

The Protective Property of Equipotent Bronchodilating Doses of Inhaled KWD 2131 and Terbutaline against Allergen-Induced Bronchospasm

B. HEGARDT, O. LÖWHAGEN, N. SVEDMYR and G. GRANERUS

Medical Department of AB Draco*, Lund, Dept. of Allergology, Dept. of Medicine I; Dept. of Clinical Pharmacology; Dept. of Clinical Physiology, Sahlgrenska Hospital, University of Gothenburg, Sweden

The anti-allergic capacity of nebulized KWD 2131 in inhibiting allergen-induced bronchospasm was compared with that of terbutaline in equipotent bronchodilating doses. It was a double-blind cross-over and randomized study also including placebo. Twelve symptom-free extrinsic asthmatics participated in the trial. Equipotent bronchodilating doses of the two β -receptor-agonists were established in a histamine challenge procedure before the start of the study. Allergen challenge was performed with double concentration steps every 10 min until a $\geq 20\%$ decrease in FEV_1 was achieved. Significantly ($P < 0.001$) more allergen dose steps could be used after pretreatment with KWD 2131 and terbutaline than with placebo. No difference could be observed between the active compounds. The same allergen log dose gave a 20% decrease in FEV_1 after pretreatment with KWD 2131 and terbutaline. The active compounds' protective properties did not differ at a lower degree of allergen challenge. The plasma histamine level was not significantly changed at any point of allergen challenge after pretreatment with either placebo or the active compounds. Therefore, plasma histamine determination was of no value for evaluating the inhibition of mediator release by these drugs. It is concluded that the anti-allergic property of KWD 2131 at allergen challenge does not give any further clinical value besides the bronchodilating property.

Key words: allergen challenge; anti-allergic agent; asthma; β -receptor agonist; KWD 2131; plasma histamine; terbutaline.

Accepted for publication 29 January 1982

β -adrenoceptor stimulants have for decades been used as bronchodilators for the treatment of reversible obstructive lung diseases. These compounds also exhibit inhibition of mediator release (anti-allergic property) in a variety of sensitized *in vitro* preparations (1, 2, 17, 31).

Booij-Noord et al. (4) showed as early as 1972 that a β -agonist, fenoterol, given intramuscularly and by aerosol before antigen inhalation, inhibited the immediate bronchoconstriction. However, as bronchodilating and

anti-allergic properties of commonly used β -agonists are seen at the same concentration range (31) it is impossible to interpret whether or not an anti-allergic effect was apparent besides the bronchodilating capacity of the drug.

Sörenby showed 1977 (32) that a new β -receptor agonist, KWD 2131, which is structurally related to terbutaline, demonstrated a difference in relation between the effect on anaphylactic histamine release and the effect on the bronchial smooth muscle of guinea pig. In *in*

* Subsidiary of AB Astra, Sweden.

in vivo and *in vitro* animal studies, KWD 2131 was a 10–25 times weaker bronchodilator than terbutaline, whereas the anti-allergic property was almost equal (32, 33). Equipotency of the anti-allergic action of the two compounds was also obtained *in vivo* in the human nose (30) and skin (14).

A stepwise procedure was performed in order to clinically evaluate the anti-allergic capacity of nebulized KWD 2131 (10–13). Initially, the protective property of nebulized KWD 2131 against allergen-induced asthma was studied in individually found highest non-bronchodilating doses (0.25 mg and 0.5 mg) (12). The protection was not significantly better than that of placebo. Thereafter, an increased nebulized weak bronchodilating dose of KWD 2131 (5 mg) was compared with terbutaline in the same dose against immediate and late allergen response (13). 5 mg in nebulized solution is a normally recommended dose of terbutaline in the treatment of bronchospasm. No significant protection was seen with KWD 2131. With terbutaline an almost complete protection against immediate reaction was obtained.

The present study: 1) verified whether the 1:30 relation in bronchodilating potency of the two β -receptor agonists was the same in extrinsic asthmatics as had earlier been found in intrinsic asthmatics (10), and 2) evaluated whether a high dose of nebulized KWD 2131 (15 mg) could show a clinically better anti-allergic property than terbutaline (0.5 mg); both are equipotent bronchodilating doses. Histamine having proved to be released at allergen provocation (3, 19) was measured in plasma.

PATIENTS AND METHODS

Experimental design

Part 1. In a histamine challenge procedure KWD 2131 and terbutaline, in presumably equipotent bronchodilating doses, were compared in a single-blind, cross-over manner.

Part 2. The protection capacity of the found equipotent doses were thereafter studied in an allergen challenge trial. This study was a 3-day, double-blind, cross-over comparison with random allocation of KWD 2131, terbutaline, and placebo. The individual doses of histamine and the appropriate allergens which produced a $> 20\%$ decrease in FEV_1 had been determined by titration before the start of the trial.

The trial was approved by the Ethical Committee of the University of Gothenburg. Informed consent was obtained from all patients.

Patients

Thirteen patients with extrinsic bronchial asthma, seven female and six male, mean age 28 years (range 20–39), were selected for the study. Four were histamine challenged of whom three later participated in the subsequent allergen provocation trial which included 12 patients (Table 1).

The diagnosis was based on history of allergy, positive skin test, RAST, and bronchial provocation test. Table 1 gives pertinent, clinical data. All patients were familiar with the inhalation and measuring procedures; most of them had earlier participated in similar studies. All were known not to react to physiological saline inhalation. At the time of the study there were no signs of respiratory infection, and for at least 24 h none of the patients had been exposed to relevant allergens. They had also avoided exercise during the same period. At the time of the study, all patients were subjectively and objectively free from asthma symptoms. The highest FEV_1 value during the study was within normal predicted values except in one patient (K.F.). The baseline FEV_1 at the start of each study day varied by less than 20% in each patient except one (24%).

Some of the patients occasionally used inhaled β -receptor stimulators. When used, the drugs were withheld for 12 h before the allergen challenge procedure. None of the patients received immunotherapy. Smoking was not allowed 4 h before the study.

Table 1
Clinical data

Pat.	Age	Sex	Diagnosis	Allergen conc. (weight volume) producing $\geq 20\%$ decrease in FEV ₁	Prick test	RAST	Basal FEV ₁ value during the study Range	*Predicted value
US ^H	34	♀	ex. asthma	guinea-pig 1:2,000	++++	—	2.64–3.25	3.33
ER ^H	31	♀	"	cat 1:400	+++	3	2.10–2.40	3.11
LN ^H	33	♂	"	cat 1:2,000	+++	4	3.38–3.67	4.47
KF	21	♀	"	horse 1:128,000	++++	2	1.86–2.45	3.36
MW	24	♀	"	horse 1:1,000	+++(+)	—	3.86–4.10	3.62
MH	27	♀	"	horse 1:256,000	++++	4	2.56–2.72	3.48
MP	39	♀	"	cat 1:4,000	+++	3	2.97–3.21	3.16
S-AJ	27	♂	"	horse 1:16,000	++	1	3.13–3.64	4.65
GL	21	♂	"	horse 1:32,000	+++	1	4.56–4.79	4.83
LJ	23	♂	"	cat 1:1,000	+++	2	3.29–3.68	4.50
JB	38	♂	"	rabbit 1:125	++	2	4.54–5.17	4.29
KFo	20	♀	"	birch 1:2,000	++++	3	3.78–4.49	3.87
PE ^H	31	♂	"	cat 1:100	+++	3	4.29–4.69	4.60

* Normal range of predicted FEV₁ value (2 SD = ♀ 0.8 l; ♂ 1.1 l) Berglund et al., Acta Med Scand. 1963.

H = Patients participating in Part 1 – histamine provocation procedure.

Experimental details

The experiment started at the same time each trial day in the individual patients, as circadian rhythm of the bronchial hyper-reactivity to both non-specific and specific agents has been shown (8, 34).

Part 1. Histamine provocation

A slight modification of the earlier employed histamine challenge model (11) was made. The challenge procedure (21) was performed twice a day with 90-min intervals. Histamine chloride was administered during 2 min tidal breathing through the mouth in two-fold increased concentrations with 5-min intervals up to the point where FEV₁ had fallen to $>20\%$ from the pre-challenge value. The lung function measurements were made 0.5, 1.5, 3, and 5 min after each challenge. Ninety minutes later, when FEV₁ was back to baseline, the patients were pretreated with either 0.5 mg terbutaline or 10 and 15 mg KWD 2131 by 10 min nebulization. These doses of KWD 2131 were chosen in order to find the bronchodilating equipotent dose to 0.5 mg terbutaline. Ten minutes later,

the histamine challenge was repeated and stopped when a decrease of $>20\%$ in FEV₁ was obtained.

Part 2. Allergen provocation

The allergen provocations were carried out as a dose-response modification of the method described earlier by Löwhagen & Lindholm (20). The same individual batch of allergen was used throughout the study.

After measurement of the basal lung function, the patients inhaled placebo, KWD 2131 (15 mg), or terbutaline (0.5 mg) for 10 min. The lung function measurements were repeated 10 min later and the allergen challenge started. The first individual allergen dose used was usually two steps below the earlier titrated dose estimated to produce a $>20\%$ decrease in FEV₁ with placebo pretreatment.

The appropriate allergen was inhaled through the mouth during 2 min quiet tidal breathing in a cumulative manner, doubling the concentrations, with 10-min intervals, until a $\geq 20\%$ decrease in FEV₁ from the initial value was obtained. Lung function measurements were made immediately and 5 and 10 min after

each inhalation step. At $> 20\%$ fall in FEV_1 the measurements were continued up to 30 min. If at that point the FEV_1 did not show a tendency to normalize, the patients were given inhalation of a β_2 -stimulating agent. The allergen challenges were performed with a mean of 16-day intervals (range 3–45 days).

Measurements and equipment

Lung function. Monaghan M 403 Spirometer (Monaghan Co., Denver, USA) with attached recorder and calibrated against the Bernstein Spirometer was used to measure lung function: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and maximum expiratory flow at 50% of vital capacity ($MEF_{50\%}$). The highest value of two was used in the statistical evaluation. The percentage fall in the different lung parameters was calculated from the values immediately before the challenges after drug pre-treatment.

Histamine, allergen, saline (placebo), and the two drugs were nebulized with the same Pari Inhalierboy nebulizer (Paul Ritzau Pari-Werk GmbH and Co., Starnberg, Germany: airflow 15 l/min, particle size 0.5–5.5 μ , and nebulizer output 0.75 ml/min of continuous nebulization). The nebulizer output was checked each test day.

Plasma histamine. Plasma histamine was measured by a modified enzymatic double isotope technique (5). The method incorporates thin layer chromatography and high specific activity ^3H -SAM to increase specificity and sensitivity. All samples were run in duplicate with an intra-assay coefficient of variation of 7%. Blood was drawn from an indwelling venous catheter before drug administration and 5 min after each step of allergen challenge. Ten-minute samples were also taken after the last challenge. The samples were drawn into EDTA or heparin and immediately centrifuged at $+4^\circ C$ and 1000 g for 15 min. All plasma samples were kept frozen at $-20^\circ C$ until analysed.

Statistics

Statistical analysis was made with Wilcoxon's signed rank sum test and Student's t-test for paired samples. The former test was used to compare the number of concentration steps of the allergen challenges needed before a $> 20\%$ decrease in FEV_1 , FVC, and PEF (40% in $MEF_{50\%}$) was obtained, pre-treating with placebo, KWD 2131, and terbutaline. Student's t-test comparison was made on the calculated allergen log doses needed to obtain exactly 20% decrease in the different lung parameters (40% in $MEF_{50\%}$) after active drug pre-treatment. These doses were obtained by linear interpolation from the 10-min lung parameter values of the two last-used allergen challenge doses (Fig. 2b).

Finally, Student's t-test was also used when drug comparison was made on the FEV_1 values obtained 10 min after challenge at the allergen dose which with placebo pre-treatment gave $\geq 20\%$ decrease in FEV_1 (Fig. 2a).

RESULTS

All results are presented only as changes in FEV_1 , as FVC, PEF, and $MEF_{50\%}$ did not provide any further substantial information.

Part 1. Histamine challenge

Three patients were accounted for in the histamine challenge procedure. The fourth was disregarded because of febrile reaction to histamine. Pretreatment with 15 mg KWD 2131 and 0.5 mg terbutaline (1:30 relation) required in all patients the same provocation concentration of histamine for a $> 20\%$ decrease in FEV_1 . KWD 2131 10 mg gave less protection than both terbutaline 0.5 mg and KWD 2131 15 mg in two out of three patients. Fig. 1 illustrates the changes in FEV_1 after histamine challenges on the 3 test days in one representative patient (P.E.).

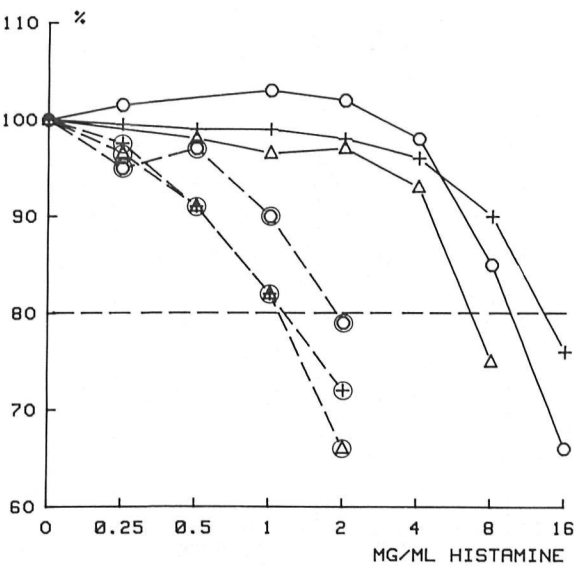


Fig. 1. Histamine challenge with saline and drug pretreatment at 3 different days in one representative patient (P.E.).

- ⊕—⊕ Pretreatment with saline day 1.
- △—△ Pretreatment with saline day 2.
- ⊙—⊙ Pretreatment with saline day 3.
- +—+ Pretreatment with 0.5 mg terbutaline 90 min after pretreatment with saline day 1.
- △—△ Pretreatment with 10 mg KWD 2131 90 min after pretreatment with saline day 2.
- Pretreatment with 15 mg KWD 2131 90 min after pretreatment with saline day 3.

Part 2. Allergen challenge

There was no significant difference between the mean initial FEV₁ values on the allergen provocation test days. Pretreatment with KWD 2131, terbutaline, and placebo did not produce any significant per cent change in FEV₁ (Table 2).

Fig. 2 illustrates the changes in FEV₁ after allergen challenge on the 3 test days in one representative patient (G.L.). Compared with placebo, pretreatment with KWD 2131 and

terbutaline lead to a similar shift of the dose-response curve to the right.

After the two active compounds, the same mean of 3.8 dose steps of allergen compared to 2.2 with placebo could be given before a fall of $\geq 20\%$ in FEV₁ was reached. After KWD 2131, this shift was seen in all patients and after terbutaline in 11 patients. The difference between active and placebo treatment is highly statistically significant ($P < 0.001$). Fig. 3 illustrates equipotent protective action of the two compounds.

Table 2
Mean initial FEV₁ values and percent changes 10 min after drug pretreatment

Pretreatment	Mean ($\pm$ SEM) initial FEV ₁ value	Mean ($\pm$ SEM) % change in FEV ₁	
Placebo	3.37 $\pm$ 0.26	-1.2 $\pm$ 1.65 (NS)	NS
KWD 2131	3.42 $\pm$ 0.26	+3.2 $\pm$ 1.56 (NS)	
Terbutaline	3.43 $\pm$ 0.30	+2.9 $\pm$ 1.37 (NS)	

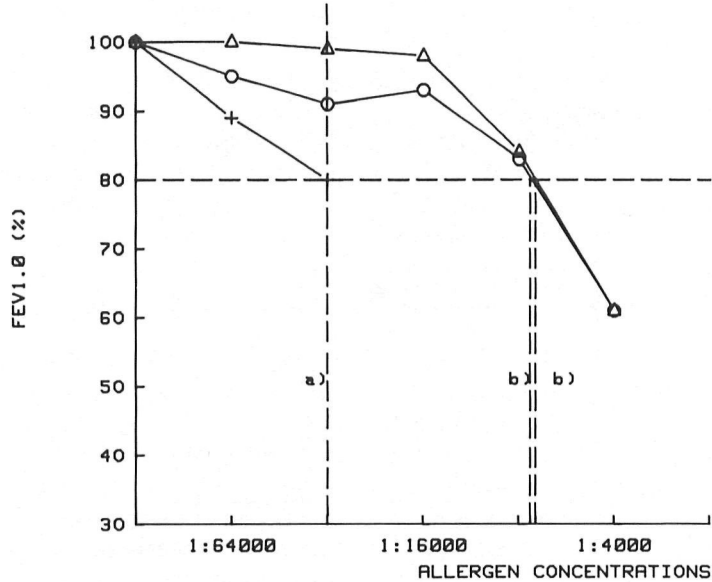


Fig. 2. FEV₁ in per cent of baseline after pretreatment with placebo (+—+), 0.5 mg terbutaline (Δ—Δ), and 15 mg KWD 2131 (O—O) at allergen provocation in one representative patient (G.L.).

- a) The allergen concentration leading to $\geq 20\%$ decrease in FEV₁ after placebo pretreatment and no significant difference in protection between KWD 2131 and terbutaline at this allergen concentration.
- b) The calculated allergen log-dose producing a 20% decrease in FEV₁ after pretreatment with KWD 2131 and terbutaline. In this case, it was -3.86 (absolute conc. 1:7258) and -3.89 (absolute conc. 1:7797), respectively.

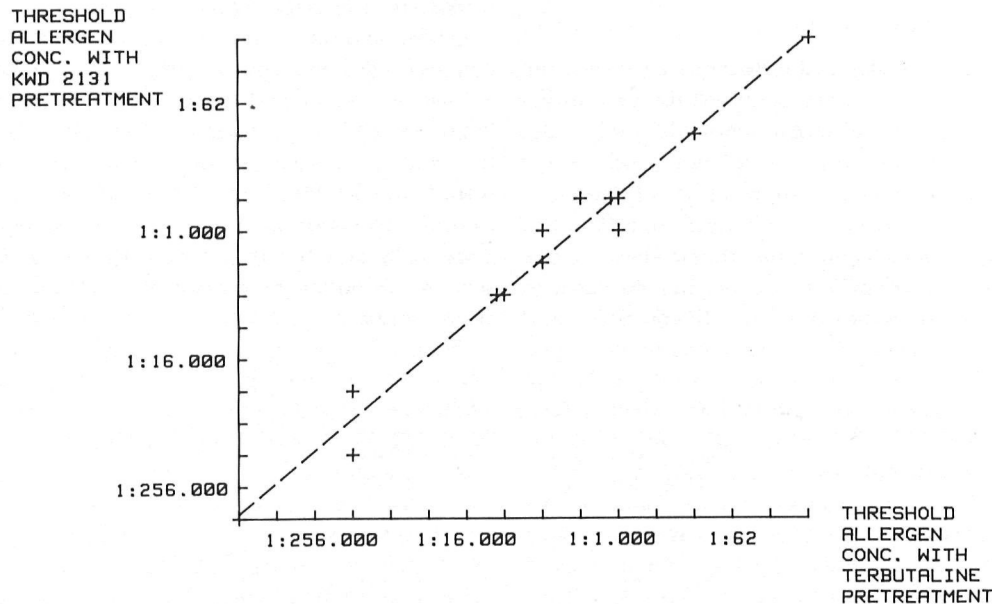


Fig. 3. Individual threshold allergen concentration leading to $\geq 20\%$ decrease in FEV₁ pretreating with equipotent bronchodilating doses of KWD 2131 and terbutaline. Dashed line is the line of identity.

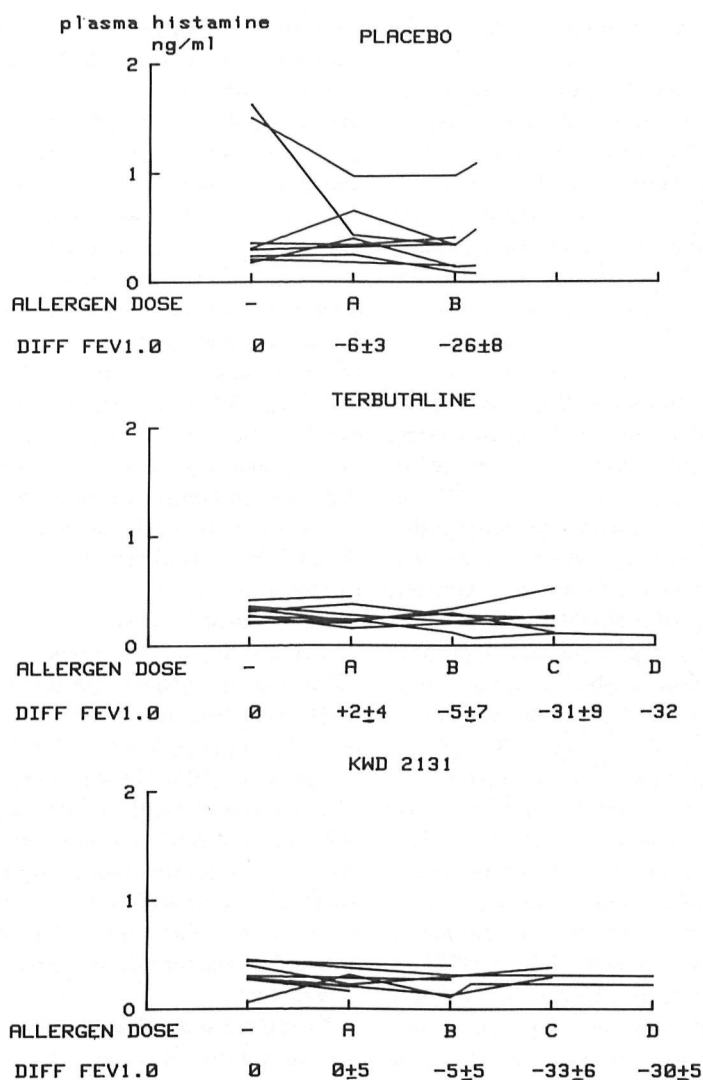


Fig. 4. Plasma histamine in peripheral venous blood in eight asthmatic patients before and after challenge with increasing doses of allergen. The patients were pretreated with placebo, terbutaline 0.5 mg and KWD 2131 15 mg. Blood was drawn 5 min after each step of allergen challenge.

Allergen dose A = $1/4-1/2$ of dose B.

" " B = The dose giving significant decrease in FEV_1 ($\geq 20\%$) after pretreatment with placebo.

" " C = Dose B $\times 2$.

" " D = Dose B $\times 4$.

The reduction in FEV_1 in per cent (mean $\pm$ SD) compared to prechallenge value is given under each allergen dose.

The calculated mean allergen log-dose producing a decrease of 20% in FEV_1 pretreating with KWD 2131 and terbutaline was -3.20 ± 1.10 (mean $\pm$ SD) (absolute conc. 1:1584) and -3.24 ± 1.08 (mean $\pm$ SD) (absolute conc. 1:1737) respectively. The difference is non-

significant. Not even at an allergen challenge dose which gave $\geq 20\%$ decrease in FEV_1 after pretreatment with placebo was there any significant difference in protection between the two active compounds.

The result is illustrated in one representative patient in Fig. 2.

Plasma histamine was measured in eight patients. The mean $\pm$ SD pre-challenge histamine level was 0.30 ± 0.10 ng/ml ($n = 23$). After allergen challenge there was no significant change irrespective of pretreatment with either placebo or active compounds at any point of measurement (Fig. 4).

DISCUSSION

This study shows that KWD 2131 and terbutaline in nebulized equipotent bronchodilating doses give similar protection against bronchial allergen challenge.

The clinical evaluation uses a stepwise procedure. In an earlier study in *intrinsic* asthmatics (10), KWD 2131 proved to be an approximately 30 times less potent bronchodilator than terbutaline. However, as the patients with symptom-free extrinsic asthma with less pathological changes such as mucus stagnation and oedema are more sensitive to KWD 2131 (11) than the *intrinsic* asthmatics (10), it was necessary to check in a few patients whether the same was the case with terbutaline; thus the 1:30 bronchodilating ratio was still valid. As pretreatment with 0.5 mg terbutaline and 15 mg KWD 2131 in the three patients led to the same histamine concentration being required for a $\geq 20\%$ decrease in FEV₁ and earlier human *in vitro* (28) and *in vivo* studies (10) had shown the same bronchodilating ratio between the two compounds, these bronchodilating doses were considered equipotent.

The present study included two repeated histamine challenge procedures with only 90 min intervals. This way, histamine challenge with and without drug pretreatment could be performed in one single day. The reproducibility of this test system proved satisfactory with a coefficient of variation of 23% (21). Also Ruffin et al. (27) found a good reproducibility at repetitive histamine challenge procedures with 30, 40, 60, or 120 min intervals within 1 day.

A study of the protection capacity of drugs against bronchial allergen challenge can use different procedures. The most common one is to

use only one allergen challenge dose, which in intensity produces a $\geq 20\%$ decrease in FEV₁, and to see the inhibition potential by drug pretreatment (4, 18, 23, 24, 25). This model was used in earlier KWD 2131 and terbutaline studies evaluating the inhibitory effect of the two compounds on allergen-induced bronchospasm (12, 13). Another method is to use dose-response procedures. Few investigators have used this model in drug evaluations (16, 22, 29). In the present study this type of provocation was considered necessary, as the bronchodilating doses of the drugs were expected to give complete protection (ceiling effect) in a one-dose challenge procedure.

A dose-response procedure will also be more informative and make possible a comparison of the two drugs at different intensities of allergen provocation.

Our statistical analysis has considered three points on the dose-response curve. First: the 10-min value after pretreatment with KWD 2131 and terbutaline at the allergen dose, which after pretreatment with placebo gave $\geq 20\%$ decrease in FEV₁ (Fig. 2a). The other two points were chosen where the main reactions took place (Fig. 2b). As we do not have enough support to construct a mathematical model curve to include all points, and as there is little information to be gained where small changes take place on the curve, we considered the choice statistically satisfactory.

In the present study, KWD 2131 showed for the first time in a series of studies (12, 13) protection against allergen challenge. This effect seems to be due to the bronchodilating capacity of the drug rather than the anti-allergic activity. This conclusion was drawn as KWD 2131 did not show a better protection than terbutaline in an equipotent bronchodilating dose.

Kaliner concluded from partly old and partly new data in 1980 (15) that skin, lung and nasal mast cells uniformly respond. The reason for the lack of a plus effect of KWD 2131 besides the bronchodilating capacity, however, could be that the human lung mast cells do differ from mast cells in other human tissues such as nose and skin where a selective anti-allergic

property of KWD 2131 has been found (14, 30). Indication that this could be the case is given by investigators such as Pearce et al. (26) and Greaves et al. (9). Another reason for the lack of a plus effect of KWD 2131 could be that the human lung mast cells differ from other species such as guinea pig (32, 33); thus the found selective anti-allergic property in this species is not relevant in *homo*. Species difference has recently been shown between isolated human lung mast cells and rat peritoneal mast cells (7). However, the *in vitro* human lung data (28) does not favour lack of anti-allergic selectivity of KWD 2131 even if it is less so than in guinea pig lung (32, 33). Therefore, the present data and earlier obtained data (12, 13) suggest that the anti-allergic property of KWD 2131 and probably also of other β -stimulators is of limited clinical value at an acute bronchial allergen challenge.

An increase of histamine in plasma and of histamine and methylhistamine in urine after allergen challenge procedures have been shown by both Bhat (3) and Löwhagen et al. (19). These investigators also found a correlation between the mediator increase and the FEV₁ decrease. Pretreatment with DSCG and ICI 74.917 at one-dose allergen challenge protected against FEV₁ decrease and resulted in a smaller increase of histamine excretion (19). In the present study, plasma histamine seemed to be a poor index of mast cell degranulation *in vivo* and could not be used to further evaluate the drugs investigated. However, the lack of plasma histamine increase does not necessarily infer that histamine was not released in the lung during an asthmatic attack. Most of the histamine liberated might very well be metabolized in the lung tissue before reaching the blood stream. Possibly the challenge procedure, consisting of several repeated provocations with increasing allergen doses, functionally meant such a slow release to the blood that no rise in plasma histamine occurred. Recently it has been demonstrated in sensitized dogs that the same allergen dose given repeatedly within short intervals produced none or much smaller increase in plasma histamine concentration than the first provocation; yet the bronchial reaction

was not diminished (35). These results suggest an impaired diffusion of histamine or exaggerated histamine degradation in repeated allergen challenges.

The results obtained throw doubts upon the relevance of the different *in vitro* and *in vivo* test systems which assess mast cell histamine release in the search for anti-allergic drugs in the treatment of asthma. In this respect, our results agree with those obtained with the sodium cromoglycate analogues (6).

In this study only the acute phenomena concerning the clinical efficacy of KWD 2131 and terbutaline have been considered. Long-term treatment might have offered a better result. Studies to evaluate the long-term value of terbutaline in comparison with DSCG in extrinsic asthmatics are in progress.

ACKNOWLEDGEMENTS

The study was supported by grants from the Medical Faculty of the University of Gothenburg and the Swedish National Association against Heart and Chest Diseases. AB Draco also provided financial support. We thank Mrs Barbro Balder for skilful technical assistance and Carl-Johan Lamm for statistical analyses.

REFERENCES

1. Assem, E. S. K. & Schild, H. O.: Inhibition by sympathomimetic amines of histamine release induced by antigen in passively sensitized human lung. *Nature* 224, 1028–1029, 1969.
2. Assem, E. S. K. & Schild, H. O.: Inhibition of the anaphylactic mechanism by sympathomimetic amines. *Int. Arch. Allergy* 40, 576–589, 1971.
3. Bhat, K. N., Arroyave, C. M., Marney, S. R., Stevenson, D. D. & Tan, E. M.: Plasma histamine changes during provoked bronchospasm in asthmatic patients. *J. Allergy Clin. Immunol.* 58, 647–656, 1976.
4. Boij-Noord, H., Quanjer, Ph. H. & de Vries, K.: Protektive Wirkung von Berotec® bei Provokationstesten mit spezifischer Allergeninhalation und Histamin. *Int. J. Clin. Pharmacol., Suppl.* 4, 69–72, 1972.
5. Brown, M. J., Ind, P. W., Causon R & Lee, T. H.: A novel double-isotope technique for the enzymatic assay of plasma histamine: Application to estimation of mast cell activation assessed by antigen challenge in asthmatics. *J. Allergy Clin. Immunol.* 69, 20–24, 1982.
6. Church, M. K. & Gradidge, C. F.: The activity of sodium cromoglycate analogues in human lung *in vitro*: a comparison with rat passive cutaneous anaphylaxis and clinical efficacy. *Br. J. Pharmacol.* 70, 307–311, 1980.
7. Ennis, M.: Histamine release from human pulmonary mast cells. *Agents Actions* 12, 60–63, 1982.

8. Gervais, P., Reinberg, A., Gervais, C., Smolensky, M. & de France, O.: Twenty-four-hour rhythm in the bronchial hyperreactivity to house dust in asthmatics. *J. Allergy Clin. Immunol.* 59, 207–213, 1977.
9. Greaves, M. W., Yamamoto, S. & Fairley, M.: IgE-mediated hypersensitivity in human skin studied using a new in vitro method. *Immunology* 23, 239–248, 1972.
10. Hegardt, B., Löwhagen, O. & Svedmyr, N.: New β -agonist, KWD 2131, compared with terbutaline in asthmatics. A cumulative dose-response study. *Allergy* 35, 105–112, 1980.
11. Hegardt, B., Löwhagen, O. & Svedmyr, N.: Histamine-induced bronchospasm. Its reproducibility and usage in clinical evaluation of the subthreshold bronchodilating dose of a new β -agonist, KWD 2131. *Allergy* 35, 113–121, 1980.
12. Hegardt, B., Löwhagen, O. & Svedmyr, N.: Evaluation of the protective effect of a new β -agonist, KWD 2131, on allergen-induced bronchospasm. *Allergy* 35, 413–419, 1980.
13. Hegardt, B., Pauwels, R. & Van Der Straeten, M.: Inhibitory effect of KWD 2131, terbutaline, and DSCG on the immediate and late allergen-induced bronchoconstriction. *Allergy* 36, 115–122, 1981.
14. Hegardt, B. & Arner, B.: Evaluation of the inhibition of allergen-induced intracutaneous reactions by a new β -agonist, KWD 2131, and by terbutaline. *Eur. J. Respir. Dis.* 62, 352–359, 1981.
15. Kaliner, M. A.: Is a mast cell a mast a mast cell? *J. Allergy Clin. Immunol.* 66, 1–4, 1980.
16. Katcher, M. L. & Reed, C. E.: Prevention of antigen-induced bronchoconstriction by lodoxamide ethyl, a new orally active anti-allergic drug. *J. Allergy Clin. Immunol.* 66, 223–226, 1980.
17. Lichtenstein, L. M. & Margolis, S.: Histamine release in vitro: Inhibition by catecholamines and methylxanthines. *Science* 161, 902–903, 1968.
18. Löwhagen, O. & Lindholm, N. B.: Clinical evaluation of some anti-allergic drugs by use of the allergen challenge test. In Pepys, J. & Edwards, A. M. (eds.): *The mast cell – its role in health and disease*, pp. 332–336. Pitman Medical Publishing Co. Ltd., 1979.
19. Löwhagen, O., Granerus, G. & Wetterqvist, H.: Studies on histamine metabolism in allergen-induced asthma. *Allergy* 35, 521–529, 1980.
20. Löwhagen, O. & Lindholm, N. B.: Standardized allergen provocation test. Variation in bronchial response. *Allergy* 35, 349–356, 1980.
21. Löwhagen, O. & Lindholm, N.: Standardized histamine provocation – short-term and long-term variation in bronchial response. *Europ. J. Respir. Dis.* (In press).
22. Martin, G. L., Atkins, P. C., Dunskey, E. H. & Zweiman, B.: Effects of theophylline, terbutaline, and prednisone on antigen-induced bronchospasm and mediator release. *J. Allergy Clin. Immunol.* 66, 204–212, 1980.
23. Pauwels, R., Lamont, H. & Van Der Straeten, M.: The effect of oral doxantrazole on allergen-induced bronchospasm. *Acta Allergol.* 31, 239–244, 1976.
24. Pauwels, R., Lamont, H. & Van Der Straeten, M.: The inhibition of allergen-induced bronchospasm in man by oral BRL 10833. *Clin. Allergy* 6, 471–478, 1976.
25. Pauwels, R. & Van Der Straeten, M.: Drugs that modify mast-cell function: Their mode of action. In Pepys, J. & Edwards, A. M. (eds.): *The mast cell – its role in health and disease*, pp. 61–68. Pitman Medical Publishing Co. Ltd., 1979.
26. Pearce, C. A., Greaves, M. W., Plummer, V. M. & Yamamoto, S.: Effect of disodium cromoglycate on antigen-evoked histamine release from human skin. *Clin. Exp. Immunol.* 17, 437–440, 1974.
27. Ruffin, E. W., Alpers, J. H., Crockett, A. J. & Hamilton, R.: Repeated histamine inhalation tests in asthmatic patients. *J. Allergy Clin. Immunol.* 67, 285–289, 1981.
28. Strandberg, K., Pegelow, K.-O., Persson, C. G. A. & Sörenby, L.: Anti-anaphylactic and bronchodilating action of a β -adrenoceptor stimulator, KWD 2131, in human lung tissue. *Allergy* 34, 221–224, 1979.
29. Street, J. O., Rosenthal, R. R., Norman, P. S. & Hood, D. B.: Inhibition of antigen-induced bronchospasm by fenoterol. *J. Allergy Clin. Immunol.* 65, 172–173, (abstract), 1980.
30. Svensson, G.: Effects of topical use of β -adrenoceptor stimulants on nasal mucosa. Rhinomanometric evaluations in experiments with terbutaline and KWD 2131. II. Nasal provocation tests with hay fever patients in asymptomatic period. *Acta Otolaryngol.* 90, 130–138, 1980.
31. Sörenby, L.: The β -adrenoceptors of the lung mediating inhibition of antigen-induced histamine release. *Eur. J. Pharmacol.* 30, 140–147, 1975.
32. Sörenby, L.: A new β -adrenoceptor stimulant, preferably with anti-anaphylactic effect. Thesis, pp. 1–14. University of Uppsala, Sweden, 1977.
33. Sörenby, L.: Personal communication, 1977.
34. de Vries, K., Goei, J. T., Booij-Noord, H. & Orie, N. G. M.: Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int. Arch. Allergy* 20, 93–101, 1962.
35. Zimmermann, I., Bugatho de Almeida, A. A. & Ulmer, W. T.: Plasma-Histaminkonzentration in Verlauf wiederholter Antigenbelastung des bronchopulmonalen Systems. *Res. Exp. Med. (Berlin)* 177, 101–109, 1980.

Address:

Birgitta Hegardt
Medical Department
AB Draco
Box 1707
S-221 01 Lund
Sweden

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.