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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

Abstract
Objective: To assess the effect of a long-acting inhaled β2-agonist, salmeterol (SM), compared to a short-acting inhaled β2-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 (FEV1) 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. 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 β2-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 β₂-agonist, differs from conventional β₂-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 β₂-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 β₂-agonist, with that of inhaled salbutamol (SB) (or albuterol), a short-acting β₂-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 (FEV₁) 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.

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 FEV₁ 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 (PaCO₂) and a decrease in pH during the MD, though the magnitude of the change was small. Neither oxygenation, assessed by the PaO₂/FIO₂ 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 PaCO₂ and the fall in