acute asthma, although a trend was detected favouring its combination with injected  $\beta$  agonists.<sup>8</sup>

The overall cardiovascular responses did not differ significantly between the combined treatment and salbutamol alone, except for the faster heart rate observed in the combined group. This is supported by symptoms of palpitation which were more common in this group. Tachycardia, which was seen in all patients at the beginning of treatment, improved with the improvement in lung function in both groups. The incidence of arrhythmia was similar in both groups but no patient had a sufficiently severe arrhythmia to cause haemodynamic disturbances. The incidence of arrhythmia was relatively small and tended to be transient, partly because the serum theophylline concentration was maintained within the therapeutic range in most patients. This is in keeping with the findings of others.<sup>9</sup> The incidence and the severity of cardiac arrhythmias has been shown to increase when the aminophylline concentration exceeds the therapeutic range.<sup>10</sup> Although the incidence of cardiac arrhythmia was similar, the incidence of side effects in our study and others<sup>4,10</sup> was substantially higher in those patients treated with a combination of aminophylline with a  $\beta$  adrenergic agent.

We conclude that the addition of aminophylline infusion increases the toxicity, but not the efficacy, of nebulised salbutamol in the treatment of acute severe asthma.

Figure 1 Mean peak expiratory flow (PEF) values in group A and group B during the course of treatment. No significant difference was seen between the two groups.

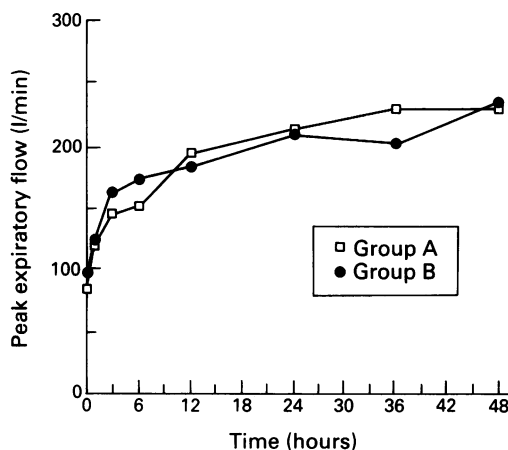
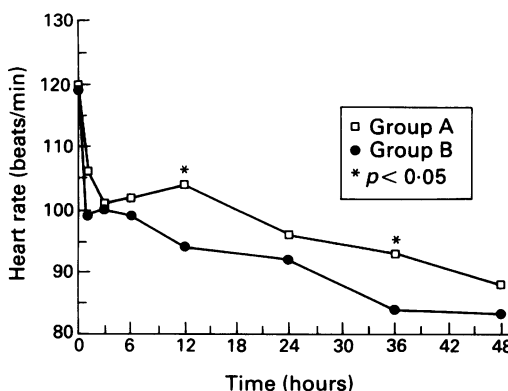


Figure 2 Mean heart rates in group A and group B during the course of treatment. The rate is significantly higher in group A than group B at 12 and 36 hours of treatment.



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## Adventitia

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### Breathless on Everest – II

Everest is not climbed in the normal sense of climbing a mountain; you must lay siege to it. This means setting up camps at several levels. Apart from base camp there is usually a Camp 1 just above the icefall at 19 000 feet and then an advanced base camp, or Camp 2, at the head of the Western Cym at 23 000 feet. Camp 3 is based half way up the Lhotse face at 24 500 feet and Camp 4 on the South Col at 26 000 feet. On the South Col you look down into Tibet or Nepal and seem to be looking out over the whole of the rest of the world. The summit of Everest lies just above you and seems tantalisingly close.

I promised myself that I would cross the icefall and try to make some measurements at advanced base camp. I made measurements of spirometry, alveolar oxygen concentration, and arterial oxygen saturation at Camp 2 and was quite pleased with the data obtained, but then heard that because two of the climbers were incapacitated, one with altitude sickness and the other with a recurring back injury, I was to be added to the climbing team. This meant that I could have a crack at the summit. It was with terrible apprehension that I left Camp 2 on 5 May 1993, heading up this most frightening mountain. We made Camp 3 quite well without oxygen and, despite being very breathless, managed to get there in good time. We settled into our tents for the rest of the day to try to get some sleep before leaving early the following morning for Camp 4 on the South Col. I was very demoralised when the first assault team joined us back at Camp 3. They had left 24 hours earlier but had been forced back by the weather before the Geneva Spur. For me, the most inexperienced member of the team, the fact that Britain's best Himalayan climbers were turning round and coming back wrecked my rather fragile courage. The next day, however, our climbing leader John Barry decided we should give it a crack.

The sun was out and the winds were moderate but the hypoxia was terrible. We were now using oxygen at 2-3 l/min, but even so could only manage three or four steps and then had to take 20 breaths. I now know what it feels

like to have end stage emphysema. It seems that anything you do – eating, talking, sitting down and standing up, or taking a single step – causes so much breathlessness that you think you are never going to make it. We eventually did make it, but climbing only 1500 feet up from Camp 3 to Camp 4 on the South Col took us eight hours. The view from there was breathtaking.

The conditions on the South Col were nothing like the pictures that appeared in the Sunday newspapers. There were certainly discarded oxygen bottles, there were even one or two bodies, but the image of a rubbish dump was completely misplaced. I was not, however, doing well myself. We took the oxygen off on the South Col and I quickly became disorientated and confused. I tried to lie down in the snow and go to sleep but luckily I was spotted by the other members of the team who got me into the tent, into my down gear and sleeping bag, and put me on oxygen at 3 l/min. I slept fitfully but awoke the next morning feeling a great deal better. I even felt well enough to make some measurements. I measured alveolar  $P_{O_2}$  and arterial saturation on each of the four of us on and off oxygen. The resting arterial oxygen saturations of the group were under 70% and, in my case, this did not improve much with oxygen. Clearly I was developing pulmonary oedema and had to get down which required help from a colleague to leave the South Col. I clipped onto the fixed ropes and stumbled and fell most of the 3000 feet back to the safety of Camp 2. After two days of recuperation there we descended to base camp. Two days later I found myself escorting Harry Taylor, another member of our team, back to Britain. He had made the second British oxygenless ascent of Everest, but he had suffered the terrible consequences of frostbite, snow blindness, and pulmonary oedema. We were lifted by helicopter from base camp to Kathmandu and within 24 hours I was back in Glasgow. My overwhelming sensation was of relief that once again I could breathe normally.

ANDREW J PEACOCK