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Intravenous Theophylline After Beta$_2$-Agonist Treatment in Severe Acute Asthma. Effect on Patients Who Are Not Pre-treated with Theophylline

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ABSTRACT

The effect of i.v. theophylline after high-dose ß$_2$-agonist treatment in severe acute asthma was studied in 30 patients from a multicentre study who reported not having taken theophylline during the last 24 hours. One hour after the start of inhaled or i.v. salbutamol treatment, all patients received 6 mg/kg of i.v. theophylline. The plasma concentration 30 minutes after the start of the theophylline infusion was 78 ± 13 µmol/l (mean ± SD). The mean change (Δ) in peak expiratory flow (PEF) was 8 ± 6% of the predicted 30 minutes after the theophylline infusion and 7 ± 5% 60 minutes after it. The increase in PEF was greater in this patient group than in a group of 101 patients from the same multicentre study who were on theophylline medication and were therefore given a reduced dose (3 mg/kg) (7 ± 5 vs. 4 ± 6% of the predicted value, $p<0.01$). The proportion of patients with an increase in PEF of ≥ 10% of the predicted at discharge was 27% (8/30) in the patient group in this investigation and 14% (14/101) in the group who was on theophylline treatment.

INTRODUCTION

Inhaled ß$_2$-agonists and systemically administered corticosteroids are recognized as the cornerstones of the modern treatment of acute asthma (2,16). Theophylline has subsequently been degraded to the position of a third-line drug in the current guidelines on the management of acute asthma (2,16). In fact, there are several studies in which no additional bronchodilatory effect has been found when theophylline has been administered with inhaled ß-agonists (1,6,15). A further disadvantage of theophylline is the risk of potential serious side-effects owing to the narrow therapeutic interval of the drug (4).

In a Swedish multicentre study, i.v. theophylline was given 60 minutes after inhaled and i.v. ß$_2$-agonist treatment (17). Most of the patients in the study were taking theophylline as maintenance treatment and were therefore given a reduced theophylline dose. In a subanalysis we found that only a small proportion of these patients had a clinically significant additional improvement after theophylline (9). Since the time of the multicentre study there has, however, been a change in therapy practice. As a result, most patients admitted because of acute asthma today are not on theophylline. The aim of this investigation was therefore to study the effect of i.v.

theophylline after β_2-agonist treatment in acute asthma on the subgroup of patients who had not taken theophylline during the last 24 hours before admission to the emergency room.

MATERIAL AND METHODS

Between September 1985 and January 1987 the Swedish Society of Chest Medicine conducted a multicentre study on the effect of i.v. versus inhaled salbutamol treatment in severe acute asthma (17). One hour after the start of salbutamol treatment (Ventoline, Glaxo), i.v. theophylline was given to both patient groups. An infusion of aminophylline (Teofyllamin, ACO) in a dose corresponding to 6 mg/kg of theophylline was given to patients who had not taken theophylline during the last 24 hours. The dose was reduced to 3 mg/kg in those patients who had taken oral theophylline.

In this analysis we have only included those patients who were not taking oral theophylline before treatment and were thus given a dose corresponding to 6 mg/kg of theophylline. We have excluded the patients who reported having taken bronchodilatory drugs for which no method of determining the plasma level was available; they included fenoterol, orciprenaline, isoprenaline and ipratropium bromide. This analysis thus comprised 30 adult patients (13 men and 17 women, mean age 54 years, range 18-73) who attended the emergency room with a severe acute attack of asthma (peak expiratory flow rate (PEF) of $\leq$ 50% of the patient's predicted normal value (7), pulse rate of $\geq$ 100 beats/min.). As initial treatment 15 patients received inhaled salbutamol (0.15 mg/kg x 2) and 15 received i.v. salbutamol (5 µg/kg). The infusion time for the i.v. aminophylline was 20-30 minutes.

Blood samples for the determination of plasma theophylline levels were taken before the start of treatment and 30 minutes after the start of the aminophylline infusion. Plasma theophylline levels were determined at the Department of Clinical Pharmacology at Sahlgren's University Hospital, Gothenburg, using a high-pressure liquid chromatographic method (5). Using this method, the lowest detectable level is 1 µmol/l. The coefficient of variation is 4% for a plasma level of 3 µmol/l and 3% at 55 µmol/l. Plasma levels of salbutamol and terbutaline were determined 55 minutes after the start of the salbutamol treatment. From the result of the salbutamol and terbutaline assay an estimation of the total β_2-agonist plasma concentration was made. The methods for this drug concentration assay and for the estimation of the total β_2-agonist plasma level have been described in detail elsewhere (8).

Peak expiratory flow (PEF), pulse rate and blood pressure were followed from arrival at the emergency room until 60 minutes after the start of the theophylline treatment.

The informed consent of all patients was obtained and the study was approved by all the relevant local ethics committees.

Statistics

Differences between subgroups of the population were analysed using the Mann-Whitney U test. Spearman's rank correlation test was used to analyse the correlation of the change (Δ) in PEF after the theophylline treatment with the other variables. A p-value of < 0.05 was regarded as statistically significant.The results are expressed as mean ± SD.

RESULTS

Measurable plasma levels of theophylline before treatment were found in 20 of the 30 patients (3±2 µmol/l, range 1-9). The mean P-Theophylline concentration 30 minutes after the start of the theophylline infusion was 78 ± 13 µmol/l (range 52-102) (Fig. 1).

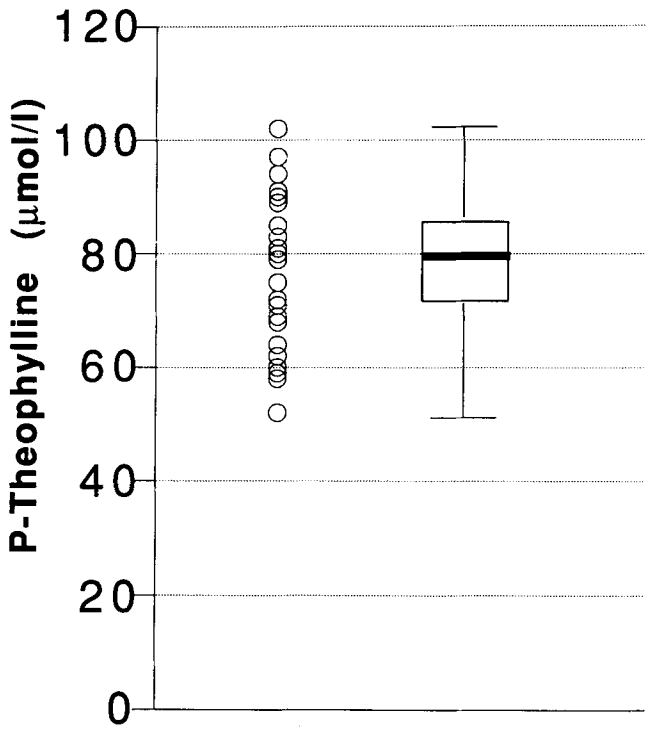

Figure 1.P-theophylline concentration 30 minutes after the start of i.v theophylline treatment (6 mg/kg) in 30 patients with severe acute asthma (individual values, median, inter-quartile range (25-75%) and range).

Following the theophylline infusion, Δ PEF was 8 ± 6% of the predicted value (40 ± 33 l/min) after 30 minutes and 7 ± 5% of the predicted (37 ± 30 l/min) after 60 minutes (Table 1).

Table 1.Peak expiratory flow, pulse rate and blood pressure before and 30 and 60 minutes after treatment with 6 mg/kg of i.v. theophylline (n=30).
(Mean ± SD) (* p<0.05, ** p<0.01, *** p<0.001, compared with before treatment.)

		Before	30 min	60 min
Peak expiratory flow	(% of predicted)	45±16	53±15***	53±15***
	(l/min)	229±82	269±86***	266±82***
Pulse rate	(beats/min)	99±21	104±21**	103±19*
Systolic blood pressure	(mm Hg)	137±25	133±21	131±19
Diastolic blood pressure	(mm Hg)	85±15	82±14	84±14

Patients treated with inhaled salbutamol displayed a significantly greater increase in PEF before the theophylline infusion than those treated with i.v. salbutamol (p<0.05). There was, however, no significant difference in Δ PEF after the theophylline treatment between the inhalation and i.v. salbutamol group (Fig. 2). At discharge (60 minutes), 8 patients had an increase of ≥ 10% of the predicted value. Four of these patients had received inhaled salbutamol and 4 i.v. salbutamol.

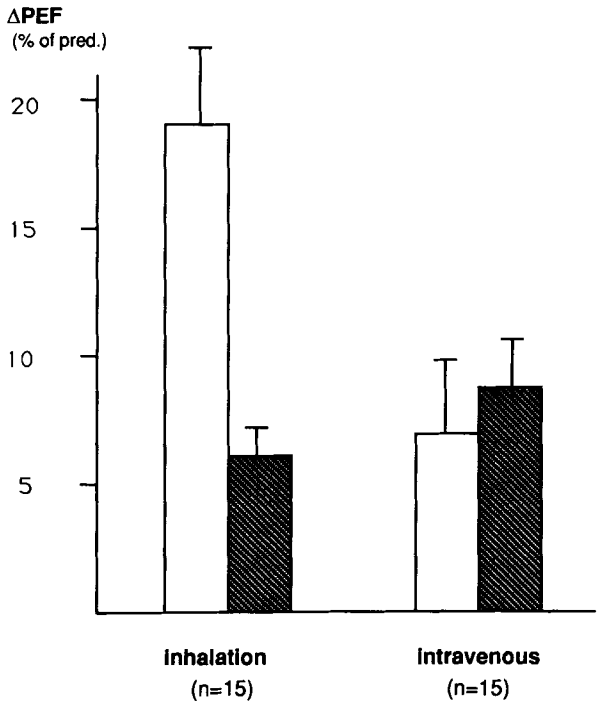

Figure 2.Change in PEF (mean and SE) 55 minutes after inhaled or intravenous salbutamol (open bars) and 60 minutes after the addition of intravenous theophylline (cross-hatched bars).

No significant correlations were found between the post-theophylline increase in PEF and age, sex, PEF before treatment, Δ PEF before theophylline, P-β_2-agonist concentration or Δ P-theophylline after treatment.

The increase in PEF after theophyline treatment was significantly greater in the study group in this investigation than in a group of 101 patients from the same multicentre study who were on theophylline medication and were therefore given a reduced theophylline dose (3 mg/kg) (8 ± 6 vs. 4 ± 6% after 30 minutes and 7 ± 5 vs. 4 ± 6% of the predicted after 60 minutes, $p<0.01$). The number of patients with an increase in PEF of ≥ 10% of the predicted at discharge was 8 (27%) in this investigation and 14 (14%) in the group who were on theophylline treatment. The average increase in PEF before the theophylline infusion was 13% of the predicted in both groups.

DISCUSSION

When designing the Swedish Society of Chest Medicine's multicentre study, the main purpose was to compare the effect of inhaled and intravenous β_2-agonist treatment in severe acute asthma. A further aim was to see whether theophylline was of any clinical use after high-dose β_2-agonist treatment. In our first report, our conclusion was that it was doubtful whether theophylline had any clinical effect after high-dose inhaled β_2-agonists (17). This conclusion was, however, criticized as being based on data which was not totally convincing (3). This caused us to make a subanalysis of the effect of i.v. theophylline on patients who were taking oral theophylline as maintenance treatment. In this investigation, there was a small group of patients who did improve rather well after i.v. theophylline. This group was characterized by having subclinical P-theophylline concentrations before treatment (9).

The Swedish multicentre study was conducted from 1985 to 1987. Since then therapy practice has changed. Maintenance treatment with theophylline has markedly declined at least in Sweden (10). A large proportion of patients who currently seek emergency treatment are therefore not on theophylline. These patients can be given a larger theophylline dose without increasing the risk of toxic side-effects. The negative correlation between plasma concentration before treatment and the treatment effect reported earlier (9) indicates that patients without theophylline pre-treatment might be most suitable for emergency treatment with i.v. theophylline. Our results partly support this hypothesis. Consequently the proportion of patients whose PEF increased by 10% or more compared with the patients predicted value after i.v. theophylline was 27% (8/30) in this patient group compared with 14% (14/101) of the patients who had taken theophylline before emergency treatment.

On the basis of previous dose-effect studies, a dose of 5-6 mg/kg theophylline is usually recommended in the treatment of acute asthma in patients who are not taking theophylline (12,16). In this study nearly all the patients reached a P-theophylline concentration of above 55 μmol/l, while none reached a concentration

above the upper limit of the therapeutic interval (110 μmol/l). We can thus confirm that a theophylline dose of 6 mg/kg is a suitable loading dose in the emergency treatment of patients who are not on theophylline medication.

As would be the case in a clinical setting, the question of whether the patients had taken theophylline before arrival or not was based on their own reports. In several of the patients we found small but measurable levels of theophylline. These might have been caused by theophylline taken earlier than 24 hours before arrival. In some patients the low theophylline levels might also have been caused by drinking tea as tea contains small levels of theophylline (13). The theophylline concentrations measured were below the level at which they could have influenced the clinical outcome.

As in our previous report (9), the effect of theophylline appears to be relatively unrelated to the β_2-agonist treatment. As a result, we found no significant difference between the effect in patients treated with inhaled or i.v. salbutamol. There was no significant correlation between the estimated P-β_2-agonist concentration before treatment and the effect of the theophylline infusion. In both our investigations the response to theophylline was also unrelated to the patient's age, sex, pre-treatment PEF or the level of change in PEF after β_2-agonist treatment. There was also no difference in PEF response to salbutamol between the patient group with and the group without theophylline pre-treatment.

Lately there has been a discussion as to whether theophylline, apart from being a bronchodilator, also has other effects of possible therapeutic value. In one American study, theophylline treatment was reported to decrease the need for hospital admission despite the fact that there was no difference in the effect on lung function between the patients who were given theophylline and the control group (18). The author suggests that this might be caused by an anti-inflammatory effect. An editorial commenting on the study speculates on a possible future rise for theophylline in asthma treatment (11). Our results are a further indication that it is perhaps not possible to completely count-out theophylline in the treatment of severe acute asthma. We conclude that after high-dose β_2-agonist treatment there is a subgroup of patients in whom i.v. theophylline produces a further bronchodilation of probable clinical value. The factors causing this interindividual difference in theophylline response are not known at present.

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