

Evaluation of the Bronchodilating and Antiallergic Properties of a Beta-Adrenoceptor Stimulant, KWD 2131, in Asthmatic Patients*

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KWD 2131 (1-(3,5-dihydroxyphenyl)-(1,1-dimethyl-2-hydroxyethyl-amino)ethanol sulphate) is a β -adrenoceptor stimulating compound that has been shown to be equipotent to terbutaline with regard to inhibition of anaphylactic histamine release from guinea pig lung tissue but less potent than terbutaline as a cardioaccelerator in this species. In the present study KWD 2131 was found to be about 5-10 times less potent than terbutaline as a cardioaccelerator, tremorogenic and bronchodilator agent on subcutaneous (s.c.) injection in man. S.c. injection of KWD 2131 in a subthreshold dose for bronchodilatation, i.e. 0.3 mg or 0.6 mg, given prior to a bronchial provocation test with specific allergen had no protective effect on the changes in specific airway conductance and peak expiratory flow in a double-blind cross-over study in 12 patients with allergic asthma.

It is concluded that KWD 2131 probably has a less selective antiallergic activity in man as compared to guinea pig and that the methodology employed for the evaluation is useful for the characterization of antiallergic drugs with bronchodilator properties.

Key words: allergen bronchial challenge tests; asthma; heart rate; KWD 2131; terbutaline; tremor bronchodilatation

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β -Adrenoceptor stimulants inhibit allergen-induced release of histamine from sensitized human lung tissue and sensitized human leucocytes (3, 7). These findings suggest a possible antiallergic action of such drug therapy in clinical work. In allergic asthma this hypothesis is difficult to prove or disprove, since the bronchodilating activity of the compounds interferes with the evaluation of an inhibitory effect on mediator release as measured by bronchial challenge tests.

Compared with terbutaline, KWD 2131 (1-(3,5-dihydroxyphenyl)-2-(1,1-dimethyl-2-

hydroxyethyl)-amino)ethanol sulphate), a recently synthesized β -adrenergic compound, is a considerably less potent relaxant of guinea pig airway smooth muscle whereas the two compounds are equipotent inhibitors of histamine release from guinea pig lung tissue (26). This activity profile of KWD 2131 prompted us to undertake a series of experiments finalized in a double-blind cross-over study of the effect of a subcutaneous injection of KWD 2131, in a subthreshold dose for bronchial relaxation, on the bronchial provocation test with specific allergen in patients with allergic asthma. This report gives the results of these studies and the methodological considerations involved.

*A preliminary report was presented at the XIII Nordic Congress of Allergology, Copenhagen 1978 (24).

MATERIAL AND METHODS

Drugs and allergens

Terbutaline and KWD 2131 were generously supplied by AB Draco, Lund, Sweden. The allergen stock solutions (1 : 10) were manufactured by Vitrum, Stockholm, Sweden. Dilutions were made with Coca's solution (saline-phenol). Freshly made dilutions were always used for the provocation tests and the batches were the same throughout the study.

Experimental design

Cardiovascular and tremorogenic activity. Six healthy volunteers of both sexes, aged 22–29 years, were given 0.25 mg terbutaline and 1.0, 2.5 and 5 mg KWD 2131 s.c. on random allocation (Latin square model) in the morning on 4 consecutive days using a single-blind protocol. The subjects had fasted, and abstained from smoking for at least 12 h prior to the study. The experiments were performed with the test subjects in the supine position and no drug was given prior to a resting period of 70 min. ECG, systemic arterial blood pressure (cuff method), and tremor activity, measured with a Grass single plane accelerometer attached to the third right hand digit and equipped with an integrator to give the cumulative outprint over a selected period of time, were recorded 5 and 10 min before drug injection. After drug administration ECG was continuously recorded for 60 min and then at 5-min intervals, whereas blood pressure and tremor recordings were made every 10 min throughout the experiments. The heart rate was determined from the ECG recordings. The participants were informed about possible side effects such as palpitations, tremor, anxiety, etc. and were requested to report any occurring symptoms.

Threshold dose determinations. In order to establish the threshold dose for the bronchodilating effect of KWD 2131 a study on eight patients with non-allergic perennial asthma was performed. Guided by the results of this

study 0.6 mg and 1.25 mg KWD 2131, 0.125 mg terbutaline and vehicle alone (placebo) were given s.c. at the same time in the morning on 4 consecutive days according to a randomized scheme (Latin square model) in a double-blind cross-over study on 12 hospitalized patients, seven males and five females aged 49–67 years. All the patients had constant asthmatic discomfort with an airway resistance of 4–12 cm/H₂O/l/sec, which decreased more than 50% after the inhalation of 0.25 mg terbutaline. The pretest values for airway resistance were not permitted to differ more than 50% on the different test days.

Long-acting adrenergic drugs and methylxanthines were withheld 12 h before the test. Isoprenaline spray was permitted if acute asthmatic symptoms occurred during the night but no later than 3 h before the test. When used, steroids and expectorants were given in the same doses and at the same time of the day throughout the experimental period. No smoking was allowed 1 h before and during the test.

Measurements of lung function (*vide infra*), heart rate and blood pressure were made 15 and 5 min before and 15, 30, 60 and 120 min after injection.

The threshold dose for bronchodilatation by KWD 2131 in patients with intermittent allergic asthma was determined by studying the influence of the drug on the bronchoconstrictor response to inhaled histamine. In each of five patients (four males and one female) the threshold dose for a histamine-induced asthmatic reaction was determined by inhalation of a series of 2-fold dilutions of a histamine chloride solution (64 mg/ml saline).

Aerosols of the solutions used were inhaled for 30 sec by means of a de Vilbiss nebulizer No. 40 operated by compressed air at a flow rate of 6 l/min. The patients inhaled normal tidal volumes from the nebulizer. After recording the resting values for specific airway conductance (SGaw) and peak expiratory flow (PEF), saline was inhaled and if there was no reduction of SGaw or PEF the challenge began with the lowest concentration of histamine

chloride (0.063 mg/ml). Increasing concentrations of histamine were inhaled until the concentration of histamine producing at least a 50% reduction of SGaw and no less than a 15% reduction of PEF was reached. This concentration of histamine was considered the threshold dose for histamine in the patient studied. The average threshold dose for healthy subjects with this technique is 32 mg/ml (28).

The patients were injected s.c. with KWD 2131 1 h later and after a further 30 min rechallenged with the threshold dose of histamine. If histamine produced no bronchoconstrictor response a lower dose of KWD 2131 was given on the following day and the histamine challenge was repeated, and so on, until no change in histamine sensitivity could be demonstrated. All histamine challenges were made at the same time of the day.

Allergen challenge. Twelve patients, six males and six females aged 19–40 years, with allergic asthma, were studied in bronchial provocation tests with specific allergen. All patients were free of symptoms at the time of the study and on no medication. Prior to the trial with KWD 2131 the lowest allergen dose provoking an asthmatic reaction on inhalation was determined as follows. A series of 10-fold dilutions of stock allergen solutions were prepared. The patients then inhaled an aerosol of 1 ml of the lowest concentration of specific allergen generated by a de Vilbiss nebulizer No. 40, and SGaw and PEF values were recorded at 5 and 15 min after inhalation. Increasing concentrations of allergen were inhaled at 15-min intervals until there was a prompt decrease of SGaw by at least 50% and/or reduction of PEF by no less than 15%. The concentration of allergen giving this response was used in the KWD 2131 trial (*vide infra*). Prior to the allergen challenge all subjects inhaled saline to identify any non-specific reactions. If the PEF value was reduced by more than 10% the patient was not accepted for further study.

In the trial 0.3 mg and 0.6 mg KWD 2131

and vehicle alone (placebo) were given s.c. 30 min prior to allergen challenge following a randomized double-blind cross-over design. There was at least 1 week between the separate challenges and they were all carried out at the same time in the morning. The pretest values for PEF were not permitted to differ more than 15% on the different test days. To check that no change in sensitivity to the allergen used occurred during the trial an additional challenge without pretreatment was finally made.

All patients participating in the various stages of the investigation received full information about the study and gave their consent. The study was approved by the Huddinge Hospital ethical committee.

Lung function tests

Total airway flow resistance (R_t) and thoracic gas volume (V_{tg}) were measured during normal breathing in a whole-body plethysmograph of constant volume type and equipped with electronic compensation for changes in temperature and humidity of the respiratory air during each breathing cycle (Siemens Siregnost FD 91). Specific airways conductance (SGaw) was calculated from the mean of three readings of R_t and V_{tg} .

Peak expiratory flow (PEF) was determined after the measurement of R_t and V_{tg} by means of a Wright peak flow meter. The best of three exhalations was taken as the patient's PEF value.

Statistics

Student's t-test was used for the statistical analyses.

RESULTS

Cardiovascular and tremorogenic activity

As illustrated in Fig. 1, s.c. injection of 1–5 mg KWD 2131 resulted in a dose-related increase in heart rate and tremorogenic activity. 5 mg KWD 2131 caused a slight increase in systolic

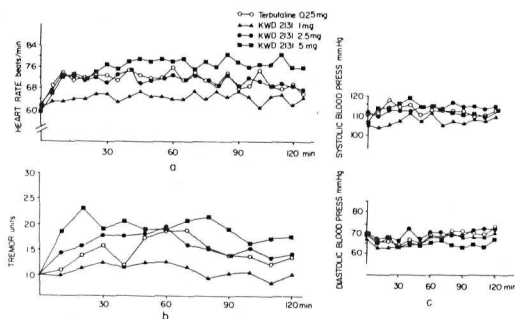


Fig. 1. Mean effects of s.c. administered KWD 2131 and terbutaline on heart rate (a), tremor (pretest value = 1.0) (b), and systemic blood pressure (c) in six volunteers.

blood pressure and a longer lasting weak decrease in diastolic blood pressure, whereas the smaller doses had no effect. For comparison, 0.25 mg terbutaline was also given and the results indicate that this dose is equipotent to 2.5–5 mg KWD for the parameters studied.

Threshold dose for bronchodilating effect

The bronchodilating capacity of a drug can be determined either by studying its effect on patients with stable chronic asthma or by investigating its protective effect against induced asthma. Both methods were used in the present study.

Chronic asthma. The effect of a s.c. injection of 0.6 mg and 1.25 mg KWD 2131, 0.25 mg terbutaline and vehicle alone on total airway flow resistance (R_t), thoracic gas volume (V_{tg}) and peak expiratory flow (PEF) was studied in a double-blind cross-over trial in 12 patients with chronic asthma. Nine patients completed the trial in accordance with the trial design. Three patients were excluded since the differences between their prevalues in airway resistance exceeded 50%. Some patients could not satisfactorily use the Wright peak flow meter and therefore the PEF readings were not considered in the statistical calculations.

As compared with the mean pretest values for airway resistance (R_{aw}), 0.125 mg terbutaline and 1.25 mg KWD 2131 had a clearcut bronchodilating effect which was statistically

significant ($P < 0.01$ and $P < 0.05$ respectively) 15, 30, and for KWD 2131 also, 60 min after administration (Fig. 2). 0.6 mg KWD 2131 and placebo did not produce any significant bronchodilating effect.

There was a statistically significant difference ($P < 0.05$) for the effects of placebo vs 1.25 mg KWD 2131, placebo vs 0.125 mg terbutaline, 1.25 mg KWD 2131 vs 0.6 mg and 0.125 mg terbutaline vs 0.6 mg KWD 2131 15 min after injection.

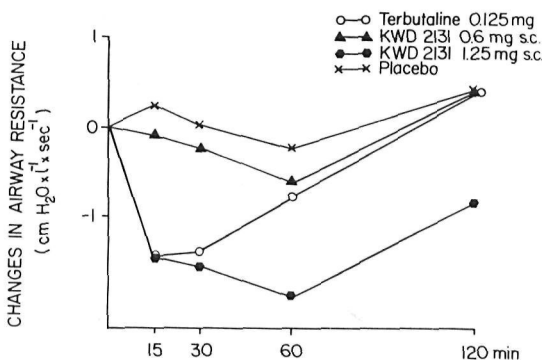


Fig. 2. Mean effects of s.c. administered KWD 2131, terbutaline and vehicle alone on airway resistance in nine patients with chronic asthma.

However, as airway resistance varies with lung volume it is important to relate resistance (or conductance) to simultaneously measured thoracic gas volume (V_{tg}). Thus when specific airway conductance (SG_{aw}) was calculated the bronchodilating effects were not as marked as indicated by R_{aw} data. Notably, the difference between the effect of 1.25 mg and that of 0.6 mg KWD 2131 was not statistically significant (Table 1).

No significant changes in heart rate or systemic blood pressure were recorded during the study period.

Histamine-induced asthma. In five patients with intermittent allergic asthma the threshold dose for bronchodilatation by KWD 2131 was determined by studying the influence of the drug on the bronchoconstrictor response to inhaled histamine. In three patients the

Table 1

Specific airway conductance ($l \cdot \text{cmH}_2\text{O}^{-1} \cdot \text{sec}^{-1}$) in nine patients before and after injection of the test drugs

		Pretest value $\cdot 10^4$	15 min after injection	30 min after injection	60 min after injection	120 min after injection
Placebo	M	216.8	-12.3	+11.2	+2.6	-5.2
	s.e.m.	33.6	11.0	24.5	18.6	27.7
KWD 2131 1.25 mg	M	209.7	+71.6	+85.3*	+126.6	+22.8
	s.e.m.	32.5	31.9	35.9	69.3	18.4
Terbutaline 0.125 mg	M	205.8	+80.8	+84.7	+59.4	+21.6
	s.e.m.	27.8	40.0	40.2	69.2	52.0
KWD 2131 0.6 mg	M	194.9	+39.2	+43.2	+53.3	+19.6
	s.e.m.	22.9	44.1	44.3	43.8	32.0

* $P < 0.05$ compared with the pretest value.

A statistically significant difference ($P < 0.05$) was obtained comparing the effects of placebo vs 1.25 mg KWD 2131, placebo vs 0.125 mg terbutaline and 0.125 mg terbutaline vs 0.6 mg KWD 2131.

histamine threshold was raised after pretreatment with 0.6 mg KWD 2131, while no change in bronchial sensitivity to inhaled histamine was demonstrated after 0.3 mg KWD 2131. Two patients were tested with 0.3 mg KWD 2131 alone and showed no change in histamine threshold value (Table 2). Consequently, patients with intermittent type of asthma seemed to be more sensitive to the bronchodilating effects of KWD 2131 than patients with perennial asthma.

Effect on allergen-induced asthma

In the concluding double-blind cross-over trial of the prophylactic effect of KWD 2131 on bronchial provocation tests with specific allergen in 12 patients with allergic asthma, 0.3 mg and 0.6 mg KWD 2131 and placebo were used for treatment. The KWD 2131 doses selected were based on the results of the threshold dose studies.

As shown in Table 3 pretreatment with

Table 2

Histamine threshold values without and with pretreatment with KWD 2131 in five patients with intermittent asthma

Patient No.	Histamine threshold (mg/ml)*		
	Without KWD	After 0.6 mg KWD	After 0.3 mg KWD
1	0.5	2	0.5
2	8	16	8
3	0.063	0.25	0.063
4	0.063	ND	0.063
5	1	ND	1

*The lowest concentration of 2-fold dilutions of a histamine chloride solution (64 mg/ml) which on inhalation produced a 50% or larger reduction of SGaw and 15% or larger reduction of PEF was regarded as the patient's histamine threshold.

ND: not done.

Table 3
Effect of subcutaneous pretreatment with KWD 2131 on allergen-induced asthma

Patient No.	Inhaled allergen conc. and injected substance	Pretest values		After allergen challenge		Change in % of pretest values	
		SGaw	PEF	SGaw	PEF	SGaw	PEF
1	<i>Horse</i>						
	10 ⁻⁵	0.218	540	0.037	275	-83	-49
	10 ⁻⁵ + placebo	0.222	515	0.017	200	-92	-61
	10 ⁻⁵ + 0.3 mg KWD 2131	0.218	560	0.010	175	-95	-69
	10 ⁻⁵ + 0.6 mg KWD 2131	0.227	500	0.044	370	-81	-26
	10 ⁻⁵	0.161	570	0.014	260	-92	-54
2	<i>Cat</i>						
	10 ⁻³	0.128	440	0.059	410	-54	-7
	10 ⁻³ + placebo	0.155	460	0.072	400	-54	-13
	10 ⁻³ + 0.3 mg KWD 2131	0.155	480	0.155	465	0	-3
	10 ⁻² + 0.3 mg KWD 2131	0.155	480	0.047	330	-70	-31 ^d
	10 ⁻³ + 0.6 mg KWD 2131	0.152	460	0.053	300	-65	-35
	10 ⁻³	0.126	450	0.038	320	-70	-29
3	<i>Cat</i>						
	10 ⁻³	0.197	520	0.042	360	-79	-31
	10 ⁻³ + placebo	0.493	510	0.058	330	-88	-35
	10 ⁻³ + 0.3 mg KWD 2131	0.172	560	0.094	475	-46	-15
	10 ⁻³ + 0.6 mg KWD 2131	0.203	560	0.116	540	-43	-4
	10 ⁻² + 0.6 mg KWD 2131	0.203	560	0.044	325	-78	-42 ^d
	10 ⁻³	0.274	540	0.083	440	-70	-19
4	<i>Cat</i>						
	10 ⁻³	0.476	500	0.077	340	-84	-32
	10 ⁻³ + placebo	0.202	510	0.021	310	-90	-39
	10 ⁻³ + 0.3 mg KWD 2131	0.286	520	0.033	330	-89	-37
	10 ⁻³ + 0.6 mg KWD 2131	0.427	500	0.033	310	-92	-38
	10 ⁻³	0.476	505	0.015	270	-97	-47
5	<i>Dog</i>						
	10 ⁻²	0.167	545	0.049	420	-70	-23
	10 ⁻² + placebo	0.159	530	0.109	510	-31	-4 ^e
	10 ⁻² + 0.3 mg KWD 2131	0.132	510	0.065	460	-51	-10 ^e
	10 ⁻² + 0.6 mg KWD 2131	0.174	530	0.111	525	-36	-1 ^e
	10 ⁻²	0.152	525	0.077	475	-49	-10 ^e
6	<i>Timothy</i>						
	10 ⁻²	0.137	425	0.011	100	-92	-76
	10 ⁻² + placebo	0.110	460	0.010	180	-91	-61
	10 ⁻² + 0.3 mg KWD 2131	0.139	430	0.007	145	-95	-66
	10 ⁻² + 0.6 mg KWD 2131	0.131	445	0.012	145	-91	-67
	10 ⁻³	0.101	425	0.035	380	-66	-11 ^b
7	<i>Birch</i>						
	10 ⁻²	0.081	460	0.026	380	-68	-17
	10 ⁻² + placebo	0.134	505	0.045	400	-67	-21
	10 ⁻² + 0.3 mg KWD 2131	0.128	465	0.039	320	-70	-31
	10 ⁻² + 0.6 mg KWD 2131	0.092	500	0.079	475	-14	-5
	10 ⁻¹ + 0.6 mg KWD 2131	0.092	500	0.022	275	-76	-45 ^d
	10 ⁻²	0.112	485	0.044	415	-61	-15

Table 3—continued

Patient No.	Inhaled allergen conc. and injected substance	Pretest values		After allergen challenge		Change in % of pretest values	
		SGaw	PEF	SGaw	PEF	SGaw	PEF
8	<i>Horse</i>						
	10 ⁻⁶	0.077	700	0.018	500	-77	-29
	10 ⁻⁶ + placebo	0.104	700	0.014	410	-86	-41
	10 ⁻⁶ + 0.3 mg KWD 2131	0.113	725	0.047	640	-58	-12
	10 ⁻⁶ + 0.6 mg KWD 2131	0.170	725	0.042	570	-75	-21
	10 ⁻⁶	0.139	710	0.046	530	-67	-25
9	<i>Dog</i>						
	10 ⁻²	0.070	280	0.020	150	-72	-46
	10 ⁻² + placebo	0.061	295	0.033	230	-46	-22
	10 ⁻² + 0.3 mg KWD 2131	0.064	250	0.019	80	-71	-68
	10 ⁻² + 0.6 mg KWD 2131	0.052	255	0.017	140	-68	-45
	10 ⁻³	0.076	285	0.046	140	-22	-51 ^d
10	<i>Horse</i>						
	10 ⁻⁵	0.094	310	0.032	230	-66	-26
	10 ⁻⁵ + placebo	0.096	360	0.043	270	-55	-25
	10 ⁻⁵ + 0.3 mg KWD 2131	0.155	400	0.104	385	-33	-4 ^c
	10 ⁻⁵ + 0.6 mg KWD 2131	0.073	300	0.009	130	-88	-57
	10 ⁻⁵	0.106	325	0.037	ND	-66	—
11	<i>Dog</i>						
	10 ⁻²	0.122	460	0.057	360	-54	-22
	10 ⁻² + placebo	0.159	510	0.025	319	-84	-39
	10 ⁻² + 0.3 mg KWD 2131	0.122	505	0.017	260	-86	-49
	10 ⁻² + 0.6 mg KWD 2131	0.159	515	0.014	230	-91	-55
	10 ⁻³	0.155	450	0.036	320	-77	-29 ^b
12	<i>Horse</i>						
	10 ⁻⁷	0.195	415	0.033	260	-83	-37
	10 ⁻⁷ + placebo	0.286	425	0.089	360	-69	-15
	10 ⁻⁷ + 0.3 mg KWD 2131	0.440	490	0.493	480	+12	-2
	10 ⁻⁶ + 0.3 mg KWD 2131	0.440	490	0.077	375	-82	-23 ^d
	10 ⁻⁷ + 0.6 mg KWD 2131	0.293	485	0.293	495	0	+2
	10 ⁻⁶ + 0.6 mg KWD 2131	0.293	485	0.154	450	-48	-7 ^d
	10 ⁻⁵ + 0.6 mg KWD 2131	0.293	485	0.053	270	-82	-44 ^d
	10 ⁻⁷	0.183	455	0.088	330	-52	-27

^aNot challenged with allergen concentration 10⁻¹

^bNot challenged with allergen concentration 10⁻²

^cNot challenged with allergen concentration 10⁻⁴

^dIncreased tolerance to allergen

SGaw: Specific airway conductance (1 · cmH₂O⁻¹ · sec⁻¹)

PEF: Peak expiratory flow (l/min)

KWD 2131 had no effect on the mean changes in SGaw and PEF produced by allergen challenge. However, patients No. 3 and 7 tolerated one 10-fold more allergen and No. 12 two 10-folds more allergen after 0.6 mg KWD 2131 than after placebo and the lower dose of KWD 2131. On the other hand, patient No. 2

tolerated one 10-fold more allergen after 0.3 mg KWD 2131 but not after 0.6 mg KWD 2131 and patient No. 5 showed less sensitivity to allergen after placebo as well as after the two doses of KWD 2131.

One of the 12 patients (No. 10) was excluded from the statistical analysis as she did

not fulfill the condition of having pre-test PEF values that did not differ by more than 15% between the trial days.

Patients No. 9 and 11 showed one 10-fold increase in sensitivity at the final control challenge while their proper trial challenges turned out similar to the initial one.

DISCUSSION

The introduction of disodium cromoglycate (DSCG) into clinical practice offered a novel approach to the treatment of allergic diseases, as the drug was assumed to act by inhibiting the release of putative mediators of the pathophysiological reactions encountered on allergen challenge (12). The successful use of DSCG in many allergic patients prompted a search for still more active drugs and in particular drugs that could be used orally. One line of research has been concerned with cromoglycate analogues and allied compounds, but progress has been slow and no drug has so far reached clinical recognition. The rediscovery that adrenergic drugs inhibit antigen-induced histamine release from chopped sensitized lung tissue introduced an alternative avenue of research (3). It was subsequently demonstrated that β -adrenoceptor stimulating drugs, theophylline and other drugs that increase the tissue cAMP content, also inhibit mediator release in allergic reactions (for references see 4, 21).

Although cAMP-raising drugs work satisfactorily in *in vitro* conditions it has been difficult to unequivocally demonstrate their inhibitory action *in vivo* due to their overall activity profile. For example, in allergic asthma any inhibitory effect on lung mediator release may be obscured by the bronchodilator action of the drug used.

However, using the skin testing technique, low doses of terbutaline were recently shown to inhibit the flare reaction produced by allergen, whereas the histamine-induced response was not influenced (15). Since terbutaline had no vascular effects *per se* it was concluded that the drug had a selective antiallergic action *in vivo*

and that this effect most likely was executed at the mast cell level.

Prior to this finding Sörenby (26) had made the interesting observation in the guinea pig that a terbutaline analogue, KWD 2131, was equipotent to the parent compound with regard to inhibition of histamine release from lung tissue, whereas it had only 1/40 of terbutaline's bronchodilator activity. This difference in activity profile between the two compounds suggested the possible synthesis of compounds with an even more favourable relation between the antiallergic property and other pharmacological actions. In addition, it provided a possible instrument to study the significance of the antiallergic effect in asthma.

In our study on asthmatic patients the bronchodilating activity of KWD 2131 was approximately 10 times less than that of terbutaline. The patients with chronic asthma were found to be less sensitive to the bronchodilating effect of KWD 2131 than the patients with intermittent asthma. The latter finding might reflect a reduced responsiveness of the bronchial β -adrenoceptors in the patients with chronic asthma. In contrast to the patients with intermittent asthma these patients were on the average older and had been treated continuously with β -adrenoceptor stimulants over a long period of time with the possible occurrence of increased tolerance.

Whether a change in tolerance occurs in asthmatic patients treated with adrenergic drugs is still a matter of controversy. Some investigators found a decrease of airway responsiveness in subjects on adrenergic drugs (17, 18, 19) while others were unable to demonstrate any such influence (5, 10, 20). The conflicting results may at least partly be due to differences in pretest therapy and baseline values among patients, and differences in doses and administration routes of administered adrenergic drugs.

In most studies evaluating the protective effect of drug treatment on bronchial allergen challenge the vital capacity (VC), the forced expiratory volume (FEV₁) or the peak expiratory flow (PEF) are used as lung

function parameters, e.g. (6, 9, 13, 22). In the present study we preferred the plethysmographic measurements of bronchial resistance and specific airway conductance together with PEF.

Plethysmographic measurements have been shown to be superior to the use of spirometry parameters with regard to sensitivity and effort independence (11, 14). The mere effort of a forced expiration in connection with spirometric studies may provoke bronchial obstruction in patients with hyperreactive airways. In such cases PEF might be preferable to FEV_1 . However, Gonsior *et al.* (14) showed that PEF gave the most erroneous results when SRaw, VC, FEV_1 and PEF were compared.

The results given in Table 3 demonstrate clearly that even when the PEF prevalues do not differ much from one day to another, e.g. as in patients No. 4 och 8 (maximally 4 and 8% respectively), the difference in SRaw prevalues can be quite large (maximally 58 and 55% respectively). However, in these patients no relationship between the pretest SRaw value and the reduction encountered on allergen inhalation was found.

The reliability of the spirometric methods is extremely dependent on patient collaboration, while the plethysmographic measurements of specific airway conductance can be performed during normal breathing. Also, plethysmographic measurements have a high degree of reproducibility (14, this study). These properties add to the advantages of the method with regard to its use in the evaluation of drug effects on bronchial allergen challenge.

Repeated allergen challenges over a short period of time might result in hypo- or hypersensitization of the patient. Using spirometric parameters, some investigators found no indication of a change in patient sensitivity to inhaled allergens (8, 9, 25), whereas others reported hypo- or hypersensitization in a few patients after repeated challenge (6, 16).

To check if there was any change in sensitivity to allergen as a result of repeated exposures to allergen during the clinical trial all patients were rechallenged after conclusion

of the trial. Ten out of the 12 patients showed no change. Two patients, however, showed an increased sensitivity to allergen by one order of magnitude. As the SRaw and PEF prechallenge values recorded at the pre-trial test and the post-trial test did not differ, hypersensitization had possibly occurred in these two cases. Yet, it seems unlikely that this change in sensitivity influenced the outcome of the trial.

In the controlled clinical trial pretreatment with KWD 2131 in subthreshold doses for bronchodilatation had no significant prophylactic effect on allergen-provoked asthma. With the method employed for challenge a drug-induced increase in tolerance by a dose increment of the allergen of at least one order of magnitude is of clinical importance (1). Studies with cromoglycate are in accordance with this view (2, 6, 23).

Why then was KWD 2131 not active in our trial? The explanations offered are: an insufficient drug concentration at the mast cell site, a less selective antiallergic action of KWD 2131 in humans as compared with guinea pigs, or that our results simply reflect that a mast cell protective effect has no significant bearing on the clinical outcome.

According to the chemico-physical properties of KWD 2131 there is no reason to believe that the drug would be distributed unevenly as compared with terbutaline. KWD 2131 is more lipophilic than terbutaline, a fact that would favour tissue penetration rather than limit it. Moreover, when large doses of KWD 2131 were given it had effect on various tissues, as reflected in its bronchodilator, chronotropic and tremorogenic activities.

Yet if the antiallergic activity of the drug is lower in humans than found in the animal experiments the titration of a threshold bronchodilator dose as done in this study could result in the administration of too low a dose to detect any significant protection in the challenge experiments. There is data to substantiate this interpretation. Thus when terbutaline and KWD 2131 were compared for inhibitory action on the allergen-induced

release of histamine from chopped passively sensitized human lung tissue the potency of KWD 2131 was approximately 0.15 times that of terbutaline (27) whereas the two compounds were equipotent inhibitors in guinea pig lung tissue (26). The relaxant potency of KWD 2131 was 0.02–0.03 times that of terbutaline when compared on isolated human bronchi (27) and a similar order of potency was found for the isolated guinea pig trachea (26).

Thus it appears that KWD 2131 is a less selective antiallergic drug in human lung tissue than in guinea pig lung tissue. As suggested by the present results the *in vitro* human lung test might therefore serve as a useful predictive instrument before commencing laborious clinical testings on new potentially beneficial antiallergic drugs. If the results of such a study are encouraging enough, the battery of methods employed in this study should be considered for the testing of drugs with additional bronchodilator activity.

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