The corticosteroid dose-response curve in asthma and how to identify patients for adjunctive and alternate therapies

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Abstract

Asthma is an inflammatory disorder of the airways and inhaled corticosteroids are the most effective agents in controlling the disease process. The corticosteroid-dose response curve has traditionally been thought of as being flat, i.e. plateaus early, with no further therapeutic response with increasing dose of medication. This is only true for mild asthma and the improvement in airway calibre that occurs as inflammation subsides. For other parameters of asthma control, the dose- response curve is shifted to the right (i.e. control takes longer to achieve) and for severe asthma and bronchial hyper-responsiveness, the curve is much steeper (an almost linear relationship). Thus, for PEFR or FEV_1, the curve plateaus at about 400-800 ug BDP equivalent per day (depending on asthma severity), whilst doses greater than 1000 ug per day control bronchial hyper-reactivity much better.

In assessing the efficacy of asthma medication, the current literature is confusing in that response criteria are chosen arbitrarily (e.g. a 10% improvement in FEV_1) and can mislead if results are extrapolated to other components of asthma control that were not studied. Thus one needs to appreciate data in the appropriate research context. Asthma control should be gauged using composite measures of as many variables in the goals of therapy as possible. Failure to achieve these goals is an indication that the ICS dose should be increased or that an additional agent should be added when one needs to limit steroid side-effects. Co-administration of LABA/ICS remains the most effective strategy (especially in the combination product), that allows for superior asthma control, with leukotriene antagonists and theophylline being alternate choices.

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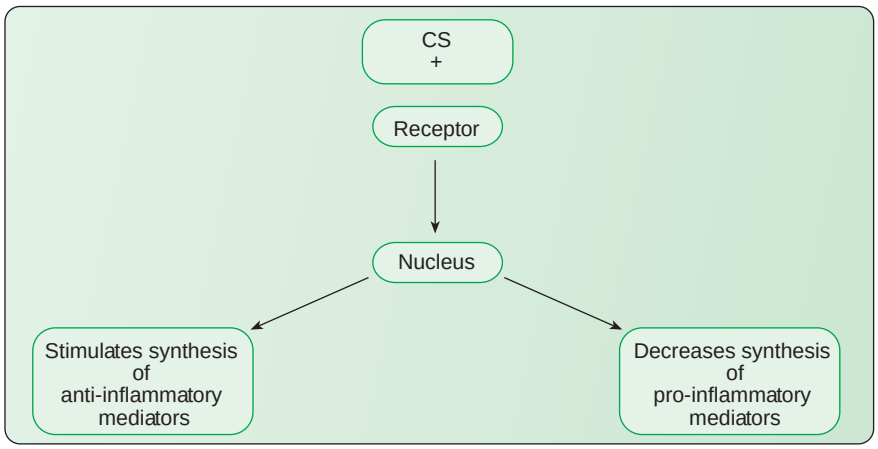
Introduction

The recognition that inflammation is the dominant process in asthma saw a shift in emphasis to anti-inflammatory therapy rather than medication, which had primarily been aimed at relieving bronchospasm.[1] Consequently, over the past decade, inhaled corticosteroids (ICS) have become the agents of choice in this respect.[2] They exert their effect by entering cells and linking with an intracellular glucocorticoid receptor, after which the complex translocates to the nucleus.[2] Here it combines with the promoter regions of the genes of numerous cytokines and mediators of inflammation, the result of which is an increase in the synthesis of anti-inflammatory mediators. The dominant effect is a decrease in the synthesis of pro-inflammatory mediators (see Figure 1). The net result is that the inflammatory cascade is checked. When inflammation has subsided, the goals of therapy have been reached: the abolition of symptoms and excessive need for

Five learning points

1. Corticosteroids exert their effect by intracellular amelioration of inflammatory mediators through a direct nuclear interaction.
2. Episodic bronchoconstriction and impaired bronchodilation are due to unrecognised inflammation.
3. The corticosteroid dose-response curve is different for different components of asthma and varies according to the severity of the illness.
4. The PEFR dose-response curve plateaus early, while the bronchial hyper-reactivity curve is steep.
5. To improve control and limit adverse events, it is better to add a long-acting beta agonist to ICS than to double the dose of ICS.

Figure 1: The principle mode of action of corticosteroids



rescue medication, the normalisation of lung function and the minimisation of the risk of exacerbations.

The next issue that became evident, however, was how to decide that inflammation was indeed under control. Theoretically, it would appear easy – the disease process is under control when inflammatory indices/parameters have normalised. This would be best achieved by means of a bronchial biopsy and, because of the variable nature of asthma, would need to be repeated at various time points to ensure that long-term suppression of the inflammation had been achieved. Clearly, because of its invasive nature, this avenue is impractical. The clinician thus has to use surrogate markers. Many of these are research tools and not available in general practice. This is precisely the problem that besets asthma control – the unavailability of these tools usually results in inadequate assessment and treatment.[3] This has also lent itself to asthma being assessed rather superficially, by symptoms alone, in the majority of patients.

We are interested in the dose response of ICS because the primary aim of treatment is to achieve complete control of the pathology of asthma and we would like to know how this can best be achieved in the most cost-effective manner. The immediate complications of poor control are well known – troublesome symptoms, decrease in the quality of life, absence from school or work and the risks associated with acute exacerbations. The long-term consequences are less well known:

- asthmatics have a more rapid rate of decline in lung function than non-asthmatics;[4]
- asthmatics with impaired lung function have a higher mortality rate;[5,6]
- untreated inflammation can lead to less reversible airway calibre, the so-called "fixed asthma", with permanent deficits in lung function and attendant morbidity.[7]

In order to understand the dose response of corticosteroids, it is constructive to examine precisely what is meant by asthma control and to consider some of the indices whereby these are measured. With regard to the former, it has become clear that there are sequential stages of asthma control – from simple to more sophisticated measures. Control can thus be viewed in three stages, as illustrated in Figure 2. Possible parameters to assess asthma control include the following:

1. Clinical parameters

The symptoms of asthma, namely cough and wheezing (especially nocturnal), lend themselves to be easily quantified and judged for control. However, wheezing is readily ameliorated by SABA and does not imply that the pathology is controlled. It is certainly true that the optimal dose of ICS will decrease the *frequency* of wheezing.

2. The PEFR

This is the simplest tool and should represent the bare minimum utilised by every practitioner. In addition to its diagnostic use (where a bronchodilator response can be measured), it has great utility in monitoring control. To be used accurately, the expected PEFR for a patient has to be derived from a normogram using age and gender. This predicted volume (or that obtained when the patient is perfectly well) represents the PB (personal best). The crucial aspect to remember here is that *inflammation causes bronchoconstriction and impairs bronchodilation*. In other words, when inflammation is controlled, the bronchi are least constricted, demonstrate the best bronchodilator response and there is a decrease in the need for rescue medication. Control is thus assessed by serial pre-bronchodilator and post-bronchodilator PEFR. Also, the within-day and day-to-day variation in PEFR (called the *PEFR variability*) should not exceed 20%. When the predicted or PB is achieved and sustained (low variability), asthma control is good.

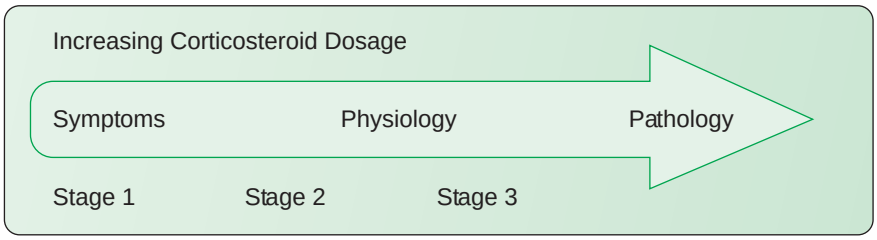
3. Spirometry

This allows us to define bronchomotor tone more accurately in the measurement of the FEV_1 and FVC (forced expiratory volume in one second and forced vital capacity). It usually takes higher doses of ICS to normalise the FEV_1 than the PEFR. Studies that have looked at normalising this parameter have shown exacerbation rates that have been two to three times better than those evident only from looking at symptoms and PEFR.[8, 9]

4. Bronchial hyper-responsiveness

This hallmark of asthma is the most intriguing. It is measured by inducing bronchoconstriction with methacholine or histamine and the provocative dose/concentration causing a 20% fall in the starting FEV_1 (the PD20/PC20) is determined. The greater the inflammation, the lower the dose required to achieve the target FEV_1 (the PD20). In the AMPUL study, a mean dose three times the BDP dose needed to normalise PEFR was required to control BHR.[8] This increased dose was superior in improving the FEV_1 and in the

Figure 2: The continuum of asthma responses**.** There are three stages of asthma control. As corticosteroid dosage is increased, the initial resolution of symptoms moves into the control of abnormal physiology (lung function tests) and then to the pathology of asthma.



histological changes on bronchial biopsy.

5. Induced sputum

To assess inflammation less invasively than by using biopsy, it is possible to attempt to analyse the bronchial milieu through sputum induction. Hypertonic saline/allergens are used and secretions from the lower airways can be encouraged and expectorated. A variety of inflammatory cells and cytokines have been elegantly studied in this manner. Green *et al*. showed that tailoring control according to a reduction in sputum eosinophils achieved better asthma control and outcomes than through the use of clinical variables alone, as laid down by the British Thoracic Society.[10] In this report, significant improvements in BHR were noted; accompanied by an approximately 60% absolute reduction in exacerbations and concomitant oral corticosteroid usage and admissions.

6. Exhaled nitric oxide

Nitric oxide (NO) is generated in inflamed airways and has been extensively studied in asthma. NO correlates with disease severity and is one of the earliest markers to decrease with steroid therapy.[11,12] A portable device is available (although somewhat costly at present) to measure exhaled NO and could prove useful in the future as a non-invasive method of monitoring asthma control.

Understanding "response" in dose-response studies

In understanding the dose-response relationship of ICS, one should first appreciate that CS exists in different potencies and that comparisons must be made at equipotent doses. Table I reflects the relative potencies of the various ICS preparations.

The dose equivalents for various corticosteroid preparations are shown above and efficacy should be compared at the appropriate dose. Ciclesonide is a new agent that has the property of being inactive per se and activated largely at the site of inflammation, namely the lung. NB. Beclomethasone-HFA refers to Qvar; no data is available for Budeflam HFA and the dose equivalent is considered 2:1 to FP.

Another area of confusion in appreciating dose-response relationships in the recent asthma literature is the inconsistency in the characterisation and standardisation of "asthma responders".[13] One question is whether the response should be considered in terms of symptoms or objective parameters or a composite of all criteria of the goals of asthma treatment. Another is whether the results are both statistically and clinically significant. The critical point is as follows (and it is absolutely crucial that the reader appreciates this): in any given study, a response is defined *arbitrarily* and the research is *powered* (i.e. pre-determined numbers of patients are selected to study that hypothesis or outcome alone). It is therefore possible that, although other benefits are observed, the study may not be powered to reach statistical significance for other, sometimes more important, parameters.

What does this mean? Each study belongs in a specific context and it is likely that the results cannot easily be extrapolated to all asthmatics. The generalist thus becomes confused because there is no consensus amongst specialist chest physicians and researchers. By way of example: in the study by Szefler et al[14], the number of patients responding to ICS and Montelukast was a maximum of 40% and 23% respectively. However, a response was defined as a prebronchodilator $FEV_1 \geq 7.5\%$; most of the subjects were mild asthmatics with a FEV_1 of close on 100% and

Table I: Fluticasone propionate equivalents of inhaled corticosteroids

	Ratio to fluticasone	Example: 500 µg FP corresponds to
Fluticasone	1	500 µg
Beclomethasone-HFA	0.8	400 µg
Beclomethasone-CFC	2.0	1000 µg
Budesonide	1.6	800 µg
Ciclesonide	1	500 µg

Figure 3: The magnitude of the FEV_1 response to ICS follows a Gaussian distribution. This must be differentiated from the *bronchodilator* response (improvement in the FEV_1 after a short-acting beta agonist), which can be equally variable (derived from the data of Price & Ostrom).

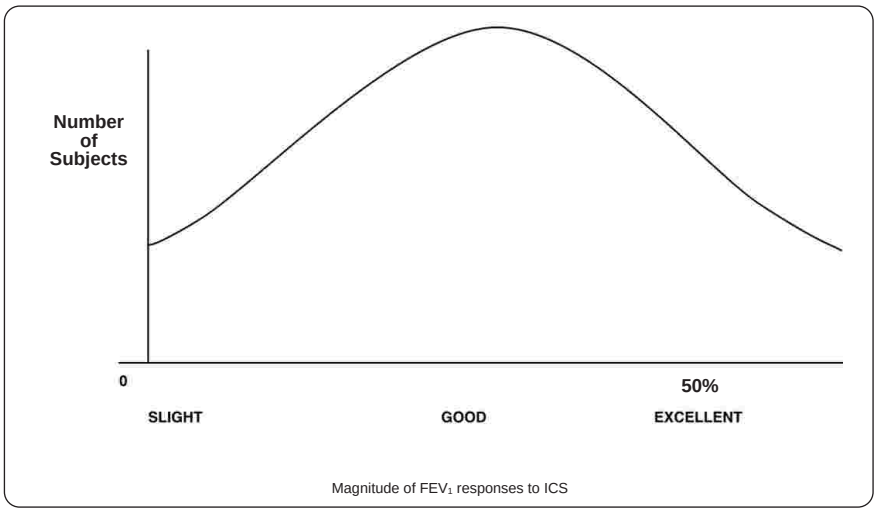
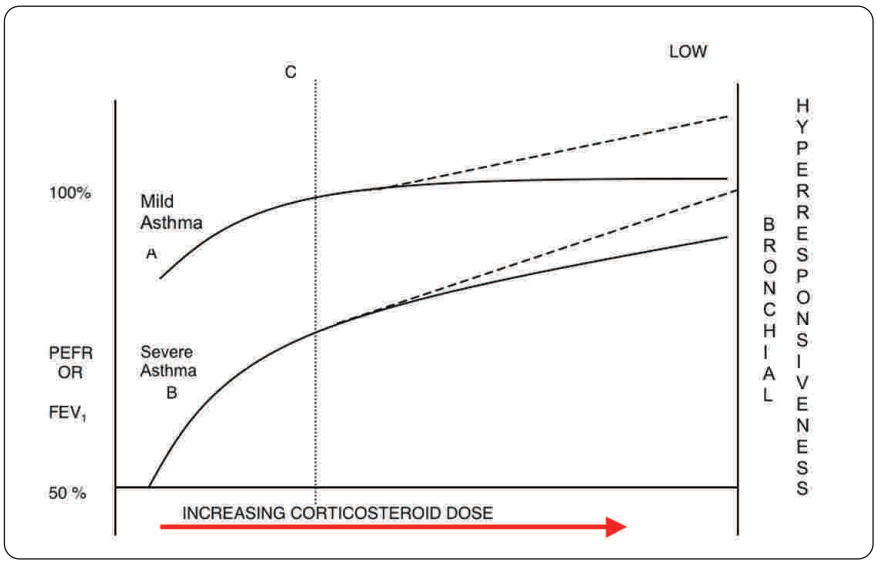


Figure 4: The dose-response curve has traditionally been considered "flat" for ICS. As can be seen, this is not true. It depends on the parameter being measured and the severity of the asthma. For example, although the mild asthmatic's curve plateaus at point C for PEFR, the more severe asthmatic's curve is still rising, with the potential for further benefit. However, if one looks at airway hyperresponsiveness (---), neither curve shows a plateau and there are continuing gains with higher corticosteroid doses. The complexity of the asthma phenotype dictates that each individual asthmatic has his or her own dose-response curve for different parameters of asthma control.



therefore the potential to improve was limited. If, for example, symptoms had also been considered, it is conceivable that a greater percentage would have shown a response. In the GOAL study[15] (Gaining Optimal Asthma Control), where fluticasone was compared to a combination of salmeterol and fluticasone, total control during the step-up therapy was measured over seven of eight weeks, not over six or even all eight weeks. The results most likely would have been very different had alternate time periods been chosen.

In a recent study of mild persistent asthma, as-needed dosing of budesonide was stated to be just as effective as regular administration, which is contrary to current best practice.[16] However, the primary outcome measure was morning PEFR, which in itself is not very robust. The therapeutic advantages of daily budesonide (greater and statistically significant improvements in pre-bronchodilator FEV_1, bronchial reactivity, sputum eosinophils, exhaled NO and asthma control scores) were under-emphasised by the authors.

Dose-response data

If one studies a population of asthmatics, the magnitude of the FEV_1 response to ICS will have a Gaussian distribution (see Figure 3), with most subjects having a good result, and some having either a poor or a very good response.[17,18]

For PEFR/FEV_1, the most therapeutic gain is achieved at ICS doses of 200 to 500 µg BDP equivalents. However, these observations are frequently, if not exclusively, in steroid-naïve or mild asthmatics and considerable inter-subject variability has been conceded.[19]

In most patients, a starting dose of 400 to 800 µg is quite adequate and is more effective than <400 µg, with >800 µg seldom warranted.[20] In patients that are somewhat therapy resistant, higher doses of ICS will be required and doses as high as 4000 µg/day have been used with good clinical effect[21] (although one would usually attempt a steroid-sparing strategy with doses >1000 µg).

Regarding bronchial reactivity, a meta-analysis of 25 studies with 963 patients showed that a high dose BDP ≥1000 µg conferred greater benefits in bronchial hyperresponsiveness than doses <1000 µg.[22]

In the study by Sont et al[8], a clinical asthma control group was compared with another group where treatment was tailored to control BHR as well. Whereas symptoms and PEFR were controlled with a mean of dose of 200µg BDP, the BHR strategy needed a mean dose of 600ug and this was accompanied by further improvements in FEV_1 and a 50%

reduction in the exacerbation rate compared to the clinical control group.

Thus, different parameters of asthma control – PEFR or absolute FEV_1, PEFR variability, risk of exacerbations and BHR – have different dose responses to ICS. Some of these aspects are illustrated in Figure 4.

Choosing add-on therapy

The need for additional therapy is judged by the adequacy of asthma control. Persistent symptoms, a frequent need for rescue medication, lung function below PB and exacerbations necessitate additional therapy after compliance and inhaler technique have been excluded as reasons for suboptimal outcomes. Deciding on the agent to use in stepped care management plans will depend on

a) reaching the plateau of ICS efficacy
b) the profile of inflammation in asthma

The latter is still being researched to discover, for example, whether there are specific genotypes and phenotypes of asthma that dictate responses to different agents that will allow us to tailor or individualise therapy in the future. Currently, ICS is used in all categories and is particularly useful in those with low pulmonary function or elevated markers of allergic inflammation, such as exhaled NO, IgE or total eosinophil count.[14]

Two meta-analyses have shown that it is better to add a LABA (long-acting beta agonist) to 400 µg of BDP/equivalent than to double the dose of ICS in the case of mild, persistent asthma.[19,23] It should also be borne in mind that the addition of a LABA (through the synergistic molecular interactions of beta and glucocorticoid receptors) is equivalent to the clinical efficacy of doubling the dose of ICS. This was also exemplified in the GOAL study.

If patients are still symptomatic on low-dose combination therapy, it would be prudent to use the higher ICS dose (up to 1000 µg) in conjunction with LABA. If necessary, even higher doses of ICS are relatively safe, especially if the alternative is oral steroids. However, these should always be used cautiously and a second controller agent is always preferable. The combination ICS/LABA product is particularly useful, as it is very effective, convenient and ensures that the ICS component is regularly used. LABA are also superior to theophylline as add-on agents.[24]

The other alternative is a leukotriene antagonist. These agents are particularly useful in children, and in those who have difficulty with coordination, who prefer a tablet and who are prone to non-compliance with inhalers.

Conclusion

Asthma is a subtle disease. Its control has to be assessed in a surrogate manner because it is difficult to monitor inflammation easily. When the goals of therapy are not realised, additional therapy is warranted. A better understanding of the dose response to ICS will assist practitioners to use therapy appropriately and safely, so that their patients can benefit.

See CPD Questionnaire, page 52

This article has been peer reviewed

References

1. Barnes PJ. Inhaled glucocorticoids for asthma. *N Engl J Med* 1995;332:868-75.
2. Barnes PJ. Efficacy of inhaled corticosteroids in asthma. *J Allergy Clin Immunol* 1998;102:531-8.
3. Rabe KF, Vermiere PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;16:802-7.
4. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194-200.
5. Lange P, Ulrik CS, Vestbo J. Mortality in adults with self reported asthma. Copenhagen City Heart Study Group. *Lancet* 1996;347:1285-9.
6. Huovinen E, Kaprio J, Vesterinen E, Koskenvuo M. Mortality of adults with asthma: a prospective cohort study. *Thorax* 1997;52:49-54.
7. Busse W, Elias J, Sheppard D, Banks-Schlegel S. Airway remodeling and repair. *Am J Respir Crit Care Med* 1999;160:1035-42.
8. Sont JK, Willems LNA, Bel EH et al. Clinical control and histopathological outcome of asthma when using airway hyperresponsiveness as an additional guide to long term treatment. *Am J Respir Crit Care Med* 1998;159:1043-51.
9. Turner MO, Taylor D, Bennett R, Fitzgerald JM. A randomized trial comparing peak expiratory flow and symptom self-management plans for patients with asthma attending a primary care clinic. *Am J Respir Crit Care Med* 1998;157:540-6.
10. Green RH, Brightling CE, McKenna S et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.
11. Lang MJ, Leung DY, White CW. Comparison of exhaled nitric oxide to spirometry during emergency treatment of asthma exacerbations with glucocorticoids in children. *Ann Allergy Asthma Immunol* 1999;82:161-4.
12. Kharitonov SA, Barnes PJ, O'Connor B. Reduction in exhaled nitric oxide after a single dose of nebulised budesonide in patients with asthma. *Am J Resp Crit Care Med* 1996;153:A799.
13. Stempel DA, Fuhlbrigge AL. Defining the responder in asthma therapy. *J Allergy Clin Immunol* 2005;115:466-9.
14. Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. Characterization of within-subject response to fluticasone and montelukast in childhood asthma. A study for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. *J Clin Allergy Immunol* 2005;115:233-42.
15. Bateman ED, Boushey HA, Bousquet J, et al. GOAL Investigators Group. *Am J Respir Crit Care Med* 2004;170:836-84.
16. Boushey HA, Boushey HA, Sorkness CA, King TS et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519-28.
17. Price DB, Hernandez D, Magyar P, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;58:211-6.
18. Ostrom NK, Decotiis BA, Lincourt WR. Comparative efficacy and safety of low-dose fluticasone propionate and Montelukast in children with persistent asthma. *J Pediatr* 2005;147:213-20.
19. Sin DD, Man J, Sharpe H, Gan WQ, Man SF. Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. *JAMA* 2004;292:367-76.
20. Powell H, Gibson PG. Initial starting dose of inhaled corticosteroids in adults with asthma: a systematic review. *Thorax* 2004;59:1041-5.
21. Ayres JG, Bateman ED, Lundback B, Harris TAJ. High dose fluticasone propionate, 1 mg daily, versus fluticasone propionate, 2 mg daily, or budesonide, 1.6 mg daily, in patients with chronic severe asthma. *Eur Resp J* 1995;8:579-86.
22. Currie GP, Fowler SJ, Lipworth BJ. Dose response of inhaled corticosteroids on bronchial hyperresponsiveness: a meta-analysis. *Ann Allergy Asthma Immunol* 2003;90:194-8.
23. Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005;60:730-4.
24. Davies B, Brooks G, Devoy M. The efficacy and safety of salmeterol compared to theophylline: meta-analysis of nine controlled studies. *Respir Med* 1998;92:256-63.