

Histamine-Induced Bronchospasm

Its Reproducibility and Usage in Clinical Evaluation
of the Sub-Threshold Bronchodilating Dose of a New β -Agonist, KWD 2131

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The reproducibility of the histamine challenge in seven asymptomatic patients with extrinsic asthma, provoked four times each with 1-2 weeks interval, was investigated. The method was thereafter used in order to find the sub-threshold bronchodilating dose of a new β -agonist KWD 2131 with a preferably anti-allergic property. Selection of patients and methodology of the histamine challenge procedure were carefully standardized. Histamine was administered during quiet breathing at 3-min intervals in a step-wise cumulative manner up to a point where $>20\%$ decrease in $FEV_{1.0}$ was reached. The pooled intra-individual standard deviation was 4.6% in $FEV_{1.0}$, 5.0% in PEFR, and 4.7% in FVC.

Pretreatment with KWD 2131, before histamine challenge, showed that the sub-threshold dose for bronchodilatation was 0.5 mg in nine patients and 0.25 mg in three patients compared with 1 mg in patients with intrinsic asthma. It was important to perform individualized dose-titration of the sub-threshold bronchodilating dose of KWD 2131 before initiation of a subsequent allergen provocation study.

Key words: β -agonist; bronchial provocation; bronchodilatation; histamine; KWD 2131; reproducibility; standardization.

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As is well known, patients with bronchial asthma show a hyper-reactivity to exogenously administered histamine (9, 12, 15, 28, 42). This hyper-reactivity is also seen in normal subjects during upper respiratory infection (17). There is no significant difference in bronchial response to histamine between patients with allergic and those with non-allergic asthma (26). This hyper-reactivity to mediators is apparent (9) also during asymptomatic phases.

Bronchoconstriction in man resulting from inhaled histamine has been thought to act partly on irritant receptors to trigger reflex bronchoconstriction via vagal parasympathetic fibres (31, 36). Other studies also

show a more direct effect on the smooth muscle of the airways (10, 24).

Histamine is suggested to be a natural mediator released by bronchial mast cells and involved in the pathogenesis of asthma. After allergen- and exercise-provocations, increase in plasma histamine has been found (6, 18). A histamine release has also been noted in patients with extrinsic and intrinsic asthma during a period of severe exacerbation (27, 35).

KWD 2131 is a β -adrenoceptor stimulant with preferably anti-allergic (inhibition of mediator release) property (37) thereby differing from the β_2 -stimulating, structurally related compound terbutaline (38).

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KWD 2131 should therefore give us a tool to prove the value of the anti-allergic property of a β -agonist in the prophylactic treatment of patients with extrinsic asthma, a preliminary report of which was presented at the 13th Scandinavian Congress of Allergology 1978.

In order to prove this in an antigen provocation procedure, we first need to find the biggest dose devoid of bronchodilating effect in each patient with extrinsic asthma.

An earlier bronchodilating study in patients with intrinsic asthma had indicated 1 mg KWD 2131 by inhalation to be the mean dose devoid of bronchodilating effect (23). But 50% of the patients showed clinically significant bronchodilatation; therefore we chose 0.5 mg as the starting dose.

Histamine provocation should be a suitable model for evaluating bronchodilating drugs in patients with extrinsic asthma during their symptomfree intervals. This test model was earlier used to evaluate new bronchodilating drugs both in normal and in asthmatic subjects (1, 3-5, 7, 8, 13, 21, 25, 29, 43). However, data on the reproducibility of the histamine provocation technique has been sparse and often limited (16, 20, 44). Since we completed our study, two studies by Cockcroft et al. (14) and Juniper et al. (24) showed a good reproducibility of histamine challenges when repeated four times within 14 days or twice within a week.

The aim of the present study was: 1) to establish under standardized conditions the

reproducibility of histamine challenge in symptomfree extrinsic asthmatic patients; 2) to use this method to find an individual dose of KWD 2131 devoid of bronchodilating effect in the same type of patients.

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

PATIENTS AND METHODS

Part 1: Reproducibility of histamine-provoked bronchospasm

Seven patients with extrinsic bronchial asthma were included in the study. The diagnosis was based on history of allergy, positive skin test, RAST, and bronchial allergen provocation test (Table 1). They were subjectively and objectively free from asthmatic symptoms, and had no respiratory infection. Only three patients were moderate smokers. Smoking was not allowed for 4 h before the study. Occasionally some patients used β_2 -stimulators by aerosol (salbutamol or terbutaline) and/or disodium cromoglycate (DSCG), but no other drugs. When drugs were used they were not permitted for 12 h prior to the allergen challenge procedure. The basal FEV_{1.0}-value in the individual patient was not allowed to differ by more than 15% from day to day. In the individual patient, the study started at the same time each day after 15 min rest.

Each patient was histamine challenged on four different occasions. The provocation

Table 1
Clinical data (Part I)

Patient	Sex	Age, years	Diagnoses	Allergen	Skin test prick	RAST
A.F.	F	24	Ex. Asthma	Cat	4+	4
L.N.	M	30	Ex. Asthma	Cat	4+	3
Å.B.	F	25	Ex. Asthma	Cat	5+	3
K.-H.V.	M	23	Ex. Asthma	Dog	2+	2
P.E.	M	30	Ex. Asthma	Cat	3+	0
L.A.	F	30	Ex. Asthma	Cat	4+	2
E.R.	F	28	Ex. Asthma	Birch	3+	3

procedures usually took place at 1–2-week intervals. The interval between two provocations in two patients were 1 day and 6 weeks, respectively.

Lung function measurements; Forced Vital Capacity (FVC), Forced Expired Volume in One Second $FEV_{1.0}$, and Peak Expiratory Flow Rate (PEFR) were performed in duplicate using the Monaghan M403 Spirometer (Monaghan Co., Denver, USA) with attached recorder. The highest value was used in the statistical evaluation.

Histamine and saline were nebulized with Pari Inhalerboy 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). The nebulized solution was delivered into a mask covering mouth and nose.

After basal spirometry, nebulized saline was administered for 2 min of quiet tidal breathing. If more than 10% reduction in $FEV_{1.0}$ is obtained 3 min after completion, the patient was excluded from the study. The histamine solution was thereafter administered in increasing doses.

The challenge procedure was performed as follows: Histamine was administered at 3-min

intervals in a step-wise cumulative manner starting with an individualized dose titrated earlier. The minimum dose was 0.1 mg/ml in five inhalations. If 3 min after the challenge, less than 20% decrease in $FEV_{1.0}$ was obtained, 10 and thereafter (if necessary) 20 inhalations of the same concentration of histamine were administered. If this dose did not produce a significant fall, a 10-fold higher histamine concentration was used and the same procedure repeated up to a point where more than 20% decrease in $FEV_{1.0}$ from the base-line was found during the first provocation day in each patient.

Ventilation was measured before, $\frac{1}{2}$, and $2\frac{1}{2}$ min after each inhalation procedure. At significant fall, the spirometric measurements were continued up to 30 min. In the following three challenge periods the same doses were used as in the first provocation, except that the lowest doses without effect were excluded.

The individual per cent fall in FVC, $FEV_{1.0}$, and PEFR at different times after each histamine dose was calculated from the value obtained before the challenge (after saline). For each individual, the standard deviation between days for the maximum per cent fall at the selected dose was calculated. These

Table 2
Clinical data (Part II)

Patient	Sex	Age, years	Diagnoses	Allergen	Prick ^a test	RAST
E.J.	F	39	Ex. Asthma	Hamster	3+	—
L.A.	F	30	Ex. Asthma	Birch	4+	2
B.T.	F	29	Ex. Asthma	Birch	4+	2
J.B.	M	31	Ex. Asthma	Rabbit	6+	—
K.S.	M	26	Ex. Asthma	Cat	4+	2
E.R.	F	28	Ex. Asthma	Cat	3+	3
L.N.	M	30	Ex. Asthma	Cat	4+	3
A.F.	F	24	Ex. Asthma	Cat	4+	4
U.S.	F	30	Ex. Asthma	Birch	3+	0
I.S.	F	37	Ex. Asthma	Cow	5+	0
B.A.	F	42	Ex. Asthma	Dog	1+	3
J.S.	M	47	Ex. Asthma	Horse	3+	2

^a Aas, K., & Belin, L.: A standardized system of reference for reaction to skin tests. *Acta Allergol.* 29, 229–230, 1974.

Table 3
Initial value of FEV_{1.0}

Name	FEV _{1.0} (l)				Max. % diff. between initial values
	Day 1	Day 2	Day 3	Day 4	
A.F.	3.00	3.04	3.09	2.75	11
L.N.	3.96	3.69	4.20	3.71	12
A.B.	3.45	3.44	3.41	3.63	6
K.-H.V.	6.33	6.64	6.70	6.96	9
P.E.	4.62	4.62	4.74	4.52	5
L.A.	2.57	2.71	2.73	2.62	6
E.R.	2.44	2.39	2.44	2.40	2

standard deviations were pooled to a common intra-individual value.

Part II: Titration of the individual sub-threshold bronchodilating dose of nebulized KWD 2131

Twelve patients with extrinsic bronchial asthma and with the same inclusion criteria as in Part I were studied (Table 2). Four of them were included in the previous reproducibility study.

The histamine challenge study was designed as a single-blind 2-3-day procedure.

The first day established the dose of histamine that caused more than 20% decrease in FEV_{1.0}.

The second day, and when needed the third day, determined the sub-threshold bronchodilating dose of nebulized KWD 2131. This was considered to be a dose which gave less than 15% difference in maximum % FEV₁ decrease compared with control histamine challenge. The first pretreatment dose was 0.5 mg. If the difference compared with control histamine challenge was more than 15%, 0.25 mg was also given. KWD 2131 was administered for 15 min. The histamine challenge procedure was performed 15 min after completion of the drug administration.

The histamine challenge procedure was the same as presented in Part I. As lung function measurement, only FEV₁ was used as PEFR and FVC did not add any further information in Part I. Student's *t*-test was used in the statistical evaluation.

RESULTS

Part I

The inclusion criteria were fulfilled by all patients. The differences in initial values (before saline) of FEV₁ between the 4 days were less than 12% for each patient (Table 3). The change after saline was <10% (range +4.5 to -5.4%).

Histamine induced a dose-dependent decrease in all parameters. The individual mean maximum per cent fall in FEV₁ was obtained in most cases 2½ min after each challenge. Fig. 1 shows individual results and illustrates that the lung function had returned close to baseline 30 min after the last challenge (mean -4.1, range -12% to +5%). A cumulation effect was seen, and it became most apparent at the highest dose. A typical curve illustrating this process is seen in Fig. 2.

Table 4 lists the individual maximum decrease in FEV₁ in the 4 days. The difference in per cent decrease was 1-15% (mean 5.1%). Table 4 also lists the intra-individual standard deviation for each patient and also the pooled value for the group. The pooled intra-individual value was 4.6 in FEV₁, 5.0 in PEFR, and 4.7% in FVC.

Part II

The results show that three of the patients were protected from histamine-induced bronchospasm with 0.5 mg KWD 2131 (>15% difference from the histamine control). These

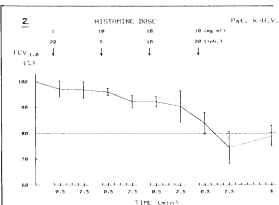
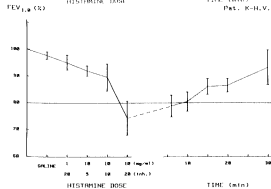
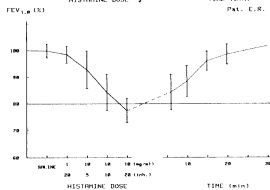
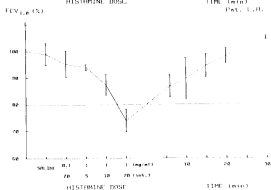
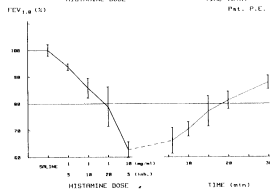
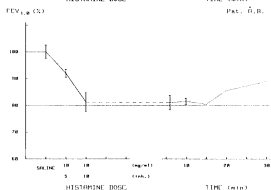
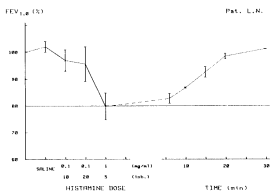
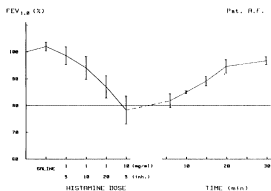


Fig. 1. Maximum per cent decrease in FEV_{1.0} (mean $\pm$ S.D.) after increasing doses of inhaled histamine in seven patients challenged at four occasions each. The right-hand parts show the FEV_{1.0} values 6-30 min after the last dose.

Fig. 2. Per cent decrease in FEV_{1.0} (mean $\pm$ S.D.) at $\frac{1}{2}$ and $2\frac{1}{2}$ min after increasing doses of inhaled histamine in one patient challenged at four occasions.

Table 4

Maximum decrease in FEV_{1.0} measured as per cent change from baseline (after saline)

Name	Dose	Max % diff.	Days 1-4, % decrease				S.D. (% Days 1-4)
			1	2	3	4	
A.F.	10 mg/ml 5 inh.	13	-28	-24	-25	-15	5.6
L.N.	1 mg/ml 5 inh.	11	-29	-18	-23	-19	5.0
A.B.	10 mg/ml 10 inh.	7	-21	-23	-16	-22	3.1
K.-H.V.	10 mg/ml 20 inh.	15	-23	-25	-20	-35	6.5
P.E.	10 mg/ml 5 inh.	7	-39	-38	-41	-34	2.9
L.A.	1 mg/ml 20 inh.	9	-31	-23	-22	-27	4.1
E.R.	10 mg/ml 20 inh.	9	-18	-20	-22	-27	3.9
							Pooled S.D.: 4.6 21 df

patients were also given 0.25 mg, which proved ineffective (Table 5).

The mean maximum per cent decrease in FEV₁ after the histamine control was 30% and after pre-treatment with individualized non-bronchodilating doses of KWD 2131, 31.5% (Table 5). This difference was not statistically significant.

DISCUSSION

The present study has shown that histamine challenges gives a satisfactory reproducibility in symptomfree extrinsic asthmatics under standardized conditions. This test model was considered suitable to find the individual sub-threshold bronchodilating dose of the new β -agonist KWD 2131.

In recent years, several investigators have tried to standardize the histamine challenge procedure (11, 12, 39-41). Our model differs from that of Cockcroft et al. (13) but the two results closely resemble each other. They found a mean difference in per cent maximum fall in FEV_{1.0} of 5.5% for the same inhaled histamine

concentration repeated twice. In the present study, the mean difference was 5.1% between four repeated challenges.

To standardize the histamine procedure, we considered the patients' lung function before each provocation. The necessity of such a precaution can be argued, as earlier investigators found that, within certain limits, there was no relation between airway calibre and bronchial reactivity (30, 34, 44), whereas others found it necessary (2, 13, 14, 24). All patients in the present study were used to the procedures and were known to produce reproducible FEV_{1.0}-values. They had no recent respiratory infections and their initial FEV₁-values were close to those predicted. The challenges were performed every day at the same time, which was important, as a fluctuation in sensitivity over 24 h has been found (16).

In order to account for possible cumulative dose effects when a series of histamine challenges are performed, each day's challenge was done in the same manner, apart from excluding the first day's lowest, not effective,

Table 5

Maximum per cent decrease in FEV₁ after histamine challenge and after pretreatment with sub-threshold bronchodilating doses of KWD 2131 (Part II)

Patient	Dose histamine	Histamine (control)	0.5 mg KWD 2131
E.J.	1 mg/ml 20 inh.	-4.5*	-31
L.A.	1 mg/ml 10 inh.	-27	-22
B.T.	1 mg/ml 20 inh.	-34	-4 -34 ^b
J.B.	1 mg/ml 10 inh.	-38	-16 -29 ^b
K.S.	10 mg/ml 10 inh.	-35	-42
E.R.	10 mg/ml 5 inh.	-32	-17
L.N.	1 mg/ml 10 inh.	-27	-31
A.F.	10 mg/ml 5 inh.	-25	-22
U.S.	1 mg/ml 10 inh.	-29	-44
I.S.	1 mg/ml 5 inh.	-45	-46
B.A.	1 mg/ml 10 inh.	-34	-2 -37 ^b
J.S.	10 mg/ml 10 inh.	-30	-23
Mean		-30.0 ^a	-31.5 ^a
± S.E.M.		2.8	2.7

*10 mg/ml 10 inh. = -27^a.

^b 0.25 mg KWD 2131.

concentrations. Juniper et al. (24) suggested that no cumulative effect is produced with doubling the dose every 5th min. However, we used 3-min intervals between the challenges, which means a faster increase in dose, and found a cumulative effect that became more apparent with increasing histamine doses.

In different laboratories, the inhalation technique differs. A group of investigators (11) selected by the programme directors of the A.A.D.C. (Asthma and Allergic Disease Centers) in the USA suggests "that all breaths of histamine should be delivered from functional residual capacity to inspiratory capacity" (total lung capacity). Cockcroft et al. (12, 13), as in the present study, used tidal volume breathing. This manoeuvre is easy for the patients and will minimize influence on lung mechanics (19) and give a more even distribution of particles administered to the lung (22, 32).

An earlier study in intrinsic asthmatics with relative stable reversible bronchospasm showed 1 mg KWD 2131 to be the mean sub-

threshold bronchodilating dose (23). Fifty per cent of these patients showed a small but clinically significant bronchodilatation after this dose. It was therefore considered necessary to test the bronchodilating effect individually in patients with exogenous asthma. We found that 0.5 mg gave bronchodilatation in three patients, making it necessary to further decrease the dose to 0.25 mg. This agrees with the results of Pegelow & Strandberg (33) who found that some patients with extrinsic asthma were more sensitive to a β -agonist than patients with intrinsic asthma. However, in two patients (E.J. and U.S.) an increase in the KWD 2131 dose over 0.5 mg might have been possible.

Another bronchoconstricting agent could have been chosen. Metacholine challenge is often used and its reproducibility is rather well established. Juniper et al. (24) have shown a good correlation between histamine and metacholine provocations. As the presented studies are to be followed by a subsequent allergen provocation study, we used histamine,

it being a natural mediator shown to be released during allergen challenge.

These results indicate the necessity for an individualized dose titration of the sub-threshold bronchodilating effect before the initiation of allergen provocation in the same patients.

We now intend to evaluate the prophylactic effect of 0.5 and 0.25 mg KWD 2131 in an allergen provocation procedure in the same patient group.

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