

New β -Agonist, KWD 2131, Compared with Terbutaline in Asthmatics

A Cumulative Dose-Response Study

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The equipotent bronchodilating doses of terbutaline and a new β -agonist KWD 2131 with a relatively stronger anti-allergic (inhibition of mediator release) than bronchodilating effect given in nebulized form was estimated in eight patients with intrinsic asthma. The subthreshold bronchodilating dose of KWD 2131 was also evaluated. The study was a 2-day, single-blind cross-over comparison between cumulative doses of KWD 2131 (0.5 mg to 12 mg) and terbutaline (0.05 mg to 1.2 mg). Both drugs gave a dose-dependent bronchodilating effect as measured spirometrically. It was already statistically significant at the 0.05 mg dose of terbutaline, but not until the cumulative 1.5 mg dose (0.5 + 1 mg) of KWD 2131. The median value of the bronchodilating potency of terbutaline relative to KWD 2131 was 30. The influence of the two substances on tremor and the cardiovascular system was minimum and clinically unimportant.

The search for the subthreshold bronchodilating dose of KWD 2131 was of interest, as this dose was to be used in a subsequent antigen provocation study in order to selectively evaluate KWD 2131's anti-allergic property. The mean subthreshold bronchodilating dose of KWD 2131 was 1 mg. However, four of the eight patients showed bronchodilatation at the 1 mg dose, and two of the four also at 0.5 mg.

Key words: bronchodilatation, dose-response curves, KWD 2131, terbutaline

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KWD 2131 is a new β -agonist (Fig. 1) structurally related to terbutaline. Similar to terbutaline, KWD 2131, in animal studies, exhibits both anti-allergic (inhibition of mediator release) and bronchodilating properties (23). KWD 2131's profile of action is changed compared with terbutaline. Whereas terbutaline shows anti-allergic effect and tracheal smooth muscle relaxation in the same concentration range in *in vitro* studies in guinea pigs (22), KWD 2131 shows appreciable anti-

allergic effect in concentrations where the tracheal smooth muscle relaxation is weak (23). Therefore KWD 2131 should provide a tool to prove the value of the anti-allergic property of a β -agonist in the prophylactic treatment of patients with extrinsic asthma which was preliminary reported at the 13th Scandinavian Congress of Allergology 1978.

Terbutaline is a well-known β_2 -stimulant and in the treatment of asthma is used orally, parenterally, by pressurized aerosol, and by nebulized solution.

The present study had two objects: We

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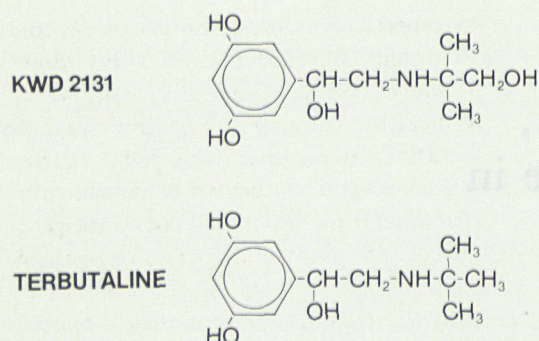


Fig. 1. Chemical structures of KWD 2131 and Terbutaline.

wished to find the equipotent bronchodilating doses of terbutaline and KWD 2131 given in nebulized form. Earlier *in vivo* (24) and *in vitro* (23) pharmacological studies in guinea pigs had indicated that the bronchodilating potency of KWD 2131 was 10 and 25 times weaker respectively, than that of terbutaline. We also wished to find the subthreshold bronchodilating dose of KWD 2131 in order to use it in a subsequent antigen provocation study evaluating selectively KWD 2131's anti-allergic property in prophylactic treatment of patients with extrinsic asthma.

The study was approved by the Ethical Committee of the University of Göteborg, informed consent being obtained from all patients.

PATIENTS AND METHODS

Eight patients, three female and five male, mean age 49 (range 31–66) were studied. Table 1 gives pertinent clinical data. All had relatively constant asthmatic discomforts and fulfilled the inclusion criteria of having pretreatment FEV₁-values that did not differ by more than 20% on the 2 days of experiment. All had earlier taken part in similar studies and were well versed in inhalation and measuring procedures. The reversibility of bronchospasm was $\geq 20\%$ measured as an increase in FEV₁ 15 min after two inhalations of isoprenaline (0.16 mg). Bronchodilator agents, sympathomimetic amines type, were withdrawn 12 h and theophylline derivatives 36 h before the trial began, which took place at the same time on both days and was performed in a strictly standardized way. Patients on inhaled steroids continued this treatment.

The study was a 2-day, single-blind cross-over comparison between KWD 2131 and

Table 1
Clinical data

Patients	Sex	Age	Weight	Cig./day	Diagnosis	Treatment
A.M.	♀	42	46	Exsmoker since 4 years ago	asthma chronic bronchitis	BecR IAR OBR IBR
E.Z.	♂	48	70	5–6	asthma	OBR IBR
H.E.	♂	53	98	12	asthma	OBR IBR
M.B.	♀	57	67	—	asthma	IBR OBR
L.L.	♂	49	93	—	asthma	IBR OBR
A.M.	♀	42	51	—	asthma	OBR IBR
K.J.	♂	31	73	10–15	asthma	BecR IBR OBR
T.N.	♂	66	69	12	asthma chronic bronchitis	OBR IBOD

BecR = Becotide inhalation regularly

IAR = inhaled anticholinergics regularly (Sch 1000)

IBR = inhaled β -stimulants regularly (salbutamol or terbutaline)

IBOD = inhaled β -stimulants on demand

OBR = oral β -stimulants regularly

terbutaline with random allocation of the 2 consecutive days.

Forced expiratory volume in 1 sec (FEV_1) was performed with Bernstein Spirometer. Two measurements were made on each occasion, the highest value being used in the statistical evaluation. Heart rate and blood pressure were studied with continuous ECG recordings and cuff method, respectively. The skeletal muscle tremor was registered with a Grass accelerometer according to a standardized method by Thiringer & Svedmyr (30). Throughout the study, pulse, blood pressure, and tremor were registered immediately before the lung function tests. The patients' basal values in the chosen parameters were recorded after a 60-min rest. Thereafter, 5 ml physiological saline was inhaled via a Bird Nebulizer for 15 min. Measurements were again made 5 and 30 min after this procedure. KWD 2131 and terbutaline were thereafter given in increasing cumulative doses, 0.5, 1.0, 2.0, 4.0, and 12 mg, and 0.05, 0.1, 0.2, 0.4, and

1.2 mg, respectively, with 45 min between the 15 min inhalation procedures. This dose relation was chosen as previous subcutaneous data in healthy volunteers had indicated a potency ratio between the drugs of 1:10 (18). Measurements were performed 5 and 30 min after each inhalation period. The patients were not allowed to swallow and had to rinse their mouths at the end of each inhalation procedure in order to minimize the amount absorbed from the stomach (5, 13, 14, 16). All the changes were calculated from the 30-min post-physiological saline value and expressed as per cent changes from base line. Two statistical methods were used for analysis of the data: Student's t-test and parallel lines regression. Significances reported refer to two-sided alternatives.

RESULTS

All patients showed stable basal FEV_1 -values. The difference in pre-values from day to day

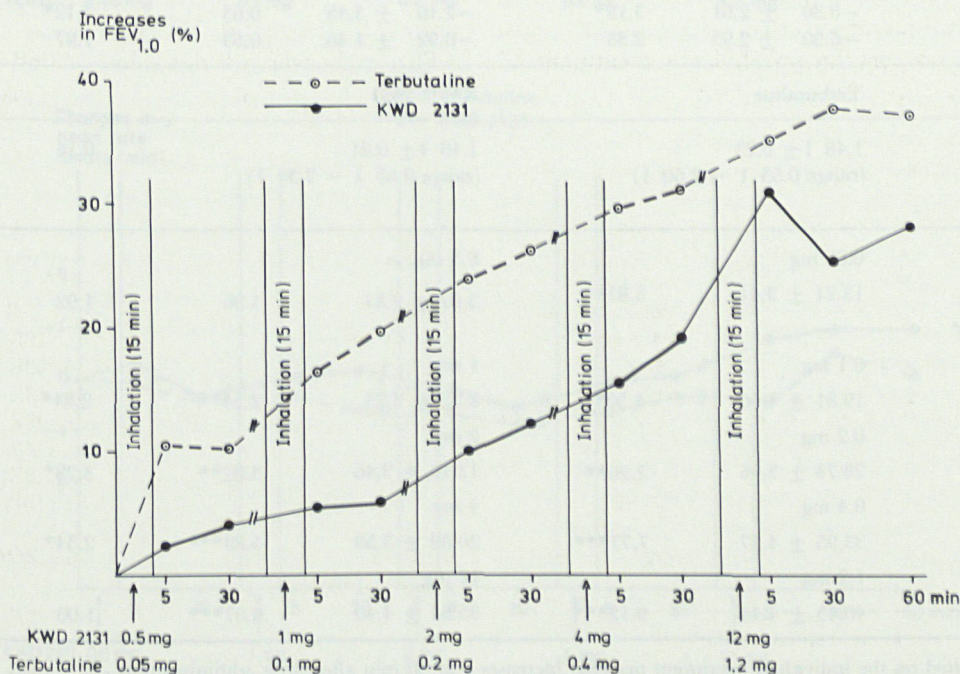


Fig. 2. Mean per cent changes from baseline in eight experiments. Measurements 5 and 30 min after each inhalation procedure.

was $\leq 10\%$ except in one case (17%). A small but statistically significant mean per cent decrease in FEV_1 after saline was seen on the day terbutaline was given 8.3 ± 2.6 (mean $\pm$ s.e.m.; $P < 0.05$). This was not the case on the day KWD 2131 was given 2.2 ± 3.5 (mean $\pm$ s.e.m.; $P > 0.05$) (Table 2). The cardiovascular and tremorogenic response after saline was insignificant and did not differ between days.

Both drugs gave a dose-dependent bronchodilating effect (Fig. 2). This was statistically significant already at the 0.05 mg dose of nebulized terbutaline but not until a cumulative 1.5 mg dose (0.5 + 1.0 mg) of KWD 2131 (Table 2). The mean increase was strongest at the 30-min measurement, except after the

lowest terbutaline dose and the highest KWD 2131 dose. There was a statistically significant difference in the increase of FEV_1 between the two drugs in three of five doses where the relation between terbutaline and KWD 2131 was 1:10 (Table 2). The bronchodilating potency of terbutaline relative to KWD 2131 was estimated for each patient using parallel lines regression of the 30 min response value, measured as increase from baseline, on log dose. For seven patients the relative potency showed a median value of 30. For one patient the relative potency was undetermined as no bronchodilatation was obtained despite earlier found bronchial reversibility of $>20\%$ after isoprenaline.

The influence of the two substances on

Table 2

$FEV_{1,0}$ mean of initial values and mean maximum per cent changes from baseline. Mean $\pm$ s.e.m. ($n = 8$)

	Physiological saline	t_0	Physiological saline	t_0	t_0 diff
Before	1.56 ± 0.21		1.50 ± 0.21		1.67
5 min	-8.30 ± 2.61	3.19*	-2.16 ± 3.45	0.63	3.12*
30 min	-6.90 ± 2.93	2.35	-0.92 ± 1.46	0.63	1.97
	Terbutaline		KWD 2131		
Before (Base- line)	1.48 ± 0.23 (range 0.55 1 – 2.60 1)		1.49 ± 0.21 (range 0.65 1 – 2.50 1)		0.16
Max % changes ^a	0.05 mg 13.21 ± 3.41	3.87**	0.5 mg 5.62 ± 2.87	1.96	1.92
	0.1 mg 19.81 ± 4.40	4.50**	1 mg 8.22 ± 3.23	2.54*	2.84*
	0.2 mg 28.74 ± 3.96	7.26**	2 mg 13.19 ± 3.46	3.82**	3.28*
	0.4 mg 33.95 ± 4.37	7.77***	4 mg 20.89 ± 3.58	5.83***	2.54*
	1.2 mg 40.45 ± 4.44	9.12***	12 mg 35.50 ± 4.40	8.07***	1.00

^aCalculated on the individual maximum per cent increases 5 or 30 min after drug administration

* $P < 0.05$

** $P < 0.01$

*** $P < 0.001$

tremor and the cardiovascular system was minimum and clinically unimportant (Fig. 3). Only the highest dose of terbutaline (1.2 mg) gave a statistically significant, but clinically

insignificant, i.e. < 1.6 (30), increase in tremor ratio. Heart rate was increased by a mean of 4 ± 1.7 beats/min ($P < 0.05$) after 12 mg KWD 2131. Terbutaline gave no significant

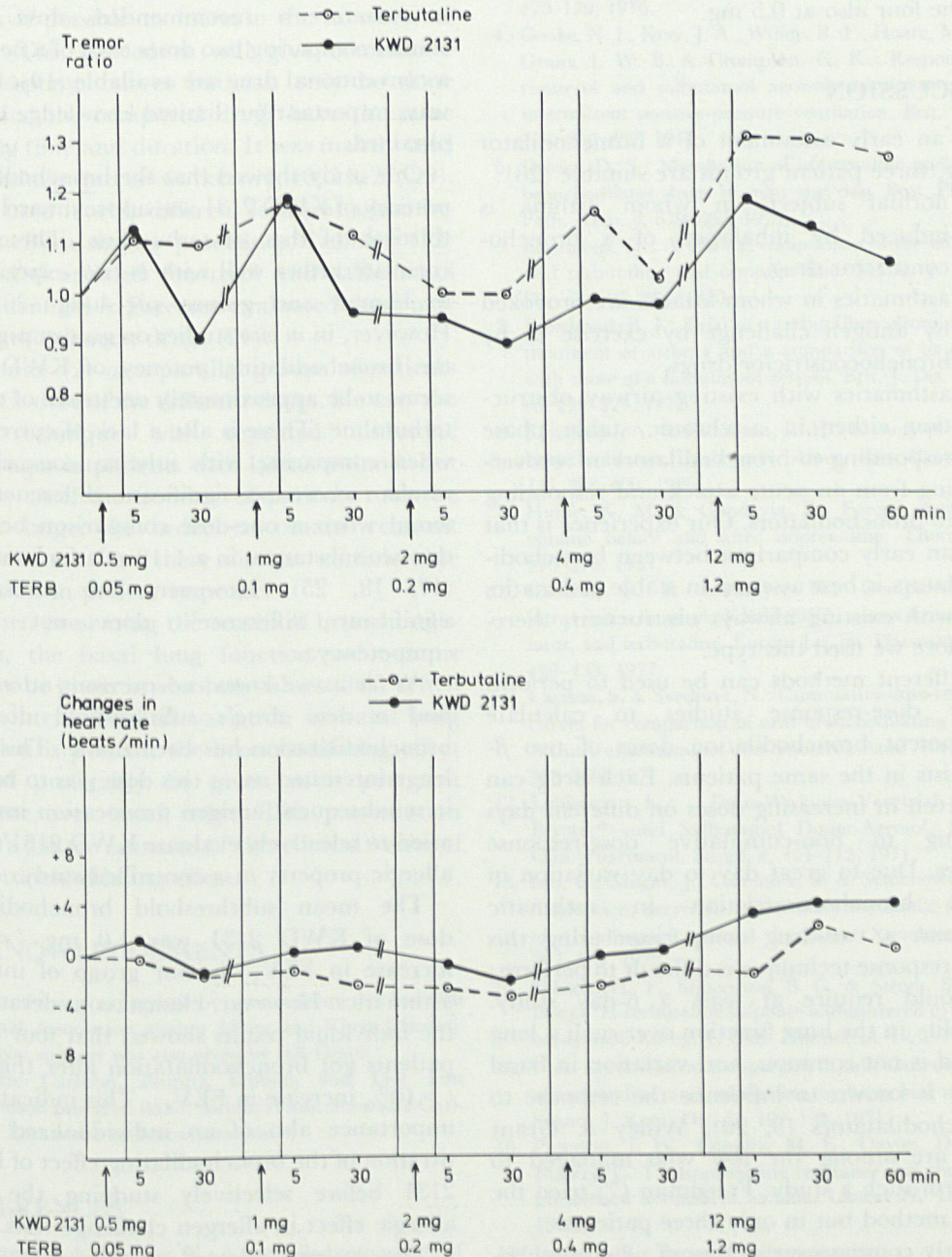


Fig. 3. Tremor ratio and heart rate. Mean changes from baseline in eight experiments. Measurements 5 and 30 min after each inhalation procedure.

increase in heart rate; neither of the drugs significantly changed the blood pressure.

The mean subthreshold bronchodilating dose of KWD 2131 was 1.0 mg. However, four of the eight patients showed bronchodilatation at this dose ($> 10\%$ increase in FEV_1) and two of the four also at 0.5 mg.

DISCUSSION

For an early assessment of a bronchodilator drug, three patient groups are suitable (28):

- normal subjects in whom asthma is induced by inhalation of a bronchoconstrictor drug,
- asthmatics in whom attacks are provoked by antigen challenge by exercise or by bronchoconstrictor drugs,
- asthmatics with existing airway obstruction either in a chronic stable phase responding to bronchodilators or recovering from an acute attack and responding to bronchodilators. Our experience is that an early comparison between bronchodilators is best assessed in stable asthmatics with existing airways obstruction; therefore we used this type.

Different methods can be used to perform early dose-response studies to calculate equipotent bronchodilating doses of two β -agonists in the same patients. Each drug can be given in increasing doses on different days leading to non-cumulative dose-response curves. Due to great day to day variation in basal bronchoconstriction in asthmatic patients, a two-drug comparison using this dose-response technique is difficult to perform; it would require at least a 6-day study. Stability in the lung function over such a long period is not common, and variation in basal value is known to influence the response to bronchodilators (9, 20). Willey & Grant (31) are among the few who managed to perform such a study. Freedman (7) tried the same method but in only three patients.

Early comparative studies of new bronchodilating drugs have often been performed on three consecutive days (3, 4, 6, 8, 15). This

limitation is because the large day-to-day variation of the basal lung function in asthmatic patients makes a longer period of study most difficult. These studies usually compare two doses of the new drug with placebo or the established drug given in the manufacturer's recommended dose. Also studies comparing two doses each of a new and a conventional drug are available (19). In this way, important but limited knowledge will be obtained.

Our study showed that the bronchodilating potency of KWD 2131 was approximately one-thirtieth of that of terbutaline. These data correlate rather well with *in vitro* experiments in human and guinea pig lung (26, 23). However, in *in vivo* studies on guinea pig (24), the bronchodilating potency of KWD 2131 seems to be approximately one-tenth of that of terbutaline. There is also a lack of correlation when comparing with subcutaneous clinical results, where no significant difference was found when a one-dose comparison between the two substances in a 1:10 relation was used (17, 18, 25). However, "no statistically significant difference" does not prove equipotency.

As far as we know, no previous attempt to find a new drug's subthreshold dose for bronchodilatation has been made. This challenge interested us, as this dose was to be used in a subsequent antigen provocation investigation to selectively evaluate KWD 2131's anti-allergic property in a controlled study.

The mean subthreshold bronchodilating dose of KWD 2131 was 1.0 mg ($< 10\%$ increase in FEV_1) in our group of intrinsic asthmatics. However, clinical consideration of the individual results showed that four of the patients got bronchodilatation after this dose ($> 10\%$ increase in FEV_1). This indicates the importance also of an individualized dose-titration of the bronchodilating effect of KWD 2131 before selectively studying the anti-allergic effect in allergen challenge tests.

The patients selected to take part in the subsequent study have relatively normal lung function; therefore histamine challenge pro-

cedure could be used to find the individual subthreshold dose for bronchodilatation. These studies are in progress.

Another approach is to give increasing doses of each drug on 1 day. This method solves the problem with instable lung functions and makes it possible to increase the numbers of doses. This procedure will give cumulative dose-response curves but can only be done provided the compared drugs have the same latency time and duration. It was mainly used by Svedmyr and co-workers (1, 10, 11, 27, 29). They used it with different forms of administration. By a similar procedure, Leblanc (12) compared inhaled fenoterol and salbutamol and Shenfield & Paterson evaluated three new sympathomimetic drugs (21).

Beumer (2) uses parallel groups of patients for each dose of the different drugs. He uses the trial technique with repeated histamine challenges in patients with latent asthma. But in this case, the number of patients must be much larger in order to obtain relevant information, as there is a considerable variation in patient response.

When presenting the results of bronchodilators, the basal lung function value must always be given in absolute values (28). When large interindividual variation in basal lung function is present, the bronchodilating effect should preferably be given as a per cent increase over basal value. This presentation gives a better estimate of the clinical value of the bronchodilating effect.

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REFERENCES

- Bennis, J. & Svedmyr, N.: A controlled comparison of salbutamol and terbutaline inhaled by IPPV in asthmatic patients: A dose-response study. *Scand. J. Resp. Dis. Suppl.* 101, 113-117, 1977.
- Beumer, H. M.: Vergleichende Untersuchungen zur protektiven Wirkung von Alupent® und Th 1165a gegenüber Histamin beim Menschen. *Int. J. Clin. Pharmacol. Suppl.* 4, 75-81, 1971.
- Cockcroft, D. W., Donevan, R. E. & Copland, G. M.: Carbuterol: A double-blind clinical trial comparing carbuterol and salbutamol. *Curr. Ther. Res.* 19, 170-179, 1976.
- Cooke, N. J., Kerr, J. A., Willey, R. F., Hoare, M. V., Grant, I. W. B. & Crompton, G. K.: Response to rimiterol and salbutamol aerosols administered by intermittent positive-pressure ventilation. *Brit. Med. J.* 4, 250-252, 1974.
- Davies, D. S.: Metabolism of isoprenaline and other bronchodilator drugs in man and dog. *Bull. Physio-Path. Resp.* 8, 679-682, 1972.
- Formgren, H.: A clinical comparison of the effect of oral terbutaline and orciprenaline. *Scand. J. Resp. Dis.* 51, 195-202, 1970.
- Freedman, B. J.: Trial of a terbutaline aerosol in the treatment of asthma and a comparison of its effects with those of a salbutamol aerosol. *Brit. J. Dis. Chest* 66, 222-229, 1972.
- Funahashi, A. & Hamilton, L. H.: A study of a new bronchodilator: Carbuterol. *Amer. Rev. Resp. Dis.* 113, 398-400, 1976.
- Hume, K. M. & Gandevia, B.: Forced expiratory volume before and after isoprenaline. *Thorax* 12, 276-278, 1957.
- Larsson, S. & Svedmyr, N.: Comparison of intravenous ibuterol (KWD 2058), a new bronchodilator, and terbutaline. *Europ. J. Clin. Pharmacol.* 11, 429-433, 1977.
- Larsson, S. & Svedmyr, N.: Cumulative dose-response curves for comparison of oral bronchodilating drugs. A study of salbutamol and fenoterol. *Ann. Allergy* 39, 362-366, 1977.
- Leblanc, K.: Dosis-Wirkungs-Vergleich von Berotec®-und Salbutamol Dosier-Aerosol. *Int. J. Clin. Pharmacol. Suppl.* 4, 104-112, 1971.
- Lin, C., Magat, J., Calesnick, B. & Symchowicz, S.: Absorption, excretion and urinary metabolic pattern of ³H-albuterol aerosol in man. *Xenobiotica* 2, 507-575, 1972.
- Nilsson, H. T., Simonsson, B. G. & Ström, B.: The fate of ³H-terbutaline sulphate administered to man as an aerosol. *Europ. J. Clin. Pharmacol.* 10, 1-7, 1976.
- Nou, E.: A clinical comparison of subcutaneous doses of terbutaline and adrenaline in bronchial asthma. *Scand. J. Resp. Dis.* 52, 192-198, 1971.
- Paterson, J. W., Conolly, M. E., Davies, D. S. & Dollery, C. T.: Isoprenaline resistance and the use of pressurised aerosols in asthma. *Lancet* 24, 426-429, 1968.
- Pauwels, R.: Personal communication.
- Pegelow, K.-O. & Strandberg, K.: Abstract. 13th Scandinavian Congress of Allergology 1978. *Allergy* 33, 333, 1978.

19. Riedel-Dibbern, E. & Leblanc, K.: Kontrollierter Vergleich von Berotec®—und Salbutamol Dosier-Aerosol. *Int. J. Clin. Pharmacol. Suppl.* 4, 129–133, 1971.
20. Shenfield, G. M., Hodson, M. E., Clarke, S. W. & Paterson, J. W.: Patterns of response to isoprenaline in asthmatic patients. *Brit. J. Dis. Chest* 69, 273–278, 1975.
21. Shenfield, G. M. & Paterson, J. W.: Clinical assessment of bronchodilator drugs delivered by aerosol. *Thorax* 28, 124–128, 1973.
22. Sörenby, L.: The β -adrenoceptors of the lung mediating inhibition of antigen-induced histamine release. *Europ. J. Pharmacol.* 30, 140–147, 1975.
23. Sörenby, L.: A new β -adrenoceptor stimulant preferably with anti-anaphylactic effect, p. 1–14. University of Uppsala, Sweden, 1977.
24. Sörenby, L.: Personal communication.
25. Stiksa, G.: Personal communication.
26. Strandberg, K., Pegelow, K.-O., Persson, C.-G. & Sörenby, I.: Anti-anaphylactic and bronchodilating action of a beta-adrenoceptor stimulator, KWD 2131, in human lung tissue. *Allergy* 34, 221–224, 1979.
27. Svedmyr, K., Mellstrand, T. & Svedmyr, N.: A comparison between effects of aminophylline, proxiphylline, and terbutaline in asthmatics. *Scand. J. Resp. Dis. Suppl.* 101, 139–146, 1977.
28. Svedmyr, N.: Clinical trials in asthma. *Scand. J. Resp. Dis. Suppl.* 103, 65–68, 1979.
29. Svedmyr, N., Malmberg, R. & Thiringer, G.: The effect of a new adrenergic β_2 -receptor-stimulating agent (Rimiterol, R 798) in patients with chronic obstructive lung disease. *Scand. J. Resp. Dis.* 53, 302–313, 1972.
30. Thiringer, G. & Svedmyr, N.: Evaluation of skeletal muscle tremor due to bronchodilator agents. *Scand. J. Resp. Dis.* 56, 93–102, 1975.
31. Willey, R. F. & Grant, I. W. B.: Effects of oral salbutamol and pirbuterol on FEV₁, heart rate and blood pressure in asthmatics. *Br. J. Clin. Pharmacol.* 3, 595–600, 1976.

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