

A New β_2 -Adrenoceptor Agonist – D2343 – with Long Duration

Inhalation Comparison with Terbutaline in Asthmatics

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A new β_2 -adrenoceptor agonist D2343 has been shown in a human i.v. study to be less potent than terbutaline. Animal experiments showed an increased affinity to lung tissue and a longer bronchodilating effect than terbutaline when inhaled. In a randomized single-blind, crossover comparison, 2.5 and 5 mg D2343 and 5 mg terbutaline were inhaled by eight asthma patients. We found that 5 mg of D2343 was equipotent to 5 mg terbutaline in bronchodilatory effect measured with FEV₁. The duration was longer with an increased bronchodilation ($P < 0.01$) 6 h after D2343 inhalation compared with terbutaline. The mean fall in FEV₁ 3–6 h after inhalation was significantly greater with terbutaline than with D2343 ($P < 0.05$). Thus, this study shows that inhaled D2343 has a longer bronchodilating effect than terbutaline.

Key words: β_2 -adrenoceptor agonists; duration of effect; skeletal muscle tremor; heart rate.

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D2343 (1-(4-hydroxyphenyl)-2- 1,1-dimethyl-3-(2-methoxyphenyl)propyl-amino ethanol, HCl) is a new β_2 -adrenoceptor agonist with some α_1 -adrenoceptor blocking effect (1, 4, 5). In an earlier i.v. study in asthmatics we showed D2343 to be 4–6 times less potent as a bronchodilator than terbutaline. The same potency difference was shown in the measurements of skeletal muscle tremor and heart rate. In this i.v. study there was a tendency towards longer duration with D2343 than with terbutaline.

Animal studies have shown that D2343 has an increased affinity to lung tissue when time-concentration curves were compared with those of plasma, liver and brain (8). Terbutaline did not show this separation of affinity (2). Guinea pig studies have also shown a prolonged bronchodilating effect of D2343 compared with terbutaline (6). The aim of the present study was to evaluate equipotent bronchodilating doses of D2343 and terbutaline and to com-

pare the duration of effect after inhalation treatment.

PATIENTS AND METHODS

Study design

The study was a single-blind randomized, crossover comparison between two inhaled doses of D2343 (2.5 mg and 5 mg) and 5 mg terbutaline, given with a Bird ventilator.

The study was approved by the Ethics Committee of the University of Göteborg.

Patients

Eight patients with intrinsic asthma were included in the study (Table 1). None of the patients had an acute exacerbation of obstruction at the time of study. All patients had proved to have a constant airway obstruction

with a reversibility in FEV₁ of 34–77% after inhalation of 5 mg terbutaline with a Bird ventilator. The basal value of FEV₁ was not allowed to differ more than 20% between the experiment days.

Inhaled and oral β_2 -adrenoceptor stimulants and inhaled anticholinergics were withdrawn 12 h and theophylline derivatives 36 h before each experiment. Corticosteroid treatment was unchanged during the trial. Previous drug treatment is shown in Table 1.

Experimental details

After a light breakfast the patients arrived at the laboratory at 7.30 a.m. The patients were seated in a semi-recumbent position during the experiment. After 60 min of rest the basal values were measured. The following measurements were performed in the following order:

- 1. Heart rate from a continuous ECG.
- 2. Skeletal muscle tremor with an accelerometer method described earlier (9).
- 3. FEV₁ with a Collin's survey spirometer, the highest of at least two values was recorded.

After measurement of basal values the drug (2.5 mg, 5 mg D2343 or 5 mg terbutaline) was inhaled, dissolved in 5 ml saline. D2343 was given in its chloride form. The inhalation was administered with a Bird ventilator (Mark 7 respirator, inspiratory pressure 15 cm H₂O,

flow rate 10) for 15 min. After inhalation the mouth and pharynx were rinsed. The above mentioned measurements were repeated 15, 30 min, 1, 2, 3, 4, 5, and 6 h after inhalation. After the 6 h measurement the patients inhaled 1.25 mg terbutaline (5 inhalations) from a standard metered dose aerosol (Bricanyl®) and a new measurement of FEV₁ was performed 5 min later. Lunch was served about 210 min after the inhalation.

Statistical methods

Means and standard error of the mean (SEM) are presented.

Areas under the curve (AUC) have been calculated for the individual values of change in FEV₁ (1) and for tremor ratios during 6 h.

Duration of action has been evaluated by comparing the effect of presumably equipotent doses after 6 h. The fall in effect has been studied by calculating the individual regression lines according to the least squares method for changes in FEV₁ 3–6 h after inhalation. The slope of these lines was then used to calculate the FEV₁ mean fall/h. Comparison between mean values was studied by paired Student's t-test. Differences were considered statistically significant when *P* < 0.05.

RESULTS

FEV₁ (Fig. 1). Inhalation of 5 mg terbutaline and D2343 showed maximal effect similar to

Table 1
Clinical details of patients

Sex	Age	Height (cm)	Weight (kg)	Cig./day	Diagnosis	Basal FEV ₁	Reversibility (%)	Previous drug treatment
1 M	63	176	81	–	A	1.53	52	IB OB OT
2 M	60	181	85	–	A	1.49	77	IB OB OC
3 M	63	184	82	–	A	1.79	53	IB OB OT IC
4 M	60	180	98	–	A + C	1.23	34	IB IC
5 M	65	180	78	–	A	1.74	39	IB OB IC
6 F	55	156	60	–	A	1.23	65	IB OB OT
7 M	58	175	78	–	A	1.19	50	IB OT IC
8 F	54	168	98	5–6	A + C	1.65	49	IB OB OT IC OC

A = asthma; C = chronic bronchitis; O = oral; I = inhaled; B = β_2 -stimulant; T = theophylline; C = corticosteroid.

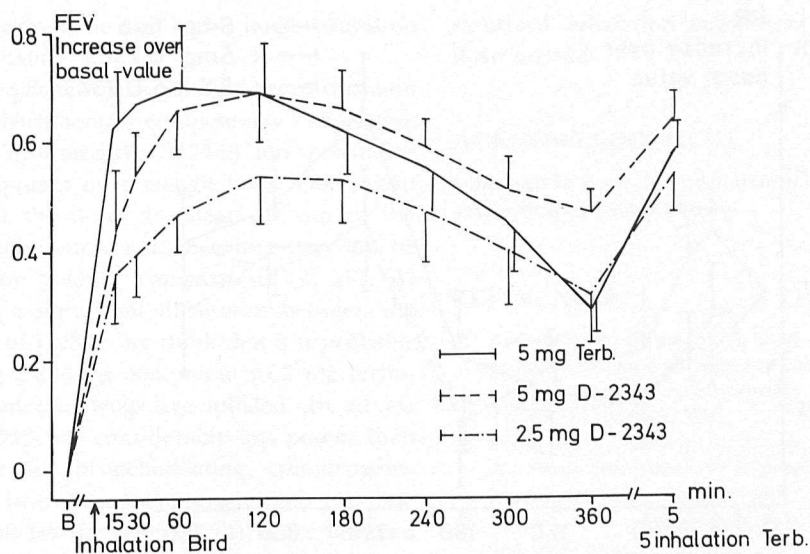


Fig. 1. Mean change of FEV₁ from basal value (B) ($\pm$ SEM) 15–360 min after inhalation of 5 mg terbutaline (basal value 1.48 ± 0.08 l), 5 mg d 2343 (1.45 ± 0.09 l) and 2.5 mg D2343 (1.52 ± 0.07 l) and 5 min after inhalation of 1.25 mg terbutaline from an MDI.

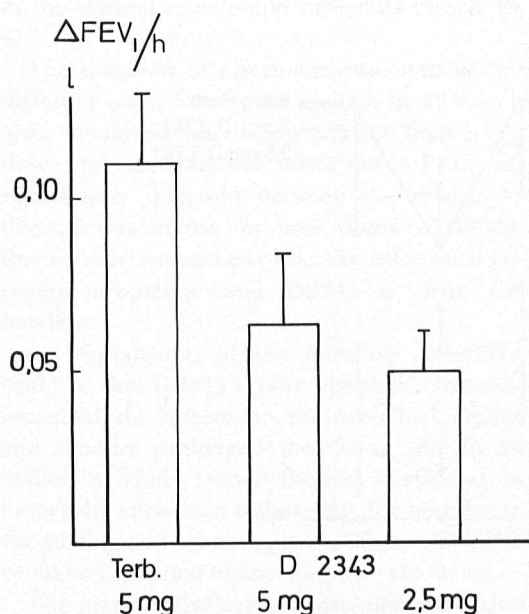


Fig. 2. Mean fall in FEV₁/h 3–6 h after inhalation.

that achieved by inhalation of 1.25 mg from a metered dose aerosol at the end of the experiment. There was a tendency towards a more

rapid effect after terbutaline inhalation; however, the difference was not significant after 15 min.

The AUC showed almost identical values after 5 mg of terbutaline and D2343. There was a significant AUC difference ($P < 0.01$) between the two doses of D2343.

Six hours after inhalation FEV₁ showed a difference between 5 mg terbutaline and 5 mg D2343 (0.19 ± 0.05 l, $P < 0.01$).

The mean fall in FEV₁/h (Fig. 2) was 0.11 ± 0.01 l after 5 mg terbutaline, after 5 mg D2343 0.06 ± 0.02 l and after 2.5 mg 0.05 ± 0.01 l. The differences between both doses of D2343 and terbutaline were significant ($P < 0.05$). There was no significant difference between the two doses of D2343.

Heart rate (Fig. 3). After lunch there was a slight increase in heart rate. There was no significant difference between the different treatments.

Skeletal muscle tremor (Fig. 4). There was a significant, although very low effect of 5 mg of both D2343 and terbutaline on skeletal muscle

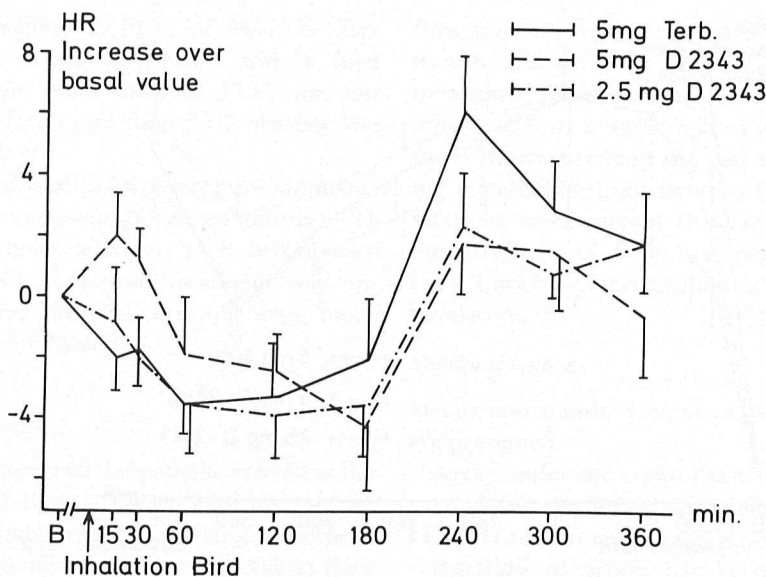


Fig. 3. Mean change from basal value (B) of heart rate 15–360 min after inhalation of 5 mg terbutaline (basal value 66 ± 3 bpm), 5 mg D2343 (66 ± 4 bpm) and 2.5 mg D2343 (65 ± 2).

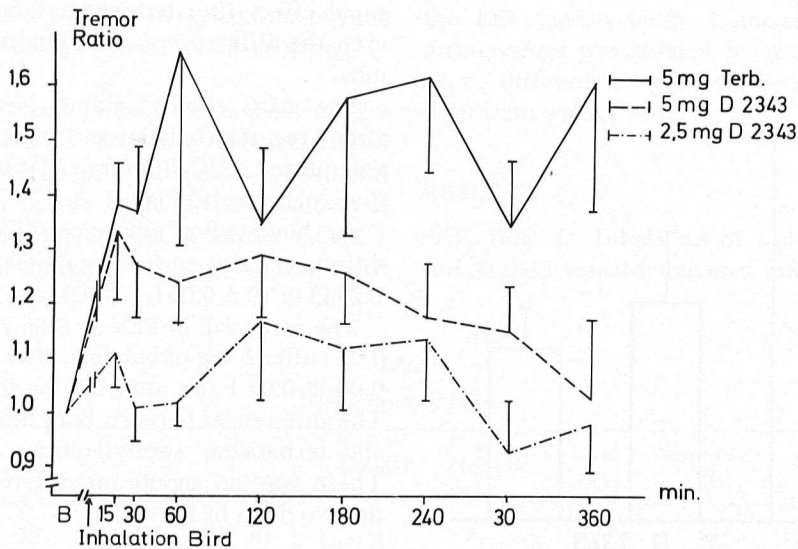


Fig. 4. Tremor ratio 15–360 min after inhalation of 5 mg terbutaline, 5 mg and 2.5 mg D2343.

tremor measured as AUC during 6 h. AUC for 5 mg terbutaline tended to be greater than for 5 mg D2343, although not statistically significant.

DISCUSSION

This study showed that the bronchodilating effect of inhaled D2343 was equipotent mg for

mg with terbutaline and had a longer duration than terbutaline.

A prerequisite for the evaluation of duration is the establishment of equipotency. The data in this study indicated that D2343 and terbutaline were equipotent on a weight basis. One might argue that the doses are near the top of the dose-response curve and therefore may not be optimal for potency comparisons (7, 10). As there was a significant difference between the two doses of D2343, we think that it is probable that 5 mg D2343 is equipotent to 5 mg terbutaline when the drugs are inhaled. In an i.v. study D2343 was considerably less potent than terbutaline for bronchodilating, tremorogenic as well as heart rate increasing effects (4). One explanation for the potency difference between inhaled and i.v. treatment could be that D2343 had a more rapid liver metabolism than terbutaline. The tendency towards less skeletal muscle tremor in the present study pointed to the same, as the i.v. study produced no evidence for a difference in the β_2 -adrenoceptor effects in the skeletal muscle and bronchial muscle (3, 4).

The duration of effect was evaluated in two different ways. Firstly, the change in FEV₁ 6 h after inhalation was different after both 5 mg doses and, secondly, the mean fall in FEV₁ was significantly different between the drugs. As this fall was similar for both doses of D2343, this further strengthens that the difference between terbutaline and D2343 is drug dependent.

An explanation of the duration difference could be that D2343's more lipophilic character increased the affinity to the bronchial muscle and thereby prolonged the action (8). In an earlier i.v. study D2343 showed a tendency to longer duration than terbutaline, for both bronchodilating and tremorogenic effects, which also could be explained by the lipophilic character.

The increased affinity to lung tissue, and the indications of a more rapid metabolism together with longer duration, makes D2343 more useful for inhalation treatment. It is therefore of interest that further studies of the inhalation route are made, preferably using

standard inhalation equipment as a standard dose aerosol.

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