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Perspectives in β_2 -agonist therapy: Vox clamantis in deserto vel lux in tenebris?*

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β -Adrenergic agonists are compounds of simple chemical structure that are useful in the treatment of asthma and other pulmonary diseases characterized by reversible airway obstruction. These drugs act through stimulation of β_1 - and β_2 -receptors on cells, resulting in alterations in adenylyl cyclase and elevations in intracellular cyclic adenosine monophosphate (AMP).¹ The net effect in the airways is relaxation of smooth muscle with bronchodilatation, increased ciliary beat frequency, and a reduction in mucus viscosity.^{2,3} They also have significant actions on the heart, liver, and skeletal muscle.^{2,3} The first clinically useful drug of this class was isoproterenol, which appeared as a metered-dose inhaler in 1957. Although a potent bronchodilator, isoproterenol has a very short half-life and major dose-dependent inotropic and chro-

Abbreviations used

AMP:	Adenosine monophosphate
FEV ₁ :	Forced expiratory volume in 1 second
PC ₂₀ :	Provocative concentration causing a 20% fall in FEV ₁
PEFR:	Peak expiratory flow rate

notropic cardiac properties. To overcome these problems, the catechol moiety of isoproterenol was altered to produce longer acting β_2 -agents (i.e., metaproterenol, terbutaline, albuterol, pirbuterol, fenoterol, and others) that have selective action on the bronchi.^{2,3} The enhanced durations of activity and reduced side effects of these newer drugs have had a profound impact on patient care. With them, it became possible to try to maintain a state of continuous bronchodilatation, and treatment strategies quickly moved from simply relieving acute episodes of airway narrowing as they appeared, to attempting to prevent their occurrence by regularly scheduled medication. As a result, β_2 -agonists became the mainstay of asthma therapy, and increasingly larger numbers of patients began to be exposed to greater quantities of these drugs worldwide.

Shortly after their introduction, fears about the safety of β -agonists began to appear. In the 1960s, an increase in deaths in patients with asthma and chronic bronchitis in certain countries was associ-

*A voice crying in the wilderness or a light in the darkness?

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ated statistically with the availability of a high-dose formulation of isoproterenol.⁴ Because the mortality rate fell to baseline after this product was removed from the market and because the use of isoproterenol has been superseded by the more selective agents, which have fewer untoward consequences, the problem appeared to be solved. Recently, however, concerns have been expressed that even the newer drugs may be harmful when taken continuously three or four times daily.⁵⁻⁷ For reasons that are unclear, these viewpoints were accepted with little dissent and much sensationalism with the result that limited use, or even withdrawal, of β_2 -sympathomimetics has been advocated.^{7,8} However, whenever dispassionate evaluations of the strength of the current evidence have been undertaken, similar degrees of certitude have not been forthcoming,^{9,10} and so the matter remains a source of confusion for practitioners and patients alike. In this article, the data underlying the present controversy over the use of β_2 -agonists will be critically analyzed so that a perspective on the types and magnitude of risks involved can be formulated.

TOXICITY

The toxicity of the β_2 -agonists has been detailed previously,^{2,3} and only the salient features will be presented here. Because the incidence and intensity of side effects are dependent on the dose of drug reaching the target organs, the oral and parenteral routes of administration produce the greatest adverse consequences. Statistically, tremor is the most common untoward event. It is a specific β_2 activity and is seen with all agents of this class. Tremor disappears with continuing drug use and does not have any long-term health implications. When large quantities of β_2 -agonists are used (as in the treatment of status asthmaticus), increases in blood glucose, lactate, pyruvate, and ketones have been observed, as well as decreases in potassium.¹¹⁻¹³ Usually, such metabolic events are minor in degree, but the additional hypokalemia can potentiate that produced by steroids or diuretics. Fortunately, the latter is a rare occurrence and one that is readily reversed.

The toxic effects of greatest concern are those that have an impact on the heart. With the current drugs, the major cardiac events are palpitations and tachyarrhythmias. Sinus tachycardia is the most prevalent phenomenon and is due to a reflex increase in heart rate as a result of peripheral vasodilatation.^{2,3} Like tremor, it disappears with time. At high doses β_2 -agonists can also have a

direct stimulatory effect on the myocardium. Although ventricular arrhythmias have been observed with the nonselective sympathomimetics, significant cardiac toxicity has not been reported with the new β_2 compounds in therapeutic amounts, even when arrhythmias are specifically sought with Holter monitoring.¹⁴⁻¹⁶ In fact, symptomatic sinus tachycardia appears to be an infrequent occurrence. In a multicenter trial comparing albuterol and salmeterol (a long-acting albuterol congener recently released in the United States), only two of 234 subjects complained of rapid heart rates during the 3 months of observation.¹⁶ The national surveillance study in the United Kingdom of 25,180 patients taking salmeterol or albuterol also found cardiac problems to be distinctly uncommon.¹⁷ One hundred twenty-two subjects had their sympathomimetics withdrawn because of rapid heart rates. Ninety-eight of these had palpitations, 19 complained of tachycardia, and five had arrhythmias. Of the 39 cardiovascular deaths in this series, none were due to altered cardiac rhythms (myocardial infarctions = 21, congestive heart failure = 7, cerebral vascular accidents = 5, pulmonary emboli = 4, hypertension = 1, ruptured aneurysm = 1). This information was graciously supplied at my request by Drs. W. Castle and R. Fulton of the Glaxo Research Institute. Thus although the potential for myocardial side effects certainly exists with the β_2 -agonists, myocardial side effects are not a major clinical concern in prescribed doses.

PURPORTED DETRIMENTAL EFFECTS

The potential adverse reactions to β_2 -agonists, in addition to the standard toxicity, that have been expressed in the literature are: aggravation of hypoxemia,^{18,19} toxicity of the propellants in metered-dose inhalers,^{18,20} augmented dose of allergen as a result of bronchodilatation,^{21,22} paradoxical bronchospasm,⁷ heightened airway reactivity,^{7,23,24} tolerance or tachyphylaxis,^{7,25-28} increased morbidity from loss of asthma control,^{5,7,29} and a high mortality rate.^{7,30,31} The first two are mainly of historical interest, and the third is a theoretic construct. The remainder constitute the majority of current concerns, and as will be developed, the database in support of each is not sufficiently compelling to afford uniform acceptance.

AGGRAVATION OF HYPOXEMIA AND CONCERNS WITH PROPELLANTS

All sympathomimetics, including the β_2 -agonists, can produce acute alterations in ventilation-

perfusion relationships in patients with asthma, thereby causing arterial oxygen levels to fall.^{19, 32} This phenomenon, however, is of little clinical significance because it is very short-lived and rarely of sufficient magnitude to lower arterial saturation.³² Thus it is not a major problem. The toxicity of the fluorocarbon propellants in metered-dose inhalers has been extensively studied after early reports raised the possibility that they sensitized the myocardium to endogenous catecholamines and could conceivably contribute to asthma mortality.²⁰ Here too, the expressed concerns turned out to be largely groundless, and the data demonstrate that the nonmedicinal components contained in pressurized aerosols do not cause problems for patients with asthma, except in cases of the most flagrant abuse.³³⁻³⁵ Nonetheless, even this potential will disappear in the near future when the current propellants are phased out of production by international treaty.

AUGMENTED DOSE OF ALLERGEN

It has been suggested that the regular administration of β_2 -sympathomimetics, through their amelioration of the early response to antigen, may inadvertently allow excessive exposure to immunologically active substances with the production of magnified delayed reactions that would then lead to worsening asthma symptoms.^{21, 22} Additionally, it has been hypothesized that the mast cell-stabilizing properties of these compounds may be detrimental and interfere with the antiinflammatory activities of heparin.³⁶ Although interesting, both of these postulates are purely theoretic, and there are no data to support either. In fact, if the first circumstance actually developed, such masking of symptoms should also occur with long-acting bronchodilators such as sustained-release theophylline. These drugs produce persistent airway dilatation while modulating the physiologic reactions to antigens,³⁷ yet they are not associated with worsening asthma via subliminal allergen exposures. Moreover, it is not entirely clear why inhibition of mast cell degranulation by β_2 -agonists should evoke adverse results, when that associated with cromolyn or nedocromil is a sought-after therapeutic effect.

PARADOXICAL BRONCHOSPASM

Shortly after the appearance of isoproterenol, its ability to worsen pulmonary function and asthma symptoms in isolated patients was recognized.³⁸ In recent years, scattered case reports of severe bronchospasm after aerosol administration of the selec-

tive β_2 -agonists have also been published,^{39, 40} prompting admonitions regarding safety.⁷ Although dramatic, paradoxical bronchospasm is an extremely rare event. From 1974 to 1988, 88,546,239 metered-dose inhalers were distributed to patients with asthma in the United States, and only 126 instances of this complication were reported to the Center for Drug Evaluation and Research of the Food and Drug Administration (i.e., 1.4 occurrence/million canisters dispensed).⁴¹ Similar findings exist for nebulizer solutions. From 1983 to 1988, 58 instances of bronchospasm occurred among 19,358,290 distributed nebulizer solutions (3 occurrences/million units dispensed). Obviously, this phenomena is not a major public health problem in terms of prevalence and does not require restriction of the use of β_2 -agonists.

HEIGHTENED AIRWAY REACTIVITY

This section deals with the suspected effects of β_2 -agonists on the intrinsic responsivity of the airways and not with the action of these drugs in providing immediate protection against various provocative stimuli. The latter will be covered subsequently in the section on tolerance. It is commonly written that the scheduled, continuous use of β_2 -sympathomimetics worsens bronchial hyperresponsiveness,^{7, 22, 42} and one postulate holds that even small drug-induced changes in this parameter could cause the proportion of patients with uncontrolled asthma to increase.^{22, 43} Although these views have made their way into asthma treatment guidelines,^{7, 44} there does not appear to have been a critical assessment of the quality of the evidence on which they are based. For example, there are no objective data from any source that demonstrate that β_2 -agonists have transformed the severity of asthma by enhancing airway sensitivity, and, for reasons to be discussed, the likelihood of this being a valid hypothesis is remote (see the section on increased morbidity). The quoted trials purported to show positive effects are also problematic. These studies examined the consequences of treatment with inhaled glucocorticoids and β_2 -agonists^{23, 24} and regular versus as-needed use of fenoterol on bronchial responsiveness,⁵ but the results are far from conclusive. (Because the last article cited⁵ is concerned primarily with the influence of intermittent and scheduled uses of β_2 -agonist on lung function and asthma control, its contents are analyzed in detail in the section on increased morbidity. Suffice it to say here that the portions of this

work related to bronchial hyperresponsiveness contrast with the findings in other trials.²⁹)

In the first investigation,²³ the difference between the budesonide and terbutaline arms was statistically significant, but no analysis was presented to indicate that there were any meaningful group changes in provocative concentration causing a 20% fall in FEV₁ (PC₂₀) before and after administration of the sympathomimetic. In point of fact, the tabular data in this article demonstrate that the β -agonists did not have any consistent statistical influence on mean airway reactivity over the course of observation. After 1 month of terbutaline treatment, PC₂₀ slightly, but statistically significantly, worsened; however, the values spontaneously returned to baseline by the second month. Values then remained constant for the next 2 months, fell significantly at the next observation point, and once more returned to pretreatment levels for the rest of the study. Obviously, such a pattern is not indicative of a meaningful physiologic effect, and this work does not support the hypothesis with which it is associated. The second positive study cited above also compared terbutaline and budesonide but used both histamine and propranolol to quantitate the airway responses.²⁴ In this trial terbutaline was associated with a minor, but statistically significant, worsening of bronchial reactivity as measured by histamine inhalation after 2 weeks of therapy, but the effect was gone by 4 weeks. From the data in this portion of the trial, the most that one can conclude is that the event, if real, is a transient one that disappears quickly with time and is therefore of marginal importance. On the other hand, the response to propranolol was amplified at both points of observation. Hence, in this work, 4 weeks of treatment with terbutaline caused airway responsiveness to both return to and worsen from baseline simultaneously, depending on the stimulus. Obviously, this is a clinical impossibility, and the internal inconsistencies of such data preclude them from serving as universally acceptable examples of adverse consequences. Most recently, albuterol was said to enhance airway reactivity in a group of five patients with asthma and 10 patients with chronic obstructive pulmonary disease.⁴⁵ The reported changes were small (19% reduction in PC₂₀) and required a full year for development. The first finding is typical but the second is a major departure from previous studies (see above). Further, a separate statistical analysis for the patients with asthma was not presented, so it is not clear which group was responsible for the findings. As concerning as these

differences are, the major flaw, however, is a lack of continuity of data collection. One third of the subjects, at one or more of the observation points, did not have measurements made of the index variable, airway reactivity. In the statistical analysis the missing data were simply estimated. Consequently, the impact of this work is quite limited. It is essential to appreciate that the lack of any important influences of β_2 -agonists on airway reactivity in the articles cited in this paragraph is not unique, nor is it due to a bias in selection of references. Rather the absence of any meaningful effect is representative of all of the observations in the literature on this subject,^{25, 29, 46-49} including two large multicenter trials involving 193 patients.^{29, 47} In terms of overall balance, it is difficult to escape the conclusion that there is little convincing evidence that β_2 -agonists alter the intrinsic responsiveness of the airways of asthmatic patients in an adverse fashion.

TOLERANCE

Loss of bronchodilatation

It is well known that persistent use of β_2 -sympathomimetics results in tolerance or down-regulation of many of the extrapulmonary activities of these drugs. Tremor, tachycardia, lymphocyte receptor number, and plasma cyclic AMP levels—to name a few—all decrease in these circumstances.⁵⁰⁻⁵² None of these changes, however, are indicative of what goes on in the airways of asthmatic patients, and attempts at extrapolation have been uniformly unsuccessful. The only clinically relevant sequela of the development of tolerance in patients would be a progressive reduction in bronchodilatation, a loss of protection from appropriate provocative stimuli, or a diminution in the ability to reverse induced obstruction as the dose of medication or the duration of therapy increases. The first possibility has been repetitively sought over the years, but it has never been convincingly demonstrated.^{50, 52-57}

A few investigations have purported to find a small reduction in bronchodilatation,⁵⁸⁻⁶¹ but as with the changes in airway reactivity, the patterns are difficult to explain physiologically. The sine qua non of time dependence is strikingly absent in these works, and some authors describe reduced responsiveness to a β -agonist at 1 or 2 hours after acute administration, but not after 3 or 4 hours⁵²; whereas others report the reverse.⁶⁰ Further, tolerance has been said to have been present with one set of pulmonary function measures and not with similar indices in the same investigation.⁶¹ Newer works have uniformly been negative,^{16, 52} and they,

in combination with previous data,^{50, 53-56} confirm that a loss of bronchodilatation is not an important consideration. The typical consequence of prolonged administration of β_2 -agonists is a slight decline in the duration of activity.⁵⁷ There are no clinical counterparts associated with this phenomenon, and even any potential difficulties with dosing will disappear completely with the availability of the new long-lasting compounds.

Loss of protection to provocative stimuli

Since 1988, four articles have appeared that allege that β_2 -sympathomimetics can be associated with a reduction in protection against the airway constriction evoked by stimuli such as histamine,²⁵ methacholine,²⁶⁻²⁸ AMP,²⁷ and antigen.²⁸ As with the alterations in airway reactivity and downregulation of the bronchodilator actions of β_2 -agonists reviewed above, the overall data are inconsistent and difficult to fit into a pattern. In the first work investigators from Nottingham found that the prophylactic action of terbutaline against histamine-induced constriction was reduced significantly after 14 days of treatment, even though the intrinsic reactivity of the tracheobronchial tree had improved.²⁵ This trial conflicts with a subsequent study by this group in which statistically significant effects could not be found in a similar experiment.⁶² It also contrasts with a previous work in which albuterol provided unchanging defense against histamine for 6 weeks.⁴⁹ Because histamine can induce tachyphylaxis by itself,⁶³⁻⁶⁵ when given in the intervals used in the positive investigation,²⁵ it is not clear what role, if any, this factor played in the results.

A Dutch group working with salmeterol observed a diminution in the ability of the drug to protect against methacholine.²⁶ According to the numeric, rather than the graphic, data in this investigation, salmeterol raised the PC₂₀ over 800% immediately, but this effect was not sustained, and by 28 days had decreased by 75%. Thereafter, it remained stable for the duration of the study (56 days). Time dependence was absent, and a progressive loss did not develop. Others have subsequently confirmed this effect.^{26a} In the third article, 1 week of terbutaline was said to reduce the acute responsiveness to methacholine and AMP significantly from 2.7 to 2.2 and 3.8 to 1.7 doubling doses, respectively.²⁷ Reanalyzing this study with the untransformed data from the tables, however, demonstrates that terbutaline did not have any greater effect on methacholine than did placebo (PC₂₀ terbutaline before vs after treatment =

-30.4%; PC₂₀ placebo before vs after treatment = -28.4%; $p = \text{NS}$). In the AMP portion, the placebo effect was a 17.4% decrease in PC₂₀ contrasted with a 57.8% fall with the active component for a net reduction of 40.4%. Therefore the β_2 -agonist only influenced AMP, and not methacholine. Such specificity is difficult to explain physiologically or pharmacologically, and one cannot help but question its meaning, particularly because part of this investigation refutes the Dutch work cited earlier.

The final article in this series demonstrated that 2 weeks of salbutamol treatment resulted in a significant loss of protection from antigen and methacholine as measured by a shift in the number of doubling doses of agonists required to reduce the FEV₁ by 20%.²⁸ It also implied that the β_2 -agonist produced an increase in the intrinsic bronchial responsiveness to antigen. Again, analysis of the untransformed data provides a different perspective. In the antigen arm paired comparisons using the mean pre- and postintervention differences between placebo and salbutamol in the subjects who have complete data (Table 2) do not show any significant effects.²⁸ With this analysis, the decrease in allergen PC₂₀ between the baseline data for the β_2 -agonist periods also disappears. The diminution in methacholine prophylaxis remains, but it is quite small (i.e., percent change in PC₂₀ in the placebo period before and after salbutamol = $16.0\% \pm 4.8\%$ SEM; percent change in PC₂₀ in the salbutamol period before and after salbutamol = $11.2\% \pm 3.8\%$).

The quantitative reevaluation of the data in each of these studies was not undertaken solely to contest the respective authors' conclusions but also to make a point regarding the meaning of the findings. If different analysis of the same data can make an alleged detrimental effect come and go, how important can it be in terms of overall health consequences? In this context it is imperative to understand that even if the data in all of the above studies are accepted at face value, their clinical significance remains questionable. The prophylactic action of the β_2 -agonist always remained greater than placebo by a factor of 2 or more and never fell below the pretreatment baseline.²⁵⁻²⁷ Hence, the drugs continue to protect. Further, none of these trials are therapeutically relevant. Patients will not encounter any of the nonspecific stimuli used in their daily activities, and knowledgeable clinicians would never recommend a bronchodilator as the sole preventive agent to forestall the effects of antigen. Equally germane is

the fact that there are no data that show that the capability of β_2 -agonists to ameliorate newly formed acute obstruction from any cause is compromised by long-term use. This really is the critical issue. If the drugs continue to reverse induced or spontaneous bronchospasm, then a diminution in preventive ability would not be detrimental to the patient because it would not interfere with therapy in any fashion.

Can long-term use of β_2 -agonists produce a loss of protection against asthma precipitants, such as exercise, for which these drugs would ordinarily be used? Here too, the data are inconclusive. One experiment suggested that oral agents could have this effect but aerosolized formulations of the same drug did not.⁶⁶ Most recently, investigators in the United Kingdom reported that tachyphylaxis may develop in response to the functional antagonism of salmeterol against exercise-induced bronchospasm.⁶⁷ Salbutamol was said to afford significantly more prophylactic benefit against an exercise challenge commencing 6 hours after administration on day 1 of a 4-week trial than at its end. Reduced protection was not found at 12 hours after administration. Unfortunately, the design of this investigation did not permit the authors to verify when or even if their subjects took the medication before undergoing the exercise provocation. Equally importantly, data were not provided to demonstrate that the exercise challenges were uniformly applied from trial to trial. The authors did not give any information as to how they monitored and controlled critical variables, such as the temperature and water content of the inspired air and the level of ventilation.⁶⁸

Rebound increases in reactivity

One group has presented evidence that suggests that cessation of β -agonists can be associated with a short-lived (2- to 3-day) rebound increase in airway reactivity.^{6,62} As with other features of the β_2 -agonist story, analytic uncertainties cloud the interpretation. In both studies the rebound effects are only present when comparisons with placebo are made. Examination of the data does not indicate any change in airway responsiveness when the initial and final values in the β_2 -agonist sections are contrasted. Thus the active drugs per se did not induce the reported change; it was the placebo arm that changed. This is not a sophistic point, for placebo use in treatment of asthma routinely alters lung function. Further, in the first trial β_2 -agonist withdrawal did not affect FEV₁, whereas in the second, FEV₁ fell by 10%. This decrease is difficult

to understand because the reduction in FEV₁ was not associated with changes in peak expiratory flow rate (PEFR), or symptom scores during the time of interest. Because FEV₁ and PEFR are statistical subsets, it is not clear how the airways could narrow sufficiently to cause forced expiratory volume to fall without changing the rate at which air was expelled. Once more, clinical relevance is also an issue, for others have not found any type of rebound phenomenon when they searched for it.²⁶

INCREASE IN ASTHMA MORBIDITY

As pointed out in the introduction, β_2 -agonists have been traditionally used on a continuous basis in an effort to achieve and maintain the best state of lung function possible. In so doing, it was thought that asthma morbidity would be reduced. The data in support of^{69,70} and against⁷¹ such arguments have been reviewed, and it is fair to say that the superiority of regular over intermittent symptomatic use for the majority of patients has never been conclusively proven. Four years ago, this matter was taken a step further when it was suggested that continuous treatment with β_2 -agonists could actually be detrimental.⁵ Of the 64 patients randomized to receive fenoterol or placebo 4 times daily for 24 weeks in a crossover, double-blind study, 40 were said to fare much better on the as-needed regimen. They had fewer symptoms and higher values for PC₂₀. Unfortunately, this article only presented the percentage of patients showing a change in the parameters assessed; and essential objective data on signs, symptoms, quantities of drugs used, and lung function were not provided. Consequently, it is not possible to validate the authors' conclusions.

The most disturbing feature of this study, however, is the magnitude of the physiologic changes that are allegedly driving the symptoms heralding the loss of asthma control. When these data were published in a subsequent article,⁷² they turned out to show remarkably small effect. The average difference in FEV₁ between the regular and as-needed regimen for the duration of observation was only 5.3%. A change of this magnitude, even though statistically significant, is simply too diminutive to have any clinical meaning or to cause any symptoms whatever.⁷³ If alterations in pulmonary mechanics did not produce the observed effect, what did?

The answer may lie in the type of analysis used. Improvement, or lack thereof, was not examined in the standard manner by comparing the differences between the means and variance of the clinical

indices in both arms of the parent investigation. Rather, it was arbitrarily defined by a hierarchy of "markers of control." If significant differences for each variable were not all in the same direction, then need for short courses of prednisone, morning PEFR, nocturnal bronchodilatation use, nocturnal symptoms, daytime symptoms, evening PEFR, and daytime bronchodilatation use, in that order, were used to decide which regimen showed better asthma control. This means that in a situation in which morning PEFR was the only significant improvement and all of the other parameters remained constant, worsened, or changed randomly, the patient could be judged to be better. Obviously, such an approach contravenes usual clinical experience, and its validity needs objective verification before it could be universally accepted.

Supporters of the theory that β_2 -agonists increase asthma morbidity point to a multicenter Dutch study²⁹ as confirming the above-mentioned investigation.⁵ It, however, does not do so in any particulars. This trial included patients with 51 asthma and 93 patients with chronic bronchitis and showed that those given salbutamol on a scheduled, four times daily, regimen had a more rapid decline in lung function over 24 months than did a parallel group taking this agent only as needed. Curiously, a separate analysis of rate of loss of FEV₁ was not presented for the patients with asthma and those with bronchitis, even though such an analysis was undertaken for PC₂₀. Hence, one cannot distinguish which group accounted for the phenomenon. This is a major impediment to reaching a sound conclusion because a cardinal feature of chronic bronchitis is an accelerated reduction in forced expiratory volumes and flows. Unlike the study cited above,⁵ there were no differences in symptoms, general well-being, exacerbations of airway obstruction or PC₂₀ between regimens.

If lung function and disease control were deteriorating in asthmatic patients in a meaningful fashion with β_2 -agonists, could this go undetected for so long? On the basis of the widespread use of these compounds around the world and the commonality of asthma, the answer appears to be no. Given that in the United States alone, there are 10 million or more patients with asthma consuming tens of millions of different sympathomimetic inhalers per year, plus oral formulations, for more than a decade, the chances of adverse reactions being manifest clinically, if they were occurring on the time scales described, would be quite high. Even if 5% of those at risk showed the findings

alleged in the above-mentioned studies, in short order there would be an ever increasing population comprising tens to hundreds of thousands of patients with worsening asthma. Such numbers are not trivial signals, and it would require a great stretch of the imagination to suggest that they have gone unrecorded (see below).

INCREASED ASTHMA MORTALITY RATES

In an attempt to explain the rise in deaths caused by asthma that have been reported in some countries,⁷⁴ attention has turned toward the possibility that β_2 -agonists were contributing to the process. Epidemiologic data from New Zealand first suggested that treatment with fenoterol could be associated with an increase in asthma mortality rates.^{30, 75, 76} Although the validity of the original findings were challenged on technical grounds, the effect continued to be observed when the methodological problems were corrected.³⁰ The strength of this association, and the reasons for it, however, are still a matter of some debate. The findings seem to be specific to fenoterol because the control populations in those New Zealand studies used other β_2 -agonists and did not have an increase in deaths.^{30, 75, 77} In fact, all studies to date in this population have excluded a class effect of the sympathomimetics.⁷⁷ Although it is true that fenoterol may be less β_2 -selective than other agents,⁷⁸ this factor does not necessarily confirm cause and effect. The association between death and fenoterol use may simply have derived from the positioning of fenoterol in the marketplace as better serving the more severely ill patient. The asthma mortality rate in New Zealand rose dramatically from 1974 to 1979 and fell sharply thereafter.^{77, 79} During this time, consumption of β_2 -agonists of all types, including fenoterol, increased steadily.⁷⁹ Fenoterol, which was introduced in 1976, did not reach its peak market share until years after the decline in deaths began and sales were maintained long after the death rates reached pre-epidemic levels. Consequently, the purported fenoterol-asthma mortality rate relationship does not seem to coincide in time. Moreover, countries such as Germany and Belgium have used fenoterol extensively but have been spared an epidemic of asthma fatalities.⁷⁸

A nested case-controlled study from Canada showed a relationship between asthma mortality rate and the quantity of β -agonists taken over a year.⁶ In the original publication, consumption of 2 or more canisters of fenoterol or albuterol per month was said to be associated with an increased

risk of death. (The risk was greater with fenoterol, perhaps for the reasons discussed above.) In a follow-up analysis involving the entire cohort of patients with asthma, the limit was lowered to 1.4 canisters per month.³¹ If correct, these findings are indeed damning. However, they do not appear to be true for a number of reasons.

First and foremost, the epidemiologic investigations have only noted an association. They have not demonstrated causality. This is an extremely important point, for the authors of the Canadian studies have clearly lost sight of the quantities of medications involved. One 200-dose canister of albuterol contains only 20 mg of drug, whereas a 300-dose fenoterol metered-dose inhaler can have as much as 60 mg (fenoterol is marketed in 200- and 300-dose canisters containing either 100 or 200 μ g drug/activation; information provided by Boehringer Ingleheim, U.S.A.). Ignoring that only 10% to 15% of each puff reaches the lungs and that quantities of fenoterol administered were greater than albuterol because of its formulations, the amounts said to be deadly (i.e., 1.4 to 2.6 canisters/month) would equal doses of albuterol ranging from 38 to 52 mg/month and doses of fenoterol from 84 to 156 mg/month. Even with the maximum values, the quantities in question are actually less than what a patient would receive if he or she took the recommended oral doses of each drug for 5 and 21 days, respectively (i.e., albuterol 4 mg three times daily for 5 days = 60 mg; fenoterol = 2.5 mg three times daily for 21 days = 158 mg). At the lower levels the situation is even more unrealistic. If increased risk of death really began to accelerate at 1.4 canisters/month, that would mean that 3 days of oral albuterol administration and 11 days of oral fenoterol administration would put patients in jeopardy. Yet in the study in question, the odds ratio for adverse reactions for any oral β -agonists was less than that for inhaled compounds, theophylline, and oral corticosteroids, respectively, and equal to that for inhaled glucocorticoids. Thus simplistically put, this group of investigators is arguing that small amounts of drug given by inhalation are more lethal than much larger quantities administered orally, even though the blood levels of the latter are far higher.² This scenario does not seem very likely. A far more appealing possibility is that disease intensity drives drug use in these and other studies and not the converse.

Second, a good case can be made that the authors are overstating the magnitude of the problem. Only 46 deaths occurred in the entire cohort of 12,301 asthmatic patients evaluated. Incorporation of "near deaths" expands the database markedly, but the definitions used to identify these individuals (i.e., a $Paco_2$ greater than 45 mm Hg or intubation) are too imprecise to allow such patients to add meaningfully to the issue under study. Fully 10% of adults and children with asthma seeking care for acute episodes in emergency departments fulfill the first criterion without having any risk for death at all.⁸⁰⁻⁸³ Moreover, it is well established that a single $Paco_2$ value at one point in time does not predict the patient's course.⁷³ Elevated levels fall with appropriate treatment well short of the need for assisted ventilation. Intubation may be a better indicator of the intensity of a given attack, but it cannot necessarily be used as a surrogate for "near death" unless one has objective documentation that the procedure was performed solely because of impending suffocation. Too often this is not the situation and without information on the number of subjects in this category and the circumstances surrounding this intervention, the authors' contentions cannot be validated.

These points of confusion probably account for why the Canadian observations show up as such a minor effect in a meta-analysis⁸⁴ and do not concur with those from New Zealand,⁷⁷ Sweden,⁷⁰ or Great Britain⁸⁵ in which no relationship between deaths caused by asthma and overall β -agonist use has been found. In fact, in Great Britain sales of β_2 -agonist inhalers have tripled in the last decade while the number of deaths caused by asthma has remained stable. The studies in question also do not correspond with observations, indicating that very high doses of β -agonists such as those used in compressor-driven nebulizers are not associated with a higher mortality rate.⁸⁶ A person in North America using albuterol nebulizer solution 4 times daily for a month would in effect be consuming the equivalent of 15 metered-dose inhalers as a minimum. In Europe and elsewhere the quantity could be double this amount. The Canadian observations also do not fit well with the circumstances surrounding deaths caused by asthma in the United States. The mortality rate among persons 5 to 34 years of age is considerably and consistently higher among nonwhites than whites and tends mainly to be found in large urban areas such as Chicago and New York.⁸⁷ Approximately 20% of all deaths caused by asthma developed in these regions even though only 6.8% of the population at risk resides there. Many of these persons live in the inner city where access to and continuity of health care are great problems. If excess β -agonist medication is

contributing to deaths caused by asthma in the United States, it seems to be doing so quite selectively.

CONCLUSION

A critical analysis of the available data underlying the current controversy regarding the use of β_2 -agonists does not support the existence of major adverse reactions, and internal and external inconsistencies in the published material preclude the identification of any recognizable pattern of untoward health effects. Contrary to what is written, there is no convincing evidence that these drugs unfavorably modulate the responsiveness of the tracheobronchial tree in patients with asthma or reduce the protection from constrictor stimuli in a clinically meaningful way. The purported increase in asthma morbidity that has been associated with scheduled use of β_2 -agonists remains contentious because of problems with the analysis, the paucity of the physiologic changes, and the lack of confirmation of a loss in asthma control in other studies with similar designs. The case for β_2 -agonists as a class causing an increase in the asthma mortality rate is also not very compelling. Fenoterol, because of the strength of its formulation and its market positioning, may have been associated with deaths caused by asthma because it was used more frequently in patients whose disease was unstable and difficult to control. The Canadian studies suggesting a class effect do not reconcile their findings with the negative results around the world, incorporate a population of questionable relevance in the analysis, and claim that quantities of inhaled drug equivalent to a few days of oral medication increase the risk for death. β_2 -agonists are not perfect or a panacea, but they are the best drugs that we have for managing the acute symptoms of asthma. When used appropriately, alone or in combination with other modalities, they will continue to provide a reliable and dependable means of controlling asthma morbidity.

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