

obstruction not uncovered by a test with inhaled beta-adrenergic agonists, although one study has pointed to individual differences in the dose-response to oral theophylline and beta-2-agonist (terbutaline).

Anticholinergic drugs

In obstructive lung disease, inhaled ipratropium and oxitropium gives a bronchodilation. When tested in patients in "stable" condition the maximum effect is seen from 40 mg ipratropium. In allergic bronchial asthma, the bronchodilation from inhaled anticholinergic drugs seem inferior to the effect from an inhaled beta-agonist but in older, non-atopic patients the bronchodilations from an anticholinergic have been found equal or superior to inhaled beta-agonists.

Oral antihistamines

Antihistamines can improve resting lung function in a dose dependent manner. This effect has not been used systematically as a test for reversible airways obstruction.

Corticosteroids

Oral and inhaled corticosteroids may in some patients with airway obstruction improve dynamic and static lung volumes 3-9 h after dosing and it has been possible to show that this effect is dose dependent. This has been called the acute effect of corticosteroid.

Several days of corticosteroid treatment may be necessary to achieve an improvement in lung function as the effect is slow in onset and also longer lasting than the action of bronchodilators. Most patients respond during the first week of treatment. No correlation seem to exist between the immediate responsiveness to an inhaled beta-2-adrenergic agonist and the response to corticosteroids.

Bronchodilation can be achieved from drugs with different mechanism of action. The underlying disease mechanism may determine the responsiveness to the pharmacological agent applied. Several drugs often have to be tested to determine their role in a patient and as the acute response to a bronchodilator does not exactly predict a therapeutic response in long term treatment the clinical benefit from a treatment should always be determined. The response to single doses of a bronchodilator does not seem to define disease entities but simple shows the ability of the substance to influence airway calibre at that particular moment.

The assessment of reversibility: short-term

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The objectives for short-term assessments are to prove the efficacy of drugs:

- in acute stages, e.g. acute severe asthma,
- after short-term application, mainly after a single dose or a few applications and repeated measurements of the parameters of airways obstruction within some hours,
- in an acute model.

For the clinician, most important information comes from the comparison of pharmacodynamic effects of different drugs. For such purposes the differences between baseline values at different days and the minimal improvement, which has to be achieved with a standard drug has to be defined prospectively, e.g. $R_t \geq 25\%$, $FEV_1 \geq 15\%$.

In an acute trial the efficacy may be described as follows:

- onset of action,
 - maximum efficacy,
 - duration of the plateau,
 - duration of a clinical relevant effect, e.g. $FEV_1 \geq 15\%$.
- AUEC_{limit} which may be defined as $FEV_1 \geq 15\%$.

There are many different questions to be proved in an acute trial:

- single dose studies of different drugs,
- different doses of one drug (dose-finding-study),
- cumulative dose of one drug to find out the maximum efficacy,
- repeated doses of one drug in different time intervals to compare the different formulations, e.g. for theophylline preparations.

Looking at the bronchospasmolytic effect of a new compound we obtain information which is clinically relevant: this does not apply to the provocation test model. Nevertheless such tests are often used because this model can nicely be standardized.

It may be applied in different modifications:

- the protective effect of different doses of one drug or of different drugs to a constant stimulus is compared,
- threshold doses are evaluated.

The test may be performed after a single application (when the efficacy is expected to be maximum) or under steady state conditions.

The assessment of drugs is mainly concerned with their protective effect but the challenge may be used to look at the reversibility of bronchoconstriction induced by different stimuli such as allergens, mediators, drugs, exercise, cold air or SO₂.

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The efficacy of drugs may be assessed by their influence on mucociliary clearance. The criterion is the abbreviation of the elimination-half-time of radio-label-particles, e.g. TE⁹⁹. The interesting information of such tests is that not the so called secretolytics, but beta-agonists and theophyllin are effective. However the message is rather artificial and the clinical relevancy of such effects give rise to some doubts.

There is a wide spectrum of objectives for acute clinical trials. Compared are:

- different substances representing one class, e.g. beta-agonist with respect to the relation of effects and side effects and especially to the duration of action,
- different types of drugs such as beta-agonists *versus* theophylline,
- different routes (oral, inhalative, sc, iv),
- different types of aerosol generation or particles (MDI, nebulizer, powder, different shapes and volumes of spacers *etc.*),
- different formulations,
- different dosing intervals,
- combinations of different drugs to look at synergistic effects.

Acute clinical trials are easier to perform than subacute or longterm trials. But even in acute studies we are faced with one big problem: the patient.

The ideal patient in the biometric point of view may be characterized as follows: highly cooperative, stable, even in case of stopping the medication for hours or several days. But nevertheless he has to fulfil the criteria of manifest asthma.

The real patient in real life is quite different. Compliance is limited (with respect to the use of drugs and to the frequency of measurements prescribed by the protocol) unstable and needs some medication - or does not suffer from asthma. The design of protocols has to take into account these conditions otherwise, violations are preprogrammed.

What can we learn by clinical trials for the management of COPD-patients? For several reasons it may be difficult to judge the results of clinical trials:

- the labels for the diseases and therefore the selection criteria are different in different countries,
- the question has to be answered whether significant differences are clinically relevant,
- principally we have to judge whether results coming from selected patients and elaborated by more or less artificial methods are applicable for clinical practice,
- and finally, what does an acute effect mean for long term treatment?

Acute clinical trials give valuable information about potency of a drug, onset and duration of action in comparison with placebo or standard drugs or different routes of application or formulations.

The relevancy of different models for clinical application the results decrease from: bronchospasmolytic effect, protection in challenge test, influence on mucociliary clearance.

In every single case the effect of drug and the optimal dose has to be evaluated individually. Fortunately there are simple and reliable methods available such as peak flow recordings and the diary.

Long-term treatment in asthma and COPD

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Therapy of asthma and COPD currently consists of bronchodilating agents and agents with anti-inflammatory properties. The acute (within hours) and short-term (within days) effects of these agents are reasonably well established. The effects of long-term (within months) treatment are less certain. In this respect the question whether therapy influences the outcome of the disease is of major importance. This short and incomplete review deals with acute, short-term, and long-term effects of beta-adrenergic and anticholinergic bronchodilators and corticosteroids in particular with respect to airway obstruction and hyperresponsiveness.

Beta-adrenergic drugs

Beta-adrenergic drugs are the most widely used drugs in the treatment of patients with airflow obstruction. Administration of beta-adrenergic agents results in fast bronchodilation, caused by stimulation of the

beta-adrenergic receptor on bronchial smooth muscle cells. Moreover, beta-adrenergic drugs diminish mediator release from mast cells and mucosal oedema formation, and may modulate neurotransmission in parasympathetic ganglia. The well established acute protective effect of beta-adrenergic drugs against bronchoconstriction after provocation with histamine, methacholine, and cold air are possibly related to these latter effects. Their acute effects on airway hyperresponsiveness [1] and FEV₁ are, although not yet completely understood, quite clear. But what are the effects of a longer duration of treatment?

There are many studies on the short-term treatment with beta-adrenergic drugs. In general, baseline FEV₁ which is measured at least 8 h after withdrawal of the drug, does not change. KRAAN *et al.* [2] treated in a double-blind, cross-over design, 17 asthmatics during 4 weeks with terbutaline 2 mg per day, and with budesonide 0.8 mg per day. They observed no changes in baseline FEV₁ in the terbutaline treatment period, FEV₁ being measured 12-16 hours after the last drug inhalation. Other studies have demonstrated similar effects of beta-adrenergic drugs on baseline FEV₁.

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