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Regular beta-agonist therapy - the quality of the evidence

In a recent issue of the Journal, LOFDAHL and SVEDMYR [1] discussed the evidence for and against a deleterious effect of regular inhaled beta-agonist therapy in asthma. Seven studies were quoted in support of the benefits of regular therapy [2–8], in contrast to one recent study which showed adverse effects [9]. We have carefully reviewed each of the seven studies quoted, examining the quality of the evidence on which arguments for and against regular beta-agonist therapy in asthma are made.

SHEPHERD *et al.* [2] gave 18 asthmatics regular or as needed salbutamol in a one week cross-over trial. Despite the use of twice as much inhaled bronchodilator (10.8 *versus* 5.7 puffs per day), symptoms were unchanged. The only significant change was a higher evening peak flow rate during regular therapy, which is to be expected as measurements were made within a few hours of use of the bronchodilator. This "beneficial" effect was also seen in our study of regular fenoterol, in which all other parameters generally indicated a deterioration in control of asthma [9].

VAN AS [3], reported a study by Benjamin, showing increased peak flows (whether morning or evening is not stated) in eight patients treated for one year with regular oral and inhaled hexaprenaline, and in 10 patients treated with regular oral and inhaled fenoterol. On the basis of that study, Van As recommended, "bronchodilators clearly must be administered regularly each day in full dosage". The original study of Benjamin has apparently never been published, and so the data cannot be independently assessed for validity.

COCHRANE [4] reported an unblinded, uncontrolled, retrospective review of 14 patients, who were given regular inhaled salbutamol for one or two weeks. He stated that, "unfortunately data of bronchodilator usage on a puff-to-puff basis were not accurately recorded". The mean of thrice daily peak flow rates (recorded in the morning, early evening and at bedtime) increased by 8%. This improvement could be consistent with a short-term effect of beta-agonist on evening peak flow rates, as seen in our study [9] and in that of SHEPHERD *et al.* [2], and may not reflect long-term benefit. The small numbers, short duration, inadequate data recording and open nature of the investigation preclude use of this investigation to support a beneficial effect of regular therapy.

ZELLWEGER *et al.* [5] compared regular use of dry powder salbutamol 400 μg *q.i.d.* with *p.r.n.* use in 52 adult asthmatics in a double-blind, 4 week, cross-over study. There were no significant difference between the two regimes with regard to symptoms, morning and evening peak flow rates, and spirometry, despite use of more that twice as much salbutamol during regular therapy (2,148 μg *vs* 800 μg). The only indicator favouring regular treatment was patient preference; that preference was not consistent with the objective data. The published illustrations in fact show a fall in morning peak flow of about 20 $l \cdot min^{-1}$ in the group initially given regular therapy, with return to baseline during *p.r.n.* treatment.

Despite being frequently cited in support of regular beta-agonist therapy, the study by BESWICK *et al.* [6] also suggests the contrary. In this randomized, placebo-controlled, cross-over study, 17 asthmatics were given salbutamol, 200 μg *q.i.d.*, or placebo for 12 months with rescue doses as required, then crossed over to the alternative regime for 3 months. Those initially taking regular therapy had stable (but lower) peak flow rates throughout the study period. Those using salbutamol only as needed showed an increase in mean peak flow of 32 $l \cdot min^{-1}$ above baseline by 12 months, which was reversed by a decrease of 63 $l \cdot min^{-1}$ in peak flow when regular therapy was instituted. It is, therefore, impossible to regard these data as supportive of regular therapy.

VANDEWALKER *et al.* [7] added oral or inhaled terbutaline, each for two weeks, to the treatment of asthmatics on maintenance theophylline. Only 13 out 32 subjects completed the study; five dropped out because of worsening asthma, seven because of side-effects, and seven others failed to complete both trial periods. In those who tolerated the treatment regime, addition of oral or inhaled beta-agonist asthma symptoms and peak flow. However, there was no adequate control period, *i.e.* treatment with *p.r.n.* beta-agonist alone without theophylline, and the very high drop-out rate makes the study difficult to interpret.

SMITH *et al.* [8] added inhaled terbutaline 500 μg *q.i.d.* to an optimal dose of theophylline in 10 patients for on week, and then substituted placebo for either terbutaline or theophylline for two 2 week periods with 1 week intervals back on combination therapy. Asthma control, as judged by peak flow rates and symptoms, was better during the one week periods of combination therapy than during monotherapy with either agent. However, in this study, there was again no placebo period with only *p.r.n.* beta-agonist with which comparisons could be made, and the study periods were very short.

None of these studies quoted by LOFDAHL and SVEDMYR [1], or any other available studies, support long-term regular therapy with inhaled beta-agonist

drugs. Two of these studies in fact reveal deleterious trends, similar to those that we reported with use of regular inhaled fenoterol [9]. It is surprising that studies of such short duration and small size, which are inadequately controlled, should have been accepted as evidence favouring regular beta-agonist therapy.

Set now against these inadequate studies is one specifically designed, large double-blind, placebo-controlled, year-long, randomized clinical trial with appropriate wash-out periods and sensitive analysis, which showed that regular use of inhaled fenoterol was deleterious in long-term control of asthma [9]. Of 57 subjects showing better control in one or other treatment period, 40 (70%) were better controlled using beta-agonist only as needed and deteriorated when given regular fenoterol ($p=0.003$). Mean forced expiratory volume in one second (FEV_1) declined 0.15 *l* ($p<0.005$), mean vital capacity (VC) declined 0.12 *l* ($p<0.05$), diurnal variation in peak expiratory flow increased from 9.8 to 17.5% ($p<0.0005$) and airway responsiveness increased (geometric mean provoking concentration producing a 20% fall in FEV_1 ($PC_{20}FEV_1$) to methacholine fell from 1.63 to 1.15 $mg \cdot ml^{-1}$, $p=0.003$). All but one major exacerbation necessitating hospitalization or temporary withdrawal from the study occurred whilst subjects were taking regular inhaled beta-agonist.

The increase in asthma mortality in New Zealand from 1976 onward was related in time with the marketing of fenoterol metered dose inhaler in a dose of 200 μg per puff, which contrary to the statement by LOFDAHL and SVEDMYR [1], was never sold over-the-counter in New Zealand. Initial studies of deaths from asthma in New Zealand raised concerns regarding recognition and management of severe life-threatening attacks [10, 11], but did not address the issue of why those who died had asthma of such severity as to be at risk of a fatal episode. The finding that regular or frequent use of a potent beta-agonist increased asthma morbidity provides a highly plausible explanation for the recent epidemic of asthma deaths in New Zealand, and for the epidemic of asthma deaths which followed the introduction of high dose isoprenaline in several countries in the 1960s.

When used frequently, whether for "maintenance" therapy on a regularly scheduled regime, or for recurrent breakthrough symptoms, beta-agonists have the potential to increase morbidity and, by extrapolation, mortality. Evidence of short-term benefit from use of beta-agonist cannot be used to argue in favour of their long-term use. The data contained in the studies cited by LOFDAHL and SVEDMYR [1] do not negate our concern about the long-term adverse effects of these drugs on the severity of asthma.

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Beta-agonists - still more friends than foes

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We are grateful for the opportunity to reply to the letters from Haas and Staudinger and from Sears and Taylor on our editorial "Beta-agonists - friends or foes" recently published in this journal [1]. We would also like to add further data to the current discussion about long-term effects of short acting β_2-adrenoceptor agonists.

The changes in mortality shown in the figure by the authors from Boehringer Ingelheim are similar to the figures for fenoterol, shown previously by CRANE *et al.* [2], and they add data on the increase of salbutamol use during the same period. The increase in use of β_2-adrenoceptor agonists is parallel to the figures seen both in Sweden and in the UK (see below). However, as previously indicated, there were no indications in the New Zealand data that salbutamol was related to the increase in asthma mortality [3].

Several points in the letter by Staudinger and Haas are very much in accordance with our own views. We believe, as do other authors [4], that fenoterol was selectively prescribed to high-risk asthmatics. This is probably due to the high dose of active drug in the fenoterol metered dose inhaler (MDI). The data from the Saskatchwan study did show an increased odds ratio for asthma death or near death for both fenoterol and salbutamol [5]. This certainly shows that those patients who had an increased death rate were the same patients who used the highest doses of both β_2-adrenoceptor agonists probably because they were instructed to do so.

Concerning the pharmacological properties of fenoterol, it clearly has a higher intrinsic activity, both on the β_1- and the β_2-adrenoceptors, than salbutamol which is only a partial agonist [6]. However, salbutamol has a much lower efficacy on the β_1-adrenoceptor, whereas on the β_2-adrenoceptor, in most pharmacological systems, the effect seems to be close to the efficacy of isoprenaline [6]. We admit that receptor binding studies do not show any relevant difference between fenoterol and salbutamol in terms of β_2-adrenoceptor selectivity. However, high doses of fenoterol may still cause a more pronounced stimulation on the β_1-adrenoceptors due to a higher β_1-adrenoceptor efficacy, which certainly explains the marked tachycardia after treatment with fenoterol seen in some New Zealand studies. Indeed, the study that we quoted [7] recorded tachycardia relatively late after inhalation of isoprenaline or fenoterol, but we believe it is appropriate to evaluate the effect after some time when the peak effect of isoprenaline and fenoterol has worn off. Thus, we consider that the comparison between the two drugs is appropriate, and it is evident that fenoterol has more pronounced cardiac effects when given in the doses supplied by the ordinary MDI [8].

Staudinger and Haas mention the differences between a cross-over design and a parallel design in the evaluation of asthma control. Obviously, these authors favour the cross-over design. In our experience, it is very difficult to perform a good cross-over study of long-term asthma control, because it may be difficult to prove that the patients are in a comparable state when entering both treatment periods. Therefore, well-designed studies evaluating asthma control are more easily to be done in parallel group designs.

In reply to the letter by Sears and Taylor, we admit that several of the older studies evaluating regular use of β_2-adrenoceptor agonists *versus* on-demand use had methodological defects. However, about 150 patients in total have been involved in these studies, without showing any clear disadvantageous effect of regular treatment, and this number is far greater than the number of patients recently presented as evidence that stopping regular use of β_2-adrenoceptor agonists is beneficial in asthma patients.

We agree that better studies have to be done, and we think that the huge recently performed trials with long-acting β_2-adrenoceptor agonists are good examples of such studies [9–11]. They all show an improved asthma control in several thousand patients. Several studies have been of long duration, and it is even more evident that in these conditions a parallel group design has to be used. These studies have been performed both in mild and in more severe asthmatics, in young patients as well as elderly. They most often present the original values of measurements instead of individually transformed variables, like in the study presented by Sears *et al.* [12]. The studies on long-acting β_2-adrenoceptor agonists show that long-term treatment with continuous β_2-adrenoceptor stimulation improves asthma control and decrease symptoms, but they do not exclude that patients with continuous need for asthma treatment should also be on maintenance treatment with inhaled glucocorticosteroids.

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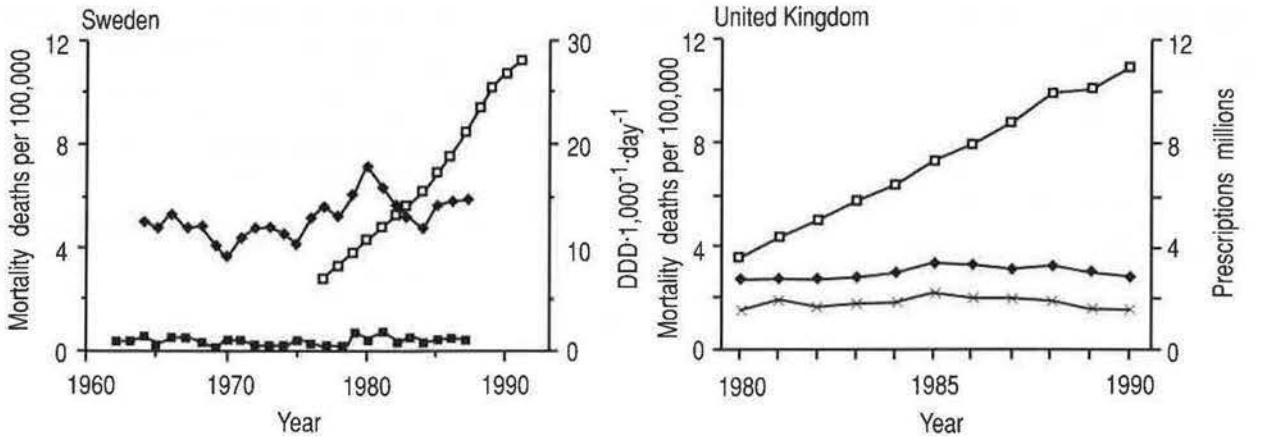

Fig. 1. – Asthma mortality data compared to prescription of inhaled β-agonists in Sweden and the UK. DDD: defined daily doses. Data from the UK were kindly supplied from the Committee on Safety of Medicines and published with their permission. —□—: inhaled β-agonists; —◆—: mortality, total; —■—: mortality, 0–34 yrs. —×—: mortality, <65 yrs.

Thus, if there is a consensus between Professor Sears group and ourselves, that would be: let us continue to perform and report better studies on the long-term effect, of asthma treatment, by doing this we will know better how we can improve the situation for the rising numbers of asthmatics throughout the world.

In a recent study in children comparing treatment with terbutaline (0.5 mg *q.i.d.*) alone with terbutaline *p.r.n.* [13], the regular terbutaline treatment did not cause deterioration of asthma control, thus contradicting the results by SEARS *et al.* [12]. Furthermore, a study in patients with chronic obstructive pulmonary disease, performed with regularly inhaled terbutaline (1 mg *q.i.d.*) compared to regular placebo with on demand terbutaline in both groups, showed better morning and evening peak expiratory flow (PEF) values, as well as a decreased number of asthma exacerbations during regular terbutaline treatment, this also contrasts the opinion that regular treatment with β_2-adrenoceptor agonists deteriorates the control of the disease [14].

Finally we would like to add some data from Sweden and UK for the discussion on regular treatment with short-acting agonists (fig. 1). In Sweden the asthma mortality has been almost unchanged since the early sixties. The total asthma mortality showed a small increase during the early eighties, but the mortality in the low age group has remained unchanged. This is true in spite of a tremendous increase of the use of inhaled β_2-adrenoceptor agonists during the 15 years. Similar changes in prescription habits have also been recorded in the UK where there was an almost threefold increase in the prescriptions of β_2-adrenoceptor agonists during the eighties. In spite of this both total mortality and mortality in the low age group have been constant throughout the decade. These data from Sweden and UK do not represent epidemiological studies, but if β_2-adrenoceptor agonists would have a major negative influence on asthma mortality, changes would have been seen in the asthma mortality in these countries where the use of β_2-adrenoceptor agonists has been increasing to very high levels compared to other countries.

The main take home knowledge acquired from the debate during the last year is that patients who need to increase their dose of these drugs should be re-evaluated concerning their asthma treatment, and that patients who regularly need bronchodilating therapy should also receive treatment with inhaled glucocorticosteroids to assure an effect on the inflammatory events associated with asthma. We still think that the β_2-adrenoceptor agonists are more friends than foes in the treatment of asthma.

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