Plasma levels and effects of salbutamol after inhaled or i.v. administration in stable asthma

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ABSTRACT: The response and plasma levels of inhaled (0.15 mg·kg⁻¹) and intravenous salbutamol (5 µg·kg⁻¹) were studied in 12 patients who had previously been included in a study of acute severe asthma and were now in a stable phase. The maximal value for change (Δ) in plasma salbutamol compared with the pretreatment value was higher after i.v. than after inhalation treatment (59 ± 30 nmol·l⁻¹) but the areas under the curve (AUC) during 90 mins after treatment were similar for the two administration routes. The inter-individual differences in peak plasma salbutamol and AUC for Δ plasma salbutamol were much greater after inhalation than after i.v. infusion. Immediately after treatment there was a greater increase in pulse rate (mean ± 17 ± 6 beats·min⁻¹) and lower serum potassium level (mean ± 0.3 mmol·l⁻¹) after i.v. than after inhalation treatment. The increase in peak expiratory flow (PEF) measured 90 min after the start of treatment (85 ± 31 l·min⁻¹) and as AUC was significantly higher after inhalation than after i.v. treatment.

Six patients had received i.v. treatment in the acute asthma study; in these patients ΔPEF immediately after i.v. treatment was significantly lower in the stable situation (+49 ± 115 l·min⁻¹). There was also a significant difference in the effect on the pulse rate immediately after i.v. treatment, with a decrease in the acute asthma and an increase in the stable asthma situation (+5 ± 16 beats·min⁻¹).


β₂-agonists are commonly used as first line treatment in all forms of asthma [1]. The treatment can be administered either by inhalation or systemically, i.e. intravenously, subcutaneously or orally. In several studies the effects of inhaled and infused β₂-agonists in the treatment of acute asthma have been compared: in several studies these alternative routes were found to be equally effective [2-5] and in others intravenous infusions seemed to be more effective in relieving bronchoconstriction in severe asthmatic attacks [6, 7]. In a Swedish multicentre study of 176 patients with acute severe asthma, salbutamol was, however, found to be more effective when given as a high-dose inhalation than when infused intravenously [8].

The principal aim of the present study was to compare the plasma levels, anti-asthmatic effects and systemic effects of inhaled and intravenous salbutamol treatment in doses which are used in the emergency treatment of acute asthma [8]. A further aim was to compare the effect of the treatments in acute asthma with that in a non-acute situation. The study was therefore conducted on asthmatic patients who had previously taken part in the acute asthma study and who now were in a stable phase.

Material and methods

The study lasted from June to September 1988. Twelve patients (mean age 54 yrs (range 33-71), 6 men and 6 women), were recruited from the Swedish multicentre study of acute asthma performed two years earlier. These twelve lived in Uppland. All the patients had bronchial asthma as defined in the earlier study [8]. No patient had severe heart disease or hypertension. The patients anti-asthmatic maintenance treatment is presented in table 1. All the patients were now in a stable phase - e.g. they had no acute asthmatic symptoms for at least two weeks. They all gave informed consent and the study was approved by the Ethics Committee of the Medical Faculty at Uppsala University.

The patients were instructed not to take oral β₂-agonist drugs for 24 h or inhaled β₂-agonists for 6 hours prior to the two treatments described below. Each patient received both of the following treatments: A: Inhalation of 0.15 mg·kg⁻¹ of nebulised salbutamol (Ventoline, Glaxo) in an undiluted solution (5 mg·l⁻¹) from a Pari-Inhalier Boy. This nebuliser, which is driven by compressed air, is reported to produce a mass median particle diameter of 9.7 mm, with an intrapulmonary deposition of 35% of
The treatments were given on separate days with an interval of 2 days to 3 weeks. The order of the treatments was randomized so that half of the patients received the inhalation treatment first and the other half the i.v. treatment first. Both treatments were given at approximately the same time of day in ten of the 12 patients. One patient received the infusion 3 hours later than the inhalation (11 a.m. and 8 a.m. respectively), while another patient was given inhaled treatment 4 hours later than the infusion (1 p.m. and 9 a.m. respectively).

Blood samples for salbutamol and potassium assay were drawn before, immediately after, and 15, 30, 45, 60 and 90 min after treatment. After centrifugation the plasma was removed, frozen and stored in a freezer (−20°C) until analysed. Salbutamol was assayed by a gas chromatographic mass spectrometric method [10]. Potassium in serum was analysed by flame photometry.

The following measures of the effect of the salbutamol treatment were recorded before, immediately after treatment and 30, 60 and 90 min after the start of the treatment: Peak expiratory flow rate (PEF), using a Wright peak flow meter. The PEF value was also compared with the patient’s predicted value (%PEF) [11]. Pulse rate by palpitation of the radial artery. Diastolic and systolic blood pressures, measured with a sphygmomanometer. Side-effect score: the patients were actively asked about the following symptoms, which they rated from 0 (none) to 3 (severe): headache, nausea, abdominal symptoms, palpitations, tremor, and any other symptoms.

The area under the curve (AUC) for change (Δ) in plasma (p) salbutamol, PEF and pulse rate from 0 to 90 min was calculated by the trapezoidal rule from a plot of the measured values versus time on linear co-ordinates [12].

The results were compared with those obtained in the same patients in the acute asthma study 2 years earlier [8].

### Statistics

A non-parametric paired test (Wilcoxon test) was used for analysing the significance of differences between the effects of the two modes of therapy and between those of the therapy given in the acute and stable situations.

To test the correlation between the plasma level of salbutamol measured as change from baseline (Δ p-salbutamol) and the effect variables Δ PEF, Δ pulse rate, Δ blood pressure and Δ potassium, the following procedure was carried out: the correlation coefficient was calculated for each patient and the Wilcoxon test was applied to the coefficients. The correlation between the peak Δ plasma salbutamol level and the effect of the treatment was tested with Spearman’s rank correlation test.

A p value of less than 0.05 (two-tailed test) was considered significant. The results are presented as mean±SD.

### Results

There were no significant differences as regards any of the measured variables before the two treatments. The mean duration of inhalation was 13 min (range 10–15 min), whereas all i.v. infusions were given during 10 min.

#### Salbutamol plasma levels

All patients claimed to have refrained from taking oral β₂-agonists for 24 h and inhaled β₂-agonists for 6 h prior to the study. In one patient (patient 9), however, the salbutamol level was 31.8 nmol·l⁻¹ before the inhalation but was not measurable before the i.v. treatment. This patient was therefore excluded whenever the two modes of therapy were compared. In addition measurable salbutamol levels were found in three patients before the
inhalation treatment (4.6, 6.3 and 9.2 nmol·l⁻¹), and in two before the i.v. treatment (4.6 and 9.2 nmol·l⁻¹).

The individual changes in the plasma salbutamol level after treatment are presented in Table 2 and Fig. 1. The peak increase in the plasma level was greater after the i.v. treatment than after the inhalation in all patients (58.8 (16.2) vs 30.2 (21.0) nmol·l⁻¹ p<0.001). The mean Δ p-salbutamol level was significantly higher 15 min after and significantly lower 60 and 90 min after the start of the i.v. treatment compared with the inhalation treatment (Fig. 2).

After i.v. treatment there was a significant positive intra-individual correlation between Δ p-salbutamol and Δ pulse rate (p<0.01) and between Δ p-salbutamol and Δ systolic blood pressure (p<0.05). A significant negative correlation was found between Δ p-salbutamol and Δ diastolic blood pressure (p<0.05) after i.v. treatment. After inhalation treatment there was no significant correlation between plasma salbutamol and cardiovascular effects.

For the group as a whole no significant correlation was found in either treatment alternative between the maximal increase in the plasma level and the effect of the treatment (Δ PEF, Δ pulse rate, Δ blood pressure or Δ serum potassium) at any time point.

There was a ten-fold inter-individual variation in AUC for Δ p-salbutamol after the inhalation, while the variation was much lower after i.v. treatment (Table 2). Four patients had a higher AUC value for Δ p-salbutamol after the inhalation than after i.v. treatment. All of these patients had a higher AUC for Δ pulse rate and three of them had a lower AUC for Δ PEF after inhalation than after i.v. treatment. Of the seven patients who had

<table>
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<th>Patient</th>
<th>Max. level (nmol·l⁻¹)</th>
<th>Time of max. (min)</th>
<th>AUC (nmol·l⁻¹·h)</th>
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<td>i.v.</td>
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range 11 - 77 38 - 85 12 - 90 10 8 - 82 19 - 44

Table 2. Maximal increase in plasma salbutamol concentration, time of maximal concentration and area under the curve (AUC) for Δ p-salbutamol from before treatment to 90 min after its start.

Fig. 1. Plasma salbutamol concentrations after intravenous and inhaled salbutamol treatment.
Fig. 2. Changes in plasma salbutamol, serum potassium, peak expiratory flow rate and pulse rate (mean±SE) after intravenous and inhaled salbutamol (*p<0.05, **p<0.01).

Fig. 3. Patterns of response to intravenous and inhaled salbutamol treatment in two patients.
a lower AUC for Δ salbutamol after the inhalation than after i.v. administration, 6 had a higher AUC for Δ PEF. These two patterns of response to the treatment are presented in fig. 3. For the group as a whole there was no significant difference in mean AUC for Δ p-salbutamol between the inhalation and the i.v. treatment (31.5 (23.2) vs 28.5 (7.6) nmol l⁻¹ h⁻¹).

Systemic effects

There was a significantly larger increase in pulse rate immediately after the i.v. treatment than immediately after the inhalation treatment (17 (9) vs 6 (9) beats per min, p<0.05) (fig. 2). There was no significant difference in the mean AUC values for Δ pulse rate obtained after the i.v. and inhalation treatments.

A decrease in serum potassium was noted in all the patients after the i.v. salbutamol infusions at all observations. There was no decrease 15 min after inhalation, but 8 patients showed a decrease between 30 and 90 min after this treatment. The mean maximum decrease in potassium was -0.3 mmol l⁻¹ after both treatments (range -0.2 to -0.6 after i.v. and +0.1 to -0.7 after inhalation treatment). There was a significant difference in the change in serum potassium 15 min after treatment (-0.2 (0.2) after i.v. and +0.1 (0.3) after inhalation treatment, p<0.05) (fig. 2). No significant correlation between Δ p-salbutamol and Δ potassium was found after either treatment.

The main side-effects of the treatment were heart palpitations and tremor. Two patients reported moderate palpitations immediately after the i.v. treatment and one patient reported moderate palpitations 30 min after both the inhaled and i.v. treatment. Five patients reported moderate or severe tremor immediately after i.v. treatment, while the number had decreased to two, 30 min after the start of this treatment. Two patients had moderate or severe tremors immediately after the inhalation and four patients 30 min after the start of this treatment. No significant differences in side-effect scores were found between the treatments at any point in time.

Effect on PEF

There was a tendency towards a greater increase in PEF after inhalation than after i.v. infusion throughout the study period, but the difference was only statistically significant 90 min after treatment (fig. 2). The mean AUC for Δ PEF was higher after inhalation than after i.v. treatment (6840 (5760) vs 3130 (3360) l, p<0.05); this difference was greater in the patients with the lowest pre-treatment PEF-values (r=0.7, p<0.05)

Effect in comparison with the acute asthma situation

A comparison was made between the effect of the salbutamol treatment in this study and the effect for the same patients in the acute asthma study. The baseline pulse rates before the intravenous and inhalation treatments in this study were significantly lower (86 (13) and 86 (15) vs 114 (14) beats per min, p<0.01) and PEF higher (310 (124) and 320 (124) vs 202 (36) l min⁻¹ p<0.01) than in the acute asthma situation. In the six patients who had received i.v. treatment in the acute asthma study the increase in PEF immediately after i.v. treatment was significantly less pronounced in the stable situation (49 (61) vs 115 (63) l min⁻¹) The individual responses to the treatment are presented in fig. 4. There was also a significant difference in the effect on the pulse rate immediately after i.v. treatment, with a decrease in the acute situation and an increase in the stable situation (-5 (17) vs +16 (7) l min⁻¹) (fig. 5). In the group of six patients who had been treated with inhaled salbutamol in the acute asthma study no significant differences in the effects of inhalation treatment on PEF and pulse rate were found.

The plasma salbutamol levels 55 and 90 min after i.v. treatment in the acute asthma study (n=6) were compared with those found at 60 and 90 min in the present study. These values were 9.3 (4.8) vs 10.9 (3.1) and 1.4 (4.9) vs 7.3 (2.7) nmol l⁻¹ at the earlier and later time points respectively. The differences were statistically non significant.

![Intravenous salbutamol 5 µg·kg⁻¹](image)

![Inhaled salbutamol 0.15 mg·kg⁻¹](image)

Fig. 4. – Peak expiratory flow (% of the predicted) before and immediately after intravenous and inhaled salbutamol treatment of acute and stable asthma.
Discussion

β₂-agonists are considered to be the treatment of choice in acute asthma, but the optimal route of administration has been discussed for many years [13]. In the Swedish multicentre study of acute severe asthma 0.15 mg·kg⁻¹ of inhaled salbutamol produced a greater degree of bronchodilation than 5 μg·kg⁻¹ of i.v. salbutamol, but the systemic effects (change in pulse rate and blood pressure) of the two treatments were similar [8]. In order to study the plasma levels after inhaled and i. v. salbutamol treatment and correlate these to the effects of the treatment a follow-up study was made.

In the present study i. v. infusions of 5 μg·kg⁻¹ of salbutamol produced a high peak and a rapid decline in the plasma salbutamol concentration in all patients. The inhalation treatment was followed by a slow increase in plasma salbutamol with a lower peak value in all patients. The i. v. infusion had more pronounced haemodynamic effects (tachycardia, higher systolic blood pressure and hypokalaemia) immediately after the treatment than the inhalation therapy, corresponding to the higher initial plasma salbutamol value. When the plasma salbutamol increase was measured as AUC from the start of to 90 min after treatment, however, there was no significant difference between the treatments, and correspondingly there was no difference in systemic effects measured as AUC for Δ pulse rate or as maximum decrease in serum potassium. Thus, although the inhaled dose was approximately 30 times greater than the intravenous, the systemic availability from the start to 90 min after treatment seems to have been approximately equal in the two modes of treatment.

As in our acute asthma study [8] the inhalation treatment had a better anti-asthmatic effect than the i. v. treatment in most patients. In the present study it was especially the patients with a high degree of bronchial obstruction before treatment that fared better on inhalation than on i. v. infusion.

With the i. v. treatment the effect/side-effect ratio was more favourable in the acute than in this non-acute situation. Thus the side-effects of the treatment were more pronounced in the stable situation. The probable reason for this is that in patients with severe acute asthma there is a sympathetic drive on arrival which decreases during treatment and masks adverse cardiovascular effects of the treatments [14, 15]. The fall in heart rate after treatment of acute asthma is thus due to the improvement of the asthma and not a direct effect of the drug. The β₂-agonist treatment resulted in a higher degree of bronchodilation in the acute than in the stable phase, but this might partly be explained by the lower pre-treatment PEF values in the acute situation.

As in earlier studies [16, 17], there were large interindividual variations in the plasma level pattern after the inhalation treatment. The time of onset of the peak salbutamol value also varied. In nine of the 12 patients, however, the peak value was observed within 45 minutes. Shenfield et al. have suggested that this early increase in plasma salbutamol is caused by absorption into the bronchial circulation and hence reflects the proportion of the dose that has reached the lung, whereas the proportion that has been swallowed is absorbed later, with peak values occurring after 2 to 3 h [18]. It is therefore somewhat surprising that in the patients with a higher AUC for Δ plasma salbutamol after inhalation the AUC for Δ PEF was often lower after this treatment than after i. v. infusion.

It is concluded that there is a large inter-Individual variation in plasma level pattern after inhaled treatment. The average systemic availability of 0.15 mg·kg⁻¹ of inhaled salbutamol is, however, approximately equal to that of 5 μg·kg⁻¹ of i. v. salbutamol. The inhaled salbutamol dose produces a better anti-asthmatic effect and a lower maximal pulse decrease than the intravenous one in stable asthma.

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References


