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Effects of inhaled salmeterol and salbutamol (albuterol) on morning dips compared in intensive care patients recovering from an acute severe asthma attack

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Abstract Objective: To assess the effect of a long-acting inhaled β_2-agonist, salmeterol (SM), compared to a short-acting inhaled β_2-agonist, salbutamol (or albuterol, SB), on the occurrence of morning dip (MD) in patients recovering from an acute severe asthma attack (ASA).
Design: Prospective study
Setting: 18-bed, medical intensive care unit (ICU) in a university hospital.
Patients: 19 patients suffering from an ASA.
Interventions: Serial measurements of the peak expiratory flow rate (PEFR), arterial blood gases, vital capacity and forced expiratory volume in one second (FEV_1) were performed from admission. All patients were first treated with i. v. methyl prednisolone and i. v. SB. Once the PEFR was stable and > 35 % of predicted value, i. v. SB was stopped while i. v. steroids were maintained, and patients were randomised to either inhaled SB (9 patients, 400 μg every 4 h) or inhaled SM (10 patients, 100 μg every 12 h).
Results: The mean admission PEFR was 26.1 ± 11.7 % of the predicted value and was not different between the two groups. MD was more frequent with SB (6/9 patients) than with SM (4/10). The severity of MD, expressed in l/min fall in PEFR, was higher in SB than in SM (106 ± 25 vs 55 ± 37; $p < 0.05$).
Discussion: MD is frequent in ASA. In ASA, SM appears to reduce the frequency and the severity of MD more than SB. The clinical implications of this observation, particularly a lowering of mortality and a shortening of the ICU stay, remain to be investigated.

Key words Asthma · Acute severe asthma · Morning dip · Salbutamol · Albuterol · Salmeterol

Introduction

Nocturnal symptoms and worsening of asthma at the end of the night are common features in asthma patients [1–3]. The nadir of the peak expiratory flow rate (PEFR) at this time is called morning dip (MD) [4]. At the present time, the cause(s) of this nocturnal worsening is unknown. Although a circadian rhythm of changes in airway calibre is observed in normal persons, the range of these changes is much greater in patients with asthma [5, 6]. There are probably several coexisting factors, including vagal tone [7], body temperature [8], allergens [9] and a variation of hormones [10] favouring and/or causing this airway instability. Furthermore, in the hospital, respiratory arrests due to asthma, sometimes leading to death, are more common at the end of the night [11–13] and probably correspond to the MD observed at this time.

Until recently, the available inhaled bronchodilators, due to their short half-life, could not cover the full 8 h of a normal night's sleep, so that many studies on nocturnal asthma were conducted with oral theophylline or oral sustained slow-release β_2-agonists. Though these treatments are sometimes effective in reducing noctur-

nal symptoms, many patients cannot tolerate therapeutically effective doses [14–17]. Salmeterol (SM), a new inhaled β_2-agonist, differs from conventional β_2-mimetic drugs in that it produces bronchodilatation for up to 12 h after a single inhaled dose [18, 19]. This may be due to the long lipophilic side chain that permits persistent binding and repeated stimulation at the β-adrenoceptor site. Salmeterol is effective in increasing the morning PEFR value and in reducing the nocturnal symptoms in patients with chronic stable asthma [20–23], but, as far as we know, has never been tested in patients recovering from an episode of acute severe asthma in an intensive care unit.

The aim of our study was to compare the effect of inhaled SM, a long-acting β_2-agonist, with that of inhaled salbutamol (SB) (or albuterol), a short-acting β_2-agonist, on the prevalence and intensity of MD in patients recovering from an acute asthma attack, since a decrease in or abolition of the MD might reduce mortality for such patients.

Patients and methods

Patients were admitted into the medical intensive care unit (ICU) for an acute severe asthma attack, defined as a PEFR of less than 35 % of the predicted value and blood gases showing hypoxaemia with either normocapnia or hypercapnia. The present prospective study was approved by the Ethical Committee of the University Hospital of Geneva and all patients gave informed consent, except the patient who was intubated, for whom consent was obtained from next of kin.

According to a standard treatment policy in our institution, all patients were treated with supplemental oxygen by face mask, i.v. prednisolone (Ultracorten H; 3–5 mg/kg per day given in six daily doses) and i.v. SB (= albuterol, Ventolin; 5–30 μg/min). Once the blood gas values were normalized and the PEFR was > 35 % of the predicted value and stable (i.e., showing less than 10 % variability, defined as the difference between the highest and the lowest values of PEFR, divided by the lowest value times 100) during the day and during the night, the i.v. SB was withdrawn and nebulization of SB with decreasing doses over 8 h were instituted (2.5 mg at 8 a.m., 1.25 mg at 12 a.m., 1.25 mg at 4 p.m.). The patients were then randomly assigned either to inhaled SM (Serevent), 4 inhalations of 25 μg twice daily, or inhaled SB 2 inhalations of 200 μg six times a day, given by a metered-dose inhaler connected to a spacer (Volumatic). The i.v. prednisolone was held constant throughout the study at the same dose as at admission (3–5 mg/kg), and the use of theophylline or ipratropium bromide was not allowed. Antibiotic therapy was prescribed by the attending staff if necessary.

PEFR was measured every 2 h during 24 h from the end of the i.v. SB administration, by using a Wright peak flow gauge. The forced expired volume in 1 s (FEV_1) and the forced vital capacity (FVC) were measured every 4 h with a portable spirometer (Micro Medical, Rochester, England). The highest value among three attempts for each measurement was recorded. Samples for arterial blood gases were drawn from the arterial line at the same time as the PEFR measurement was made. MD was defined as a difference of more than 15 % in PEFR between the highest diurnal reading and the 4 a.m. reading from the first night after randomization was conducted [2, 4]. No supplementary treatment was instituted during the study.

Statistical comparison of the prevalence of MD between the two treatment groups was performed using a chi-square test, or Fisher's exact test, when appropriate. The fall in PEFR, age, duration of asthma, height and weight of both groups were compared using an unpaired Student's *t*-test. The heart rate, respiratory rate, blood pressure and blood gas results were compared using a paired Student's *t*-test. All *p* values were based on two-sided tests, and a *p* value of 0.05 or less was considered to indicate statistical significance. The StatView II Abacus Concept statistical package for the Apple Macintosh was used.

Results

Nineteen asthmatic patients took part in the study, 9 in the SB group and 10 in the SM group. Only 1 patient was intubated and required mechanical ventilation for 12 h (SB group). There were no dropouts. The characteristics of all the patients are given in Table 1. Both treatment groups were similar with respect to all variables. Table 2 gives the patients' characteristics just before randomisation to the SB or SM group. As on admission, no difference between the two groups could be found at this time. Table 3 shows the results of the pulmonary function tests. Patients in the SB group suffered a higher prevalence of MD (6/9 vs 4/10). MDs were also worse, i.e., deeper in the SB groups as expressed either in l/min fall in PEFR or in percentage decrease in PEFR (106 ± 25 vs 55 ± 37 l/min and 37.5 ± 9.4 vs 23.4 ± 6.4 %, cf. Table 3). Figure 1 shows the PEFR values during the night in the patients presenting a MD. At midnight and 2 a.m., both groups showed a slight fall in PEFR, while at 4 a.m. the SB group exhibited a larger dip. After the MDs, PEFRs improved in both groups, the 8 a.m. recording being close to the highest diurnal value of the preceding day. The FEV_1 and FVC results were not interpretable: indeed, most patients could not produce sufficiently long expiration through the spirometer without experiencing bouts of intense coughing, a common finding after a severe asthma attack. Nevertheless, PEFR measurements were reliable because of the short exhalation time needed for the measurement recorded very early in the expiration phase.

Table 4 shows some of the haemodynamic and blood gas measurements at the time of the best diurnal PEFR and at the time of the MD. There was a significant increase in the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and a decrease in pH during the MD, though the magnitude of the change was small. Neither oxygenation, assessed by the PaO_2/FIO_2 in ratio between the partial pressure of oxygen in arterial blood and fractional inspired oxygen, nor heart rate nor blood pressure was different during the MD. There was no correlation between the increase in $PaCO_2$ and the fall in

Table 1 Patients' general characteristics at admission. Values are mean ± SD or numbers (*PEFR* peak expiratory flow rate, *pHa* arterial pH, $PaCO_2$, PaO_2 partial pressure of carbon dioxide and of oxygen in arterial blood, FIO_2 fractional inspired oxygen, *BEa* arterial base excess)

	Salbutamol	Salmeterol	p^a
Number of patients	9	10	
Sex (F/M)	7/2	6/4	
Age (years)	44.3 ± 22.8	36.7 ± 16.3	NS
Height (cm)	164 ± 10	169 ± 15	NS
Weight (kg)	64.6 ± 12.6	71.3 ± 34.8	NS
Duration of asthma (years)	18.2 ± 18.0	14.3 ± 11.4	NS
History of nocturnal asthma symptoms	3	4	
Atopic status	3	4	
Previous history of acute severe asthma	2	3	
Regular use of inhaled β_2-mimetics	7	7	
Regular use of inhaled steroids	4	5	
PEFR at admission (% predicted value)	28.6 ± 11.6	25.4 ± 12.1	NS
pHa at admission	7.29 ± 0.13	7.36 ± 0.06	NS
$PaCO_2$ at admission (kPa)	7.06 ± 2.9	6.63 ± 0.85	NS
PaO_2/FIO_2 at admission (kPa)	37.5 ± 8.5	36.5 ± 5.5	NS
BEa at admission (mEq/l)	−2.6 ± 4.3	−2.1 ± 3.4	NS

[a] Student's *t*-test

Table 2 Patients' characteristics at the time of randomisation. Values are mean ± SD

	Salbutamol	Salmeterol	p^a
Time from admission into ICU to randomisation (h)	21.1 ± 25.0	19.9 ± 12.0	NS[a]
Need for mechanical ventilation before randomisation (*n*)	1	0	NS[b]
PEFR (% predicted value)	55 ± 12	46 ± 21	NS[a]
PEFR variability under i.v. SB (%)	6 ± 2	5 ± 3	NS[a]
pHa	7.40 ± 0.06	7.40 ± 0.04	NS[a]
$PaCO_2$ (kPa)	4.3 ± 0.3	4.5 ± 0.6	NS[a]
PaO_2/FIO_2 (kPa/FIO_2)	40 ± 8	34 ± 7	NS[a]
BEa (mEq/l)	−2.6 ± 4.3	−2.1 ± 3.4	NS[a]

[a] Student's *t*-test
[b] Chi-square test

Table 3 Characteristics of morning dips (MDs)

	Salbutamol	Salmeterol	*p*
Number of MDs/number of patients	6/9	4/10	NS[a]
Maximal PEFR fall (l/min)	106 ± 25	55 ± 37	< 0.05[b]
Maximal PEFR fall (%)	37.5 ± 9.4	23.4 ± 6.4	< 0.05[b]

Fall in PEFR indicates the difference in PEFR between the highest diurnal value and the 4 a.m. recording
[a] Fisher's exact-test
[b] Student's *t*-test

PEFR during the MD nor between the fall in pH and in PEFR. There were no difference in haemodynamics or blood gases between the SB and SM groups.

Discussion

In this study, we demonstrated that inhaled SM, 100 μg twice daily, compared with inhaled SB 400 μg six times a day, produced a better controlled, i.e. a more stable, PEFR during the night in patients recovering from an acute severe asthma attack.

SM has already been compared to SB, a short-acting β_2-agonist, in patients with stable chronic asthma [20–23]. SM produced an increase in the FEV_1 over 12 h and in the morning PEFR, as well as a decrease in the number of nights of disturbed sleep and an improvement in the quality of sleep, assessed by electroencepha-

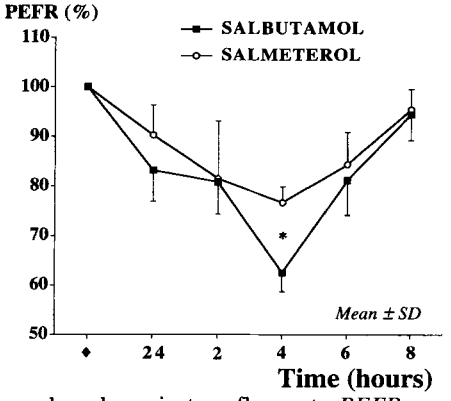

Fig. 1 Nocturnal peak expiratory flow rate *PEFR*, expressed as a percentage of the highest diurnal value (◆) recorded during the day preceding the night shown on the graph. * $p < 0.05$

lography. In our study, we investigated the effects of inhaled SM or SB in ICU patients recovering from an acute severe asthma attack, a clinical situation in which, as far as we know, no previous information exists on the comparative efficacy of both agents.

Several methodological points of our study should be clarified.

First, the dose of SM that we used, 100 μg twice a day, was higher than the 50 μg twice a day usually recommended. This is due to the fact that most studies have been conducted on chronic stable asthmatic patients. The patients we have investigated were just recovering from an acute severe asthma crisis. Moreover, the switch from i.v. SB to the inhaled β_2-mimetic was done in a short period of time, so that we decided to conduct our study with the maximal recommended doses. This was done – as requested by our Ethical Committee – in order to avoid an abrupt deterioration of the asthma control. Despite the fact that Bennett et al. [24] have recently demonstrated that the systemic effects of inhaled SM on heart rate and blood pressure were more important than the effects of inhaled SB, we did not notice any difference in the heart rate, respiratory rate or blood pressure between the SM or SB groups during the night, suggesting that both treatment regimens were probably equipotent.

Second, because every patient did not inhale the β_2-mimetic at exactly the same time of the day, we cannot exclude that the effects of SM or SB could have been different due to different times of administration. However, the diurnal and nocturnal PEFR profiles were quite similar within groups of "morning dippers", on either SB or SM, whereas the magnitude of the MDs were different, as shown in Fig. 1, between the two groups of patients when considered by the treatment option. Furthermore, MD, as defined, occurred effectively at around 4 a.m. (4.2 ± 0.8 h a.m., mean ± SD). In addition, although we did not assess the subjective tolerance to SM or SB, no patient in either group needed a rescue treatment during the study because of worsening asthma. All this suggests that the time of administration of the drugs, provided that the duration of action of the medication is accounted for, is not essential for stabilizing the airway tone in patients recovering from an attack of acute severe asthma.

Other authors have already published data on asthma and long-acting β_2-mimetics. Rabe et al. [25] investigated the effects of formoterol and SM on airway responsiveness over 24 h in mildly asthmatic patients, by measuring the FEV_1 every 4 h. Both drugs were superior to placebo in controlling the airway tone, but a circadian rhythm of airway tone and responsiveness, with a worsening of the FEV_1 at 4.30 a.m., was still detectable. In our study, 6/9 patients in the SB and 4/10 patients in the SM group developed an MD, despite aggressive anti-asthmatic medication, although the magnitude of the fall in PEFR was less important in the SM group. This may indicate that the better airway stability of SM compared to SB is predominantly due to the longer stimulation of the β_2-adrenoceptor of airway smooth muscle, but that there still exists a circadian rhythm of airway inflammation. This airway tone instability is not controlled by β_2-mimetics, despite the fact that SM has some anti-inflammatory properties [26]. To support the role of inflammation in nocturnal asthma, recent studies have shown a decline of endothelin-1 and an increase in eosinophilic cationic protein and lymphocyte count in bronchoalveolar lavage fluid taken at 4 p.m. and 4 a.m. [27, 28]. These findings do not prove that these inflammatory changes indeed cause nocturnal asthma, but

Table 4 Haemodynamic and blood gas values in patients presenting a morning dip (comparison between the parameters recorded with the highest diurnal PEFR vs during MD)

	Highest diurnal PEFR	Morning dip	*p*
Respiratory rate (breaths/min)	23 ± 5	22 ± 5	NS
Heart rate (beats/min)	87 ± 13	78 ± 13	NS
Systolic blood pressure (mm Hg)	117 ± 17	117 ± 18	NS
Diastolic blood pressure (mm Hg)	62 ± 9	62 ± 9	NS
pHa	7.42 ± 0.03	7.39 ± 0.03	< 0.05[a]
$PaCO_2$ (kPa)	4.5 ± 0.7	4.7 ± 0.5	0.05[a]
BEa (mEq/l)	−1.9 ± 2.9	−2.2 ± 3.3	NS
PaO_2/FIO_2 (kPa/FIO_2)	38 ± 8	35 ± 8	NS

[a] Student's *t*-test

they suggest a role for inflammatory mediators in potentiating airway inflammation. On the other hand, we cannot be sure that such an inflammatory component may have participated in the MD that we observed in our patients, because we did not perform bronchoalveolar lavage while our patients received high doses of i. v. corticosteroids. Furthermore, autonomic nervous system activity affecting the airway narrowing in our patients cannot be excluded, as our patients did not receive ipratropium bromide, which has been shown to reduce nocturnal asthma [29].

We could not assess the effect of SM on morbidity (i. e. the length of stay in the ICU and/or other parameters) and mortality in our study due to the small number of patients. It is well known that a marked diurnal variation in PEFR entails a heightened risk of asthma recurrence, and, sometimes, of death, in the days following ICU discharge [13]. It is thus possible that the better stability of the PEFR with SM may reduce mortality in patients recovering from an acute severe asthma attack and discharged to the ward, but this remains to be studied with larger numbers of patients. The high prevalence (52 %) of patients presenting an MD in our study indicates that a high proportion of patients remains at risk after an acute severe asthma attack, despite subjective improvement and normalization of blood gases, and that serial assessment of the PEFR is still mandatory when managing such patients.

Finally, another potential benefit of using SM instead of i. v. SB in these patients could be to reduce the costs of hospitalization. In our ICU, the mean length of stay for acute severe asthma patients is less than 4 days [1993–1996, 89 acute asthma patients; length of stay (mean ± SD): 3.37 ± 2.25 days]. The cost for 24-h treatment with i. v. SB (5 μg/min) is about U. S. $ 40, whereas it amounts to only around U. S. $ 3 for 200 μg of inhaled SM. Thus, the switch from SB to SM would only result in a small cost savings, unless treatment using SM could reduce the length of stay by allowing the transfer of a patient, once weaned from a continuous i. v. infusion, to an intermediate care unit, where aerosol therapy could be more easily undertaken.

We conclude that in patients recovering from an acute severe asthma attack inhaled SM 100 μg twice a day is more effective than inhaled SB 400 μg six times a day in reducing the prevalence and intensity of MD as assessed by serial PEFR measurements. This could reduce the mortality for such patients and shorten their ICU stay, but these points remain to be investigated in a larger population. In addition, MD seems to be frequent, when systematically looked for, in patients recovering from an acute asthma attack in the ICU setting.

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