

Comparison of dose-response effects of inhaled beclomethasone dipropionate and budesonide in the management of asthma

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The dose-response effects of inhaled beclomethasone dipropionate (BDP) and budesonide (BUD) administered b.i.d. with the aid of metered dose aerosols were studied in 128 patients (67 men and 61 women, mean age 53 years) suffering from asthma bronchiale. The study was designed as a multi-centre, double-blind, four-period cross-over study, followed by a single-blind double placebo period. BDP was administered in doses of 400 and 1000 µg, and BUD in doses of 400 and 800 µg. The results in terms of peak expiratory flow (PEF) in the morning and evening, daily symptoms score and use of inhaled β_2 -agonists did not reveal any clinically significant differences between the drugs or between high (800 µg BUD, 1000 µg BDP) and low (400 µg BUD/BDP) doses. However, statistically significant differences were recorded for the corresponding parameters when comparing the placebo with preceding steroid periods. Adverse effects consisting mainly of oropharyngeal candidiasis, hoarseness and cough occurred in 54 of 468 treatment months (12%). The carry-over effects of inhaled steroids are longer lasting than was previously assumed.

Key words: asthma; beclomethasone dipropionate; budesonide; carry-over effects; dose-response effects; inhaled steroids.

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CLINICAL ASPECTS

Inhaled steroids are effective in moderately severe asthma. No clinical differences exist, however, between BUD and BDP in a dose range of 400 to 1000 µg. Doubling a low dose (400 µg) of inhaled steroids does not produce any clinical benefit. Inhaled steroids have longer lasting carry-over effects than previously assumed.

Inhaled steroids have the properties of low systemic potency coupled with a high topical anti-inflammatory potency. They are well established in the management of asthma (3, 9). Inhaled beclomethasone dipropionate (BDP) in a mean dose of approx. 400 µg daily is shown to be the equivalent of 5-8 mg of oral prednisone (4, 7) and, in a retrospective study of 293 asthmatics, 27% of the patients were able

to stop taking oral steroids and 62% experienced an overall improvement in asthma control with BDP in doses of 500-2000 µg daily (15). Topically inhaled steroids have also proved to be particularly effective in patients with moderately severe asthma who are not receiving systemic corticosteroids (8, 23). BDP has been available for more than 10 years and has proved to be an effective control in the

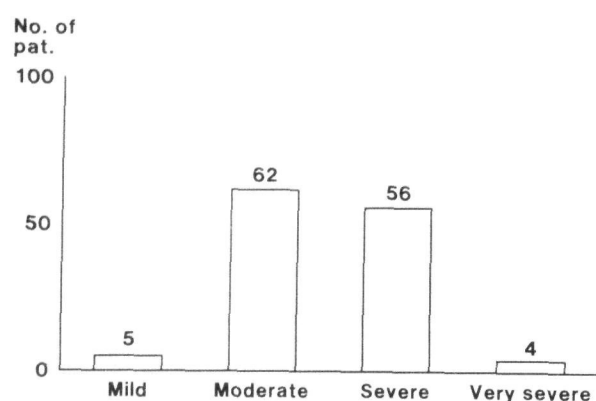


Fig. 1. Severity of asthma as estimated by the physician.

majority of such patients in doses of between 200 and 400 μg daily (8). In placebo-controlled studies inhaled steroids have been shown superior to placebo treatment in terms of pulmonary function and the use of supplementary bronchodilators (17). Budesonide (BUD) is a new, inhaled corticosteroid, which has proved effective in the treatment of chronic asthma in children (13) and adults (12). In pharmacological studies of animals (6) and humans (14) it has been claimed that BUD has an improved ratio between the topical anti-inflammatory and systemic effects when compared with BDP.

Increasing the dose of BDP from 400 to 800 μg or more has been followed by spirometric and clinical benefits (7) and it is claimed that inhaled steroids have a dose-response relationship (21). Very few prospective studies comparing inhaled corticosteroids have been conducted (9, 20).

The aim of the present study was to compare the dose-response effects of BDP and BUD administered twice daily with the aid of metered dose aerosols to patients who were currently in need of inhaled steroids, but who were not controlled satisfactorily by the low (400 μg BDP or BUD) dose.

PATIENTS AND METHODS

The subjects of this study were 128 patients (67 men and 61 women), with a mean age of 53 years (range 18–77 years), who had asthma bronchiale as defined by the American Thoracic Society (1). None had signs of cardiovascular disease or diabetes mellitus. The mean duration of their obstructive disease was 13 years (range 1–60 years).

13 patients (10%) were smokers and 49 (38%) ex-smokers. The severity of asthma from the clinical history was assessed by the physician with the aid of a 4-degree scale (mild, moderate, severe, very severe, Fig. 1). An allergic basis for asthma was found in 32 patients (25%).

The reversibility of the airway disease was estimated along the following lines: during a stable phase of the disease the patients showed a reversibility of their airway obstruction by an improvement of at least 15% in their FEV_{10} , FVC or PEF, 10 min after inhaling 200 μg of salbutamol via an inhaler, or a 20% variation in their morning PEF during the run-in period. 117 (91.4%) were receiving regular treatment with a β_2 -agonist (salbutamol, terbutaline, fenoterol, rimiterol) in the form of a metered dose aerosol, and 91 patients (71%) were using oral β_2 -agonists (salbutamol, terbutaline). Oral theophyllines were being used by 83 patients (64.8%).

Regarding the use of steroids, the inclusion criteria were as follows: only patients were included who were currently in need of inhaled steroids in doses ranging from 400–800 μg and who were not controlled satisfactorily by the low (400 μg) dose (expressed as at least one exacerbation of their asthma in the last 12 months requiring additional therapy, or recur-

Table 1
Number (No.) of patients diagnosed with diseases other than asthma

	No.
Hypertension	11
Hypertension, arthrosis of left hip	1
Hypertension, status post-myocardial infarction	1
Hypertension, perniciousa, hyperuremica	1
Polyposis nasi	2
Sinusitis	2
Rhinitis	3
Eczema	1
Duodenal ulcers	1
Gastritis	1
Tendency to cardiac arrhythmias	1
Pain in joints	1
Crural ulcera	1
Obesitas	1
Total	28

rent wheezing or episodes of dyspnea on the 400 µg dose). Patients who were currently taking regular oral corticosteroids were excluded. Patients who had taken intermittent short courses, but not more than 3 per year, were allowed to participate in the study. They did, however, have a 2-week period free from oral steroids before starting the run-in period.

Twenty-eight patients were suffering from other diseases (Table 1) and 27 of them were receiving treatment for their concurrent disease. The study was designed as a multi-centre, double-blind, four-period cross-over study, followed by a single-blind double placebo period. This final period was used to assess any carry-over effects caused by the study drugs. There was a pre-trial run-in period of 2 weeks during which the patients learned the procedure of recording peak expiratory flow measurements twice daily and filling in a daily record card. Each treatment period lasted for at least 4 weeks. The entire study therefore took a total of at least 22 weeks. Recruitment took place during weeks 36 to 42 of the calendar year.

A total of 128 patients were studied at eight centres. The randomisation took place according to a 4 × 4 Williams square. Each centre studied 16 patients.

The patients were allocated each of the following four treatment regimens:

- a) BDP 200 µg b.i.d.
- b) BUD 200 µg b.i.d.

- c) BDP 500 µg b.i.d.
- d) BUD 400 µg b.i.d.

The four possible orders of treatment were abcd, bcda, cdab and dabc. The fifth period was a single-blind regimen.

Each patient had access to a bronchodilator aerosol which they were instructed to use as required for immediate relief from any exacerbation of their symptoms. All other anti-asthma medication remained constant throughout the study period. Any necessary changes were clearly recorded on the physician's record form. Whenever necessary, exacerbations were treated with a 7-day standard short reducing course of oral steroids using the following dosages: 3.5 mg, 3.0 mg, 2.5 mg, 2.0 mg, 1.5 mg, 1.0 mg, 0.5 mg of betamethasone. If patients required a short course of steroids in the 4th week of any treatment period, they continued with the drug that caused the deterioration until the end of the short course and then started the new treatment period.

There were two types of form on which information was recorded: a daily record card on which patients recorded their daily medication, symptoms (Table 2) and PEF using a mini-Wright peak flowmeter, and a physician's record card on which patient details, clinical history and lung function results obtained at the clinic were recorded.

Any adverse events were recorded on the patient's record card and discussed with the physician during the regular visits to the clinic between the treatment periods. The study was conducted according to the Declaration of Helsinki adopted by the 18th World Medical Assembly in 1964 and revised by the 29th World Medical Assembly in Tokyo in 1975. Approval of the study was obtained from the Regional Ethics Committees.

Some of the variables were recorded in diaries by the patient every day. Only the last 14-day period of each active treatment was analysed. The mean value of these variables for the period – contributing a maximum of 14 days for active drug periods and 28 days for the placebo period – was calculated for each patient. When comparing active drug with placebo only those periods of active drug treatment that immediately preceded

Table 2

Assessing overall symptoms twice daily in the morning (symptoms from evening to morning) and in the evening (symptoms from morning to evening) with the aid of a 4-degree symptom score

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- 0 = No problems, not noticed any asthma, slept peacefully.
 - 1 = Slight problems, been aware of asthma, but this has not affected daily activities or sleep.
 - 2 = Moderate problems, troubled by asthma and this has affected daily activities and disturbed my sleep.
 - 3 = Severe problems, troubled a great deal by asthma. Unable to carry out my daily activities and had a very disturbed night.
-

the placebo period were used. When a patient deteriorated and had to begin oral corticosteroid treatment, only the data obtained prior to this deterioration was used in the evaluation.

All comparisons between BDP and BUD (active drugs) versus placebo were performed using Fisher's test for paired comparisons (5), which is a non-parametric test. The two-sided test was used.

RESULTS

Before the start of the trial the mean FEV₁ without inhaled β_2 -agonists for at least 8 h was 1.9 l/min, which corresponds to 61 % of the predicted normal FEV₁ value (3.08 l/min). The subsequent reversibility test revealed a mean FEV₁ reversibility of 26.3 % after 200 μ g of salbutamol via an inhaler. Lung function tests (FEV₁) performed during visits to the clinic showed a significantly higher FEV₁ ($P < 0.01$) on treatment with 1000 μ g BDP than at the end of the subsequent placebo period. There were no other significant differences in the FEV₁ values obtained on visits to the clinic for the different treatments. A comparison of equivalent doses of beclomethasone and budesonide reveals that a statistically significant ($P < 0.05$) reduction in the symptom score in the morning was recorded for 400 μ g BDP compared with 400 μ g BUD, and that an increased PEF was recorded following 400 μ g BDP compared with 400 μ g BUD both in the morning and evening ($P < 0.05$).

Surprisingly, 400 μ g BDP produced a significantly higher PEF ($P < 0.05$) than 1000 μ g BDP in the evening (significance by chance?). No other statistically significant differences in symptom score, β_2 -inhaler usage or PEF were recorded when comparing equivalent doses of the two drugs or the two different dose levels of the two agents.

When the preceding active treatment period was compared with the corresponding placebo period, significantly lower symptom scores were recorded in the morning and evening for 400 μ g ($P < 0.01$) and for 1000 μ g BDP ($P < 0.01$ and $P < 0.05$, respectively) and for 400 μ g BUD ($P < 0.05$) in the morning. For inhaled β_2 -agonists, significantly fewer puffs were

recorded in the evening for 400 μ g BDP ($P < 0.05$) and 800 μ g BUD ($P < 0.05$) and for 1000 μ g BDP ($P < 0.05$ and $P < 0.01$, respectively) in the morning and evening when compared with the corresponding placebo period. A significantly higher PEF was found in the morning and evening for 400 μ g ($P < 0.01$) and 1000 μ g ($P < 0.05$) BDP compared with the corresponding placebo period.

Two active treatment periods were excluded from the calculations in one patient due to throat discomfort during one period and a death in the family during another. A further eight patients failed to complete one treatment period satisfactorily; four because of poor compliance, one because of anxiety about steroid medication due to a public debate on the toxicity of inhaled steroids, two because of dryness in the mouth and palpitation cordis, respectively, and one patient who was hospitalised because of pneumonia. The above-mentioned periods were excluded from the statistical evaluation. Twenty-eight patients failed to complete the trial. Eleven patients were unable to complete all the active treatment periods and dropped out of the study. Of these patients, seven were excluded because a deterioration in their asthma made them unwilling to complete the study. One patient refused to complete the study because of anxiety about inhaled steroids, one was excluded during the first period because of pregnancy, one because of poor compliance, and one patient dropped out due to the occurrence of a retinal ablation during period 4.

Seventeen patients were unable to complete the placebo period and had to begin corticosteroid therapy again. A mean of 11.2 days (range 0–23 days) was recorded for the 17 patients before relapse. The data on these patients from the placebo period has only been included in the statistical evaluation up to the date of their relapse when they returned to steroid treatment. The remaining patients (100, 78 %) were able to complete the placebo period.

Fig. 2 shows the proportion of patients with a morning PEF of more than 80 % of the mean value in the preceding active treatment period. There was a continuous deterioration in airway obstruction, expressed as a fall in PEF, during

the entire placebo period. However, there were no statistically significant differences between patient groups in the placebo period with regard to type or dosage in the preceding active period. The number of patients in whom a clinical examination produced evidence of candida infection in the mouth and throat is shown in Fig. 3. A statistically significant increase in the incidence of candida infections was observed following treatment with 800 µg BUD compared with 1000 µg BDP ($P < 0.05$) and with 400 µg BUD ($P < 0.01$). However only one of the 13 patients displaying candidiasis following 800 µg BUD required treatment. No patient displayed signs of candidiasis during the placebo period.

The most common adverse effects were coughing due to inhaled steroids, throat irritation and hoarseness. One patient reported hoarseness and throat irritation in all the trial periods, including the placebo period, and one patient reported nasal bleeding three times whilst being treated with 800 µg BUD. The numbers of patients reporting side effects, apart from candidiasis, are shown in Table 3. During 468 months of treatment side effects from the upper airways were reported in 54 months (12 %).

DISCUSSION

The results of our study reveal very few significant differences when comparing the two drugs, and we were unable to demonstrate that the higher doses (800, 1000 µg) had a better effect than the low doses (400 µg). Our study therefore

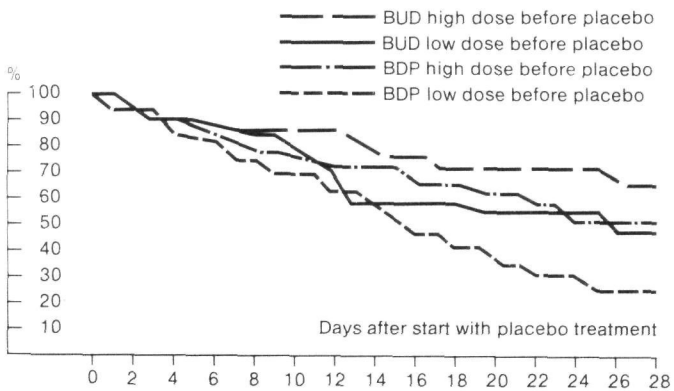


Fig. 2. Proportion of patients with a morning PEF of more than 80 % of the mean value in the preceding active treatment period. Patients with a value below 80 % of the mean, or requiring steroids, are counted as below.

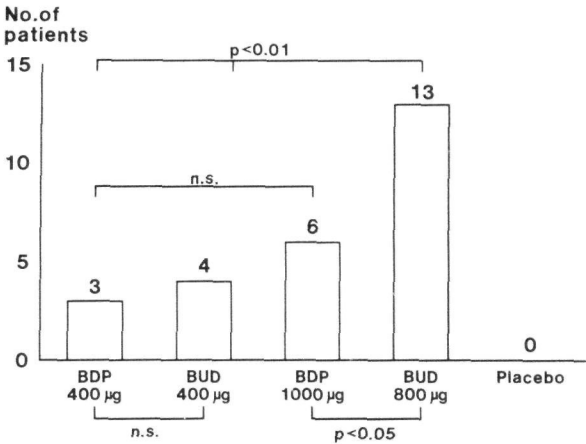


Fig. 3. Number (No.) of patients displaying mouth and throat candida infections on different treatments.

indicates that there are no clinically important differences between BDP and BUD administered twice daily in the dose range 400–1000 µg. These results correspond well with earlier comparative studies of BDP and BUD in doses of 200 µg daily in children (16) or 400 µg daily in adults (23), whereas in a recent survey of 200 µg BDP and BUD administered twice daily an increase in the PEF in the morning and evening was found in children receiving BUD (2). In 28 patients requiring a mean dose of 887.5 µg of BDP a double-blind, single cross-over study comparing 1500 µg of BDP and 1600 µg of BUD administered daily in two doses revealed no significant differences in the control of asthma during the two 6-week treatment periods (11). In light of the previous and present data, it would appear justified to assume clinical equipotency between BDP and BUD in the treatment of chronic asthma. In earlier studies it has been claimed that inhaled steroids have a dose-response relationship (7, 10, 21, 22). We were unable to demonstrate any such relationship. It could be argued that this was due to the assumption that the patients involved in our study were mild asthmatics who were not in need of inhaled steroids. We do not consider this to be true. We believe that our patients were in need of steroid treatment; statistically significant differences were recorded for symptom score, the number of additional puffs of β_2 -agonists and their PEF when comparing the placebo period with the preceding steroid periods. Our study shows that doubling the dose of 400 µg of BDP or BUD is not sufficient to obtain additional effects.

Table 3
Number of patients reporting side effects during the different treatment periods

	Budesonide		Beclomethasone		Placebo
	400 µg	800 µg	400 µg	1000 µg	
Cough	1		3	2	1
Cough and throat irritation				1	
Cough and hoarseness		1			
Hoarseness	4	6	3	5	
Hoarseness and throat irritation	2	1	2	4	1
Throat irritation	1	3	6	5	
Dry mouth	1		1		
Unpleasant taste		1			
Nasal bleeding		1			
Total	9	13	15	17	2

It might be that beneficial effects could be obtained by increasing the dose even further, as has been shown in a previous study of 24 asthmatics where an increase in the dose from 400 to 1600 µg of BUD significantly improved the clinical status of patients with severe steroid-dependent asthma (22).

Our study finished with a single-blind placebo period. Although we registered a significant deterioration in asthma control, we were nevertheless surprised that so many patients were able to complete this period. We think this may have been due to longer lasting carry-over effects of inhaled steroids than previously suggested (9). This is of great importance when conducting further studies to compare inhaled steroids. Such studies should be of a parallel group design in order to avoid carry-over effects. With this in mind we evaluated the first period of our study separately in terms of the differences between the high and low doses of inhaled steroids in order to avoid carry-over effects from the high doses. This approach enabled the first month of active steroid treatment in our study to be regarded as a parallel group study. However, even with this approach no significant differences could be registered between low and high doses of inhaled steroids.

Candidiasis, hoarseness, coughing and dysphonia are common adverse effects of inhaled

steroid treatment. They are mostly regarded as a nuisance rather than a threat (20). The adverse effects can be alleviated by measures which reduce the amount of drug deposited or retained in the oropharynx by such means as tube extensions and spacers (18) and mouth-rinsing after use. In the present study the patients were instructed in increased oral hygiene, but no spacers or extension tubes were used. Despite this, side effects occurred in only 12 % of the treatment months. This may be partly due to the twice daily administration regimen, since the degree of oropharyngeal complications has been shown to correlate with the dose regimen (fewer adverse reactions with b.i.d. compared with q.i.d.) and the size of the daily dose (19).

The presence of oropharyngeal candidiasis was estimated clinically by the physician in attendance. The number of patients with oral candidiasis increased with the high BUD dose compared with all other treatments. This should be interpreted with considerable caution since the majority of cases with oral candidiasis were not confirmed by culture and only one patient received antimicrobial therapy.

In conclusion, our study revealed no clinically significant differences between BDP and BUD in the dose range of 400–1000 µg. In patients receiving low-dose therapy (400 µg),

doubling the dose did not produce any clinical benefits. The carry-over effects of inhaled steroids are longer lasting than has been previously assumed.

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REFERENCES

1. American Thoracic Society, committee on diagnostic standards for nontuberculous respiratory disease: Definition and classification of chronic bronchitis, asthma and pulmonary emphysema. *Am Rev. Respir. Dis.* 85, 762-768, 1962.
2. Baran, D.: A comparison of inhaled budesonide and beclomethasone dipropionate in childhood asthma. *Br. J. Dis. Chest* 81, 170-175, 1987.
3. Berglund, E., Löfdahl, C. G. & Svedmyr, N.: Dosing of inhaled corticosteroids and therapeutic goals in asthmatic patients. *Eur. J. Respir. Dis.* (editorial) 65, 319-320, 1984.
4. Boc, J. & Thulesius, O.: Treatment of steroid-dependent asthma with beclomethasone dipropionate administered by aerosol. *Curr. Ther. Res.* 17/5, 460-466, 1975.
5. Bradley, J. W.: Distribution-free statistical tests. Prentice-Hall, London, 68-86, 1968.
6. Brattsand, R., Thalén, A., Roempke, K., Källstrand, L. & Gruvstad, E.: Development of new glucocorticosteroids with a very high ratio between topical and systemic activities. *Eur. J. Resp. Dis.* 63, Suppl 122, 62-73, 1980.
7. British Thoracic and Tuberculosis Association: A trial of inhaled corticosteroids in patients receiving prednisone. *J. Dis. Chest* 70, 95-103, 1976.
8. Brown, H. M. & Storey, G.: Treatment of allergy of the respiratory tract with beclomethasone dipropionate steroid aerosol. *Postgrad. Med. J.* 51, Suppl. 4, 59-64, 1975.
9. Clark, T. J. H.: Steroids in asthma. A reappraisal in the light of inhalation therapy. ADIS Press, New Zealand, 1983.
10. Costello, H. J. & Clark, T. J.: Response of patients receiving high dose beclomethasone dipropionate. *Thorax* 29, 571-573, 1974.
11. Ebdén, P., Jenkins, A., Houston, G. & Davies, B. H.: Comparison of two high dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 µg/day) and budesonide (1600 µg/day), for chronic asthma. *Thorax* 41, 869-874, 1986.

12. Ellul-Micallef, R., Hansson, E. & Johansson, S. Å.: Budesonide: a new corticosteroid in bronchial asthma. *Eur. J. Resp. Dis.* 61, 167-173, 1980.
13. Field, H. V., Jenkinson, P. M. A., Frame, M. H. & Warner, J. O.: Asthma treatment with a new corticosteroid aerosol, budesonide, administered twice daily by spacer inhaler. *Arch. Dis. Childh.* 57, 864-866, 1982.
14. Johansson, S. Å., Andersson, K. E., Brattsand, R., Hedner, P. & Gruvstad, E.: Topical and systemic glucocorticoid potencies of budesonide and beclomethasone dipropionate in man. *Eur. J. Clin. Pharmacol.* 22, 523-529, 1982.
15. Smith, M. J. & Hodson, M. E.: High dose beclomethasone inhaler in the treatment of asthma. *Lancet* 265-269, 1983.
16. Springer, C., Avital, A., Maayan, C. H., Rossler, A. & Godfrey, S.: Comparison of budesonide and beclomethasone dipropionate for treatment of asthma. *Arch. Dis. Child.* 62, 815-819, 1987.
17. Taylor, B. & Norman, A. P.: Betamethasone 17-valerate in childhood asthma. *Acta Paediatr. Scand.* 64, 234-240, 1975.
18. Toogood, J. H., Baskerville, J., Jennings, B., Lefcoe, N. M. & Johansson, S. Å.: Use of spacers to facilitate inhaled corticosteroid treatment of asthma. *Am. Rev. Respir. Dis.* 129, 723-729, 1984.
19. Toogood, J. H., Jennings, B., Baskerville, J., Andersson, J. & Johansson, S. Å.: Dosing regimen of budesonide and occurrence of oropharyngeal complications. *Eur. J. Respir. Dis.* 65, 35-44, 1984.
20. Toogood, J. H., Jennings, B., Baskerville, J. & Lefcoe, N. M.: Personal observations on the use of inhaled corticosteroid drugs for chronic asthma. *Eur. Respir. J.* 65, 321-338, 1984.
21. Toogood, J. H., Lefcoe, N. M., Haines, D. S. M., Jennings, B., Errington, N. & Chuang, L.: A graded dose assessment of the efficacy of beclomethasone dipropionate aerosol for severe chronic asthma. *J. Allergy Clin. Immunol.* 59, 298-308, 1977.
22. Tukiainen, P. & Lahdensuo, A.: Effect of inhaled budesonide on severe steroid-dependent asthma. *Eur. J. Resp. Dis.* 70, 239-244, 1987.
23. Willey, R. F., Godden, D. J., Carmichael, J., Preston, P., Frame, M. & Crompton, G. K.: Comparison of twice daily administration of a new corticosteroid budesonide with beclomethasone dipropionate four times daily in the treatment of chronic asthma. *Br. J. Dis. Chest.* 76, 61-68, 1982.

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