

Beta-agonists - friends or foes?

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There is, today, general agreement that inhaled β_2 -agonists are the drugs of choice in acute asthma attacks, both at home and in the emergency room. However, the place for β_2 -agonists in maintenance treatment is, at present, under debate.

Adrenaline, for inhalations or for *i.v.*, use was introduced several decades ago and was shown to have an immediate effect on asthma attacks. Later, isoprenaline was used, both by the systemic and the inhaled route. During the sixties, there was an increased death rate among asthmatics in countries where inhaled isoprenaline in high concentration was used. With the introduction of the β_2 -selective agonists salbutamol and terbutaline more than 20 yrs ago, effective means for bronchodilation without serious cardiac side-effects were available for asthmatic patients. These drugs were preferably used for inhalation treatment [1-3]. During the seventies, treatment with inhaled β -agonists was used as the first step in the maintenance treatment of asthma in many European countries. Several studies showed that regular treatment with inhaled salbutamol or terbutaline gave better asthma control than "on demand" treatment [4-11].

Epidemiological studies

There was a slight increase in asthma mortality in many countries around 1980. In New Zealand this increase started in 1976 and was very pronounced. It was found, at an early stage, that the increased mortality was related to a lack of information about the asthma diseases in patients and their relatives and to a poor general level of education. At that time, drugs *per se* were not implicated as a cause of increased mortality [12].

The high mortality rate has since been correlated specifically to inhaled treatment with fenoterol [13, 14]. The latter studies have been criticized [15-17] mainly for control group selection and misclassification of drug exposure. This criticism was for a large part eliminated in a third study [18] in which the odds ratio (death risk) for patients using inhaled fenoterol was 2.7 compared to 0.5 for salbutamol. Thus, the New Zealand studies indicate that there is a difference between fenoterol and salbutamol, and

that fenoterol seems to be associated with an increased risk of mortality.

The rise of asthma deaths in New Zealand occurred soon after the introduction of fenoterol. One suggested explanation for this association could be that the highly potent drug fenoterol, taken in relatively high concentration, gives such a pronounced relief of symptoms that it delays the admittance to hospital in acute, very severe asthma. This is similar to the events reported during the sixties when there was an increased death rate among asthmatics in countries where isoprenaline for inhalation in high concentration (Isoprenaline Forte[®]) was available [19]. The decrease of the epidemic in the sixties occurred when general awareness of the problem increased and patients were better controlled and taken care of in the acute situation. Furthermore, in the early eighties fenoterol was sold over the counter in New Zealand, as was isoprenaline in several countries in the sixties. The decrease in mortality in New Zealand began when general awareness of the problem developed, before the use of fenoterol was reduced, in a similar fashion to the events in the sixties.

A retrospective epidemiological survey performed in 1.1 million inhabitants in Saskatchewan, Canada, has recently been reported at the European Respiratory Society (ERS) meeting in Brussels. The investigators gathered 12,301 patients with 10 prescriptions of asthma drugs from 1978 to 1987. There were 44 cases of death and 85 cases of near death related to asthma in the population during this 10 yrs period. This study was performed as a case-control investigation with a matched control group within this population without any fatal or near fatal events. An increased odds ratio was found, as expected, for death and near death events for most drugs used in asthma treatment. This effect was most impressive for fenoterol, but also for salbutamol where the authors found a similarly increased odds ratio. They even found a dose-response effect on the odds ratio for fatal events for both drugs. The very low death rate is surprising and, therefore, it would have been important to also evaluate the asthma death rate before inhaled β_2 -agonists were introduced, in order to make sure that the introduction of β_2 -agonists has increased the death rate. Such an increase has not occurred in *e.g.* Sweden. A critical factor in a study of this kind is the choice of controls, as patients with acute severe asthma attacks should be treated with high doses of β_2 -agonists during the attacks. Another problem with studies of this kind is

the general poor compliance with prescribed regimens. The most likely interpretation of the results is that the patients with fatal events had, appropriately, taken more inhaled β -agonists than the controls due to more severe disease. The only conclusion of the study is then that severe asthmatics have a higher probability of dying.

Regular β_2 -agonist treatment - asthma control

SEARS *et al.* [20] found, in a New Zealand study, that regular inhalation of fenoterol, specifically, was associated with deterioration of asthma control in the majority of 64 subjects, regardless of concomitant treatment. Of 57 who differed between treatments with regular inhaled fenoterol or β_2 -agonists on an intermittent "as needed" basis (*p.r.n.*), 17 (30%) improved on regular treatment, whereas 40 (70%) improved when given a β_2 -agonist *p.r.n.* The authors concluded that regular inhalation of β_2 -agonists may be an important causal factor in the almost worldwide increase in morbidity from asthma. One important point when evaluating these patients is that they had a mild asthma, with a need of only 2.9 inhalations daily during the *p.r.n.* treatment period and, therefore, it is doubtful whether these patients needed regular use of β_2 -agonists. Furthermore, we cannot critically evaluate the data, as no absolute values for any parameters are shown.

From their data, SEARS *et al.* [20] make generalizations, which seem inappropriate. Firstly, they used fenoterol, and we are doubtful whether their conclusions from results with fenoterol can be extrapolated to other short-acting beta-stimulators. Secondly, they concluded that long-acting inhaled drugs such as formoterol and salmeterol, might have the same deteriorating effect as fenoterol (see below).

Fenoterol differs in several aspects from other β_2 -agonists. In human bronchial smooth muscle, fenoterol is considerably more potent than salbutamol [21] and yet it is marketed in doses which are twice those of salbutamol. Fenoterol is a full agonist on the β_1 -adrenoceptor, whereas salbutamol and terbutaline are only weak partial agonists [22]. For the same bronchodilating effect, fenoterol gives a more pronounced hypokalaemia and tachycardia than, *e.g.* salbutamol [23–27]. In asthmatics, fenoterol gives an even more pronounced tachycardia than an equipotent bronchodilating dose of isoprenaline [28]! In patients with asthma, regular fenoterol, but not terbutaline, reduced baseline airway calibre [29].

These differences between fenoterol and salbutamol/terbutaline may explain the difference between the results reported by SEARS *et al.* [20] and the seven studies discussed in the introduction, which showed a better control with regular bronchodilator treatment [4–11]. The high efficacy and the full agonist activity on the β_1 -adrenoceptor makes fenoterol more like the non-selective drug isoprenaline, at least in high doses. As suggested by PEARCE *et al.* [19], there are similarities

between the current epidemic in New Zealand and the increased asthma mortality in the sixties, when intake of Isoprenaline Forte[®] was certainly involved in fatal events. With the introduction of these highly effective drugs in New Zealand in the sixties and in the mid seventies, respectively, there was a risk that patients relied on the very potent bronchodilation, with an increased risk of deterioration with hypoxia and of cardiac arrhythmias. With increased awareness of this risk and better acute treatment the mortality decreased.

Salbutamol has been used as a reference drug in studies with the long-acting drugs formoterol and salmeterol. These studies have included several thousand patients. In most studies it has been noted that regular treatment with salbutamol in the control groups have a better asthma control compared to the situation before the regular treatment during the run-in period [30–34]. This indicates that regular treatment with salbutamol gives a better asthma control than "on demand" treatment. In a comparison with regular theophylline, regular use of salbutamol gave a better asthma control [35]. In recent studies, symptomatic and regular salbutamol treatments and regular salmeterol treatment were compared [11]. The highest number of asthma exacerbations was seen in the group with symptomatic salbutamol treatment (32% of patients), whereas the group treated regularly showed exacerbations in 23% compared to 16% in the salmeterol group. This contrasts with the effects and conclusions seen in the New Zealand study.

Effects on bronchial responsiveness

A rebound increase in bronchial hyperresponsiveness, as seen after cessation of regular treatment with the available short-acting inhaled β_2 -agonists [36], could be responsible for a nocturnal deterioration during regular maintenance β_2 -agonist treatment as the bronchodilating effect wears off during the night. In the study of SEARS *et al.* [20] the adverse effect on asthma control was primarily seen as nocturnal symptoms, nocturnal inhaled use and morning peak flow values. Inhalation of glucocorticosteroids slightly attenuates bronchial hyperresponsiveness. BENATTI *et al.* [37] showed that addition of regular salbutamol medication affords a further decrease; this was tested 12 h after the last salbutamol inhalation, indicating that inhaled glucocorticosteroids counteract the rebound effect and change it to a more pronounced protection. Similar results were achieved by WOOLCOCK *et al.* [38]. These results are also in contrast to the data presented by SEARS *et al.* [20].

Another recent two year study by a Dutch group [39] compared regular and symptomatic treatment with salbutamol or ipratropium bromide. The groups with symptomatic treatment initially showed higher forced expiratory volume in one second (FEV_1) values than those who were randomized to continuous treatment. It was found that patients on regular treatment had a more rapid decline of FEV_1 than those on symptomatic

treatment. However, this was true for both bronchodilators. The authors did not report any change in histamine concentration provoking a 20% fall in FEV₁. Therefore, this study does not indicate that β_2 -agonists *per se* are harmful. Possibly, the bronchodilation could increase the inflammatory burden on the patient as suggested by the authors. The difference in initial basal values might have been of importance for the outcome of the study.

The Swedish experience

In Sweden the general recommendation from the early seventies to the mid eighties has been to use regular treatment with inhaled β_2 -agonists as a first step in treatment of patients with a daily need for asthma medication. From the mid eighties inhaled corticosteroids, together with regular or *p.r.n.* use of inhaled β_2 -agonists, have been recommended. In fact, the highest amount of inhaled β_2 -agonists per capita in Europe has been used in Sweden [40]. The prevalence of asthma in different parts of Sweden has been well studied in 18 yr old conscripts in 1971 and 1981 [41]. The prevalence was almost unchanged in the southern part of Sweden, whereas in the northern, colder part of the country the prevalence was doubled from about 2 to 4%. This change has been ascribed to the changed indoor climate, achieved by the much improved insulation of old and new houses owing to the "oil crisis" in the seventies. Moreover, these insulation efforts were subsidized by the Swedish government. The use of inhaled β_2 -agonists was equivalent in different parts of Sweden.

The Swedish experience does not indicate that the increased prevalence of asthma is caused by the use of inhaled β_2 -agonists. In other parts of the world, increases in asthma prevalence have been found without a relationship to the use of inhaled β_2 -agonists [42]. The asthma mortality in Sweden has been almost unchanged for more than 30 yrs, except in elderly people, despite this increased prevalence of asthma (about 0.2 deaths per 100,000 inhabitants in the 5-34 yr age group, in total approximately 20 cases per year in about 8 million inhabitants) [43]. In 1979-1981 there was a small increase in deaths, which, was however, unrelated to drug treatment [44].

Swedish data have also shown that after the introduction of salbutamol and terbutaline (fenoterol has had a very low market share) sick leave decreased, number of days in hospital decreased, and the national cost for the disease was reduced [45], and this occurred before any widespread use of inhaled corticosteroids.

Thus, the Swedish experience fails to give any support for the view that regular inhaled β_2 -agonists are deleterious in asthma.

Long-acting β_2 -agonists

Concerning the extrapolation made by SEARS *et al.* [20] from fenoterol to the new long-acting drugs

formoterol and salmeterol, it should be pointed out that these new drugs have been evaluated more thoroughly in prospective studies than the older drugs. It has been shown that inhaled formoterol and salmeterol attenuate the late asthmatic reaction and the following increase in bronchial hyperresponsiveness [46-48]. We found [49] that an improvement in lung function remained up to one week after discontinuation of salmeterol treatment, contrary to the rebound effect after stopping regular terbutaline [36]. This may indicate a preventive effect and gives no indication of any rebound phenomenon.

Several prospective studies have been performed in more than 3,000 patients for up to one year, with both formoterol and salmeterol. These studies have shown a better asthma control, improved ventilatory lung function with decreasing nocturnal symptoms, less pronounced bronchial hyperresponsiveness and no rebound phenomenon, as well as less need for rescue bronchodilating therapy. These results were reported at the Societas Europae Physiologiae (SEP) meeting in Freiburg 1989, the SEP-Societas Europae Physiologiae Clinical Respiratoriae (SEPCR) meeting in London 1990, and recently at the ERS meeting in Brussels 1991. No long-term studies with either formoterol or salmeterol have shown any tendency towards development of tachyphylaxis to β_2 -adrenoceptor stimulation.

Conclusion

In our opinion, inhaled β_2 -stimulators are more friends than foes in the treatment of asthma. Further long-term studies with currently available salbutamol or terbutaline will shed more light on the question of whether these drugs could have any deleterious effects in the treatment of asthma. The new long-acting drugs formoterol and salmeterol have been shown to give improved asthma control in long-term studies. At present there is not enough evidence that they could safely be used without inhaled corticosteroids.

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