

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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The influence of short-term treatment with beta-adrenergic drugs on baseline airway hyper-responsiveness, as measured at least 8 h after withdrawal of the drug, is more complicated. KRAAN *et al.* [2] showed an increase in airway hyperresponsiveness to histamine and propranolol after two weeks of treatment with terbutaline. After four weeks of treatment, however, a small improvement of PC_{20} was observed, and after two weeks of withdrawal of terbutaline PC_{20} returned to pre-study levels. Thus, short-term treatment seems to result in a temporary increase in airway hyper-responsiveness which recovers during continued administration, and disappears rapidly after wash-out. However, more studies of longer duration are necessary to confirm these findings.

An important issue in long-term treatment with beta-adrenergic drugs is the development of decreased sensitivity. *In vitro*, it has been demonstrated in human blood lymphocytes that incubation with beta-adrenergic drugs results in a decrease of beta-adrenergic receptor number (down regulation), and on longer term a decreased signal transduction from receptor to intracellular structures (uncoupling). There is also *in vivo* evidence of tolerance to beta-adrenergic drugs following long-term treatment. TASHKIN *et al.* [3] investigated 261 non-atopic patients with COPD in a randomized, double-blind, 90 day, parallel-group trial, and treated them with either ipratropium bromide 40 mcg four times daily, or with metaproterenol 1.5 mg four times daily. No changes in baseline FEV_1 were observed during both treatment regimens, but the response to metaproterenol changed significantly during the study, and became smaller and shorter of duration. However, the development of subsensitivity seems not of large clinical significance. Ongoing studies have to be awaited to analyse the effects of long-term treatment, especially with regard to airway hyperresponsiveness.

Anticholinergic drugs

Anticholinergic agents are known as potent bronchodilators, and are widely used in the treatment of asthma and COPD. They block muscarinic receptors which are located in the parasympathetic ganglia, on postganglionic fibres, on airway smooth muscle, and possibly on submucosal glands. In particular older patients with chronic airflow obstruction show an equal or even better response to clinically used doses of anticholinergic agents in comparison with beta-adrenergic drugs. This may be due to a reduction in number and function of beta-adrenergic receptors with age, but another explanation may be the larger relative contribution of vagal tone to airway obstruction in COPD. Anticholinergic agents provide only a small acute protection against stimuli provoking bronchial obstruction, which is considerably smaller than the protection offered by beta-adrenergic drugs. The mechanism of this action is not fully understood.

What are the effects of short-term and long-term treatment with anticholinergic agents on FEV_1 and PC_{20} ?

It has been suggested by some investigators that treatment with anticholinergic agents can modulate basal vagal tone. Several studies in patients with asthma and COPD, including the above mentioned study of TASHKIN *et al.* have dealt with this hypothesis. They observed no change in baseline FEV_1 after short-term or long-term treatment with anticholinergic agents. Things are less clear with respect to effects on airway hyperresponsiveness. Thus far, no data are available in literature.

As for the beta-adrenergic drugs, the question of subsensitivity to anticholinergic agents after long-term treatment arises. In the study of TASHKIN *et al.* [3] just as in most other studies, no changes in bronchodilator response to ipratropium bromide were observed during the treatment period. From a pharmacological point of view it is plausible that hypersensitivity to the agonist will occur in the presence of a blocking antagonist. This also applies for the parasympathetic system in the lung: an up-regulation of muscarinic receptors is suggested by the finding of an increase in sensitivity to methacholine after vagotomy and after regular use of ipratropium bromide, the latter being transient. In general however, the clinical significance of subsensitivity to anticholinergic agents after long-term administration is probably limited. Future prospective studies are necessary in this respect.

Corticosteroids

Corticosteroids are extensively used in the management of chronic airway obstruction in particular after the introduction of inhaled agents such as beclomethasone dipropionate and budesonide. Corticosteroids are known to influence many important steps in the inflammatory process which now is generally considered to contribute to airway obstruction and airway hyperresponsiveness.

The acute and short-term effects of oral and inhaled corticosteroids in asthma are relatively well established: airway obstruction and hyperresponsiveness, which together may reflect the inflammatory processes in the lung, decrease after 1-2 weeks of treatment. A faster effect on FEV_1 , which occurs after 4-6 h, has even been suggested. These effects are dose dependent, and it is obvious that a certain corticosteroid dose results in a distinct dampening of inflammation which is, however, individually determined. There is some evidence that this lowered degree of inflammation can even be maintained after reduction of the initial dose of corticosteroids. The largest achievable decrease in inflammation is also individually determined, and depends on many endogenous and exogenous factors. The next question with respect to long-term treatment is whether it is necessary to treat even mild asthmatics with corticosteroids, apart from short-term symptom relieve. The answer is not simple. Hardly anything is known about the significance and reversibility of changes in cells and tissues, which are induced by the chronic inflammatory process. However, we believe that the

severity of inflammation may be related to the outcome of the disease. Airway obstruction and hyperresponsiveness are known to be associated with the degree of inflammation. Therefore, it is important to investigate the relationship between airway obstruction and hyperresponsiveness and the outcome of the disease in order to obtain arguments in the discussion about the use of long-term corticosteroid treatment in asthma.

The effects of corticosteroids in patients with COPD are as yet uncertain. In general, no or only a small improvement of airway obstruction and hyperresponsiveness is found in stable patients after short-term treatment with oral corticosteroids up to four weeks. We have recently performed a randomized, 3-period cross-over, double-blind, placebo-controlled study in 9 non-allergic patients with COPD. They were treated with budesonide 1.6 mg per day for three weeks, and prednisolone 40 mg per day for 8 days. No statistical significant effects on FEV₁ and PC₂₀ histamine could be observed after any treatment period. Factors mentioned as related to the short-term corticosteroid response are the degree of reversibility, eosinophilia, and atopy [4]. It is generally acknowledged that the inflammatory process in COPD is more of neutrophilic than eosinophilic origin. This neutrophilic inflammation is thought to be very little or not at all sensitive to corticosteroids. This emphasizes the importance of accurate characterization of patients in studies on the response to corticosteroids.

Many important questions are as yet unanswered with regard to longterm corticosteroid treatment of patients with COPD. Firstly, does a longterm corticosteroid response exist? Such a long-term response could be measured for instance by diminished decrease in lung function over time, and is therefore directly related to the outcome of the disease. Some indication for such a response has arisen from retrospective studies in which it has been demonstrated that the effects of corticosteroids on FEV₁ appeared after 6-24 months of treatment with prednisolone [5]. And secondly, if a long-term corticosteroid response exists, are our measurements of the effects of corticosteroid treatment correct? Perhaps the beneficial effects of corticosteroids are reflected in increased quality of life, decreased severity

of symptoms, number of infections, exacerbations and admissions to the hospital, and mortality. Results of ongoing studies have to be awaited for arguments in this discussion.

Conclusion

Acute and short-term effects of bronchodilators and anti-inflammatory agents on airway obstruction and hyperresponsiveness are more or less known, although underlying mechanisms need further clarification. With respect to long-term treatment, it can be concluded that much intensive and time-consuming work has to be done. Focussing on at least two aspects is thereby important: the relation between number and activation of different cell types on one side, and changes and injury in lung tissue resulting in airway obstruction and hyperresponsiveness on the other side; parameters of efficacy of treatment other than FEV₁ and PC₂₀, such as complaints, number of infections and exacerbations, and mortality.

References

1. Tattersfield AE. - Effect of beta-agonists and anticholinergic drugs on bronchial reactivity. *Am Rev Respir Dis*, 136 (S4), S64-68.
2. Kraan J, Koëter GH, vd Mark ThW, Sluiter HJ, de Vries K. - Change in bronchial hyperreactivity induced by 4 weeks treatment with anti-inflammatory drugs in allergic asthmatic patients. A comparison between budesonide and terbutaline. *J Allerg Clin Immunol*, 1985, 70, 628-636.
3. Tashkin DP, Ashutosh K, Bleecker ER, Britt EJ, et al. - Comparison of the anticholinergic bronchodilator ipratropium bromide with metaproterenol in chronic obstructive pulmonary disease. A 90-day multi-center study. *Am J Med*, 1986, 81 (suppl 5A), 81-89.
4. Eliasson O, Hoffman J, Trueb D, Frederick D, McCormick R. - Corticosteroids in COPD. A clinical trial and reassessment of the literature. *Chest*, 1986, 4, 484-490.
5. Postma DS, Sluiter HJ. - Prognosis of chronic obstructive pulmonary disease: the Dutch experience. *Am Rev Respir Dis*, 1989, 140, S100-105.

Therapeutic implications of a precise diagnosis of airflow obstruction

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Airflow limitation can be caused by a variety of lung diseases including upper airway obstruction (UAO), bronchiectasis, bronchial asthma, emphysema and chronic bronchitis. In many cases, however, a definite

aetiological diagnosis cannot be made in which case the COPD term or other elusive terms are employed to label these patients.

It is evident that in some cases a precise aetiological diagnosis of airflow limitation may be followed by a specific treatment, as is the case when an UAO obstruction is diagnosed. Since many UAOs have specific treatment (surgery, laser therapy) it is important not to miss this diagnosis. However, only a few patients with

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