

Inhibitory Effect of KWD 2131, Terbutaline, and DSCG on the Immediate and Late Allergen-Induced Bronchoconstriction

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β -adrenoceptor stimulants exhibit both bronchodilating and anti-allergic activities. KWD 2131 is a new β -agonist with preferably anti allergic property.

In an earlier study, nebulized KWD 2131 in a non-bronchodilating dose (0.25 – 0.50 mg) did not give significant protection against immediate reaction.

The present study evaluated whether an increased nebulized dose of the new compound (5 mg) could protect against either immediate and/or late responses. The response was compared with a nebulized dose of terbutaline (5 mg) and with twice the recommended dose DSCG (40 mg). The study included 10 patients with known allergic asthma. It was designed as a single-blind cross-over trial with randomized allocation of the drugs. Lung functions were measured spirometrically and by body-plethysmograph; flow volume curves were drawn.

KWD 2131 gave no significant protection against immediate reaction. Both terbutaline and DSCG did so, terbutaline being more efficient. Contrary to the β -agonists, DSCG also gave protection against late response.

Key words: allergen challenge; anti-allergic agent; β -agonist; DSCG; KWD 2131; terbutaline.

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CLINICAL ASPECTS

Terbutaline and DSCG are compounds used in the treatment of bronchial asthma. DSCG is mainly used for its anti-allergic effect; terbutaline for its bronchodilating effect. KWD 2131 is a new sympathomimetic compound which *in vitro* has shown a more selective anti-allergic effect than terbutaline.

The present study compared the inhibitory effect of KWD 2131, terbutaline, and DSCG on immediate and late allergen-induced bronchospasm. Ten patients with known allergic asthma participated. None of the patients were on regular drug treatment.

KWD 2131 did not give any significant protection against immediate or late reaction. Terbutaline and DSCG treatment resulted in a significant protection. In all parameters used, significant higher absolute values were obtained with terbutaline than with DSCG before and on most points of measurements up to 180 min. Due to the bronchodilating capacity of terbutaline the absolute values 360 min after the allergen provocation agreed very closely with that of DSCG. As terbutaline also gave better initial protection, it seems that this compound should be able to provide a better clinical protection than DSCG in extrinsic asthma. A valid answer to this question can only be given if a long-term study comparing the two compounds is done.

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Bronchial provocation with allergens in sensitive patients causes two types of bronchial obstructive reactions: an immediate one, appearing a few minutes after the inhalation of the allergen and disappearing 1–2 h later; and a late reaction, starting 4–6 h after the allergen inhalation and lasting for several hours (4, 11, 21). The mechanisms of these dual reactions are still being discussed. The immediate reaction is considered the consequence of the action of mast-cell derived mediators released during an IgE-dependent immunological response. It is effectively reversed and terminated by inhaled bronchodilators (20). The late reaction possibly depends on the presence of an immediate reaction (20, 21), but the mechanisms involved are still not known.

Drugs differ in their protective effect on the allergen-induced bronchoconstriction by their selective activity on one or both of the bronchoconstrictory reaction types. β -adrenoceptor stimulants, given in regular dosages before antigen inhalation, inhibit the immediate bronchoconstriction (5, 16) but do not influence the late reaction (5, 19). Acute administration of corticosteroids, both orally and inhaled, inhibits the late reaction without significantly influencing the immediate reaction (4, 18, 21). Chronic administration of corticosteroid inhibits both the immediate and the late bronchoconstriction (17, 24). Disodium cromoglycate (DSCG) inhibits both types of reactions (4, 18, 19, 21, 22).

Sympathomimetic amines are useful therapeutic agents in the management of bronchial asthma. Their mode of action is possibly dual. β -agonists exhibit *in vitro* both a smooth muscle relaxing and a mediator release-preventing effect (2, 23, 27). The *in vivo* separation of these two activities is not easy because the end results of both activities are the same.

Martin et al. (17), however, showed that terbutaline, a well-known β -agonist, inhibits mediator-release after *in vivo* allergen challenge in man.

KWD 2131, a new β -agonist structurally related to terbutaline, shows a more selective anti-allergic effect in several *in vitro* and *in vivo* animal experiments (28, 29). KWD 2131 exhibits a weaker bronchodilating effect than equimolar

concentrations of terbutaline in animals and in man (13, 25, 28). The bronchodilating capacity is about 10 to 30 times weaker. However, the mediator release-preventing potency of KWD 2131 and terbutaline in animals and in human skin and nose is equal (12, 26, 28). However, on human lung tissue, KWD 2131 is seven times less potent than terbutaline in the prevention of allergic histamine release (25).

The discrepancy between bronchodilating and mediator release-preventing potency in two related compounds initiated studies on the relative importance of the bronchodilating and anti-allergic effect of sympathomimetics *in vivo* in man (13, 14, 15). In an earlier study, nebulized KWD 2131 in a non-bronchodilating dose (0.25 – 0.50 mg) did not give significant protection against the allergen-induced immediate bronchoconstrictory reaction (15). The present study evaluated whether an increased nebulized dose of the new compound (5 mg) gave protection against both the immediate and the late bronchial response after allergen-challenge. We compared the new drug with terbutaline and with DSCG, a known anti-allergic drug without bronchodilating capacity (6).

PATIENTS AND METHODS

Ten patients, five female and five male, mean age 26.3 years (range 22–32 years), were studied. All had known allergic asthma based on history of allergy, positive skin test, RAST, and bronchial allergen provocation test (Table 1). None of the patients had a recent respiratory infection nor did they show an actual bronchoconstriction. The basal FEV₁ was more than 80% of the predicted normal value. Patients on oral or aerosol corticosteroids were excluded from the study. DSCG had not been used 1 month before the test period; bronchodilators, if used, were discontinued for at least 12 h before each test. The nature and the purpose of the study were explained to the patients. The investigation was approved by the Ethical Committee of the University Hospital of Gent. Informed consent was obtained from all patients.

Initially, all patients were tested with 3 min aerosol of Coca's solution to exclude non-speci-

Table 1
Clinical data

Patients	Sex	Age	Diagnosis	Allergen concentration w/v (mg/ml)	Prick test	RAST
V.I.R.	♂	27	Bronchial asthma	Derm.pteron. 1.2	4+	4+
V.S.B.	♀	28	Bronchial asthma	Derm.pteron. 1.2	4+	4+
V.I.P.	♂	25	Bronchial asthma	Derm.pteron. 1.2	4+	4+
H.M.	♀	28	Bronchial asthma	Grass-pollen 0.25	4+	4+
V.C.M.	♀	24	Bronchial asthma	Derm.pteron. 1.2	4+	4+
H.R.	♂	22	Bronchial asthma	Grass.pollen 0.25	4+	4+
V.H.M.	♂	32	Bronchial asthma	Grass.pollen 0.25	4+	4+
D.V.M.	♀	26	Bronchial asthma	Grass.pollen 0.25	4+	4+
G.P.	♂	23	Bronchial asthma	Derm.pteron. 1.2	4+	4+
F.L.	♀	28	Bronchial asthma	Derm.pteron. 1.2	4+	4+

fic reactions ($> 10\%$ decrease in FEV_1). At the same time, the appropriate concentration of allergen producing a decrease in FEV_1 between 25 and 60% of the initial value was established in each patient by logarithmic increase in allergen concentration.

The same allergen concentration was used during the test days. With intervals of approximately 1 week between each test day the same allergen challenge was performed 15 min after pre-treatment with either 5 mg nebulized terbutaline, 5 mg nebulized KWD 2131, or 40 mg nebulized DSCG.

The study was single-blind cross-over with randomized allocation of drugs. The experiment began at the same time each day.

The allergens (Bencard, England) were administered via nebulization from a Wiesbadener Doppel-Inhalator with an air-flow of 61/min for 3 min. The drugs were administered by ultra-sonic nebulization (Monaghan 670 B) for 10 min. Lung function measurements were made before drug administration and before and 5, 15, 30, 60, 120, 180, 240 and 360 min after the allergen challenge. Due to practical reasons flow volume curves were omitted before drug treatments, and on the day when allergen was administered alone. The forced expiratory volume in 1 sec (FEV_1) and vital capacity (VC) were measured using a closed-circuit spirometer (Godart Expirograph). The measurements were made in triplicate. The highest value was used in the statistical evaluation. Raw,

sGaw, and TGV were measured using a constant volume body plethysmograph (Jaeger Body Plethysmograph). The mean of six consecutive manoeuvres was used in the statistical calculation. Flow volume curves were also drawn and measurement of $FEF_{25-75\%}$, $FEF_{75-85\%}$, PEF, $MEF_{50\%}$, and $MEF_{75\%}$ was made (Hewlett Packard). The starting values of the respiratory parameters on the different test days were comparable (FEV_1 -values within 17% of each other).

The absolute values and mean per cent fall in all parameters at different times after allergen challenge were calculated from the value obtained immediately before provocation. For statistical analysis, Student's t-test and Wilcoxon's signed rank sum test were used. A difference of $P < 0.05$ was considered significant.

RESULTS

Ten patients completed the study according to the procedure. The results are presented as changes in FEV_1 and sGaw; the additional parameters do not add any substantial, further information. The results from the two statistical methods were comparable. The data from Student's t-test are presented. None of the patients reacted to Coca's solution.

The relative changes

The difference in pre-value (before drug administration) from day to day was $\leq 15\%$ except

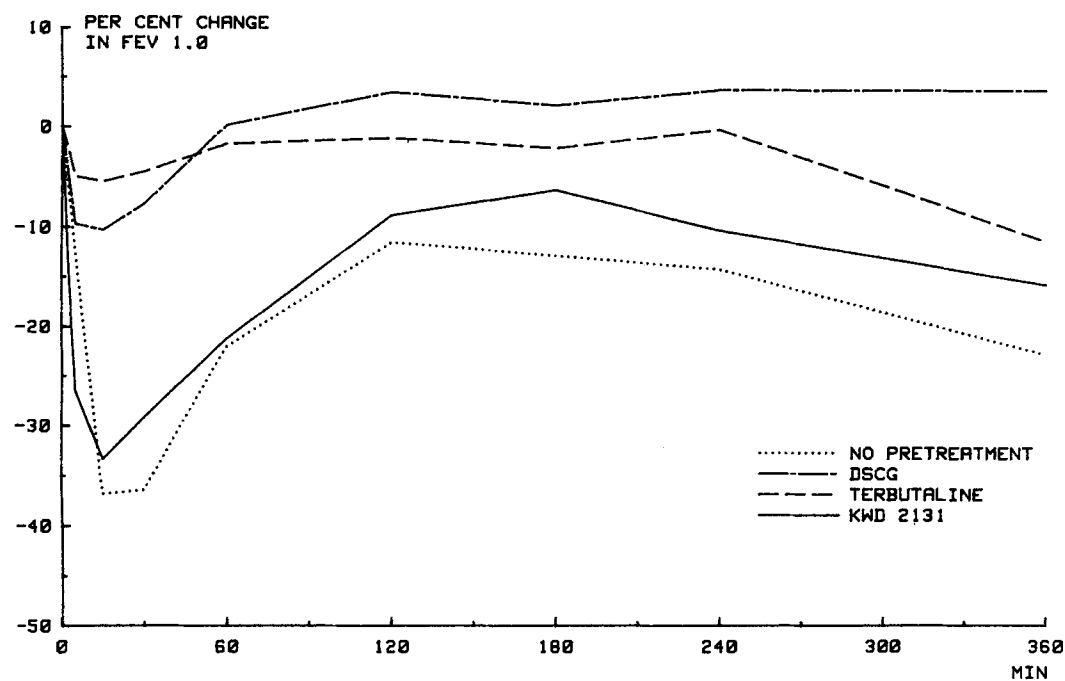


Fig. 1. Mean per cent changes in FEV₁ from the pre-challenge value on the various test days.

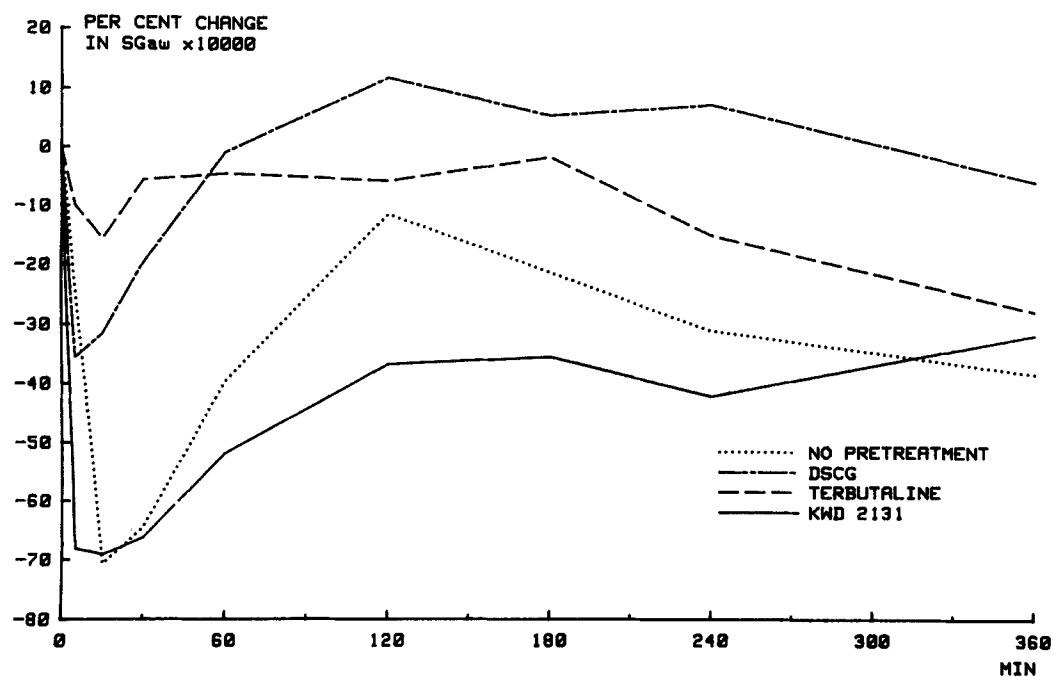


Fig. 2. Mean per cent changes in sGaw from the pre-challenge value on the various test days.

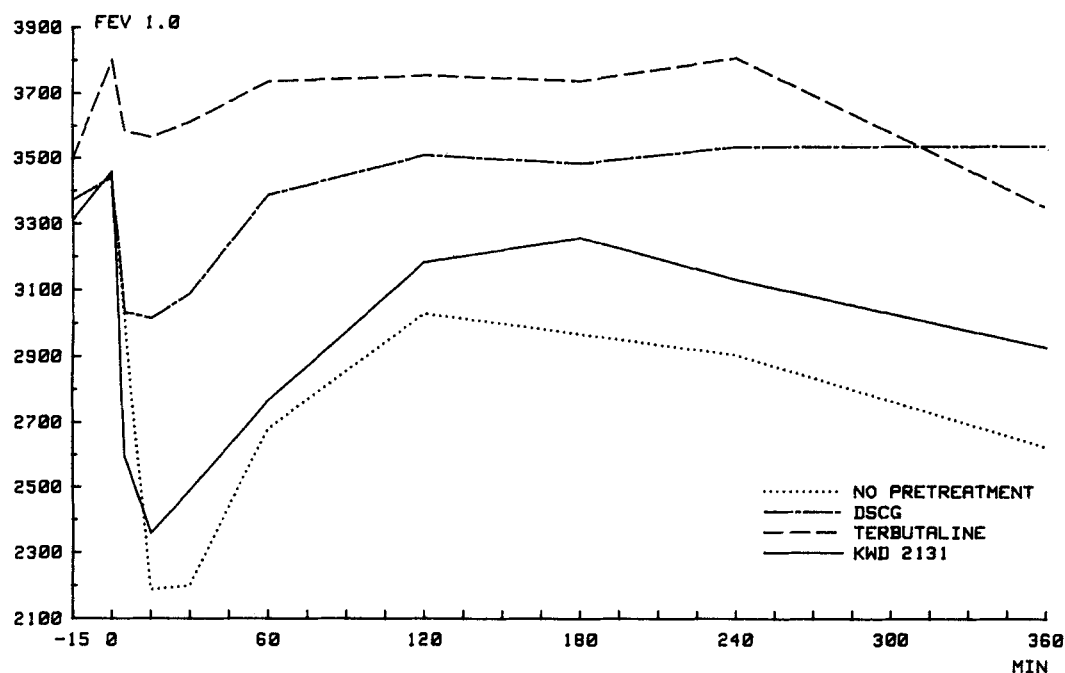
Fig. 3. Mean absolute values in FEV₁.

Table 2
Mean absolute values in sGaw (sec/cm H₂O)

Drug	Before treat- ment	Before chal- lenge	5	15	30	60	120	180	240	360 min.
Allergen		0.1374	—	0.0412	0.0489	0.0841	0.1245	—	0.0968	0.0858
DSCG	0.1396	0.1445	0.0966	0.1015	0.1169	0.1402	0.1501	0.1484	0.1524	0.1355
Terb.	0.1369	0.1848	0.1682	0.1549	0.1734	0.1731	0.1763	0.1825	0.1576	0.1344
KWD 2131	0.1115	0.1675	0.0590	0.0561	0.0593	0.0843	0.1100	0.1111	0.0990	0.1154

in one case (17%). Small but significant bronchodilatation was observed immediately after the administration of terbutaline ($10.5\% \pm 3$ (mean $\pm$ s.e.m.) increase in FEV₁, $59\% \pm 20$ increase in sGaw) and after KWD 2131 ($5\% \pm 3$ increase in FEV₁, $78\% \pm 26$ increase in sGaw). This was not the case on the day when DSCG was given.

Figs. 1 and 2 illustrate the mean per cent changes in FEV₁ and sGaw, after allergen challenge on the various test days. On the day without pre-treatment, the maximum per cent decrease in FEV₁ and sGaw during the immediate

response (15 min) was 37 and 71 and at late response (360 min) 23 and 38%, respectively.

KWD 2131 did not protect against the allergen challenge except in one instance in sGaw (120 min $P < 0.01$). DSCG and terbutaline gave significant protection for the first 2 h in FEV₁ and for 60 min in sGaw.

Significantly better protection was obtained with terbutaline than with DSCG 5 min ($P < 0.01$) and 15 min after allergen challenge in sGaw. DSCG protected against the late response at 240 and 360 min in FEV₁ and at 240 min in sGaw. In this respect, DSCG differed

significantly from terbutaline at 360 min in FEV₁ ($P < 0.01$) and at 240 min in sGaw ($P < 0.01$).

The absolute values

Fig. 3 and Table 2 illustrate the results in absolute values of FEV₁ and sGaw.

The functional parameters after KWD 2131 did not significantly differ from the values after allergen alone. Terbutaline and DSCG treatment resulted in a significantly, lesser decrease of the functional parameters ($P < 0.05 - 0.001$).

In all parameters used, significantly higher, absolute values were obtained with terbutaline than with DSCG before and on most points of measurements up to 180 min ($P < 0.05 - 0.01$). At 240 min, the values were still higher after terbutaline; however, the level of significance was not reached. Comparable absolute values were obtained 360 min after the challenge.

DISCUSSION

This investigation shows that both terbutaline and DSCG protect against the immediate reaction of an allergen challenge. This confirms the findings of Jorde (16) and Booij-Noord (5) that sympathomimetic amines inhibit the immediate reaction. After terbutaline, we observed a relative decrease in the functional parameters 4–6 h after allergen. However, in absolute values, the lung function parameters did not differ from the pre-treatment values. Similar findings were made with fenoterol, another sympathomimetic amine (19). DSCG gives a dual protection (4, 18, 19, 21, 22); however, it was not bronchodilating, as indicated by Chung (8).

The absence of protective effect with KWD 2131 was surprising. In an earlier allergen provocation study (15) 0.5 mg nebulized KWD 2131 showed a tendency to protection, and in a cumulative dose-response trial, 3.5 mg gave bronchodilatation (13). The reason for the absence of effect when a 10-times higher dose of KWD 2131 was used is not understood. At least in *in vitro* experiments, the protective effect of sympathomimetic amines is known to be considerably greater with low antigen concentra-

tion leading to a moderate allergic reaction than with high concentration (3). A difference in lung function decrease after allergen provocation in the two studies could explain the discrepancy. However, they were comparable. The delivery of the drug may have differed, but it can hardly explain the total lack of protective activity of KWD 2131.

Terbutaline gave a significant, stronger protection than DSCG in the immediate bronchial reaction. This could be due to an anti-allergic effect, a bronchodilating effect, or both. The dose of terbutaline used was high. An equal dose of KWD 2131, which according to an earlier study (13) exerts $1/30$ of the bronchodilating potency of terbutaline, and is above threshold for bronchodilation as well, was ineffective.

If we assume that the anti-allergic potency of terbutaline is comparable with that of KWD 2131, as earlier shown in *in vitro* animal lung studies (28) and also in studies in the human nose (26) and skin (12), the effect of terbutaline in this study is mainly bronchodilating.

However, an *in vitro* study in human lung (25) showed the relation in anti-allergic potency between terbutaline and KWD 2131 to be 7:1, and the corresponding relation in bronchodilating potency was 40:1. The decreased anti-allergic selectivity in *in vitro* human lung (25) and the absence of protection with KWD 2131 in this study indicates a possible species difference and a difference in man between lung mast cells and the mast cells from skin (10, 12) and nose (26). However, the fact that the tested dose of terbutaline may be somewhat more anti-allergic than that of KWD 2131 still leaves the question open whether terbutaline at least partly shows beneficial effect in the present study due to anti-allergic effect.

Pepys (20, 21) suggests that late bronchial obstructive response is always preceded by an immediate reaction. Terbutaline did not protect against the late response. Although it had a very strong effect on the immediate reaction, the lack of protection against late response could be because terbutaline might have either a 'selective' or a partial protective effect against mediator release or the bronchodilating effect had more or less ceased.

Terbutaline has been shown *in vivo* in man to protect against histamine-release after allergen challenge (17). The mediators involved in the late bronchial reaction are not known at the moment. There is indication that drugs might have selective protective activity against mediator release (1, 7, 9). However, due to the bronchodilating capacity of terbutaline, the absolute values 360 min after the allergen provocation agreed very closely with that after DSCG. As terbutaline also gave better initial protection, it seems that this compound should be able to provide better clinical protection than DSCG. A valid answer to this question can only be given if a long-term study comparing the two compounds is done.

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