Gerhard Sybrecht

Editor

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An international symposium
held during the XIIth World Congress of Asthmology,
Barcelona, 1987



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# Foreword

Inhalation therapy has become well established in asthma for several good reasons. For the patient, it provides a quick, convenient means of obtaining symptomatic relief of bronchospasm. Pharmacologically, inhalation enables small overall doses to be delivered directly to their site of action in the bronchial tree achieving maximal topical concentrations, and thus keeping systemic side effects to a minimum. However, the $\beta_2$-stimulants hitherto available have had the disadvantage of being relatively short-acting. Many patients therefore required repeated inhalations, several times daily and often during the night as well. Hence the need for a longer-acting $\beta_2$-stimulant able to produce a sustained bronchodilator effect when given only twice daily.

This symposium, held during the XIIth World Congress of Asthmology in Barcelona, first surveys the present status of $\beta_2$-adrenoceptor stimulants in asthma therapy. This review is followed by reports of clinical trials with the new long-acting compound, formoterol. Its efficacy, tolerability and duration of action are compared with those of fenoterol and salbutamol in both adults and children. The possibility that a long-acting $\beta_2$-stimulant might prove more likely to induce rapid tolerance (or tachyphylaxis) has to be considered, with so far reassuring results. Finally, the findings of additional formoterol studies presented at the Barcelona congress are summarised in the appendix.

We hope, by bringing all these papers together, to provide a critical actual appraisal of formoterol, which will help to define the future role of this new $\beta_2$-stimulant in the therapy of patients with asthma.

Gerhard Sybrecht

# Current status of β-adrenoceptor stimulants

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*Summary*

The therapeutic effects and side effects of $\beta_2$-stimulants in asthma were reviewed. $\beta_2$-stimulants and theophylline were compared in maintenance therapy and the prophylactic value of $\beta_2$-stimulants in controlling bronchial hyperreactivity discussed. Principal therapeutic effects included bronchial smooth muscle relaxation, increased mucociliary transport and inhibition of anaphylactic release of mediators and transmission through airway parasympathetic ganglia. The chief side effects were muscle tremor and tachycardia. These were compared both for intravenous and inhalation administration, the latter being the route of choice.

$\beta_2$-stimulants are relatively short acting when inhaled and cause tremor at doses high enough for maintenance therapy. Inhaled steroids with $\beta_2$-stimulants are usually given as first-line treatment, and theophylline where this fails. Inhaled $\beta_2$-stimulants are the most effective drugs to use prophylactically in parasympathetic reflexogenic bronchoconstriction. Recent development of longer-acting $\beta_2$-stimulants suggests the possibility of continuous airway control.

## *Introduction*

The efficacy of asthma therapy has increased over the past two decades. This is partly because of the introduction of relatively long-acting selective $\beta_2$-adrenoceptor stimulants which are highly effective by a variety of administration routes. The three most commonly used selective β-stimulants worldwide today – fenoterol, salbutamol and terbutaline – were discovered before Lands and co-workers subdivided the β-receptors into $\beta_1$ and $\beta_2$.

## *Therapeutic effects of $\beta_2$-adrenoceptor stimulation in asthma treatment*

The following effects of $\beta_2$-adrenoceptor stimulation have been suggested to be of therapeutic importance in asthma:

1. Bronchial smooth muscle relaxation.
2. Increase in mucociliary transport.
3. Inhibition of release of mediators.

4. Suppression of permeability oedema.
5. Decrease in pulmonary hypertension and increase in right ventricular ejection fraction.
6. Improved contractility of fatigued diaphragmatic muscle.
7. Inhibition of transmission through airway parasympathetic ganglia.

The first six of these effects are shared by both theophylline and $\beta_2$-stimulants. The most important single factor in the treatment of asthma is bronchial smooth muscle relaxation, but the other effects may also contribute to the anti-asthmatic effect, especially when the drugs are given regularly and prophylactically. Unfortunately, in clinical studies it is difficult to evaluate separately the clinical significance of the other effects.

## Bronchial smooth muscle relaxation

*Potency.* Figure 1 shows one of our early experiments on isolated human bronchial muscle contracted by a moderate dose of carbachol. The different β-adrenoceptor stimulants and theophylline derivatives all had the same

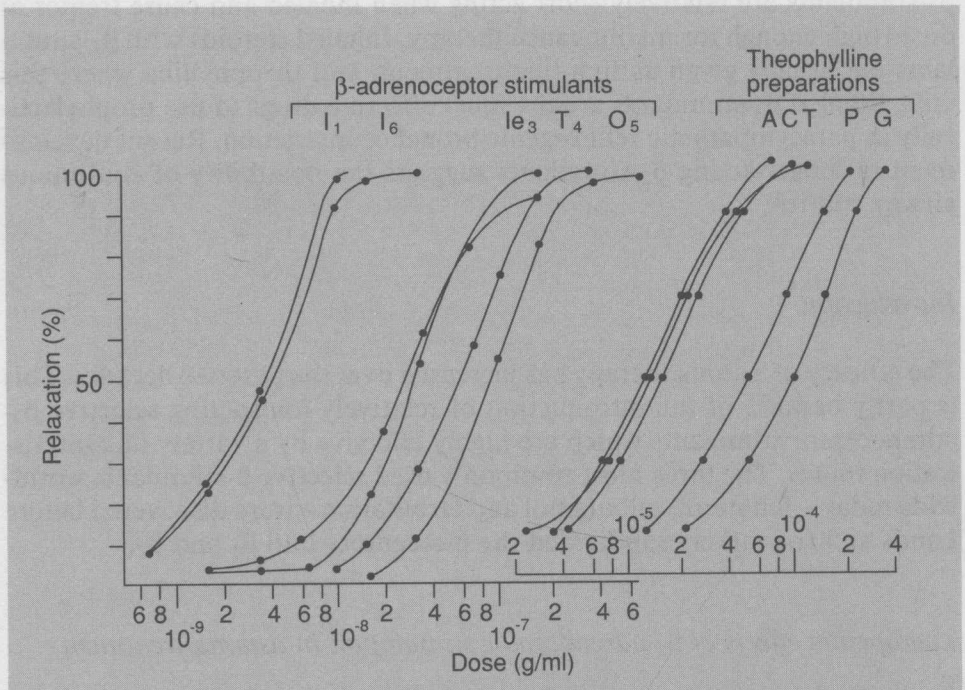


*Figure 1.* Dose-response curves for different β-adrenoceptor stimulants and theophylline preparations on carbachol-contracted human bronchial muscle in vitro. The values are means from 13 experiments. $I_1$ = isoprenaline given as the first drug; $I_6$ = isoprenaline given as the sixth drug; $Ie_3$ = isoetharine; $T_4$ = terbutaline; $O_5$ = orciprenaline; A = aminophylline; C = choline theophyllinate; T = theophylline sodium glycinate; P = proxyphylline; G = glyphilline.

maximum relaxant effect, their relative potency being proportional to the potencies found clinically. Thus the $\beta_2$-agonists are about 1000 times more potent than theophylline. Formoterol is about four times as potent as isoprenaline.
Experiments with isolated animal and human airway preparations (KARLSSON and PERSSON, 1984) show that both theophylline and $\beta_2$-stimulants relax smooth muscle in large and small airways, irrespective of whether they have been contracted by such different asthma mediators as carbacholine, histamine, 5-hydroxytryptamine, prostaglandin $F_{2\alpha}$, $LTC_4$, $LTD_4$ or substance P. Thus terbutaline and theophylline are effective functional antagonists of a large variety of potential asthma mediators at the level of the smooth muscle, probably accounting for their excellent therapeutic effect. In asthmatics their effects are superior to those of anticholinergics which only block acetylcholine and, consequently, only the reflex-mediated bronchoconstriction. The $\beta_2$-agonists and xanthines are also more effective than cromoglycate.

*$\beta_2$-adrenoceptor selectivity.* There have been difficulties in transferring selectivity data in vitro to the clinical situation.
This may be because drugs can be full or partial agonists. Approximately the same *clinical* $\beta_2$-selectivity has been established for salbutamol, fenoterol and terbutaline (SVEDMYR, 1985). Compared with this, formoterol seems to have about the same clinical $\beta_2$-selectivity, while orciprenaline, the first selective $\beta_2$-stimulant, has a lower $\beta_2$-selectivity.

### Increase in mucociliary transport

Both $\beta_2$-stimulants and theophylline have been shown to increase mucociliary transport in asthmatics, an effect that may contribute to their therapeutic efficacy (MOSSBERG et al, 1976; MATTHYS and KÖHLER, 1980). $\beta_2$-stimulants have also been shown to increase the chloride ion and water secretion into the bronchial lumen (AL-BAZZAZ and CHENG, 1979; BORSON et al, 1980), which may be one mechanism behind their increase in mucociliary transport.

### Inhibition of anaphylactic release of mediators

Histamine release from human lung mast cells is inhibited to a larger extent by $\beta_2$-agonists than by cromoglycate (HOLGATE and CHURCH, 1984). BORUM and MYGIND (1980) found that a nasal aerosol application of fenoterol protected against nasal antigen challenge. These studies show that the effects of $\beta_2$-agonists on human basophils and mast cells may be of clinical relevance.

### Suppression of permeability oedema

The vasoconstrictor action of $\alpha$-adrenoceptor-stimulating sympathomimetics is probably the most important mechanism behind their well-known decongestant action in the nasal airways. However, SVENSJÖ et al (1977)

showed that $\beta_2$-stimulants effectively prevented the mediator-induced extravasation of macromolecules in spite of an increased local bloodflow. β-agonists have direct effects on the microvascular membrane, presumably the venular endothelial cells, inhibiting macromolecular permeability (PERSSON and SVENSJÖ, 1983; PERSSON, 1988). Thus $\beta_2$-adrenoceptor stimulation is an effective way of preventing the increased venular permeability induced by different asthma mediators.
All studies to date have used concentrations of $\beta_2$-receptor stimulants larger than those obtained in plasma after systemic administration of these drugs. By inhaled administration, the antipermeability action of these drugs may be of clinical importance due to higher concentrations in the target tissue.

### Decrease in pulmonary pressure and increase in right ventricular ejection fraction

Normal *systemic* doses of both theophylline and $\beta_2$-stimulants reduce the pulmonary artery pressure and increase the right ventricular ejection fraction in patients with hypoxia (PARKER et al, 1967; AMORY et al, 1974; TEULE and MAJID, 1980; JONES et al, 1982; MACKNEE et al, 1983; WINTER et al, 1984a, 1984b). These effects can hardly be important in the normal treatment of asthma, but they may be of importance in patients with chronic obstructive pulmonary disease (COPD) (WETZENBLUM et al, 1981).

### Improved contractility of fatigued diaphragmatic muscle

Theophylline improves the contractility of fatigued diaphragmatic muscle (AUBIER et al, 1981). The same effect has also been shown with systemically administered $\beta_2$-stimulants in animal studies (in which these drugs seem to have an additive effect [HOWELL and ROUSSOS, 1984]). This effect is probably without clinical relevance in usual asthma treatment, with a comparatively low partial pressure of $CO_2$ ($PCO_2$). It might be of importance, however, when the asthmatic patient is no longer able to maintain sufficient ventilation, the $PCO_2$ begins to increase, and respirator therapy may be needed. This particular effect may also be of clinical importance in patients with COPD.

### Inhibition of transmission through airway parasympathetic ganglia

$\beta_2$-agonists block the parasympathetic ganglion transmission in the vagal nerve of ferret trachea (SKOOGH and SVEDMYR, 1984). The effect starts after some delay compared with the effect on the bronchial muscle. The potential clinical importance of this effect cannot be evaluated at the moment, but these studies indicate the possibility that part of the β-agonist effect is mediated via yet another airway target cell than the bronchial muscle.

*Side effects*

Skeletal muscle tremor is the dose-limiting factor when $\beta_2$-agonists are given systemically in maintenance therapy (FORMGREN, 1975). Tachycardia, palpitation, a slight increase in blood glucose and free fatty acids, hypokalaemia, and a certain degree of nervousness sometimes occur, especially when systemic treatment is begun. Side effects are minor after *inhalation* of normal doses of all selective $\beta_2$-adrenoceptor stimulants, if they occur at all.

Tremor

There is no evidence to date that $\beta_2$-receptors in skeletal muscle and bronchial muscle are different (LÖFDAHL et al, 1982, 1984). Although there is a considerable individual variation in tremor response, the most regular responders may shake so much that fine movements are impossible (THIRINGER and SVEDMYR, 1975). However, prolonged treatment with $\beta_2$-stimulants makes the skeletal muscle tolerant, whereas the sensitivity of the airway smooth muscle remains essentially unchanged. Thus these drugs should be introduced in a reduced dosage until skeletal muscle tolerance develops. Despite this, some individuals cannot tolerate even reduced systemic doses.

Cardiovascular effects

The cardiac stimulation is mainly reflexogenic, mediated through a $\beta_2$-induced peripheral vasodilation. Thus both tremor and tachycardia are, in principle, $\beta_2$-mediated effects and both are dose dependent. Therefore, when selective $\beta_2$-stimulants are given parenterally or orally, maximal bronchodilation cannot be achieved in moderately obstructed patients without a clinically significant simultaneous increase in pulse rate.

Inhalation

The administration of a drug by inhalation has several advantages since the drug is delivered directly to the affected area. Rapid onset of action and high efficacy can be obtained by a low dose, and the incidence of unwanted side effects can thereby be reduced. Maximal $\beta_2$-selective stimulation in the lung can be achieved with one of the new $\beta_2$-selective agonists given by the inhaled route.

Figure 2 shows a comparison of the bronchodilating effect and the side effects of terbutaline given intravenously and by a metered dose inhaler (MDI) (THIRINGER and SVEDMYR, 1976). Intravenous doses exceeding the recommended therapeutic levels did not produce maximal relaxation of the bronchial muscle in patients with endogenous asthma, but they did increase the heart rate by 20 beats/min and more than doubled the skeletal muscle tremor. When terbutaline was given by inhalation, the same degree of bronchial

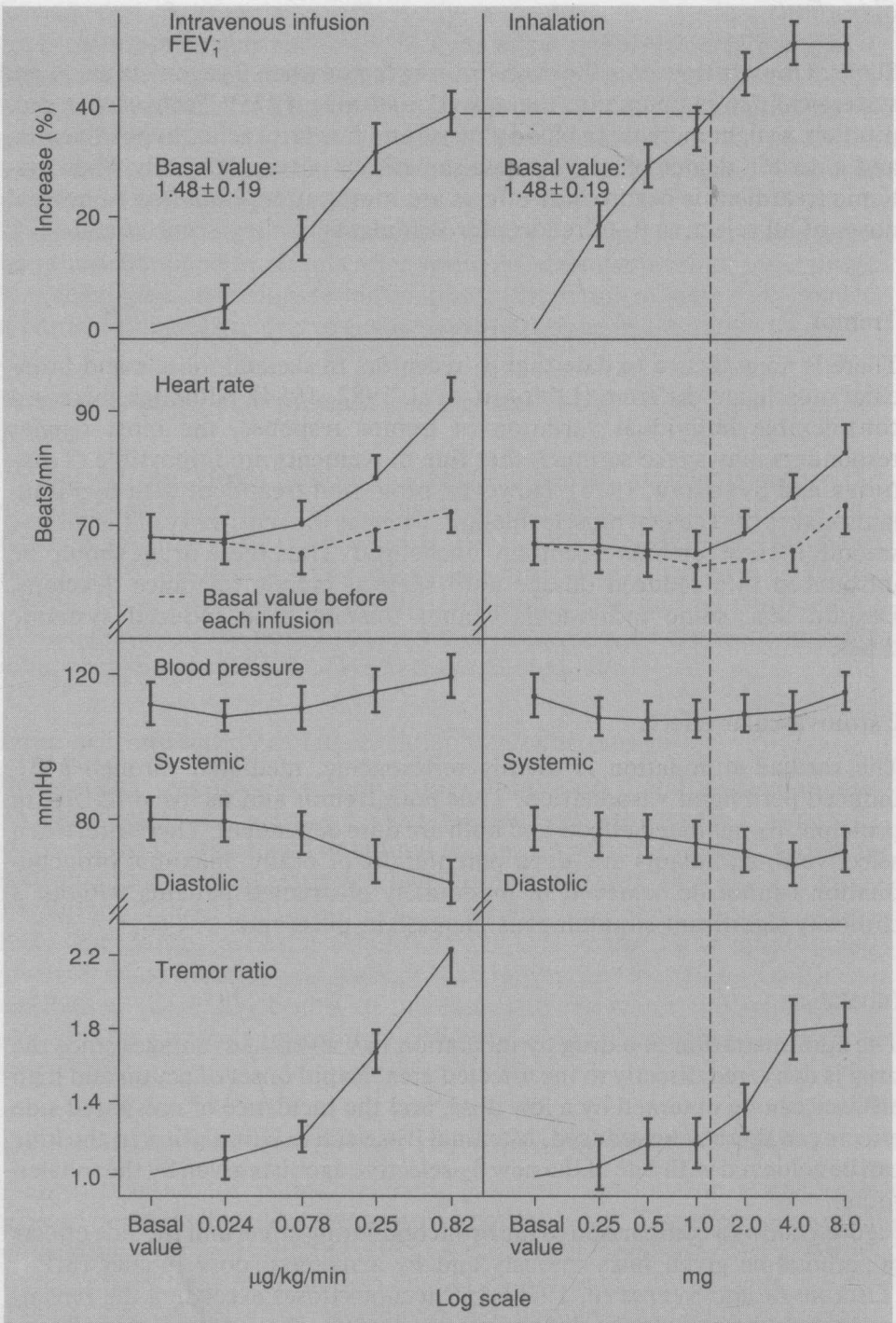


*Figure 2.* Mean (± s.e.) effects in ten patients of increasing doses of terbutaline by intravenous infusion (during six minutes) and by dose aerosol on $FEV_1$, heart rate (dotted line = heart rate just before the next dose), blood pressure, and skeletal muscle tremor in asthmatics. (From: THIRINGER and SVEDMYR, 1976.)