

Bronchodilator intake and plasma levels on admission for severe acute asthma

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ABSTRACT: We have measured the plasma levels of salbutamol, terbutaline and theophylline in 140 patients (70 men, mean age 57 yrs) arriving for emergency treatment with severe acute asthma. The aim of the study was to investigate how the measured plasma levels correlated with the reported bronchodilator intake and whether the pretreatment β_2 -agonist levels influenced the effect of emergency salbutamol treatment.

We found a highly significant correlation between the reported 24 h dose and the measured plasma concentrations for all three drugs. A plasma concentration $<40 \mu\text{mol}\cdot\text{l}^{-1}$ was found in 63 of the 107 patients who had taken theophylline, while no patient had a plasma concentration $>110 \mu\text{mol}\cdot\text{l}^{-1}$. A plasma concentration above the suggested therapeutic range was found in 23 of the 95 patients who had taken terbutaline ($>30 \text{nmol}\cdot\text{l}^{-1}$) and in 12 of the 98 patients who had taken salbutamol ($>60 \text{nmol}\cdot\text{l}^{-1}$). A significant negative correlation was found between the initial plasma β_2 -agonist levels and the bronchodilation after *i.v.* salbutamol treatment ($5 \mu\text{g}\cdot\text{kg}^{-1}$), while there was no clear indication that high plasma β_2 -agonist levels reduced the bronchodilator effect of a high dose of inhaled salbutamol ($0.15 \text{mg}\cdot\text{kg}^{-1} \times 2$).

We conclude that some patients arriving with acute asthma have high blood concentrations of β_2 -agonists, which possibly limit the response to *i.v.* β_2 -agonist treatment, while the effect of high-dose inhaled β_2 -agonists appears to be related to a lesser degree to the drug concentration on arrival. In this study overtreatment with theophylline appears to be uncommon.

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The most dramatic manifestation of bronchial asthma is the severe acute attack which requires emergency treatment and is potentially life-threatening. On such an occasion the patient has usually taken anti-asthmatic drugs at home, and this may be important when it comes to choosing the emergency room treatment.

The plasma levels of theophylline in patients arriving with acute asthma have been measured in a number of studies [1-5], while the plasma levels of β_2 -agonist drugs on arrival with acute asthma have been studied less often [1, 6]. Also, very little is known about the way the medication prior to hospital admission affects the outcome of acute asthma treatment. In one study there was no difference in the effect of emergency treatment with β -agonists between patients who had or had not taken β -agonists prior to hospital admission [7]. It has, however, been indicated that patients who have high plasma levels of β_2 -agonists on arrival improve less well on emergency treatment with β_2 -agonists than those who have lower levels [6].

The aim of this investigation was to study the plasma levels of bronchodilator drugs in patients admitted to hospital with acute severe asthma and to correlated

these with the reported drug intake. A further aim was to study the possible influence of pretreatment β_2 -agonist plasma levels on the effect of β_2 -agonist treatment in severe acute asthma.

Material and methods

Between September 1985 and January 1987, the Swedish Society of Chest Medicine conducted a multicentre study of the effect of *i.v. versus* inhaled salbutamol treatment in severe acute asthma [8]. One hundred and seventy six patients from 11 hospitals were included in this study. All of the patients had asthma defined according to our previous paper [8].

In this subsequent analysis we have excluded the patients who reported having taken bronchodilator drugs for which no method of determining the plasma level was available; they included fenoterol, orciprenaline, isoprenaline and ipratropium bromide. Patients who had received injection treatment with terbutaline or theophylline prior to arrival were also excluded. This study, thus, comprised 140 adult patients (70 men and 70 women, mean age 57 yrs, range 18-74 yrs) 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 [9], pulse rate of ≥ 100 beats \cdot min $^{-1}$) with bronchodilator treatment before admission restricted to salbutamol, terbutaline and theophylline, alone or in any combination.

The patients were randomly allocated to treatment in two parallel groups:

1. One group ($n=72$) was treated with an inhalation of 0.15 mg \cdot kg $^{-1}$ body mass of salbutamol (Ventolin, Glaxo) in an undiluted solution (5 mg \cdot ml $^{-1}$) using a Pari Inhaler Boy nebulizer (Paul Ritzau, Pauli Werk). After 30 min the treatment was repeated, making a total dose of 0.30 mg \cdot kg $^{-1}$.

2. The other group ($n=68$) received intravenous treatment with an infusion of 5 μ g \cdot kg $^{-1}$ of salbutamol (Ventolin, Glaxo) (50 μ g \cdot ml $^{-1}$), administered for 10 min.

Venous blood samples were taken before the start of treatment. After centrifugation the plasma was recovered, frozen and stored in a freezer (-20°C) until it was analysed at the Department of Clinical Pharmacology at Sahlgren's University Hospital, Gothenburg.

Salbutamol and terbutaline were assayed simultaneously using a gas chromatographic mass spectrometric method [10]. Using this method, concentrations as low as 1 nmol \cdot l $^{-1}$ can be detected. The coefficient of variation is 8% for a salbutamol level of 6 nmol \cdot l $^{-1}$ and 4% at 59 nmol \cdot l $^{-1}$. Some studies indicate that the therapeutic plasma level for salbutamol is about twice as high as that of terbutaline [12–16]. On the basis of this we estimated the total β_2 -agonist plasma concentration by multiplying the terbutaline levels by two and adding this value to the salbutamol level value (P -terbutaline $\times 2 + P$ -salbutamol).

Plasma theophylline levels were determined using a high-pressure liquid chromatographic method [11]. With this method the lowest detectable level is 1 μ mol \cdot l $^{-1}$.

The PEF (Wright Peak Flow Meter), pulse rate and blood pressure were measured prior to the start of treatment, immediately after each inhalation or infusion, and 30 and 55 min after the start of treatment.

The patients were interviewed about their medication during the 24 h prior to admission. A calculation was made of the total 24 h intake in relation to the patient's body mass (mg \cdot kg $^{-1}$). In inhaled form, salbutamol is about twice as potent as terbutaline [17]. An estimation of the total inhaled β_2 -agonist dose was obtained by multiplying the inhaled salbutamol dose by two and adding this to the terbutaline dose.

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

Statistics

The differences between the study groups were analysed using Pitman's test. The influence of the pretreatment plasma levels and inhaled drug doses on

the effect of the treatments was analysed using Mantel's test and linear regression [18]. The effect of differences in PEF in the patient group was also eliminated using Mantel's test. The correlation between reported drug dose and plasma levels was analysed using simple regression analysis.

A difference in p -values of less than 0.05 (two-tailed test) was considered significant.

Results

Drug intake

Current terbutaline medication (oral or inhaled) was reported by 95 patients and salbutamol medication by 98. The most common combination of β_2 -agonists was inhaled salbutamol and oral terbutaline ($n=50$). All but eight patients reported having used inhaled β_2 -agonists within the 24 h prior to arrival. All of these eight patients had taken oral β_2 -agonists and six had also taken oral theophylline. The number of inhalations varied considerably among the 128 patients who had used β_2 -agonist metered dose inhalers (MDI); 22 patients had taken less than eight puffs and 18 patients more than 24 puffs of their MDI (terbutaline 0.25 mg \cdot puff $^{-1}$ or salbutamol 0.1 mg \cdot puff $^{-1}$). Oral β_2 -agonists had been taken by 111 patients and theophylline (oral or rectials) by 107. All the patients who had taken theophylline had also used oral or inhaled β_2 -agonists. Eighty six patients had taken both oral β_2 -agonists and theophylline. The patients' reported drug intake is presented in table 1. In addition to the bronchodilator treatment, 85 patients had taken topical corticosteroids (beclomethasone or budesonide), 37 had taken oral corticosteroids (prednisolone or betamethasone), and one patient had taken disodium chromoglycate.

Drug plasma levels

The plasma levels of the β_2 -agonist drugs are presented in table 2. A plasma terbutaline concentration of more than 30 nmol \cdot l $^{-1}$ was found in 23 of the patients. Twelve patients had a plasma salbutamol concentration of more than 60 nmol \cdot l $^{-1}$.

The median plasma level of theophylline was 36 μ mol \cdot l $^{-1}$ (range 0 – 98 μ mol \cdot l $^{-1}$). Twenty one patients had plasma theophylline levels of between 55 – 110 μ mol \cdot l $^{-1}$. Sixty three patients had a plasma theophylline concentration of below 40 μ mol \cdot l $^{-1}$.

The number of patients who reported having taken a drug but who had no measurable plasma levels were as follows: four (4%) for terbutaline (all oral), nine (9%) for salbutamol (all aerosol), and one (1%) for theophylline.

Five patients (11%) who had not reported taking terbutaline had measurable plasma levels of terbutaline, the values ranging from 1 – 30 nmol \cdot l $^{-1}$. Nine patients (21%) who had not reported taking salbutamol had measurable plasma concentrations of salbutamol, the

values ranging from 1–38 nmol·l⁻¹. Twenty three patients who had not reported taking theophylline had measurable plasma theophylline levels, the values ranging from 1–38 μmol·l⁻¹. Of these, three (9%) patients had values of over 10 μmol·l⁻¹.

Table 1. — Reported bronchodilator drug intake of 140 patients during the 24 h prior to arrival with severe acute asthma

Drug	Median intake		Range mg
	n	mg	
Terbutaline dose aerosol	35	3.5	1–15
Terbutaline tablets	82	15	5–25
Terbutaline nebulization	6	10	5–20
Salbutamol dose aerosol	93	1.2	0.2–7.5
Salbutamol tablets	29	8	4–12
Salbutamol nebulization	13	25	2–45
Theophylline tablets	104	600	180–1200
Theophylline rectials	4	190	100–500

Table 2. — Plasma concentrations of salbutamol and terbutaline categorized on the basis of the patient's reported medication and route of administration

	Salbutamol		Terbutaline	
	n	median (range) nmol·l ⁻¹	n	median (range) nmol·l ⁻¹
All	98	17 (0–139)	95	16 (0–113)
Only oral	2	44 (39–48)	54	15 (0–68)
Only dose aerosol	57	10 (0–15)	9	4 (2–6)
Only nebulized	6	5 (3–134)	3	16 (15–29)

Reported drug intake in relation to plasma levels

A statistically highly significant correlation between the reported 24 h dose (measured as mg·kg⁻¹ regardless of the route of administration) and the plasma concentration was found for all three drugs (terbutaline $r=0.58$, salbutamol $r=0.75$ and theophylline $r=0.71$, $p<0.001$).

Treatment effects and relation to plasma levels

No significant correlation was demonstrated between the estimated total plasma β_2 -agonist level and either pulse rate ($r=0.06$) or systolic ($r=-0.13$) and diastolic blood pressure ($r=-0.08$) on arrival. A weak but significant negative correlation was found between plasma β_2 -agonist levels and PEF on arrival, when PEF was measured both as l·min⁻¹ ($r=-0.15$, $p<0.05$) and as a percentage of the predicted value ($r=-0.19$, $p<0.01$).

A statistically significant relationship was found between initially high plasma β_2 -agonist levels and less bronchodilation, a greater decrease in pulse rate and a smaller decrease in diastolic blood pressure in the group who received *i.v.* salbutamol treatment (fig. 1

and table 3). A significant negative correlation was also found between the plasma levels and PEF increase 55 min after the inhaled salbutamol treatment. After the effect of the influence of differences in PEF on arrival (measured as percentage of the predicted) was eliminated, all the correlations, apart from the one between plasma level and PEF increase in the inhalation group, remained statistically significant. Patients with an estimated plasma β_2 -agonist concentration of below 60 nmol·l⁻¹ had a significantly greater bronchodilatory effect after *i.v.* treatment than those with a plasma concentration of above 60 nmol·l⁻¹ ($p<0.01$). This difference was not observed after inhalation treatment (fig. 2).

In the 40 patients who had measurable plasma salbutamol levels but no measurable terbutaline, there were no statistically significant correlations between the plasma drug concentration and the bronchodilator effect. The regression coefficient between plasma salbutamol before treatment and PEF increase 30 min after treatment was -0.38 ($n=17$) for the *i.v.* treated and -0.22 ($n=23$) for the inhalation group.

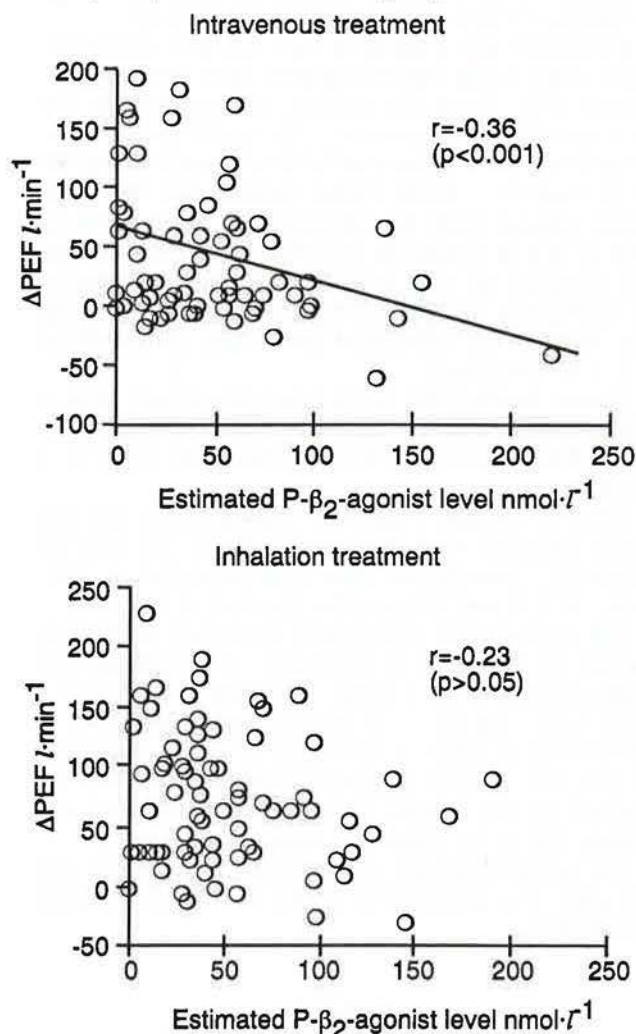


Fig. 1. — Correlation between changes in peak expiratory flow (Δ PEF) 30 min after intravenous or inhalation salbutamol treatment and the estimated plasma β_2 -agonist level (P -terbutaline $\times 2 + P$ -salbutamol) before treatment.

Table 3. — Correlation between the initial plasma beta₂-agonist levels and the effect of *i.v.* or inhaled salbutamol immediately after treatment and 30 and 55 min after the start of treatment

	Immediately after		At 30 min		At 55 min	
	<i>i.v.</i>	inhal.	<i>i.v.</i>	inhal.	<i>i.v.</i>	inhal.
ΔPEF	-- (-0.29)	0 (-0.20)	--- (-0.36)	0 (-0.23)	--- (-0.42)	- (-0.28)
Δ Pulse rate	- (-0.28)	0 (-0.12)	0 (0.03)	0 (-0.13)	0 (0.11)	0 (-0.23)
Δ Systolic blood pressure	0 (0.03)	0 (0.14)	0 (-0.06)	0 (0.23)	+ (0.27)	+ (0.24)
Δ Diastolic blood pressure	0 (0.17)	0 (0.18)	++ (0.35)	0 (-0.01)	+ (0.28)	0 (0.11)

A positive correlation is indicated by + and a negative one by - (- or +: $p < 0.05$; -- or ++: $p < 0.01$; ---: $p < 0.001$). The *r* values are presented in brackets. PEF: peak expiratory flow.

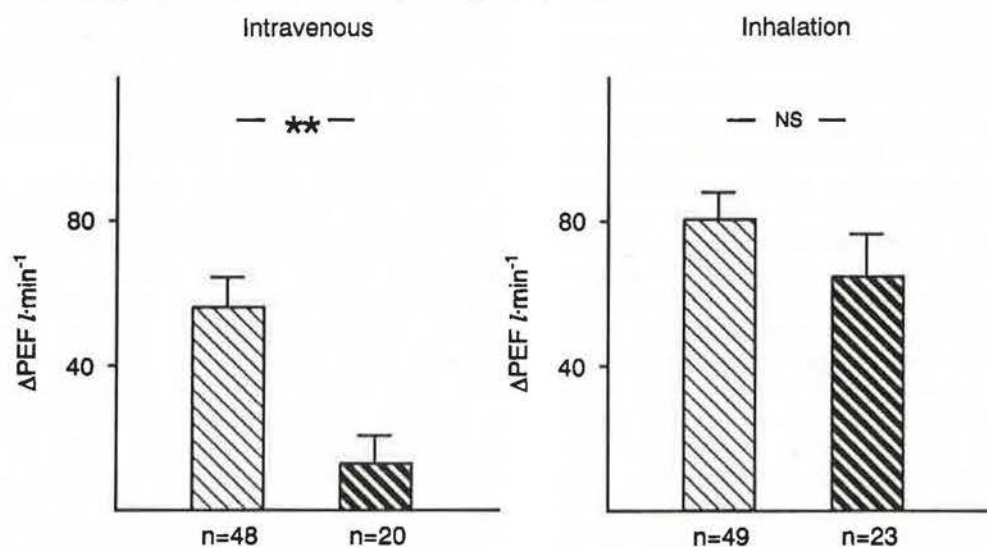


Fig. 2. — Comparison of changes in peak expiratory flow (Δ PEF) mean (SE) 30 min after intravenous or inhalation salbutamol treatment in patients with an estimated plasma β_2 -agonist level (P -terbutaline $\times 2$ + P -salbutamol) of below or above $60 \text{ nmol}\cdot\text{l}^{-1}$. **: $p < 0.01$; ns: nonsignificant; ▨: estimated β_2 -agonist level $< 60 \text{ nmol}\cdot\text{l}^{-1}$; ▩: estimated β_2 -agonist level $\geq 60 \text{ nmol}\cdot\text{l}^{-1}$.

No significant correlation was found between the reported inhaled 24 h β_2 -agonist dose ($\text{mg}\cdot\text{kg}^{-1}$) and the change in PEF after inhaled or *i.v.* salbutamol treatment.

Discussion

Some authors have suggested that the excessive use of self-administered sympathomimetic drugs in patients with acute asthma might delay hospital admission, and thus increase the risk of dying from an attack of asthma [19, 20]. Other studies have, however, indicated that patients with severe acute asthma are often undertreated [1, 21].

The question of whether patients in an acute stressful situation such as severe acute asthma can accurately report the medication they have taken is

justified. The fairly good correlation between reported drug intake and measured plasma levels in this study indicates that this was possible in most cases. There were, however, some patients in whom we found relevant concentrations of a drug which was not reported as having been taken.

Very few of the patients claimed to have taken more than the regular maintenance dose of oral bronchodilators, while a very large variation was found in the use of inhaled β_2 -agonists. In Sweden the recommended maintenance dose of the β_2 -agonist dose aerosol (terbutaline $0.25 \text{ mg}\cdot\text{dose}^{-1}$ and salbutamol $0.1 \text{ mg}\cdot\text{dose}^{-1}$) is two inhalations 4–6 times a day. At times of acute exacerbation it is, however, rational to increase this dose, and it has been suggested that the use of an aerosol involving as many as 20–24 puffs of β_2 -agonist over a period of 24 h is to be recommended on these occasions [1, 22]. Other authors

have recommended an even more frequent use of dose aerosols in acute asthma exacerbations [23]. In this study, 17% of the patients reported that they had taken less than the regular maintenance dose, while 14% had taken more than 24 inhalations.

In this study, all patients who had taken theophylline had also used oral or inhaled β_2 -agonists. It has been suggested that the lower limit of the therapeutic interval of theophylline for patients receiving this combination is $40 \mu\text{mol}\cdot\text{l}^{-1}$ [24]. Even so, the majority of the patients in this study (59%) had taken inadequately low doses of theophylline - a result which agrees with other studies of Swedish patients with acute asthma [1, 5]. None of the patients had plasma theophylline levels above the upper limit of the therapeutic interval ($110 \mu\text{mol}\cdot\text{l}^{-1}$).

The therapeutic range for systemic β_2 -agonist treatment has been less well-defined. It has, however, been suggested, in studies of stable asthma, that when plasma terbutaline levels rise to above $30 \text{ nmol}\cdot\text{l}^{-1}$ no further bronchodilation is produced, but the risk of systemic side-effects increases [13, 14]. In this study we have assumed that the therapeutic plasma levels for salbutamol is about twice as high as that of terbutaline. This assumption is based primarily on the steady-state plasma concentrations after oral terbutaline and salbutamol administration [12-16]. Plasma levels of more than $30 \text{ nmol}\cdot\text{l}^{-1}$ and salbutamol levels of more than $60 \text{ nmol}\cdot\text{l}^{-1}$ were found in 24% and 12%, respectively, of the patients in this study. The weak but significant negative correlation between plasma levels and PEF prior to treatment might suggest that patients with the most severe asthma tend to take more adrenergic treatment at home prior to hospital admission. It should be noted that there was no significant correlation between pulse rate and adrenergic drug concentration on arrival. Thus, tachycardia in patients of this kind is an effect of the acute asthmatic attack itself and not a consequence of pretreatment with bronchodilators.

A great deal of controversy exists as to whether long-term β -agonist treatment can lead to a clinically significant desensitization of bronchial β -adrenoceptors which, if it occurred, might reduce the effect of β -agonist treatment in an acute situation [25]. ROSSING *et al.* [7] found no difference in the effect of β -agonist therapy between patients with acute asthma who had or had not taken β -agonists prior to emergency room admission. BOE *et al.* found [6], however, that *i.v.* terbutaline treatment in acute asthma appeared to have less effect on patients who had very high β_2 -agonist plasma levels on arrival. Very high post-mortem drug concentrations of terbutaline and salbutamol have also been found in a significant proportion of patients who died of asthma [26]. This does not, however, necessarily imply that there is a direct relationship between high plasma concentrations and the failure of treatment. Patients with more severe asthma might, for example, be less responsive to β -agonist treatment because of oedema in the bronchial mucosa and airway mucous plugging.

In this study, a correlation was found between high plasma levels of β_2 -agonists on admission and less bronchodilatory effect by the *i.v.* salbutamol treatment, and this correlation also remained significant after eliminating the effect of differences in PEF. The clinical significance of this correlation was illustrated by dividing the patients into a low and a high plasma concentration group. The patients with an estimated β_2 -agonist concentration of below $60 \text{ nmol}\cdot\text{l}^{-1}$ had a mean PEF increase after *i.v.* treatment that was of almost the same magnitude as that following inhalation treatment, while the mean PEF increase after infused salbutamol in the group with a plasma concentration of above $60 \text{ nmol}\cdot\text{l}^{-1}$ was about a quarter of the other group's value (fig. 2). In the group that received inhaled salbutamol there was, on the other hand, considerably less indication that high plasma concentration levels resulted in a reduced effect of treatment. The reason for this might be that the drug concentration at the airway β_2 -receptors is probably higher after high-dose inhalation treatment than after *i.v.* treatment. Consequently, if the patient has some degree of β_2 -receptor desensitization, high dose inhalations are more likely to break through this hyposensitivity than *i.v.* treatment.

In conclusion, this study indicates that, in Sweden at least, very few patients appear to over-dose with their oral bronchodilators prior to hospital admission with acute asthma. On the contrary, the majority of the patients had inadequately low plasma theophylline levels. On the other hand, the use of inhaled β_2 -agonists varies a great deal. Some patients arriving with acute asthma have high blood concentrations of β_2 -agonists, which possibly limits the response to *i.v.* β_2 -agonist treatment, while the effect of high-dose inhaled β_2 -agonists appears to be related to a lesser degree to the drug concentration on arrival. This result is a further indication that inhalation is the mode of choice for administration in β_2 -agonist treatment of severe acute asthma.

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