

High-dose inhaled *versus* intravenous salbutamol combined with theophylline in severe acute asthma

Swedish Society of Chest Medicine

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ABSTRACT: In a multicentre parallel group study we studied 176 adult patients (53% men) with severe acute asthma (peak expiratory flow (PEF), 15-50% of predicted values). The effect of two doses of inhaled salbutamol (0.15 mg·kg⁻¹ × 2; 30 min apart) (n=87) was compared with that of one dose of salbutamol given intravenously (5 µg·kg⁻¹) (n=89). There was a significantly larger increase in peak expiratory flow after the first inhaled dose in the group that received inhalation treatment than in the *i.v.* treated group (69 vs 41 l·min⁻¹, p<0.05), but there was no difference in systemic side-effects between the groups. After the second inhaled dose there was a further increase in PEF, but also in systemic side-effects. These treatments were also compared in a cross-over study on 18 of the patients who returned with a second attack of severe acute asthma. The cross-over evaluation produced similar results, with a significantly larger increase in PEF after the first inhaled dose than after the *i.v.* treatment. Fifteen of the 18 patients found the inhalations more effective than the *i.v.* treatment. Theophylline (3-6 mg·kg⁻¹) was infused *i.v.* 60 min after the start of salbutamol treatment, and a significant increase in PEF was observed in both groups. A correlation between the increase in PEF and the increase in plasma theophylline concentration was only found in the group that had received *i.v.* salbutamol. The results of this study suggest that inhalation of β₂-agonists is preferable to systemic administration in treatment of severe acute asthma, and that for this treatment an inhalation dose of salbutamol of 0.15 mg·kg⁻¹ is suitable.

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Beta₂-agonists are widely used as the first-line treatment in acute asthma, but the route of administration varies between hospitals and countries. In studies with comparisons of inhaled nebulized and intravenously infused β₂-agonists in the treatment of acute asthma in adults these treatments have often been found to be equally effective in relieving bronchoconstriction [1-4], but inhalation therapy has sometimes been found to be more favourable regarding side-effects [1, 2]. Other studies have indicated, however, that intravenous infusions are more effective in relieving bronchoconstriction in severe acute asthma [5, 6].

Intravenous theophylline is often given in acute asthma together with β₂-agonists. The risk of theophylline intoxication and doubt as to whether theophylline has any clinically important additional effect when administered after optimum β₂-agonist treatment have raised the question of the appropriateness of using theophylline in acute asthma [7-9].

The principal aim of this study was to compare the effect of two high doses of inhaled salbutamol with that of one intravenous salbutamol infusion in patients with acute severe asthma. An additional purpose was to determine whether further improvement could be achieved by adding intravenous theophylline to the β₂-agonist treatment. The study was to comprise a sufficiently large number of patients to enable statistically reliable conclusions to be drawn [10].

Material and methods

Twenty five Swedish hospital departments involved in the treatment of acute asthma were invited to participate in the study. Thirteen agreed to take part and it was intended that 20 patients from each hospital should be included. An advisory group was set up by the Scientific Committee of the Swedish Society of Chest Medicine. One physician and one nurse from each hospital were appointed as the persons responsible for participation in the study. The study protocol was worked out by the advisory group together with the appointed physicians

and nurses during several pre-study meetings. The informed consent of all patients was obtained and the study was approved by all of the local ethics committees involved.

Patients

The study comprised adult patients who attended the emergency room with a severe acute attack of asthma. Such an attack was defined as a rapid deterioration in airway obstruction, severe enough to bring the patient to the hospital emergency room with a pulse rate of ≥ 100 beats·min⁻¹ and a peak expiratory flow (PEF) of $\leq 50\%$ of the patient's predicted normal value [11].

All of the patients had asthma, defined as a previous history of variable dyspnoea and wheezing and a response to β_2 -agonists, and at least one of the following additional inclusion criteria: 1) a diurnal variation in PEF of at least 25%; 2) reversibility of airway obstruction by at least 15% after β_2 -agonist treatment; 3) bronchial hyper-reactivity as demonstrated by methacholine or histamine provocation.

The patients who were excluded were those with extremely severe bronchoconstriction (PEF $< 15\%$ of the predicted value), known chronic respiratory insufficiency, severe heart disease or severe hypertension, aged more than 75 yrs and those receiving treatment with β -receptor-blocking drugs.

Since only a few physicians and nurses were to participate from each hospital, it was considered impossible to conduct this study on consecutive patients. It was therefore anticipated that the majority of the patients who were included would be those arriving at the hospital during office hours.

Procedure

The study lasted from September 1985 to January 1987. During this period 178 patients entered the study. One hospital did not include any patients, and two patients from another hospital were later excluded because of incorrectly completed records. From the remaining 11 hospitals 176 patients were included. The median number of patients from each hospital was 20, with a range of 4–22. At least one patient in both treatment groups was included from each hospital.

The study was performed as an open study in which patients were randomly allocated, in blocks of four at each centre, to treatment in two parallel groups. One group (n=87) was treated with inhalation of two doses of salbutamol and the other (n=89) with a single dose of intravenously infused salbutamol. The timing of the treatments and the times of measurements of the effects are shown in figure 1.

The patients allocated to receive inhalation treatment were given 0.15 mg·kg⁻¹ body mass of salbutamol (Ventoline, Glaxo) in an undiluted solution (5 mg·ml⁻¹) with a Pari Inhalier Boy nebulizer (Paul Ritzau, Pauli Werk). The nebulizers, which are driven by compressed air, are reported to produce a mass median particle diameter of 9.7 μ m, with an intrapulmonary deposition of 35% of the particles [12]. The nebulizers were specially obtained for this study and had not been used before. The nebulizations, which were supervised by the appointed nurse, were interrupted during expiration, and continued until the nebulizer was dry in order to reduce the wastage of the nebulized solution. The nebulization treatment was repeated after 30 min, making a total dose of 0.30 mg·kg⁻¹. The mean duration of each nebulization was 7 min (SD 4 min).

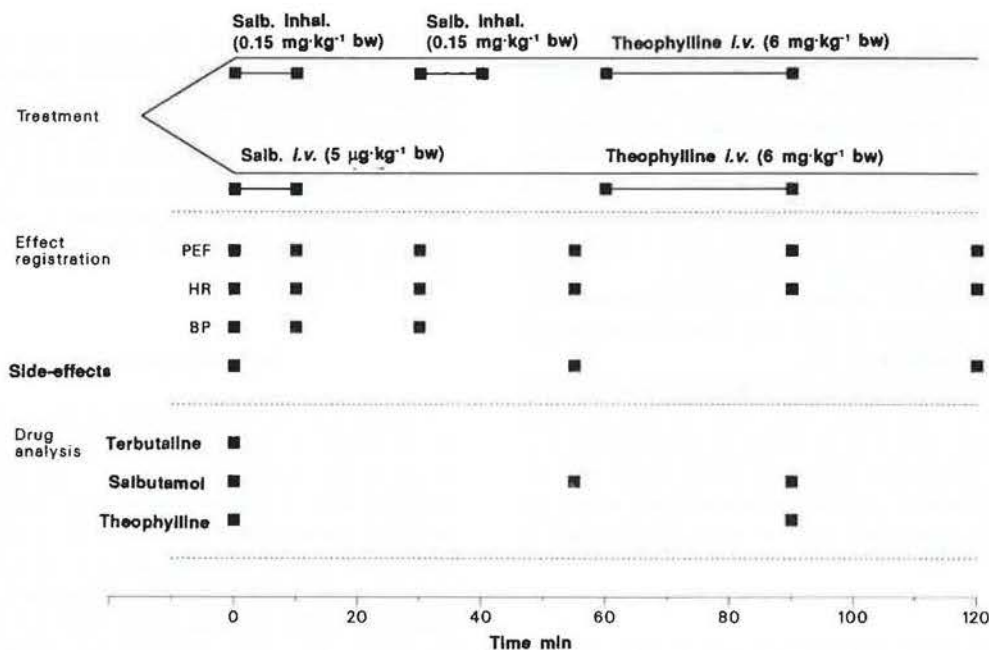


Fig. 1. – Timing of treatment, recording of effects and blood analysis. Salb: salbutamol; inhal: inhalation; PEF: peak expiratory flow; HR: heart rate; BP: blood pressure; bw: body weight.

The patients allocated to receive *i.v.* treatment were given an infusion of 5 $\mu\text{g}\cdot\text{kg}^{-1}$ of salbutamol (Ventoline, Glaxo) (50 $\mu\text{g}\cdot\text{ml}^{-1}$) over a period of 10 min. An infusion of aminophylline (Teofyllamin, ACO) corresponding to 6 $\text{mg}\cdot\text{kg}^{-1}$ of theophylline was given 60 min after the start of the salbutamol treatment. The aminophylline dose was reduced to half in patients who had taken oral theophylline during the last 24 h ($n=138$). The infusion time was 20 min at the beginning of the study but after hypotensive reactions in two patients it was later changed to 30 min. Patients who had received theophylline either by injection or by rectal applicator during the last 24 h ($n=3$) did not receive *i.v.* theophylline.

Recording of effects

The following variables were measured before the start of the treatment, immediately after each inhalation or infusion and 30, 55, 90 and 120 min after the start of the treatment: PEF, best of three values with a Wright peak flow meter (the peak flow meters were all new and calibrated.); pulse rate; systolic and diastolic blood pressure, measured with a sphygmomanometer. The patients were asked about the following symptoms before and 55 and 120 min after the beginning of the treatment: headache, nausea, abdominal symptoms, palpitations, tremor, and any other symptoms. They rated the symptoms from 0 (none) to 3 (severe).

The study was completed after 120 min and the attending physician made a final evaluation as to whether the asthmatic symptoms had improved, worsened or were unchanged, and whether the patient needed more bronchodilatation treatment. The physician was then free to give additional treatment, which in most cases consisted of *i.v.* corticosteroids. Oxygen was given at the discretion of the physician.

Drug plasma level assay

Venous blood samples were taken before and 55 and 90 min after the start of the treatment. After centrifugation the plasma was removed, frozen, and stored at -20°C until analysed. Plasma levels of salbutamol, terbutaline and theophylline were measured at the times shown in figure 1. Salbutamol and terbutaline were assayed simultaneously, using a gas chromatographic mass spectrometric method [13]. Plasma theophylline levels were determined by a high-pressure liquid chromatographic method [14].

Cross-over study

Patients who returned to the emergency room a second time with severe acute asthma ($n=18$) were eligible for a cross-over study in which a simplified protocol was used. The evaluation at the second visit was terminated after 55 min. Blood samples for plasma drug levels were not taken that time. The patients were asked to state which

treatment they preferred and the reasons for their preference.

Statistical analysis

It was calculated that 150–200 patients would be required in order to achieve a power of 90% at the level of 0.05 provided that the difference in the change in PEF between the treatments was about 15%. The differences between the study groups were analysed by means of Pitman's test. For analysing the differences within each study group, Fisher's permutation test for paired comparisons was used [15]. The influence of the severity of the bronchial obstruction before treatment on the effect of the treatments was analysed by Mantel's test [16].

For analysis of the differences between the treatments in the cross-over evaluation, Fisher's test for paired comparisons was used [15]. Comparison in terms of preference was performed by the sign test.

A difference with a *p* value of less than 0.05 (two-tailed test) was considered significant.

Results

There were no significant differences between the two study groups in their characteristics or medication on entry into the study, apart from the fact that slightly fewer in the nebulization group were receiving treatment with β_2 -agonists by nebulizers at home (table 1).

Table 1. – Patient characteristics on entry into the study (mean \pm SD or percentage of patients)

	Nebulization ($n=87$)	Infusion ($n=89$)
Age yrs	58 \pm 12	55 \pm 13
Males	49%	56%
PEF $l\cdot\text{min}^{-1}$	170 \pm 47	166 \pm 70
PEF % of predicted	33 \pm 9	31 \pm 8
Pulse rate $\text{beats}\cdot\text{min}^{-1}$	112 \pm 9	111 \pm 10
Blood pressure systolic mmHg	145 \pm 20	140 \pm 21
Blood pressure diastolic mmHg	87 \pm 11	88 \pm 12
β_2 -agonists dose aerosol	92%	89%
β_2 -agonists	37%	43%
β_2 -agonists nebulization	11%	21%
Theophylline oral	80%	76%
Corticosteroids inhalation	67%	62%
Corticosteroids oral	30%	30%
Ipratropium inhalation	5%	6%
Plasma terbutaline level $\text{nmol}\cdot\text{l}^{-1}$ ($n=124$)	22 \pm 18	24 \pm 20
Plasma salbutamol level $\text{nmol}\cdot\text{l}^{-1}$ ($n=119$)	30 \pm 29	24 \pm 26
Plasma theophylline level $\mu\text{mol}\cdot\text{l}^{-1}$ ($n=138$)	35 \pm 22	34 \pm 25

p<0.05

PEF: peak expiratory flow.

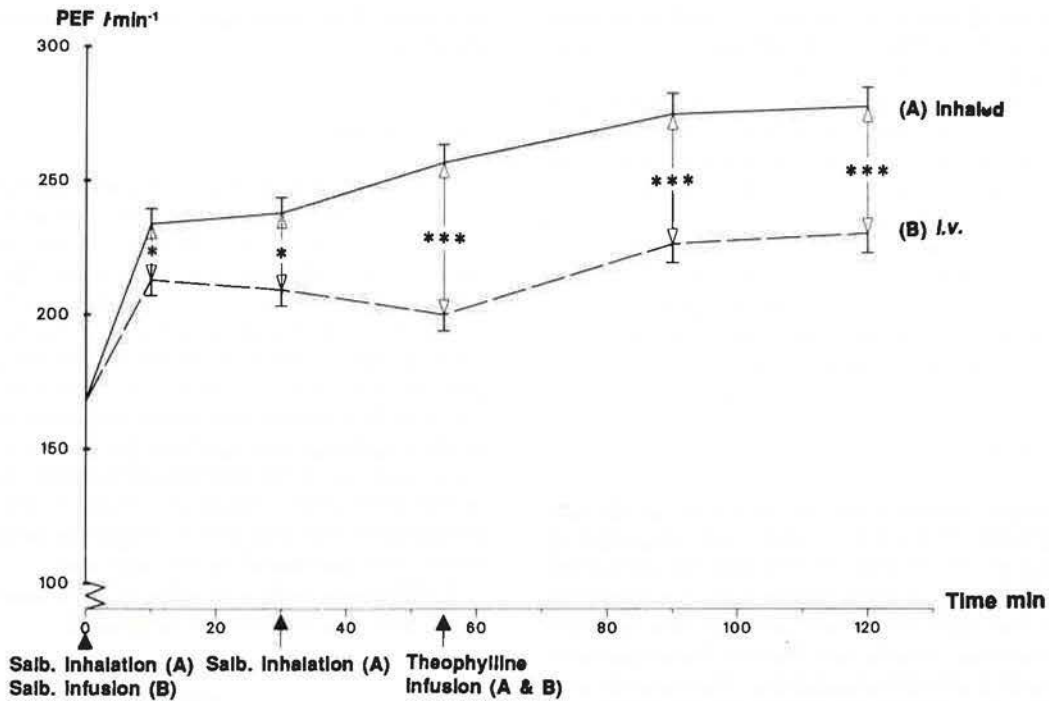


Fig. 2. - PEF (mean \pm SE) in patients treated with inhaled salbutamol (A) and intravenously infused salbutamol (B). Significance levels refer to individual changes from initial values (*: $p < 0.05$; ***: $p < 0.001$). PEF: peak expiratory flow; Salb: salbutamol.

Δ PEF at 30 min % pred

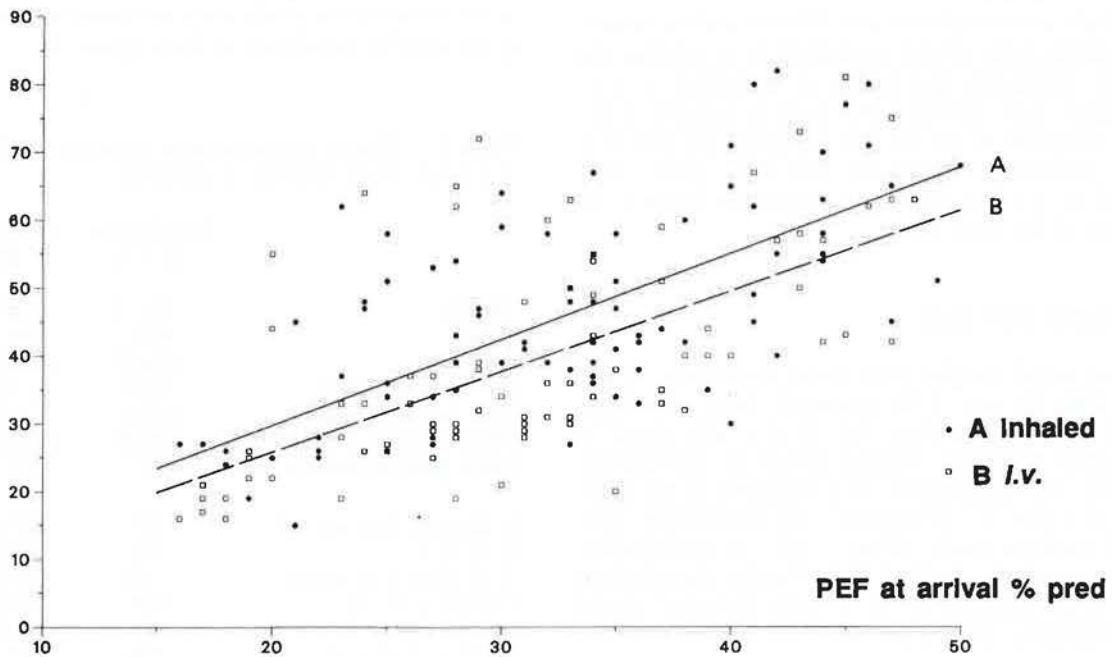


Fig. 3. - Bronchodilating effects of treatment with inhaled salbutamol (A) and of intravenously infused salbutamol (B) 30 min after the start of treatment in relation to PEF on arrival. (Regression lines and individual values). PEF: peak expiratory flow.

Effects on lung function

A larger mean increase in PEF was noted after the first inhalation than after the *i.v.* infusion. This difference was apparent immediately after completion of the

treatment and was more pronounced 30 min after the start (fig. 2). The difference between the effect of the treatments was observed irrespective of the initial degree of bronchial obstruction (percentage of predicted PEF) (fig. 3). After the second inhaled dose, there was at 55

min a significant further increase in mean PEF, whereas in the group of patients treated intravenously PEF had started to decrease at that time (fig. 2).

The volume of the nebulized solution varied from 1.4–3.0 ml. There was no significant correlation between the volume of the solution and the increase in PEF 30 and 55 min after start of inhalation treatment.

The theophylline infusions were given 60 min after the start of the salbutamol treatment, and a significant increase in the mean PEF was observed in both study groups between 55 and 90 min ($p < 0.001$) (fig. 2). There was no significant difference in the proportion of patients in whom PEF increased by $\geq 10\%$ between 55 and 90 minutes (37% in the inhalation group vs 45% in the intravenous group).

Plasma levels

In the group treated with two inhaled salbutamol doses the mean plasma salbutamol level was $67 \text{ nmol}\cdot\text{l}^{-1}$ (SD $38 \text{ nmol}\cdot\text{l}^{-1}$) after 55 min and $48 \text{ nmol}\cdot\text{l}^{-1}$ (SD $27 \text{ nmol}\cdot\text{l}^{-1}$) after 90 min. In the patients treated intravenously the levels were $28 \text{ nmol}\cdot\text{l}^{-1}$ (SD $27 \text{ nmol}\cdot\text{l}^{-1}$) after 55 min and $18 \text{ nmol}\cdot\text{l}^{-1}$ (SD $22 \text{ nmol}\cdot\text{l}^{-1}$) after 90 min. The difference in plasma levels between the treatment alternatives at 55 and 90 min was highly significant ($p < 0.001$).

The mean plasma theophylline level after 90 min was $75 \mu\text{mol}\cdot\text{l}^{-1}$ in both groups (SD $24 \mu\text{mol}\cdot\text{l}^{-1}$ in the nebulization group and $27 \mu\text{mol}\cdot\text{l}^{-1}$ in the infusion group). The increase in PEF from 55 to 90 min and the increase in the plasma theophylline concentration from arrival to 90 min correlated significantly in the intravenous group ($p < 0.001$), but not in the inhalation group.

Systemic effects

There was no significant difference in blood pressure or pulse rate between the treatment groups after the first-inhaled dose (immediately after and 30 min after treatment). After the second inhaled dose the mean diastolic blood pressure was slightly lower at 55 and 90 min (81 vs 84 and 80 vs 83 mmHg, respectively, $p < 0.05$) and the pulse rate was higher at 55, 90 and 120 min in the inhalation group than in the *i.v.* group (fig. 4). There were more complaints of tremor after 55 and 120 min among patients in the inhalation group than in the *i.v.* group (fig. 5). There were also more complaints of palpitations after 120 min in the inhalation group than in the *i.v.* group (23 vs 9%, $p < 0.05$).

Two hypotensive reactions occurred, both during the theophylline infusions. Apart from this, no severe side-effects occurred and all of the patients managed to complete their study periods.

Physician's assessment

There was less need for additional emergency treatment (48 vs 67%, $p < 0.05$) and there was a higher

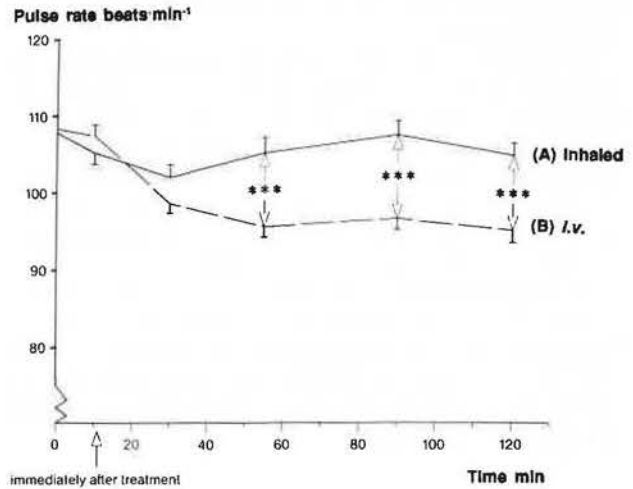


Fig. 4. – Pulse rate (mean±SE) in patients treated with inhaled salbutamol (A) and intravenously infused salbutamol (B). Significance levels refer to individual changes from initial values (***: $p < 0.001$).

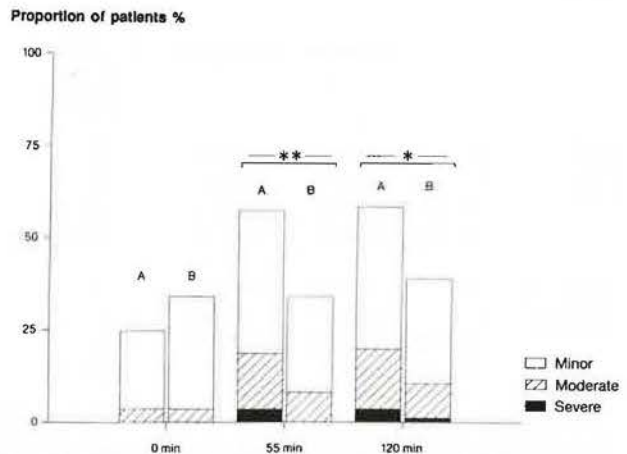


Fig. 5. – Proportion of patients with tremor before and after treatment with inhaled salbutamol (A) and intravenously infused salbutamol (B) (*: $p < 0.05$; **: $p < 0.01$).

proportion of improved asthma (92 vs 47%, $p < 0.01$) among patients receiving inhalation treatment than among those treated intravenously.

Cross-over study

In the cross-over evaluation eight patients received inhalations and ten patients *i.v.* salbutamol at their second attack of acute asthma. A larger increase in PEF was noted 30 min after the first inhaled dose than 30 min after the *i.v.* treatment (101 ± 63 vs $39 \pm 59 \text{ l}\cdot\text{min}^{-1}$, $p < 0.01$) (mean±SD). This difference in PEF increase was even more pronounced after the second inhaled dose (119 ± 68 vs $31 \pm 53 \text{ l}\cdot\text{min}^{-1}$, $p < 0.001$) (mean±SD) (table 2). On the basis of these results it was calculated that 14 patients would be needed in order to obtain a statistical power of 90% when comparing the PEF increase 55 min after the start of treatment. Using a parallel study design, 40

patients would have been required to obtain the same statistical power.

In relation to the pre-treatment values the pulse rate decreased less after the second inhalation than after the intravenous treatment (-5 ± 16 vs -11 ± 16 beats·min⁻¹, $p < 0.05$) (table 2). There was no significant difference in the change in blood pressure between the treatments, apart from the fact that there was an increase in diastolic pressure (1.5 mmHg) immediately after the inhalation and a decrease (3.9 mmHg) after *i.v.* treatment ($p < 0.01$).

Seventeen patients were asked which treatment they preferred. Fifteen preferred the inhalation treatment because it was more effective than the intravenous form. The other two patients preferred the intravenous method, one because it produced a faster effect and one because it was more comfortable.

Table 2. — PEF and pulse rate before (B) and immediately after treatment (I) and 30 and 55 min after the start of treatment (mean±sd) in the cross-over evaluation of patients who were treated twice (n=18)

		Inhalation	Intravenous	Test results of pair comparison
PEF l·min ⁻¹	B	180±50	173±49	NS
	I	263±74	227±91	NS
	30 min	281±79	212±84	$p < 0.01$
	55 min	299±87	204±78	$p < 0.001$
Pulse rate beats·min ⁻¹	B	107±13	109±13	NS
	I	104±13	108±16	NS
	30 min	102±14	102±12	NS
	55 min	103±17	97±12	$p < 0.05$

*Except for B, comparisons are made with respect to the change after the start of treatment; PEF: peak expiratory flow; NS: not significant.

Discussion

In this study, 0.15 mg·kg⁻¹ of inhaled salbutamol was found to be superior to 5 µg·kg⁻¹ of intravenously infused salbutamol in relieving bronchoconstriction in patients with an attack of severe acute asthma. Thus, in both the parallel and the cross-over study a statistically significant difference in the increase in PEF was noted after the first inhaled salbutamol dose compared with the intravenous treatment (fig. 2), while no significant difference was found in the systemic haemodynamic effects (fig. 4).

The addition of a second inhaled dose resulted in a further increase in PEF, but also caused an increase in systemic side-effects. Since only one *i.v.* infusion was given, a comparison between the two treatments after the time of the second inhalation might be somewhat misleading. Thus, the mean plasma salbutamol concentration after 55 min was much higher in the patients who had received two inhalations than in the

infusion group, and accordingly more side-effects were seen in the inhalation group at this time.

A serious drawback in many studies published on the treatment of acute asthma is their low statistical power, *i.e.* the small numbers of patients included make the risk of not detecting a clinically important difference between treatment alternatives intolerably large [10]. We therefore chose a multicentre design which made it possible to include a sufficient number of patients within a reasonable time span. On the other hand, the multicentre design with a large number of unpaid co-operating physicians led to some practical constraints, *e.g.* on the number of blood samples for drug analysis. Our results also show that the number of patients needed to achieve high statistical power is much smaller in a cross-over study than in a study with parallel groups. The difficulty involved in predicting a patient's relapse in terms of asthmatic attacks will, however, probably limit the number of cross-over studies.

It has been suggested that in patients with severe bronchial obstruction mucus plugging of the airways might prevent nebulized sympathomimetics from having an effect on the peripheral airways and that *i.v.* infusions might therefore be more effective in this condition [5, 17]. However, in our study the bronchodilating effect of the first inhaled dose was superior to that of the *i.v.* treatment, irrespective of the patient's baseline ventilatory function (fig. 3). However patients with the most severe forms of acute asthma (PEF <15% of the predicted) were not included in the study.

The inhalation treatment was preferred, both by the physicians in their assessment of asthma improvement and the need for further acute therapy, and by the patients in their preference of treatment. This further emphasizes the fact that there was a clinically important difference in the anti-asthmatic effect between the treatments.

After the theophylline infusion there was a further significant increase in PEF in both study groups. In the group treated with *i.v.* salbutamol, the mean PEF had started to decrease before the theophylline infusions were added and theophylline was therefore unquestionably of value to many patients in this group. In the group treated with salbutamol inhalations, PEF was still increasing when the theophylline treatment was added, and it is therefore uncertain whether the PEF increase in this group was a theophylline effect. Furthermore, a significant correlation between the increase in the plasma theophylline concentration and the increase in PEF was found in the *i.v.* group but not in the inhalation group.

We did not observe any severe side-effects during the β_2 -agonist treatment, but it should be noted that this study did not include patients with severe cardiovascular diseases or patients older than 75 yrs of age. We are uncertain whether the highest inhalation dose (0.30 mg·kg⁻¹) can be safely used in these patient categories.

Inhalations of large amounts of solution are time-consuming and tiring for the patients. We therefore gave the inhalations with an undiluted nebulization solution (5 mg·ml⁻¹). It has been reported, however, that

small volumes of nebulized solution lead to higher losses in the nebulizer [18], but we found no correlation between the volume of the solution and the increase in PEF after inhalation. Thus, at least in this study there are no indications that the small volumes inhaled were of negative significance. The Pari Inhalier Boy nebulizer was chosen for this study as it is the one most commonly used in emergency rooms in Sweden. The Pari Inhalier Boy nebulizer delivers particle sizes that may not be ideal [12]. It is, however, doubtful whether the particle size is crucial in this situation, as no difference in the increase in forced expiratory volume in one second (FEV_1) was found between the treatments in a study comparing the effect of a nebulized β_2 -agonist in patients with stable asthma, with use of two different flow rates generating aerosol median mass diameters of 4 μm and 11 μm , respectively [19].

When planning this study, the intention was to give as large a dose as could be considered safe. It was decided to use the doses previously suggested as being the optimum ones in terms of effects and side-effects in two dose-response studies in stable asthmatics [20, 21]. The results indicate that 0.15 $\text{mg}\cdot\text{kg}^{-1}$ of inhaled salbutamol is a threshold dose, as the repetition of this dose caused systemic side-effects and high plasma levels of salbutamol. In a follow-up study (unpublished data), however, it was found that 5 $\mu\text{g}\cdot\text{kg}^{-1}$ of *i.v.* salbutamol produces peak plasma concentration values that were even higher than those noted after the second inhaled dose in this study (59 vs 46 $\text{nmol}\cdot\text{l}^{-1}$, measured as the increase from baseline value), but the peak after the *i.v.* treatment appeared much sooner and the decline was much more rapid. This indicates that 5 $\mu\text{g}\cdot\text{l}^{-1}$ of *i.v.* salbutamol is also a threshold dose and that increasing this dose will probably cause an increase in systemic side-effects. This is also supported by other studies. In one study of treatment of acute asthma, 0.5 mg of salbutamol *i.v.* (corresponding to 8 $\mu\text{g}\cdot\text{kg}^{-1}$ with a body mass of 65 kg) produced a mean increase in heart rate of more than 20 $\text{beats}\cdot\text{min}^{-1}$ [2]. In another study in which *i.v.* terbutaline was used in acute asthma, an increase in side-effects but no further increase in PEF was observed when the dose was raised from 4 to 8 $\mu\text{g}\cdot\text{kg}^{-1}$ [22].

Our results show that inhalation of β_2 -agonists is to be preferred to systemic administration of these drugs for the initial treatment of severe acute asthma. The findings indicate that 0.15 $\text{mg}\cdot\text{kg}^{-1}$ of salbutamol is a suitable dose for this inhalation treatment. If the effect of this treatment is insufficient, there are at present no reliable guidelines in the literature as to what bronchodilating therapy should be added. The present results strongly indicate that if the inhalation of salbutamol is repeated, this will produce further bronchodilatation, but that side-effects might occur. Infusions of theophylline might be an alternative, but the effect of theophylline in this situation is doubtful [7-9]. The addition of inhaled ipratropium bromide is another possibility, since several studies have shown a further increase in bronchodilatation when this drug has been added to β_2 -agonist inhalation in the treatment of severe acute asthma [23-25].

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Salbutamol en inhalations à fortes doses ou en administration intraveineuse, en combinaison avec la théophylline dans l'asthme sévère aigu. Une étude multicentrique de 176 patients. Société Suédoise de Médecine Thoracique.

RÉSUMÉ: Au cours d'une étude multicentrique de groupe parallèle, nous avons étudié 176 sujets adultes (53% d'hommes), atteints d'un asthme aigu sévère (DEP à 15–50%

des valeurs prédites). L'effet de deux doses successive de salbutamol en inhalation ($0.15 \text{ mg}\cdot\text{kg}^{-1} \times 2$, à 30 minutes d'intervalle) ($n=87$), a été comparé avec celui d'une seule dose de salbutamol donnée par voie intraveineuse ($5 \mu\text{g}\cdot\text{kg}^{-1}$) ($n=89$). L'augmentation du débit expiratoire de pointe était significativement plus importante après la première dose par inhalation que dans le groupe traité par voie intraveineuse (69 vs. 41 $\text{l}\cdot\text{min}^{-1}$, $p<0.05$), alors qu'il n'y avait aucune différence entre les groupes en ce qui concerne les effets collatéraux systémiques. Après la seconde dose par inhalation, on note une augmentation complémentaire du DEP, mais également des effets collatéraux systémiques. Ces traitements ont été comparés également dans une étude à permutation croisée, chez 18 des patients, qui ont été réhospitalisés pour une seconde crise d'asthme sévère aigu. L'évaluation à permutation croisée a produit des résultats similaires, avec une augmentation significativement plus importante du débit de pointe après la première dose inhalée qu'après le traitement intraveineux. Quinze des dix-huit patients ont considéré que les inhalations étaient plus efficaces que le traitement intraveineux. La théophylline ($3\text{--}6 \text{ mg}\cdot\text{kg}^{-1}$) a été administrée en perfusion intraveineuse 60 minutes après le début du traitement au salbutamol, et a provoqué une augmentation significative du DEP dans les deux groupes. Une corrélation entre l'augmentation du DEP et l'augmentation de la concentration plasmatique de théophylline a été trouvée également dans le groupe qui avait reçu du salbutamol intraveineux. Les résultats de cette étude suggèrent que l'inhalation de béta₂-agonistes est préférable à leur administration systémique dans le traitement de l'asthme aigu sévère, et que, pour ce traitement, une dose d'inhalation de salbutamol de $0.15 \text{ mg}\cdot\text{kg}^{-1}$ est adéquate.

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