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Two New β_2-Adrenoceptor Agonists, D-2343 and QH 25, Studied in Asthmatic Patients

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Two new β_2-adrenoceptor agonists, D-2343 and QH 25, have been studied in asthmatic patients. Animal experiments indicated less effect on skeletal mucsle than on bronchial muscle.

D-2343 (four i.v. cumulatively increasing doses, 0.21–6.3 μg kg^{-1} min^{-1}) and i.v. terbutaline (four cumulative doses 0.07–2.1 μg kg^{-1} min^{-1}) were single-blindly compared in a randomized crossover study in eight asthmatics. It was shown that D-2343 is an effective β_2-adrenoceptor agonist with 5–6 times lower potency than terbutaline. The tremor-inducing effect of D-2343 was the same as that of terbutaline, when the same degree of bronchodilation was obtained.

The effect of QH 25 (0.25, 0.75 and 2.25 mg cumulatively) administered orally, was single-blindly compared with the effect of oral salbutamol (2, 6 and 18 mg) in a randomized crossover study in eight asthmatics. QH 25 was shown to be an effective β_2-adrenoceptor stimulant about 12 times more potent than salbutamol. The tremor-inducing capacity was the same as for salbutamol when equipotent bronchodilating doses were studied.

Key words: dose-response curves; salbutamol; selectivity; skeletal muscle tremor; terbutaline; ventilatory capacity.

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Treatment with adrenergic β_2-stimulants is one of the basal therapies in asthmatic disease. The most important therapeutic effects are bronchial muscle relaxation, decreased release of spasmogens from mast cells, increased mucociliary clearance and increased chloride ion (and water) transport over the bronchial mucosa (12). The dose-limiting side effects are skeletal muscle tremor and reflex tachycardia mainly due to peripheral blood vessel dilatation (12).

New β_2-stimulants have been synthetized with the aim to separating subpopulations among β_2-adrenoceptors to make it possible to separate therapeutic effects from side effects.

Two newly synthesized β_2-adrenoceptor agonists, D-2343 and QH 25, were in some animal experiments shown to separate bronchial muscle effect and skeletal muscle effect when compared with terbutaline (2, 5, 7, 8).

The aim of the present study was therefore to test whether D-2343 and QH 25 had less tremorogenic than bronchodilating effect when compared with two conventional β_2-adrenoceptor stimulants, terbutaline and salbutamol respectively, in asthmatics. One interesting possibility was that D-2343 was shown to have a weak α_1-adrenoceptor blocking effect (7) which could influence the bronchodilating efficiency of the drug (10, 12).

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PATIENTS AND METHODS

Study design

The studies were single-blind, randomized, crossover comparisons between cumulatively increasing doses of the β_2-agonists, in 1) between D-2343 and terbutaline by intravenous route and 2) between QH 25 and salbutamol by oral route. The study was approved by the Ethical Committee of the University of Göteborg.

Patients

The two studies were performed in 12 patients with intrinsic asthma, eight in each study. (For further data see Table 1). None of the patients had an acute exacerbation of obstruction at the time of study. All patients had previously proved to have a very constant airway obstruction with a reversibility of 20–50% after five inhalations of terbutaline sulphate (1.25 mg).

The basal value of FEV_1 was not allowed to differ more than 20% between 2 days of each experiment.

β_2-Adrenoceptor stimulants and inhaled anticholinergics were withdrawn 12 h and theophylline derivates 36 h before the study started.

Previous drug treatment is given in Table 1.

Methodological details

After a light breakfast the patients arrived at the laboratory at 7.30 a.m. The patients were seated in a semirecumbent position during the experiment. After 60 min of rest the basal values were measured.

The following measurements were performed in this order:

1. Heart rate from a continuous ECG recording.
2. Blood pressure by the cuff method and a mercury manometer.
3. Skeletal muscle tremor with an accelerometer method described earlier (14).

Table 1

Clinical details of patients

Patient	QH	D-2343	Sex	Age	Height (cm)	Weight (kg)	Cig	Diagnosis	FEV_1	Previous drug treatment
KJ	X		M	31	173	73	10–15	A	2.05	OBR IBR
TS	X	X	M	56	180	93	–	A + C	1.60	OBR IBR ICR ThR
AM	X	X	F	43	157	50	–	A + C	1.30	OBR IBR ICR IAR
ES	X		M	61	166	64	–	A	0.80	OBR IBR
TN	X	X	M	67	178	70	12	A + C	1.15	OBR IBD
EZ	X		M	48	175	69	3–4	A	1.30	IBR ICR
UF	X	X	F	57	162	50	–	A + C + E	0.85	ThR IBR ICR OBR
LL	X		M	49	176	91	–	A + C	2.75	OBR IBR
HB		X	M	69	182	100	–	A	0.65	ThR IBR ICR
AB		X	M	56	170	81	–	A	1.00	ThR IBR ICR OCR
EC		X	M	62	171	68	–	A	1.45	OBR IBR ICR OCR
EP		X	M	56		77	8–10	A + C	1.00	OBR IBR
AJ		X	M	67	190	85	–	A + C	1.00	ThR IBD

A = Asthma
C = Chronic bronchitis
E = Emphysema

O = oral
I = inhaled
B = β_2-stimulant
Th = theophylline
C = corticosteroid
A = anticholinergic
R = regularly
D = on demand

4. FEV_1 was measured with a Bernstein spirometer, and the highest value of two was registered.

After measurement of basal values the drugs were given either intravenously or orally. Five inhalations of terbutaline (1.25 mg total dose) were given after the highest dose of the drug under investigation, and the measurements were performed 5 min after the inhalations.

Part 1 – *D-2343 compared with terbutaline*

An intravenous catheter was inserted immediately after arrival at the laboratory. The infusions lasted for 6 min and the interval between infusions was 30 min. The D-2343 doses were 0.21, 0.63, 2.0 and 6.3 $\mu g\ kg^{-1}\ min^{-1}$. The terbutaline doses were 0.07, 0.21, 0.66 and 2.1 $\mu g\ kg^{-1}\ min^{-1}$. Effects were recorded 1–3 min after completion of the infusion. After the last infusion, measurements were performed every 30 min for 2 h.

The experiments were done on 2 consecutive days with either D-2343 or terbutaline: half the number of patients received D-2343 on day 1 and the other half on day 2.

Part 2 – *QH 25 compared with salbutamol*

Oral QH 25 was the only available administration. It was given in doses of 0.25, 0.75 and 2.25 mg and salbutamol in the doses 2, 6 and 18 mg. All variables were measured 30, 60, 80, 100 and 120 min after every dose. The interval between the doses was 120 min.

Statistical methods

Means and standard errors of the means are given.

To evaluate the selectivity for bronchial dilatation and skeletal muscle tremor induction in part 1 the individual regression lines for the dose-response relationships were plotted and the doses giving 0.2 l and 0.3 l increase in FEV_1 were studied concerning tremor effect in the same individual when giving the two different drugs. In part 2, where only three doses were given, intrapolation between the measured effects on different dose levels were done without calculating the regression lines, and the dose which gave 0.2 l increase of FEV_1 was calculated by intrapolation and studied concerning tremor. The comparison had to be done on an FEV_1-increase of 0.15 l in one case, 0.3 l in one case, and 0.45 l in one case, as in these cases an intrapolation to 0.2 l was impossible for both drugs. Differences were studied by paired Student's t-test. Differences were considered statistically significant when $P < 0.05$.

RESULTS

Part 1 – *D-2343 compared with terbutaline intravenously*

FEV_1 (Fig. 1). The dose response curves for D-2343 and terbutaline were quite parallel and showed that terbutaline is 5–6 times more potent than D-2343. There is a tendency towards a longer duration effect of D-2343.

It was shown that the intravenous doses, at least of terbutaline, gave maximal bronchodilation as inhalations of terbutaline did not increase FEV_1 over the increase achieved on the highest infusion dose.

Skeletal muscle tremor (Fig. 2). The dose response curves for the two drugs indicated that the potency was about 4 times higher for terbutaline compared with D-2343. Also in this case there was a prolonged effect of D-2343 during the postinfusion period.

Heart rate (Fig. 3). Parallel dose-response curves showed about 4 times increased potency for terbutaline compared with D-2343.

The *blood pressure* was not statistically different between the two treatments.

Selectivity for bronchodilating effect compared with tremor-inducing effect was studied for an FEV_1 increase of 0.2 l. Tremor ratio during the terbutaline experiment was 1.68 ± 0.60 and during D-2343 experiment 2.22 ± 0.38. The difference between the two drugs was 0.54 ± 0.59 (n.s.). Studied for an FEV_1-increase of 0.3 l, the tremor ratio for terbutaline was 2.29 ± 0.81 and for D-2343 2.77 ± 0.47. The difference was 0.47 ± 0.78 (n.s.).

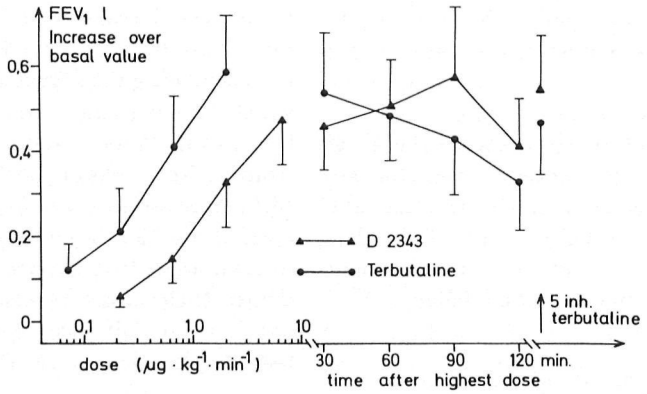

Fig. 1. Mean change of FEV_1 ± SEM (only one direction shown in the graph) after cumulatively increasing doses of D 2343 (basal value 1.08 ± 0.08) and terbutaline (1.09 ± 0.13). Postinfusion values measured 30–120min after the last infusion. To the right: values after inhalation of terbutaline (1.25 mg) 5 min after the 120 min measurement.

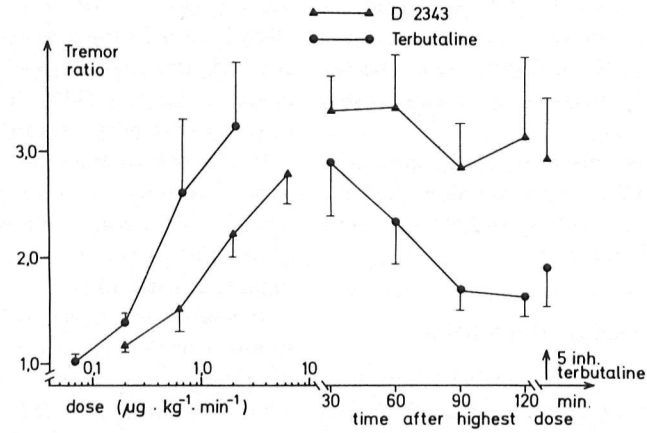

Fig. 2. Mean change of tremor ratio ± SEM (only one direction shown in the graph) after cumulatively increasing doses of D 2343 (118 ± 16) and terbutaline (150 ± 23). Postinfusion values measured 30–120 min after the last infusion. To the right: values after inhalation of terbutaline (1.25 mg) 5 min after the 120 min measurement.

Part 2 – *QH 25 compared with salbutamol*

FEV_1 (Fig 4). The Figure shows the successive measurements of FEV_1 during the whole experiment. There was a very similar increase in FEV_1 during the 2 test days with the different drugs. The individual maximal achieved effect after every dose was chosen for dose-response comparisons. Cumulative dose-response curves showed that QH 25 was about 11 times more potent as a bronchodilator than salbutamol (Fig. 5).

Skeletal muscle tremor (Fig. 6). The dose-response curves were parallel and showed about 9 times higher potency for QH 25 than salbutamol.

Heart rate (Fig. 7). After the first doses of both drugs there was a decrease of heart rate but on the two highest dose levels the increase was 6–10 beats/min. The dose-response curves were almost parallel and the difference in potency was about 13 times higher for QH 25.

Selectivity for bronchodilating effect compared with tremor-inducing effect was studied

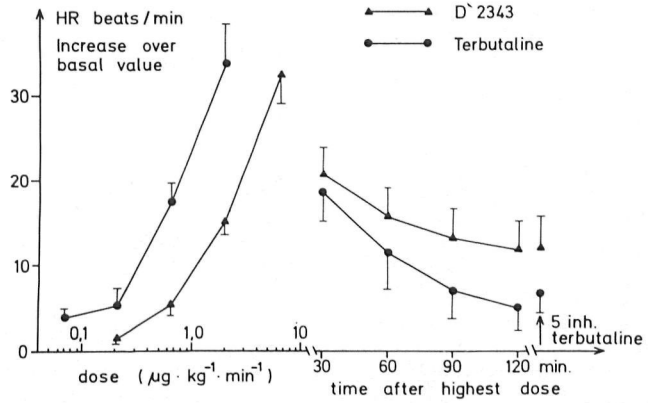

Fig. 3. Mean change of heart rate ± SEM (only one direction shown in the graph) after cumulatively increasing doses of D 2343 (67 ± 3) and terbutaline (66 ± 3). Postinfusion values measured 30–120 min after the last infusion. To the right: values after inhalation of terbutaline (1.25 mg) 5 min after the 120 min measurement.

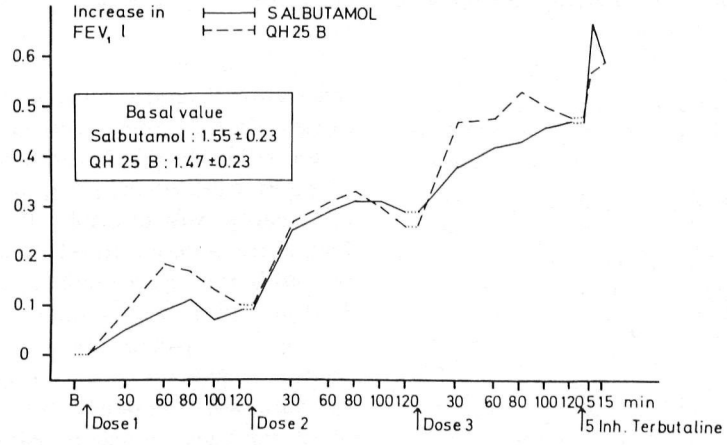

Fig. 4. Mean FEV_1 values after cumulatively increasing doses of salbutamol 2, 6 and 18 mg and QH 25 0.25, 0.75 and 2.25 mg. To the right: values after five terbutaline inhalations.

for equal FEV_1 increase for both drugs. Tremor for QH 25 was 1.79 ± 0.33 and for salbutamol 1.48 ± 0.13. The mean tremor ratio difference was 0.31 ± 0.34 (n.s.).

DISCUSSION

In the further development of β_2-adrenoceptor agonists for asthma therapy several drugs have appeared which are claimed to be more effective on bronchial muscle than on skeletal muscle, thereby decreasing tremor as the dose-limiting factor in maintenance therapy (2, 3, 5). In 1977 Larsen & Hermansen (5) found QH 25 to be more selective for bronchial smooth muscle than for skeletal muscle under certain experimental conditions. Similar observations have been made for D-2343 (2, 8) which also was shown to have an α-blocking property *in vitro*.

The present study was performed to evaluate the possible selectivity in asthmatics. D-2343 could be administered intravenously and therefore the values were more easy to evaluate. The drug could be given in very effective bronchodilating doses, so high that no further broncho-

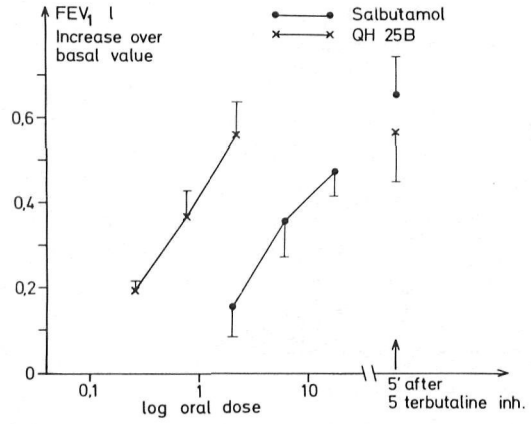

Fig. 5. Mean maximal change of FEV_1 ± SEM (only one direction shown in the graph) after oral intake of three cumulatively increasing doses of salbutamol (basal value 1.55 ± 0.23) and QH 25 (basal value 1.47 ± 0.23). To the right: values 5 min after five terbutaline inhalations (1.25 mg).

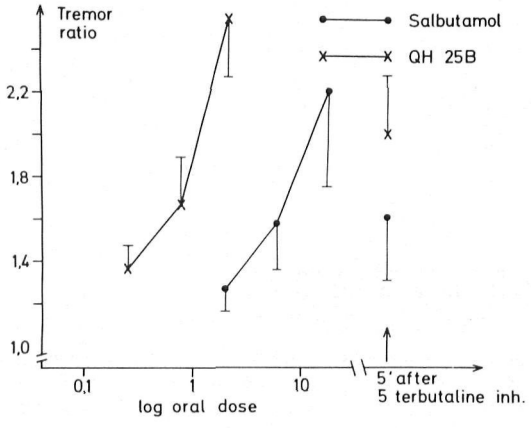

Fig. 6. Mean maximal change of tremor ratio ± SEM (only one direction shown in the graph) after oral intake of three cumulatively increasing doses of salbutamol (basal value 127 ± 39) and QH 25 (basal value 128 ± 39). To the right: values 5 min after five terbutaline inhalations (1.25 mg).

dilation could be achieved by inhalation of terbutaline at the end of the experiment. D-2343 was almost as bronchodilating as terbutaline and the increase of heart rate was equal. Thus, it was shown that D-2343 was a β_2-selective bronchodilator, but our results do not confirm those experimental results showing

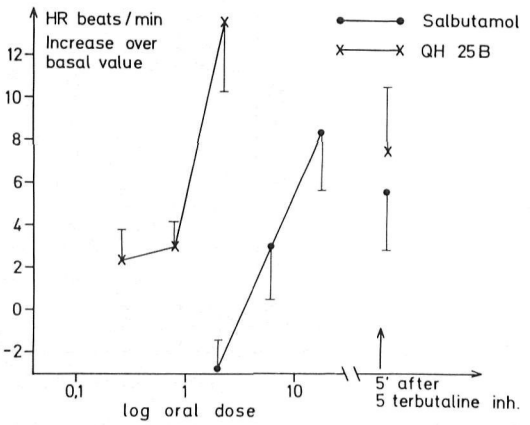

Fig. 7. Mean maximal change of heart rate ± SEM (only one direction shown in the graph) after oral intake of three cumulatively increasing doses of salbutamol (basal value 63 ± 3) and QH 25 (basal value 63 ± 3). To the right: values 5 min after five terbutaline inhalations (1.25 mg).

separation between bronchial and skeletal muscle effect in comparison with terbutaline.

The study of QH 25 had to be done with oral administration of the drug, as no intravenous formulation was available. It was shown that QH 25 was a potent β_2-selective bronchodilator but with the same tendency to give skeletal muscle tremor as salbutamol.

The discrepancies between some experimental animal results and clinical studies can be manifold. As pointed out by Andersson et al. (2) the soleus muscle preparation has proven reliable as an indicator of skeletal muscle tremor. Concerning animal studies of bronchial tone there are several pitfalls pointed out in the same paper (2):

1) the use of different spasmogens in the animal studies, 2) the different methods to estimate airway resistance, such as measurement of respiratory overflow according to Konzett & Rössler (4) and the resistance compliance method by Amdur & Mead (1), 3) furthermore, there seemed to be species differences, which also was shown by Lulich & Paterson (6).

In a study of another β_2-selective adrenoceptor agonist, clenbuterol, where results obtained with the respiratory overflow method (4) were related to results obtained on soleus muscle from cats, the findings indicated selec-

tivity for bronchial β_2-adrenoceptors (2). Clenbuterol has been studied in this laboratory in asthmatics (11). There was no preference of drug action for bronchial smooth muscle compared with skeletal muscle.

Sulfonterol, which appeared in 1975, has also been proposed to have a more pronounced effect on bronchial muscle than skeletal muscle (3). This has to our knowledge not been confirmed clinically.

The present study showed a tendency to longer duration of the D-2343-induced effect on both bronchial, skeletal muscle and heart adrenoceptors. This can be due to slower metabolism of the drug, the formation of an active metabolite, or to a different tissue distribution depending on D-2343's greater lipophilic character (9, 13).

The α-adrenoceptor blocking ability of D-2343 shown *in vitro* is interesting, as it has been shown that α-adrenoceptor agonists can increase bronchial tone (10). However, as no effect on blood pressure was seen in the present study, the dose of D-2343 was too low to significantly affect the α-adrenoceptors in the blood vessels. This could mean that no or very little effect was exerted on the bronchial α-adrenoceptors.

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