The Bronchodilator Effect of a Fixed-combination Metered Aerosol (Fenoterol and Ipratropium Bromide)

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Summary. The fixed-combination metered aerosol IK_6 (fenoterol 0.05 mg/puff, ipratropium bromide 0.02 mg/puff—Berodual, Boehringer-Ingelheim Ltd., Ridgefield, Conn.) was administered to 12 children (8 boys, 4 girls) aged $3^1/_2$ to $6^2/_{12}$ years who had extrinsic bronchial asthma. Three forms of administration, each with a different site of action, were compared: 1) Two puffs during inspiration. Probable site of action: oral cavity, pharynx, larynx, trachea, and bronchi. 2) Two puffs using an inhalational aid during inspiration. Probable site of action: pharynx, larynx, trachea, and bronchi. 3) Two puffs in the breathing interval after deep inspiration. Probable site of action: oral cavity and pharynx. The resistance of the respiratory system (R_{rs}) was measured using oscillometry for up to 360 minutes after administration. A significant decrease of the median resistance was found with all three forms of administration. The changes were Form 1—48% of baseline after 120 minutes; Form 2—47.9% of baseline after 60 minutes; Form 3—44.4% of baseline after 30 minutes. The greatest decrease was observed with form 1. The study indicates that significant bronchodilation was achieved in small children using the combination of fenoterol and ipratropium bromide administered by metered aerosol even when inhalation and the release of the puff were not synchronized. A significant bronchodilator effect was also observed in cases of severe bronchial obstruction in which transport of the active ingredients to the lower airways could not be sufficiently guaranteed. (*Key words:* asthma, bronchial; bronchodilators, combination; children, asthmatic; inhaled aerosol; metered aerosol.) *Pediatr Pulmonol 1985; 1:297–302.*

Even in the mid-1970s it was still generally accepted that broncholytic therapy with β_2-sympathomimetics had little effect on the obstructive bronchitis or bronchial asthma of young children[1–3] In 1978 studies by Lenney and Milner showed that β_2-adrenergics could be used successfully as bronchodilators at the age of 18 months and older.[4,5] The more recent data of Reinhardt et al. concluded that β_2-adrenergics may be effective in younger children if applied in sufficiently high doses.[6] The investigations of Hodges et al. and our laboratory indicated that, in addition to β_2-adrenergics, tropic acid esters could successfully treat obstructive bronchitis or extrinsic bronchial asthma in young children when administered topically.[7,8] Klabuschnigg et al. studied the efficacy of β_2-adrenergics as well as tropic acid esters in a fixed combination (Berodual metered aerosol, Boehringer-Ingelheim Ltd.) administered by metered aerosol in school children.[9]

The aim of the present study was to investigate the broncholytic effect of this combination (IK_6) when the β_2-adrenergic component was reduced to 25% per puff of the monosubstance product (Berotec metered aerosol, Boehringer-Ingelheim). Such an application has not yet been reported in young children. The study also attempted to establish whether this product can be successfully administered to young children by metered aerosol. It is known that with this form of administration a certain amount of cooperation is required for the active substance to penetrate into the lower airways; when used incorrectly, the substance reaches only the oral cavity and the pharynx. Three forms of administration with different sites of action were compared. Finally, the results of studies stating

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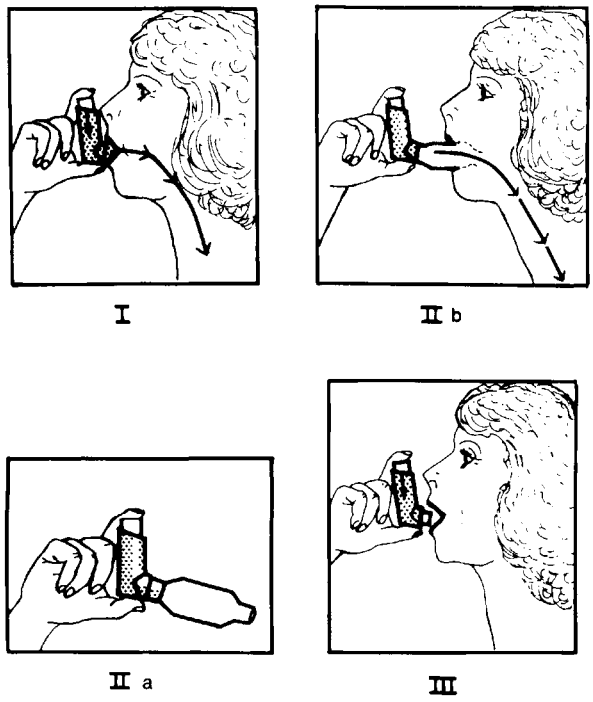

figure 1—The three forms of application of the fixed-combination metered aerosol:
I=metered dose inhaler with deep inhalation.
IIa=metered dose inhaler + inhalational aid.
IIb=metered dose inhaler with deep inhalation + inhalational aid.
III=metered dose inhaler after deep inspiration in the postinspiratory pause.

that aerosols sprayed only into the oral cavity achieved as much as 80–90% of the maximal bronchodilator capacity were reexamined.[10]

Materials and Methods

Twelve patients (8 boys, 4 girls) aged $3^1/_2$ to $6^2/_{12}$ years who had extrinsic asthma and were undergoing long-term therapy with bronchodilators were examined. Oral broncholytic agents used by the patients were discontinued at least 12 hours prior to the study, and inhalants, at least 8 hours prior. The parents were informed about the aims of the study and gave consent to the participation of their children. Prerequisites for inclusion in the study were: 1) oscillatory resistance (R_{rs}) measurements of over 150% of the predicted value on each day of the study; 2) the absence of concomitant cardiac, renal, hepatic, or metabolic disorders; 3) practice with placebo metered aerosol before the actual study.

The R_{rs} was determined using a comparative oscillation method (Siregnost FD_5, Siemens Corporation, Iselin, N.J.) and was read from the phase diagram.[11,12] The reference standards used were R_{rs} values that had been previously determined by us for young children.[13] The study lasted for 6 hours on each of the 3 days. R_{rs} was measured before and 10, 30, 60, 120, 240, and 360 minutes after the administration of two puffs of the test substance IK_6. One puff contained 0.05 mg fenoterol and 0.02 mg ipratropium bromide. The test substance was distributed in a randomized fashion on 3 consecutive days by the same physician under the same conditions for use in three different ways:

1. Two puffs of MA, synchronized with deep inhalation (deposited on the mucosa of the oral cavity, pharynx, larynx, trachea, and bronchi). This is the usual application of a metered dose inhaler (figure 1_I).
2. Two puffs MA employing an inhalational aid with deep inhalation (deposited on the mucosa of the pharynx, trachea, and bronchi). The inhalational aid was a plastic tube attached to the metered dose inhaler (figure 1_{IIa}) that reached deep into the child's mouth (figure 1_{IIb}). This allowed less substance to be deposited on the oral mucosa than did form 1. Another advantage of this form of application was that the release of the puff into the tube did not need to be syn-

table 1—Median Oscillatory Resistance (±SD) in 12 Patients with Bronchial Asthma Before and After Administration of 2 Puffs of IK_6 Metered Aerosol

	Oscillatory Resistance (mbar/l/sec)						
Forms of Administration	Before Admin.	At 10 Min.	At 30 Min.	At 60 Min.	At 120 Min.	At 240 Min.	At 360 Min.
1. 2 puffs MA *with* deep inhalation	18.50 (1.81)	10.00 (2.24)	9.40 (2.20)	9.45 (1.55)	9.35 (2.78)	12.00 (2.49)	12.75 (2.86)
2. 2 puffs MA + IA *with* deep inhalation	18.50 (4.34)	10.40 (3.42)	9.75 (1.83)	9.65 (2.41)	10.75 (2.76)	11.95 (2.83)	14.00 (4.96)
3. 2 puffs MA *after* deep inhalation	18.50 (2.04)	12.40 (2.42)	10.25 (2.22)	10.50 (2.92)	10.45 (2.82)	11.40 (2.65)	14.00 (3.28)

Abbreviations: MA = metered aerosol; MA + IA = metered aerosol plus inhalational aid.
Mean predicted value = 10.25 (±0.99).

chronous with the child's inhalation because the substance could also be inhaled from the tube.

3. Two puffs of metered aerosol after deep inhalation during the postinspiratory pause into the wide open mouth (deposited on the oral mucosa and pharynx). In this form the child had to inhale deeply and then hold his or her breath while the 2 puffs were released before exhaling (figure 1_{III}).

Changes in R_{rs} over time were studied in three different ways: 1) as absolute values; 2) as percent of baseline values; 3) as percent of predicted values. For statistical comparison of the fixed combination product we used the maximal percentage decrease compared with the baseline R_{rs} value. The percentage decrease was evaluated by variant analysis (factors: patient and product) followed by linear contrasts according to Scheffé using the SAS-program.[14] The level of significance was $P \leqslant 0.05$.

Results

Table 1 shows the median value for R_{rs} ± standard deviations for the duration of the study. Before application of the medication on each test day R_{rs} was on the average almost 200% of the normal predicted value. The maximum broncholytic effect was registered between 30 and 120 minutes after administration in all three forms of application; whereas with form 1 the lowest median was reached after 120 minutes, with form 2 the lowest was reached after 60 minutes, and form 3 after 30 minutes. These results are illustrated in figure 2. It is evident that the broncholytic effects of forms 1 and 2 were almost the same; after 360 minutes form 2 had a slightly weaker broncholytic effect than did form 1. Form 3 showed the weakest bronchodilation but the decrease in R_{rs} during this protocol did not differ significantly from that obtained with the other forms of application. As can be seen in Table 1 and figure 2, at 30 minutes all three forms recorded mean R_{rs} values that lay within the individual predicted value. Only after 360 minutes were these measurements in the upper, or slightly above the upper, range of predicted values.

Table 2 and figure 3 demonstrate the course of R_{rs} for each patient on each of the three study days. Except for patient 6 and 7, not only the bronchial (form 1) but also the buccal (form 3) administration quickly led to a significant decrease of R_{rs}. The duration of bronchodilation was almost the same for all three forms of administration in all patients except patients 9 and 11. For patient 9 the duration of action of form 2 was clearly shorter than forms 1 and 3, and for patient 11 the duration of action of form 2 was clearly longer.

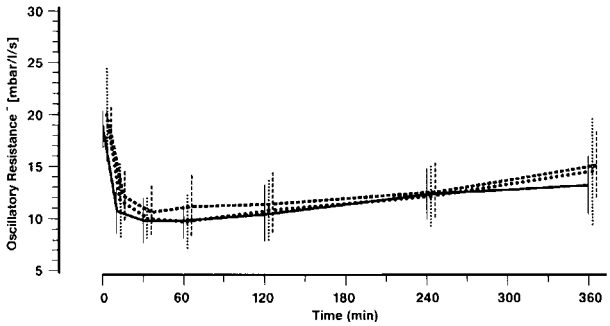

figure 2—Mean values and standard deviations for oscillatory resistance in 12 patients with bronchial asthma before and up to 360 minutes after administration of 2 puffs of IK_6 metered aerosol.

Key: _____ = metered aerosol (form 1).
. . . . . = metered aerosol with inhalational aid (form 2).
– – – – = metered aerosol, buccal application (form 3).

In the administration of metered aerosol without the inhalational aid it was difficult to coordinate inspiration with the simultaneous release of two puffs. In fact, it was only successfully done in two patients. In contrast, the inhalational aid method proved to be the easiest for all 12 patients. The buccal form was also used without problems by all 12 patients, but 10 of them considered it to be unpleasant because of the bitter taste of the metered aerosol.

Discussion

The aim of any long-term therapy must be to reduce the needed amount of medication as much as possible. In the combination product examined, the quantity of β_2-adrenergics was reduced to 25% of that in the monosubstance product and yet it produced a good bronchodilatory effect. With appropriate administration the respiratory resistance of all 12 patients was reduced by 50% and thus into the predicted normal range.

Our results show that for children a metered aerosol is not always easy to use, because small children are often incapable of simultaneously releasing the puff and inhaling. They may also reject the metered dose inhaler altogether because of its bitter taste. We therefore sought an alternative form of administration. An inhala-

table 2—Individual Values for Oscillatory Resistance in 12 Patients with Bronchial Asthma Before and After Administration of 2 Puffs of IK_6 Aerosol

			Oscillatory Resistance (mbar/l/sec)						
Patient	Day	Predicted Value	Before Admin.	At 10 Min.	At 30 Min.	At 60 Min.	At 120 Min.	At 240 Min.	At 360 Min.
	1		16.5	10.0	8.0	8.5	7.9	13.0	10.0
1	2	10.3	18.0	10.0	9.8	9.5	11.0	12.0	14.0
	3		20.0	12.0	11.0	10.5	10.2	11.0	17.0
	1		20.4	10.0	9.5	9.0	8.9	8.0	10.0
2	2	10.2	19.2	9.5	8.0	8.0	8.0	8.0	8.5
	3		20.4	9.0	9.0	9.4	8.8	10.8	12.0
	1		20.0	10.5	9.3	9.5	9.2	11.0	11.0
3	2	9.8	17.5	11.5	9.5	8.4	8.0	8.2	8.2
	3		19.6	10.0	9.5	9.0	8.8	10.5	14.0
	1		18.0	9.8	8.5	8.5	8.5	10.6	10.0
4	2	9.4	15.0	9.0	8.5	8.0	9.1	10.5	11.0
	3		16.0	14.2	9.0	8.9	9.4	11.5	13.9
	1		16.0	9.2	9.0	9.4	9.5	11.0	11.8
5	2	9.6	17.5	11.0	10.0	9.0	9.5	11.0	13.0
	3		17.0	10.8	9.0	9.3	10.0	9.6	9.8
	1		18.5	13.0	11.0	10.8	12.5	13.0	15.0
6	2	11.5	19.0	10.0	10.2	10.4	11.0	12.2	14.0
	3		20.0	15.0	14.0	17.0	16.0	14.0	14.0
	1		16.5	10.0	9.5	9.5	10.5	11.5	12.0
7	2	10.1	17.5	10.5	9.7	9.8	10.5	10.5	14.0
	3		18.5	15.0	12.0	14.0	14.0	14.0	17.0
	1		17.5	7.0	6.9	7.0	7.0	12.0	14.5
8	2	8.2	22.0	8.0	7.5	6.0	8.5	12.8	18.0
	3		14.0	7.5	7.0	6.8	8.0	10.5	12.0
	1		20.0	8.8	8.0	9.0	9.0	12.0	13.5
9	2	11.5	28.0	17.0	12.0	11.0	13.0	17.0	27.0
	3		18.5	10.8	11.3	11.0	10.8	11.8	17.0
	1		22.0	13.9	15.1	13.0	16.0	14.0	15.0
10	2	11.7	29.0	19.0	14.0	16.0	18.0	16.5	17.5
	3		21.0	12.9	14.5	15.0	14.0	17.0	21.0
	1		19.0	14.7	12.0	11.0	14.5	18.5	19.5
11	2	10.5	20.0	15.1	11.9	10.3	11.0	11.9	13.2
	3		17.3	12.8	11.9	11.9	15.8	17.8	19.0
	1		18.5	12.0	11.0	10.8	12.5	13.0	15.0
12	2	10.3	17.0	10.3	9.5	10.0	12.0	14.5	15.0
	3		18.5	14.0	9.5	10.5	10.7	11.3	12.5

Day 1 = metered aerosol with deep inhalation (bronchial; day 2 = metered aerosol plus inhalational aid with deep inhalation (bronchial); day 3 = metered aerosol after deep inhalation (buccal).

tional aid was developed for children and the elderly that can be attached to the conventional metered dose inhalers currently on the market. This makes handling much easier since the patient's inhalation and release of the puff do not need to be coordinated. Although coating of the plastic tube occurs, effectiveness was not reduced. In fact, the average reduction in R_{rs} was the same with and without the inhalational aid, but the acceptance was much better.

We wanted to determine whether IK_6 has any effect when the children were incapable of inhaling the substance due to lack of cooperation or to severe obstruction. It has been generally held that the use of the metered dose inhaler was only justified if a certain amount of the drug could reach the bronchopulmonary receptors.[15] If it could not, systemic treatment has been thought to be preferable.[16-18] The results we obtained in young children are clearly consistent with those of other studies in adults[10,19,20] in which the buccal administration of MA produced an adequate degree of bronchodilation and the effective duration was shown to differ greatly from conventional routes of administration. Several explanations for this effect have

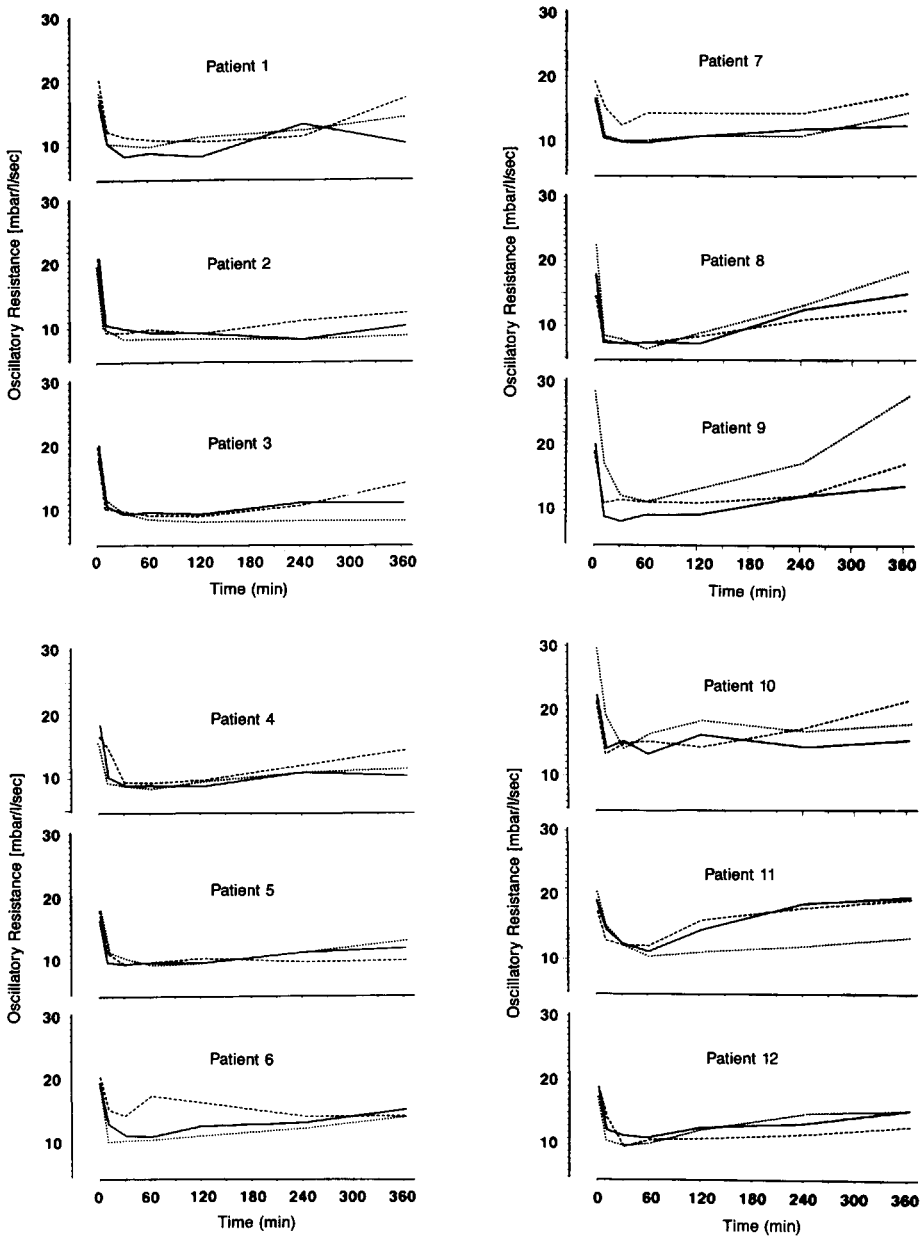

figure 3—Individual changes in oscillatory resistance before and up to 360 minutes after administration of 2 puffs of IK_6 metered aerosol using the three forms of application for each of the 12 children. *Key:* _____ = metered aerosol (form 1). · · · · · = metered aerosol with inhalational aid (form 2). – – – – = metered aerosol buccal administration.

been suggested. It is thought that the receptors of the mouth and pharyngeal mucosa mediate reflex bronchodilation.[21] The investigations of Zimmermann et al.[21,22] support this theory. They demonstrated in animal experiments that the application of a single allergen or acetylcholine onto the buccal mucosa caused bronchoconstriction. It is also conceivable that the active substance is absorbed by the oral mucosa and transported to the lung via the right heart.[23,24] Finally, it could be that the active substance reaches the trachea and bronchi by buccal administration in sufficient quantity to cause the broncholytic effect. This theory is supported by the investigations of Ruffin,[25] who studied mouthwash with fenoterol solution without obtaining any broncholytic effect. The only difference between Ruffin's method and ours is that he tested fenoterol alone, whereas we used a combination (IK_6) and applied it using a different method. Various studies that show a clear dose-related effect of β_2-sympathomimetics and atropine derivatives dispute this theory.[26,27] The fact that β_2-adrenergic substances administered as metered aerosols cause significant broncholytic effect far from their usual site of action is supported by investigations of Groth et al.,[28] who demonstrated that even the intranasal application of fenoterol metered aerosol had a broncholytic effect equal to the conventional inhalational form.

Irrespective of where the inhaled drug is even-

tually deposited, topical therapy still continues to be the treatment of choice for bronchial asthma.[29] Metered aerosols offer an effective alternative to traditional inhalational therapy using compression nebulizers, which depend on a source of energy and are considerably more time consuming. Nevertheless, one should use these nebulizers as the primary therapy in children because they offer better parental control and thus help to exclude abuse, they provide for the inhalation of more secretolytic fluid into the bronchial system, and they allow the possibility of combining several monosubstance medications.

The general opinion that metered dose inhaler aerosols should not be used in young children is no longer acceptable. Because a good broncholytic effect was achieved with the combination IK_6 administered as a metered dose inhaler, this therapeutic method can be used in certain situations such as emergencies, prior to exercise in patients who have exercise-induced asthma, and during holidays even if the children are not able to use the inhaler correctly due to age or the presence of severe airway obstruction.

References

1. Radford M. Effect of nebulized salbutamol in infants with wheezy bronchitis. Arch Dis Child 1974; 49:243.
2. Radford M. Effect of salbutamol in infants with wheezy bronchitis. Arch Dis Child 1975; 50:535–538.
3. Rutter N, Milner AD, Hiller JE. Effect of bronchodilators on respiratory resistance in infants and young children with bronchiolitis and wheezy bronchitis. Arch Dis Child 1975; 50:719–722.
4. Lenney W, Milner AD. Alpha- and beta-adrenergic stimulants in bronchiolitis and wheezy bronchitis in children under 18 months of age. Arch Dis Child 1978; 53:707–709.
5. Lenney W, Milner AD. At what age do bronchodilator drugs work? Arch Dis Child 1978; 53:532–535.
6. Rheinhardt D, Becker D, Nagel-Hiemke M, Schiffer R, Zehmich T. Influence of beta-receptor agonists and glucocorticoids on α- and β-adreno-receptors of isolated blood cells from asthmatics. Pediatr Pharmacol 1983; 3:293–302.
7. Berdel D, Kellersmann U, Magnussen H. The bronchodilator effect of inhaled fenoterol and inpratropium bromide in asthmatic children between 4 and 17 years of age. Bull Eur Physiopathol Respir *(in press)*.
8. Hodges IGC, Groggins RC, Milner AD, Stokes GM. Bronchodilator effect of inhaled ipratropium bromide in wheezy toddlers. Arch Dis Child 1981; 56:729–732.
9. Klabuschnigg A, Horak F, Rottensteiner K, Weißenbacher S, Vogt R. Kombinationsaerosol beim Asthma bronchiale im Kindesalter. Padiatr Padol 1983; 18:347–353.
10. Ulmer WT, Zimmerman I, Islam MS. Bronchodilatation: Neue Erkentnisse zu einem therapeutischen Prinzip. Inn Med 1979; 8:328–333.
11. Berdel D, Magnussen H, Holle JP, Hartmann V. Vergleich der oszillatorischen Atemwiderstandsmessung mit der Plethysmographie und Spirometrie im Kindesalter. Schweiz Med Wochenschr 1979; 109:92–94.
12. Berdel D, Holle JP, Hartmann V, Magnussen H. Die Bedeutung der oszillatorischen Atemwiderstandsmessung im Kindesalter. Klin Padiatr 1981; 193:73–76.
13. Manten J. Die Messung des Atemwiderstandes mit der Vergleichsoszillationsmethode bei gesunden Kindern. Inaugural dissertation, Rheinische Friedrich-Wilhelms-Universität Bonn, 1984; 64–71.
14. Scheffé M. In: Sachs L. Angewandte Statistik. Berlin: Springer Verlag, 1978:410.
15. Magnussen H, Macha HN. Pharmakotherapie des schweren Asthma-anfalles. Dtsch Med Wochenschr 1983; 106:1291–1295.
16. May CS, Paterson JW, Spiro SG, Johnson AJ. Intravenous infusion of salbutamol inthe treatment of asthma. Br J Clin Pharmacol 1975; 2:503–508.
17. Paterson JW, Woolcock AJ, Shenfiled GM. Bronchodilator drugs. Am Rev Respir Dis 1979; 120:1149–1188.
18. Williams S, Seaton A. Intravenous or inhaled salbutamol in severe acute asthma? Thorax 1977; 32:555–558.
19. Loellgen H, Nieding GV, Krekeler H. Bronchodilating effect of β-adrenergic substances administered orally, metered spray or metered aerosol. Atemwegs- und Lungenkrankheiten 4:401–404.
20. Rodenstein D, Stănescu DC. Mouth spraying versus inhalation of fenoterol aerosol in healthy subjects and asthmatic patients. Br J Dis Chest 1982; 76:365–373.
21. Zimmermann I, Walkenhorst M, Ulmer WT. The location of sensoric bronchoconstricting receptors in the upper airways. Respiration 1979; 38:1–11.
22. Zimmermann I, Ulmer WT, Weller W. The role of upper airways sensoric receptors on reflex bronchoconstriction. Res Exp Med 1979; 174:253–265.
23. Laros CD, Svierenga J, Vanderschueren RJGRA. A model of pathways of inhaled medicaments to their receptor sites. Respiration 1975; 32:284–293.
24. Shore SC, Weinberg EG, Duerr MH. Buccal administration of fenoterol aerosol in young children with asthma. S Afr Med J 1976; 50:1362–1364.
25. Ruffin RE, Montgomery JM, Newhouse MT. Site of beta-adrenergic receptors in the respiratory tract. Chest 1978; 74:256–260.
26. Verstraeten JM. Is there a selective indication for a para-sympatholytic (Atrovent) and for a β_2-sympathomimetic (Berotec) in asthma and asthmatic bronchitis? Acta Tuberc Pneumol Belg 1976; 3–4:130–155.
27. Ward MJ, Fentem PH, Roderick-Smith WH, Davies D. Ipratropium bromide in acute asthma. Br Med J 1981; 282:598–600.
28. Groth S, Dirksen H, Mygind N. Intranasal fenoterol in asthmatic subjects. J Allergy Clin Immunol 1984; 74:536–539.
29. von der Hardt H. Bronchospasmolytika in der Paediatrie. In: Nolte D, Lichtenfeld A. Interaktion von Vagus und Sympathikus bei Bronchialerkrankungen. München: Urban & Schwarzenberg, 1980:154–155.