Modulation of airflow limitation
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1992

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 31-12-2018
CHAPTER 10
SUMMARY AND CONCLUSIONS

Airflow limitation is a general feature in patients with asthma or COPD. Airflow limitation results from airway wall thickening and airway smooth muscle contraction, and is generally assessed by forced expirations. It may show a variable magnitude over time, especially in asthmatics. In addition, airflow limitation is stronger at night than during daytime. The studies described in this thesis deal with underlying mechanisms of airflow limitation and therapeutic intervention.

In chapter 2, combined and separate effects of corticosteroids and bronchodilators on airflow limitation and airway responsiveness are investigated in ten allergic asthmatics. Subjects were treated with budesonide (1.6 mg/day for three weeks), prednisone (40 mg/day for eight days) and placebo in a double-blind, cross-over study design. The effects of cumulative doubling doses of salbutamol and ipratropium, which were administered until a plateau was obtained in FEV₁, were measured after each period. Both treatment with budesonide and with prednisone resulted in a significant improvement of comparable magnitude in airflow limitation and responsiveness. Budesonide improved FEV₁ by 13.7 %pred and PC_{20} histamine by 2.2 DC, compared to placebo. Treatment with prednisone resulted in an increase in FEV₁ of 13.5 %pred, and an increase in PC_{20} of 1.9 DC. Salbutamol was a stronger bronchodilator than ipratropium: 26.2 %pred versus 14.7 %pred. The protective effect against histamine was also stronger for salbutamol (+4.0 DC) than for ipratropium (+1.1 DC). Finally, the effects of corticosteroids and bronchodilators on FEV₁ and PC_{20} were in general additive.

Eight non-allergic subjects with COPD took part in a study with a design similar to the one described above. Results are presented in chapter 3. Treatment with budesonide or prednisone had no statistically significant effect on airflow limitation and airway responsiveness, compared to placebo. FEV₁ after budesonide was 0.3 %pred lower than after placebo, whereas prednisone induced a small increase of 3.5 %pred. PC_{20} improved by 0.1 DC after budesonide, and fell by 0.2 DC after prednisone. Salbutamol and ipratropium caused a statistically significant bronchodilatation, which did not significantly differ between the two drugs. FEV₁ improved by 12.4 %pred after salbutamol, and by 8.5 %pred after ipratropium. Salbutamol had a significantly stronger effect on airway responsiveness than ipratropium: PC_{20} improved by 1.6 DC after salbutamol, and by 0.8 DC after ipratropium. Pretreatment with budesonide or prednisone had no influence on the post-bronchodilator levels of FEV₁ and PC_{20} histamine.

Treatment effects are commonly measured using spirometry, although the use of forced expiratory manoeuvres has several disadvantages. First, a deep inspiratory
ion affects airway diameter, depending on the level of airway responsiveness and airway hysteresis. Second, forced expirations may produce airway collapse, especially in the presence of increased airway compliance. Third, repeated forced expirations cause fatigue. These disadvantages are avoided by measuring the total respiratory resistance (Rrs), which is performed during tidal breathing with the oscillation technique. Rrs is, however, considered a less reproducible parameter than PEF or FEV₁. The effects of treatment with budesonide (1.6 mg/day for three weeks) and with prednisone (40 mg/day for eight days) on Rrs in asthmatics and patients with COPD are described in chapter 4. Changes in Rrs were compared with changes in PEF, a parameter obtained with forced expiratory manoeuvres. Corticosteroid treatment produced a decrease in Rrs in the asthmatics, compared to placebo: Rrs was 0.62 kPa.s.l⁻¹ after placebo, 0.39 kPa.s.l⁻¹ after budesonide, and 0.42 kPa.s.l⁻¹ after prednisone. By contrast, the effects of corticosteroids were not different from those with placebo in the patients with COPD: Rrs was 0.54 kPa.s.l⁻¹ after placebo, 0.54 kPa.s.l⁻¹ after budesonide, and 0.52 kPa.s.l⁻¹ after prednisone. The effects on Rrs were not essentially different from the effects on PEF.

However, there was a better correlation between changes in Rrs and PEF in the asthmatics (r=-0.74) than in the patients with COPD (r=-0.45). The lower correlation coefficient in COPD may be due to a loss of tethering forces in the airways, leading to airway collapse and subsequent airflow limitation. This mechanism is more likely to occur during forced expirations than during tidal breathing, and introduces additional measurement variation, which worsens the relation between forced expiratory and tidal breathing variables.

Young allergic asthmatics are shown to be equally sensitive to equimolar doses of histamine and cholinergic agonists, whereas (older) patients with COPD are more sensitive to histamine. A study on the influence of allergy on the sensitivity ratio for histamine and acetylcholine in older allergic (n=13) and non-allergic subjects (n=34) with airflow limitation is described in chapter 5. Mean FEV₁ was 2.05 l for allergic subjects, and 1.87 l for the non-allergic subjects, which was not significantly different. The allergic subjects had, however, a higher FEV₁, expressed as percentage of predicted: 70.2 versus 61.5 %pred. The allergic subjects were more sensitive to histamine and acetylcholine than the non-allergic subjects. Geometric mean PC_{20} histamine was 1.26 mg/ml for the allergic, and 6.59 mg/ml for the non-allergic subjects. PC_{20} acetylcholine was 3.92 mg/ml for the allergic subjects, and 19.16 mg/ml for the non-allergic subjects. The sensitivity ratio (PC_{20} acetylcholine/PC_{20} histamine) was, however, not significantly different between the two groups. Expressed on weight base, the sensitivity ratio was 1.63 for the allergies, and 1.54 for the non-allergics; expressed on molar base, the sensitivity ratio was 2.07 for the allergies and 1.98 for the non-allergic subjects. These results indicate that the presence of allergy is associated with increased sensitivity to histamine and acetylcholine, but not with a change in sensitivity ratio. In addition, our results suggest, taking other studies on the sensitivity ratio into account, that age influences the sensitivity ratio for histamine and acetylcholine, which may be due to changes in receptor...
due to changes in receptor function during ageing.

The bronchodilatory effects of the selective phosphodiesterase inhibitor zardaverine are described in chapter 6. Zardaverine has been shown to inhibit phosphodiesterase III and IV, thus producing an increase in intracellular cAMP and cGMP. It has been suggested from animal and in vitro experiments that zardaverine does not only relax smooth muscle cells, but also dampens the activity of inflammatory cells. We measured the bronchodilating potency of three doses of zardaverine in ten asthmatic patients, and compared zardaverine with salbutamol and placebo. FEV₁ at 20 minutes after inhalation (FEV₁,₂₀) of placebo was 69.2 %pred. FEV₁,₂₀ improved by 6.3 %pred after 1.5 mg zardaverine, by 6.8 %pred after 3 mg zardaverine, and by 7.1 %pred after 6 mg zardaverine; the effects of 1.5 and 6 mg zardaverine were significantly different from placebo. Time-averaged FEV₁ during the first hour after inhalation (FEV₁₁ᵣ) and during five hours after inhalation (FEV₁₁₅) were not significantly different between any of the zardaverine doses and placebo. Inhalation of salbutamol resulted in significant improvements in FEV₁₂₀, (18.8 %pred), FEV₁₁₀ (19.1 %pred), and FEV₁₁₅ (15.5 %pred), compared to placebo. Salbutamol produced higher values for FEV₁₂₀, FEV₁₁₀ and FEV₁₁₅ than 6 mg zardaverine. These results demonstrate that inhibition of phosphodiesterase III and IV results in a modest bronchodilation, which is, however, of short duration.

Diurnal variation in PEF is related to morbidity and mortality of asthma. In the study described in chapter 7, we investigated the effects of the inhaled corticosteroid budesonide and the oral long-acting β₂-agonist bambuterol on within-day and day-to-day PEF variation in allergic asthmatics. The subjects were selected on circadian PEF variation: variation in group 1 was ≥ 15 % (n=8, mean 26.5 %), and in group 2 < 15% (n=9, mean 7.2 %). Both groups were treated with a) 0.4 mg inhaled budesonide at 8 AM and 8 PM, b) 20 mg bambuterol at 8 PM, and c) placebo, during four weeks in a double-blind, randomized, cross-over study design. Subjects recorded morning (7 - 9 AM) and afternoon (4 - 7 PM) PEF. PEF variation was calculated in two ways: within-day and between-day variation. Within-day PEF variation was defined as amplitude (afternoon minus morning), expressed as percentage of the mean value (ampl %mean). Between-day PEF variation was defined as the coefficient of variation of a set of morning or afternoon recordings, which is the standard deviation as percentage of the mean value (sd %mean). The two groups did not show significantly different absolute morning or afternoon PEF values. Group 1, which was selected on a larger within-day variation, also showed a larger between-day PEF variation. Both treatment with budesonide and with bambuterol resulted in a decrease in within-day PEF variation, which was significant in both groups. Mean ampl %mean for all 17 subjects was 9.2 % during placebo, 4.8 % during budesonide, and 5.9 % during bambuterol. Only budesonide reduced between-day PEF variation: mean (n=17) sd %mean for morning PEF was 4.5 % during placebo,
2.3% during budesonide, and 4.7% during bambuterol. In group 1, the reduction of within-day PEF variation was evident within one week after the start of budesonide; between-day variation was reduced more gradually, for up to four weeks. The different effects of budesonide and bambuterol on diurnal and between-day PEF variation are probably due to different effects on airflow limitation and airway responsiveness. Budesonide produces in an indirect way relaxation of airway smooth muscle, but also a reduction of airway responsiveness and a subsequent reduction in variation of airway diameter. Bambuterol induces relatively long-term muscle relaxation, but its effect on airway responsiveness is likely to be shorter than the bronchodilatation. Thus, bambuterol may improve absolute PEF values without affecting variation.

Nocturnal symptoms are quite common in asthma, and are thought to be related to the increase in airway responsiveness at night. In chapter 8, a study on the effect of budesonide and bambuterol on nocturnal symptoms of asthma in the two groups of asthmatics, according to the protocol described in chapter 7, is presented. Additionally, the effects of these drugs on airflow limitation and airway responsiveness during a 24 hours' hospitalisation at the end of each period are described. During this hospitalisation, FEV₁ and PC₂₀ were assessed at intervals of 4 hours during 24 hours. Group 1 (PEF variation ≥ 15%) reported worse nocturnal symptom scores, and was more responsive to histamine than group 2, the difference being 1.5 DC. Treatment with budesonide and, to a lesser extent, with bambuterol had a beneficial influence on nocturnal symptom scores in both groups. In addition, both drugs significantly reduced airflow limitation and airway responsiveness at 4 AM, budesonide providing the strongest effect; the two groups did not significantly differ in response to budesonide or bambuterol. Budesonide improved FEV₁ at 4 AM by 6.9% pred and PC₂₀ by 2.1 DC, compared to placebo. Bambuterol provided an improvement in FEV₁ by 4.9% pred, and in PC₂₀ by 0.8 DC. Treatment response was significantly different between the two groups for 24-hour mean values for FEV₁, Improvements in 24-hour mean FEV₁ were only significant for budesonide: FEV₁ improved by 10.9% pred in group 1 and by 3.1% pred in group 2. Moreover, in group 1 budesonide produced a greater improvement in 24-hour mean FEV₁ than bambuterol, but not in group 2. Responses to treatment were not different with respect to 24-hour mean PC₂₀ histamine. Treatment with budesonide resulted in a significant improvement of 2.1 DC in group 1 and of 1.0 DC in group 2, compared to placebo; differences between bambuterol and placebo were not statistically significant. A remarkable observation was the change in FEV₁ (+5.5% pred) and PC₂₀ (+1.0 DC) during the 24 hours' hospitalization, probably due to low allergen loads in the hospital.

The eosinophil granulocyte is regarded as important in asthma, and may play a role in the nocturnal worsening of asthma. Circadian patterns of blood eosinophil number, serum ECP concentration, and levels of ECA and NCA were investigated as part of the study described in chapter 7. Blood samples for determination of eosinophil number, and serum ECP concentration were taken at intervals of 4 hours during 24 hours. Eosinophil numbers were highest at 1.0 AM, with a geometric mean eosinophil number of 8.3 x10⁶/₁, and ECP concentration was 30 ng/ml, resulting in a significant reduction compared to placebo. Eosinophil numbers were highest at 1.0 AM, with a geometric mean eosinophil number of 8.3 x10⁶/₁, and ECP concentration was 30 ng/ml, resulting in a significant reduction compared to placebo. Eosinophil numbers were highest at 1.0 AM, with a geometric mean eosinophil number of 8.3 x10⁶/₁, and ECP concentration was 30 ng/ml, resulting in a significant reduction compared to placebo. Eosinophil numbers were highest at 1.0 AM, with a geometric mean eosinophil number of 8.3 x10⁶/₁, and ECP concentration was 30 ng/ml, resulting in a significant reduction compared to placebo. Eosinophil numbers were highest at 1.0 AM, with a geometric mean eosinophil number of 8.3 x10⁶/₁, and ECP concentration was 30 ng/ml, resulting in a significant reduction compared to placebo. Eosinophil numbers were highest at 1.0 AM, with a geometric mean eosinophil number of 8.3 x10⁶/₁, and ECP concentration was 30 ng/ml, resulting in a significant reduction compared to placebo. Eosinophil numbers were highest at 1.0 AM, with a geometric mean eosinophil number of 8.3 x10⁶/₁, and ECP concentration was 30 ng/ml, resulting in a significant reduction compared to placebo. Eosinophil numbers were highest at 1.0 AM, with a geometric mean eosinophil number of 8.3 x10⁶/₁, and ECP concentration was 30 ng/ml, resulting in a significant reduction compared to placebo. Eosinophil numbers were highest at 1.0 AM, with a geometric mean eosinophil number of 8.3 x10⁶/₁, and ECP concentration was 30 ng/ml, resulting in a significant reduction compared to placebo. Eosinophil numbers were highest at 1.0 AM, with a geometric mean eosinophil number of 8.3 x10⁶/₁, and ECP concentration was 30 ng/ml, resulting in a significant reduction compared to placebo.
eosinophil number, and serum levels of ECP, ECA and NCA were taken at intervals of 4 hours during the 24 hours' hospitalization after the placebo, budesonide and bambuterol period. Results are presented in chapter 9. No significant differences were observed between the two groups with regard to any of the studied variables. Eosinophil count showed circadian variation: in both groups numbers were highest at night, and lowest during daytime. During placebo, geometric mean eosinophil number, averaged for 24 hours, was 372 x10⁶/l, and ECP concentration was 30.5 µg/l, for all 17 subjects. Treatment with budesonide resulted in a significant reduction in both variables: eosinophil number was 202 x10⁶/l, and ECP concentration was 15.2 µg/l. Eosinophil number and ECP concentration were 419 x10⁶/l and 29.5 µg/l, respectively, during bambuterol, which was not significantly different from placebo. No treatment effects were observed for ECA and NCA. These results suggest that the eosinophil plays a role in nocturnal asthma. In addition, they demonstrate that treatment with budesonide reduces both eosinophil number and activation, as measured with ECP.

GENERAL DISCUSSION

The studies described in this thesis demonstrate that the presence of allergic processes influences the response to treatment.

The investigated subjects with asthma and COPD of chapters 2 and 3 showed essentially different treatment responses in two ways. First, treatment with corticosteroids was beneficial in the asthmatics, but not in the subjects with COPD. The fine response to one or two months treatment with corticosteroids in asthmatic subjects probably results from a dampening or modulation by corticosteroids of the activity of several cell types which are important in the allergic process, such as lymphocytes, macrophages, and eosinophils. Pulmonary symptoms in subjects with COPD are largely due to the noxious effects of tobacco smoke, and other cell types are involved than in allergic responses. Further studies should reveal whether long-term treatment is able to diminish or repair this tobacco smoke-related damage. Second, salbutamol caused stronger bronchodilatation than ipratropium in the asthmatics, but not in the subjects with COPD. Smooth muscle contraction is the result of neurotransmitters, constrictive mediators, e.g. leukotrienes and PAF, and neuropeptides. An agonist, such as the β₂-agonist salbutamol, will induce greater relaxation in the presence of an allergic process than an antagonist (ipratropium) of only one of the smooth muscle contractile agonists (acetylcholine). More research is needed on the influence of aging on sympathetic and parasympathetic nerve system. The need for such research is emphasized by the observed change in relative sensitivity to histamine and muscarinic agents with age.

A remarkable observation was that corticosteroids and bronchodilators have an additive effect, which implies (largely) different mechanisms of action of the two classes of drugs. In this respect, it is obvious that β₂-agonists and ipratropium
produce bronchodilatation and reduction of airway responsiveness in rather
directly, by acting on receptors on airway smooth muscle. Corticosteroids act by
dampening many inflammatory cell types, resulting in reduced release of mediators. This leads to a reduction of the swelling of the airway wall and of the contraction of smooth muscle. Another class of drugs, the phosphodiesterase inhibitors, may have both 'smooth muscle-relaxant' and 'anti-inflammatory' effects. These agents may increase cAMP in smooth muscle and inflammatory cells, thus resulting in bronchodilatation. Zardaverine, a PDE III/IV inhibitor, is indeed capable of producing bronchodilatation in allergic asthmatics. This bronchodilatation is of short duration, and of smaller magnitude than that after a β₂-agonist. The value of PDE-inhibitors may, however, be determined by their action on both smooth muscle and inflammatory cells in allergic subjects, which should be addressed in future studies.

Allergic mechanisms probably also play an important role in the nocturnal worsening of asthma, characterized by a worsening of symptoms, and an increase in airflow limitation and airway responsiveness. The number of blood eosinophils was higher at night than during daytime, and a similar tendency was observed for eosinophil activity as measured with ECP. Treatment effects agree with the hypothesized increase in allergic inflammatory activity during the night. Budesonide produced a reduction in blood eosinophil numbers and ECP concentrations, which paralleled the improvement in nocturnal symptom scores, airflow limitation and airway responsiveness. Bambuterol also improved nocturnal symptoms, probably by reducing airflow limitation and, to a smaller extent, airway responsiveness. Bambuterol reduces airflow limitation more directly than budesonide by stimulation of β₂-receptors on smooth muscle cells. The importance of allergy in the investigated allergic asthmatics is indicated by the remarkable improvement in FEV₁ and PC₂₀ during the 36-hour stay in the hospital, most probably due to low allergen loads.

Allergen exposition is not the only factor responsible for the nocturnal worsening of asthma. Between-day PEF variation was still improving after 4 weeks of treatment with budesonide. By contrast, treatment with the anti-inflammatory agent budesonide produced some improvement in within-day PEF variation, but values remained rather stable during the period of four weeks. These findings indicate the importance of other factors for the nocturnal worsening of asthma in certain individuals, such as the presence of strong circadian rhythms of cortisol or catecholamines. In addition, they suggest that between-day PEF variability is more strongly related to allergic inflammatory processes in the airways than within-day variability.

CONCLUSIONS

The main findings of the studies described in this thesis are:

1. Allergic asthmatics:
   a. show a larger bronchodilatation and reduction of airway responsiveness in rather directly, by acting on receptors on airway smooth muscle. Corticosteroids act by dampening many inflammatory cell types, resulting in reduced release of mediators. This leads to a reduction of the swelling of the airway wall and of the contraction of smooth muscle. Another class of drugs, the phosphodiesterase inhibitors, may have both 'smooth muscle-relaxant' and 'anti-inflammatory' effects. These agents may increase cAMP in smooth muscle and inflammatory cells, thus resulting in bronchodilatation. Zardaverine, a PDE III/IV inhibitor, is indeed capable of producing bronchodilatation in allergic asthmatics. This bronchodilatation is of short duration, and of smaller magnitude than that after a β₂-agonist.
   b. respond equally strongly to treatment with 40 mg of zardaverine and treatment with 4 mg of terbutaline.
   c. generally show additional bronchodilatation and reduced airflow limitation and airway responsiveness.

2. Non-allergic patients with asthma:
   a. show no difference in response to the cholinergic drug, but not to the β₂-agonist.
   b. neither respond to the cholinergic drug, but not to the β₂-agonist.
   c. do not show modified nocturnal symptoms.

3. Measurement of PEFR:
   a. Measurement of PEFR technique provides a better tool for monitoring asthma. The relation between PEFR and FEV₁ is shown.

4. The presence of allergic inflammatory activity as measured with ECP.
   a. The presence of allergic inflammatory activity as measured with ECP.

5. Inhibition of phosphodiesterase: short-lasting bronchodilatation.
   a. show no difference in response to the cholinergic drug, but not to the β₂-agonist.
   b. do not show modified bronchodilatation.

6. Treatment with budesonide improves nocturnal asthma.
   a. Treatment with budesonide produces some improvement in within-day PEF variation.
   b. Treatment with budesonide produces some improvement in within-day PEF variation.

7. In subjects with a marked improvement of the nocturnal asthma, nighttime bronchodilatation is much larger than the long-acting β₂-agonist.

8. Blood eosinophils are higher at night.
   a. Blood eosinophil numbers are higher at night.
   b. Treatment with budesonide reduces blood eosinophil numbers and ECP concentrations, whereas
1. Allergic asthmatics:
   a. show a larger bronchodilatation and reduction of airway responsiveness after a \( \beta_2 \)-agonist than after an anticholinergic drug.
   b. respond equally strongly to treatment with 1.6 mg budesonide for 3 weeks and treatment with 40 mg prednisone for 8 days.
   c. generally show additive effects of bronchodilators and corticosteroids on airflow limitation and airway responsiveness.

2. Non-allergic patients with COPD:
   a. show no difference in bronchodilating effects of a \( \beta_2 \)-agonist and an anticholinergic drug, but show a stronger protective effect against histamine of the \( \beta_2 \)-agonist.
   b. neither respond to treatment with 1.6 mg budesonide for 3 weeks nor to treatment with 40 mg prednisone for 8 days.
   c. do not show modifying effects of bronchodilators by corticosteroids.

3 a. Measurement of Rrs during tidal breathing using the forced oscillation technique provides similar results as measurement of PEF.
   b. The relation between Rrs and PEF is better in asthma than in COPD.

4. The presence of allergy is associated with an increase in airway sensitivity in older subjects with airflow limitation, but does not change the sensitivity ratio for histamine and acetylcholine.

5. Inhibition of phosphodiesterase III and IV by zardaverine produces a fast but short-lasting bronchodilatation in asthmatics.

6. Treatment with budesonide results in a decrease in between-day and within-day PEF variation, whereas treatment with the long-acting \( \beta_2 \)-agonist bambuterol only reduces within-day PEF variation in subjects with asthma.

7. In subjects with asthma, treatment with budesonide produces a greater improvement of nocturnal airway responsiveness and symptoms of asthma than the long-acting oral \( \beta_2 \)-agonist bambuterol.

8 a. Blood eosinophil numbers show a circadian variation with highest numbers at night.
   b. Treatment with budesonide decreases eosinophil numbers and ECP concentrations, whereas bambuterol has no effect on either variable.