What is the role of beta-agonist bronchodilators in the day-to-day treatment of chronic asthma?

PIERRE ERNST MD MSc FRCP
Respiratory Epidemiology Unit, Department of Epidemiology and Biostatistics, and
Department of Medicine, McGill University, Asthma Unit, Montreal General Hospital Montreal,
Montreal, Quebec


The reported links of asthma morbidity and mortality to the use of inhaled beta-agonist bronchodilators are reviewed. Reports from the Saskatchewan Asthma Epidemiology Project (SAEP) suggest that it is excessive use that is linked to life-threatening asthma and that patients at highest risk can be identified by their increasing use of these medications. This is the major justification for prescribing short acting beta-agonists on an as needed basis, though there is both clinical and experimental evidence suggesting regular use of these agents may not be beneficial. New longer acting inhaled beta-agonists designed for regular use are being introduced and their exact role remains to be defined. Provisioanlly, they appear to be useful in patients whose asthma is not well controlled with optimal doses of inhaled corticosteroids. The use of these newer agents for the relief of acute bronchospasm is contraindicated because of their slow onset of action.

Key Words: Adverse effects, Asthma therapy, Beta-agonist bronchodilators

Quel est le rôle des bronchodilatateurs bêta-agonistes dans le traitement quotidien de l’asthme chronique ?

RÉSUMÉ : Les liens rapportés entre la mortalité et la morbidité de l’asthme et l’utilisation de bronchodilatateurs bêta-agonistes en inhalation sont passés en revue. Des données provenant du Saskatchewan Asthma Epidemiology Project (SAEP) laissent penser que c’est leur utilisation excessive qui est associée à l’asthme quasi-mortel, et que les patients à plus haut risque peuvent être identifiés par leur utilisation accrue de ces médicaments. Ceci est la justification majeure pour prescrire des bêta-agonistes à courte durée d’action au besoin, bien que des données à la fois cliniques et expérimentales laissent penser que l’utilisation régulière de ces agents pourrait ne pas être bénéfique. De nouveaux bêta-agonistes à longue durée d’action, en inhalation, mix au point pour une utilisation régulière sont présentés : leur rôle exact reste à être défini. Provisoirement, ils apparaissent être utiles chez les patients dont l’asthme n’est pas bien maîtrisé par des doses optimales de corticostéroïdes en inhalation. L’utilisation de ces nouveaux agents pour le soulagement d’un bronchospasme aigu est contraindiquée à cause de leur délai d’action prolongé.

THE MEDICAL PROFESSION HAS EMBRACED WITH GREAT confidence the selective beta2-agonist bronchodilators such as salbutamol, fenoterol and terbutaline for the treat­ment of bronchospasm. These agents have gradually replaced theophyllines as first line therapy not only for acute attacks of asthma where their preponderant role remains undisputed, but also in the regular treatment of the stable asthmatic (1). In this latter role, they have been used most frequently on a continuous basis, i.e. three to four times a day in order to maintain bronchodilation throughout the day and night. The short duration of action of beta-agonist bronchodilators was seen as a drawback that limited the efficacy for the treatment

Correspondence and queries. Dr Pierre Ernst, Respiratory Epidemiology Unit, Department of Epidemiology and Biostatistics, McGill University, 1300 Pine Avenue West, Montreal, Quebec H3A 1A3. Telephone (514) 398-0974, Fax (514) 398-3081.
e-mail ernst@meatops.ians.mcgill.ca

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of nighttime symptoms and was responsible for reduced com-
pliance on the part of many patients. For this reason, various
pharmaceutical companies undertook programs to develop
long acting beta-agonist bronchodilators. Two of these, sal-
meterol and formoterol, were recently introduced into the
European market, and salmeterol is now available in Canada.

An epidemic of asthma deaths among young people in
Great Britain in the mid-1980s first raised the possibility that
overuse of inhaled beta-agonist medication could be hazar-
dous (2). Several agents in use at that time were nonselective
beta-agonists such as isoprenaline. The concern regarding
their overuse contributed to the development of beta; selec-
tive agents that had fewer cardiac side effects given the
preponderance of beta receptors in the heart. Much later, an-
alarm concerning the safety of the beta selective agents was
set off by a study published by Crane and colleagues in 1989
(3), which described an association between the use of
fenoterol, one of the commonly used selective beta-agonists,
and increased risk of death from asthma in New Zealand
which, at the time, had one of the highest death rates any-
where in the world. The study design did not permit conclu-
sions to be drawn about other beta-agonists in common use
such as salbutamol. Furthermore, differences in the way the
medication history was obtained in the cases and controls
suggested the possibility of bias, which rendered the conclu-
sions of this study controversial.

SASKATCHEWAN ASTHMA EPIDEMIOLOGY
PROJECT

The Saskatchewan Asthma Epidemiology Project was
undertaken in response to this controversy. This study, based
on examination of linked computerized databases available in
the provincial region of Saskatchewan, demonstrated a dose-
response relationship between the use of inhaled selective
beta-agonists and the risk of fatal and near-fatal asthma (4).
Since it appears obvious that patients with more severe dis-
ease are likely to use more medications and are also more
likely to experience adverse outcomes, the cases of fatal and
near-fatal asthma from Saskatchewan were matched to con-
trols with a similar history of prior hospitalization for asthma
(previously shown to be one of the most important risk
factors for fatal and near-fatal asthma) as well as the presence
of other diseases that might affect outcome. Furthermore, in
a subsequent analysis, cases of fatal and near-fatal asthma
were compared with the same controls after accounting for
the influence of additional markers of severity obtained from
hospital and office charts. The association between beta-
agonists and risk of fatal and near-fatal asthma was un-
changed after this additional adjustment for severity (5).

Complementary analyses of the whole cohort of over
2,000 patients suggested that the risk of major adverse out-
comes is limited almost entirely to patients oversusing beta-
agonist medications, that is, more than once inhaler per month
(6). Furthermore, it appears that the patients at highest risk
can be identified by their increasing use of inhaled beta-
agonists over a period of several months (7). This, therefore,
formally confirms clinical experience: asthmatic patients
have a tendency to overuse inhaled bronchodilators because of
the immediate improvement of symptoms that they expe-
rience, and the resultant increase in use is paralleled with their clinical
state. Furthermore, this overuse of beta-agonists and other
bronchodilators appears to be at the expense of the use of
inhaled corticosteroids which have, in contrast to beta-
agonists, the capacity to improve the severity of asthma (8) and
to decrease the risk of fatal and near-fatal attacks (9).

The practice of prescribing inhaled bronchodilators to
be taken on a regular basis is not supported by previous data
in the literature. In a randomized study, double-blind crossover study, asthmatic patients
were found to be better controlled if they took their beta-
agonist fenoterol on an as needed basis, compared with when they were taking this medication regularly four times a day.

Some of the criteria used to judge asthma control were criti-
cized but a subsequent analysis confirmed the first impres-
sion by showing a rate of asthma exacerbations that was
higher and a time to exacerbation that was shorter among
those subjects taking the inhaled beta-agonist on a regular
basis (10). Van Schoey (10) also reported that subjects who were taking bronchodilators on a regular basis had a greater
fall in forced expiratory volume in 1 s (FEV1) over a two-year period compared with subjects who were using their bron-
chodilator on an as needed basis only.

POSSIBLE MECHANISMS

If beta-agonists do indeed increase the risk of severe attacks of asthma, and if their regular use does bring on
worsening control of asthma, what are the potential mecha-
nisms? Tachyphylaxis to the bronchodilator effects of beta-
agonists does not appear to be a problem. The bronchodilator
effect persists undiminished for prolonged periods (13). An
increase in nonspecific bronchial hyperresponsiveness to
methacholine or histamine has been found in certain studies
examining the regular use of beta-agonist therapy in the
treatment of asthma (14,15). Such changes in bronchial re-
 sponsiveness raised the possibility of a change in function of
beta-agonist receptors when they are continuously stimu-
lated. Evidence for this has been described from several
recently. Bui and colleagues (16) described defective relaxation of smooth muscle after stimulation of the beta
receptors in patients who had died of asthma. Two groups
independently reported decreases in the protective effect of
inhaled beta-agonists on induced bronchostenosis by
methacholine, which acts directly on smooth muscle, or by
adrenergic membranephore, which acts via mast cells, among
subjects who had been given either terbutaline on a regular
basis or the long acting beta-agonist salmeterol for a period
of seven days and eight weeks, respectively (17,18). Bel and
Sterk (19) have suggested that while beta-agonists delay the
onset of bronchoconstriction in response to an agonist, the
maximal degree of bronchial constriction is not decreased and the rate of bronchoconstriction may actually be in-
creased, which could make attacks of asthma more precipi-
tuous. Page (20) has proposed that the stabilization of mast
cells by beta-agonists might prevent a liberation of heparin and a loss of its protective effect on bronchial epithelium.

Most recently, Cockcroft et al (21) showed that among asthmatics, two weeks of treatment with salbutamol increases the degree of bronchoconstriction in response to allergen. This study is quite significant when one considers the very important role of allergy in the majority of asthma during childhood and young adulthood. It seems that there are several plausible mechanisms by which the use of bronchodilators on a regular basis could be responsible for a worsening asthma that might result in increased morbidity. Mitchell (22) has explained how a small increase in bronchial hypersensitivity in the general population could bring about a larger increase in morbidity, which would be most apparent in the most severe asthmatics.

Following the epidemic of asthma deaths in the 1980s, much attention was given to the possible cardiac effects of beta-agonist medications, specifically their arrhythmogenic potential. When the safety of selective beta-agonists came into question, numerous studies examined the relative cardiac toxicity of the various beta-selective agents, by using indirect measures such as tachycardia, prolongation of the Q-T interval on the electrocardiogram or the induction of hypokalemia (23). The importance of these phenomena in vivo, however, has yet to be demonstrated. It should be pointed out that the major asthma of asthma deaths occurs after days and sometimes weeks of gradual deterioration and that at autopsy, the primary abnormality is an obliteration of the airway lumens by thick mucus enriched with inflammatory and epithelial cells. The importance of asphyxia as a mechanism for life-threatening asthma was also underlined recently by the study of Molfino et al (24). Among patients coming to the emergency room in extremis, it was found that the predominant abnormality was respiratory acidosis and not cardiac arrhythmia or hypokalemia.

**ROLE OF NEW BETA2-AGONISTS**

What is the potential role of two new long acting beta-agonists, salmeterol and formoterol, in the face of guidelines for the therapy of asthma, which now emphasize earlier use of anti-inflammatory therapy and the use of short acting beta-agonists as rescue medication? The clinical efficacy of these new agents when used continuously as bronchodilators is clear and impressive (25) and these newer agents are often preferred by patients (26). Early evidence suggested these drugs might have significant anti-inflammatory activity (27), but they have not been shown to differ from the currently available agents such as salbutamol in this respect (28). Thus, we cannot expect these agents to have clinically significant anti-inflammatory effects. Salmeterol and formoterol will have an appropriate role to play among asthmatic patients who are inadequately controlled on optimal doses of inhaled corticosteroids in order to limit the need for oral corticosteroids and to improve the quality of life of such patients. They are to be avoided, however, for the treatment of acute attacks because of their delayed onset of action.
