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EXPERIENCES OF LONGTERM TREATMENT OF ASTHMA WITH TERBUTALINE*

*A Study on Frequency of
Side Effects and Therapeutic Effect*

By

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In a double-blind study, we earlier showed that terbutaline is a longacting, effective, bronchodilating drug (7). In order to study the frequency of side effects and the longterm therapeutic effect, we began in December 1968, the ambulant treatment of patients with chronic asthma with 5 mg terbutaline three times a day.

SELECTION OF PATIENTS

The patients selected for this trial were well known at the Department of Allergology. All patients suffered from chronic bronchial asthma of the intrinsic type, in some complicated by chronic bronchitis and/or emphysema. With few exceptions, all have for several years regularly visited the out-patient department for control every fourth to sixth week. They had to declare willingness to follow the instructions carefully and to appear for regular controls every month. Previously perorally given bronchodilating agents were withdrawn, but when needed, the patients were allowed to use sympathomimetic drugs for inhalation.

* Bricanyl®, AB Draco, Lund, Sweden. A new selective β -receptor stimulating agent.

MATERIAL

48 patients were treated for 6 months or more, 38 of whom were on long term treatment with steroids. The other 10 were only occasionally given steroids. The mean age for the steroid-treated group (27 female, 11 male) was 51 (20-73) years. The mean age of the group without steroids (5 female, 5 male) was 57 (24-79) years.

METHODS

In the morning between 07.30 and 09.30 every fourth week during the study the patients came fasting to the department for control of certain blood analysis, (Hgb, white blood cells, differential count, ESR, bilirubine, alkaline phosphatases, SGOT, SGPT, creatinine, free fatty acids, cholesterol, triglycerides and blood glucose), recordings of ECG and blood pressure, and medical examination. The blood analyses were made in the Department of Clinical Chemistry at the hospital with the exception of Hgb, ESR, white blood cells, and differential count, which were made at the laboratory of the Department of Allergology. The same nurse drew the blood samples and kept the laboratory journals. Statistical analysis was continuously made in order to reveal possible trends of side effects as early as possible. The statistical analysis was made according to "Student's" t-test on the differences between the initial value and the values at the different times. The following degrees of significance were used: almost significant ($p < 0.05^*$), significant ($p < 0.01^{**}$), and highly significant ($p < 0.001^{***}$). The analysis was made by means of an electronic computer, Olivetti Programma 101.

After 5-6 months of treatment, the patients answered a questionnaire regarding the therapeutic effect and possible side effects. The patient's opinion of the effect of the treatment was scored according to the answers to specified questions regarding the severity of the asthma at rest and at work, cough, expectoration, use of inhalants and steroids compared with six months before the terbutaline treatment. The scores for the different subjective variables were: 3 = much improved, 2 = improved, 1 = unchanged and 0 = worse. Independent of these answers, we classified the effect of terbutaline according to the continuously kept journals compared with the half-year before the treatment with the drug.

RESULTS

Table 1 reports the therapeutic effect and side effects. The material was divided in one steroid and one non-steroid treated group. During the six months before the terbutaline treatment began, the mean dose was 9 mg prednisolone (5-20 mg). This was significantly reduced to a mean of 7 mg

TABLE 1
Effect and Side Effects.

	No. of patients	Mean age (years)	Mean steroid dose (mg)		Therapeutic effect evaluated by the								Side effects
			Before treat- ment	During treat- ment	patients scores				investigator scores				
					3	2	1	0	3	2	1	0	
Patients with steroids	38	51	9	7	13	14	10	1	11	14	12	1	4
Patients without steroids	10	57			2	6	2		2	5	2	1	1
Total	48	52			15	20	12	1	13	19	14	2	5

The material is divided in one steroid group and one group without steroids. The mean steroid dose expressed as mg prednisolone is given for the six months before the treatment and during six months treatment by 5 mg terbutaline three times daily. The therapeutic effect was independently appraised by the patients and the investigator according to the following score system: Much improved = 3, Improved = 2, Unchanged = 1, Worse 0. The number of patients in whom side effects occurred is given.

($p < 0.01$). This figure includes three patients who were able to discontinue the steroid treatment. Previously, these three patients needed 5 mg prednisolone a day. 18 patients were able to reduce the daily doses by amounts varying from 2.5–10 mg. In three patients the mean dose of prednisolone was increased. With few exceptions, the patients' and our evaluation of the therapeutic effect agreed. However, the patients were somewhat more positive than we were. Only two patients became worse during the treatment. Of 48 patients 67 per cent had improved during the terbutaline treatment, and in 29 per cent the effect of terbutaline equalled that of previously given oral bronchodilating drugs.

A low frequency of subjective side effects was noted. Only five of the 48 patients reported new symptoms possibly due to the drug. Two patients noted 'cramps' in hands and feet.

Some patients had trembling in the early stage of the treatment. No patient complained of palpitations.

Normal ECGs did not change, nor did ECGs that were pathological at the beginning of the study.

Table 2 reports heart rate, blood pressure and the different laboratory tests.

There was an obvious decrease in the systolic and the diastolic blood pressure. This applied also to the hypertensive patients.

We could not show any reliable changes in weight, blood picture, haemoglobin, liver function, or kidney function. Neither the blood lipids nor the blood sugar were changed compared to the initial values.

SGOT and SGPT were throughout slightly increased, although not significantly. In most cases SGOT and SGPT fluctuated within the normal values, but many patients had single peak values. During the study 3 patients were taking oral contraceptives and one patient initially had a cholestasis due to gallstone passage. 4 other patients with high initial values showed unstable and still elevated values during the study. For several years, the SGOT and SGPT values of one of those patients for undetected reasons have fluctuated considerably, but are now normal. Another patient, who has had elevated SGPT values is now after 9 months treatment becoming normal.

There was no tendency for changes in the metabolic variables, apart from the triglycerides, which were significantly decreased after 3 months. No further increases were found in the few patients with pathologic blood lipids; three patients had slightly increased triglycerides and two had slightly increased cholesterol values. The blood sugar level was unchanged in the two diabetic patients. During the study, a mild diabetes was diagnosed in one patient.

Two patients have died. One man aged 64 died in chronic respiratory insufficiency. A woman aged 61 with coronary heart disease died after reinfarction and bronchopneumonia.

Three patients have discontinued the treatment and did not

TABLE 2
Mean values and standard errors of the means of the different variables investigated.

	Initial value	After treatment for 1 month	After treatment for 3 months	After treatment for 6 months
Heart rate beats/min.	83	± 2.5	86	± 2.4
Blood pressure mm Hg				
Systolic	148	± 2.8	141**	± 3.0
Hgb g%	14.0	± 0.16	13.8	± 0.17
Diastolic	91	1.4	87**	± 1.6
Differential count per cent				
White blood cells/mm ³	7000	± 350	7300	± 390
Non. segm. neutr.	1	± 0.1	1	± 0.1
Segm. neutr.	62	± 1.5	66	± 1.6
Eosinophils	5	± 0.6	5	± 0.6
Basophils	1	± 0.1	1	± 0.1
Lymphocytes	29	± 1.2	25	± 1.2
Monocytes	3	± 0.2	3	± 0.3
Thrombocytes × 1000/mm ³	187	± 8.2	170*	± 8.2
ESR mm/1 hour	11	± 1.2	12	± 1.6
Creatinine mg%	0.9	± 0.03	1.0	± 0.04
Alk. phosphatases units	5.2	± 0.25	4.9	± 0.25
Bilirubin mg%	0.5	± 0.04	0.5	± 0.02
SGOT units	21	± 2.0	24	± 1.3
SGPT units	27	± 3.2	27	± 2.6
Thymol units °	0.03	± 0.003	0.02	± 0.003
Cholesterol mg%	275	± 5.6	274	± 6.2
Triglycerides mg%	1.3	± 0.07	1.2	± 0.07
FFA µE/l †	597	± 30.1	619	± 30.1
Glucose mg% §	78	± 2.4	78	± 2.7
			80	± 2.8
			609	± 24.2
			1.1*	± 0.06
			279	± 5.8
			0.02	± 0.002
			3.1	± 3.0
			24	± 1.7
			0.6	± 0.03
			5.9*	± 0.38
			1.0	± 0.04
			12	± 1.3
			3	± 0.2
			189	± 8.3
			31	± 1.5
			1	± 0.1
			5	± 0.6
			60	± 1.8
			1	± 0.1
			7400	± 320
			84	± 2.2
			136***	± 2.5
			14.0	± 0.15
			84***	± 1.4

° 47 patients. † 45 patients. § 47 patients.

appear for control. A man, 64 years of age, stopped the drug after 6 months. During the terbutaline treatment, he discontinued prednisolone treatment. A woman aged 27 did not want to appear for blood samples and control. A man aged 43 discontinued the treatment after 2 months for the same reason.

DISCUSSION

It is difficult to evaluate the longterm effect of a certain drug in diseases with a periodic course, such as asthma. When, as in this study, previous effective symptomatic treatment is replaced by a new drug, a double-blind study against placebo cannot be performed in patients with severe chronic asthma. We preferred an open trial to a double-blind trial as the main aim of the present study was to reveal possible side-effects and secondly to study the longterm therapeutic effect of terbutaline. The bronchodilating effect has previously been proved in acute experiments (7).

However, the reduction of the steroid dose in patients with permanent need for steroids is an often used parameter to prove the therapeutic effect of a new drug. The reduction of steroid doses in this study supports the subjective evaluation of the effect made by the patients and by us. In 96 per cent of the cases, both we and the patients found the therapeutic effect of terbutaline to be as good as, or better than previously used bronchodilating drugs.

Common side effects of sympathomimetic agents: tachycardia, palpitations, and trembling, have appeared at a remarkably low frequency in this study. The pulse rate of some patients, which previously permanently in rest was high (100–110 beats per minute) decreased to 70–80 beats per minute during the terbutaline treatment. A young woman with a very therapy-resistant intrinsic asthma had for some years orthostatic reactions with typical sympathotonic changes in ECG combined with supraventricular ectopic beats. The changes were considered not to be due to heart disease

but to high endogenous and exogenous adrenergic stimulation. During the terbutaline treatment the ECG changes disappeared and the previous misuse of isoprenaline ceased. The arrhythmia and the ortostatic reaction have disappeared and the pulse rate in rest was reduced to 70-90 beats per minute.

The systolic and the diastolic blood pressures fell significantly during the terbutaline treatment. In previous studies, terbutaline slight decreased the diastolic blood pressure in asthmatic patients; after injection (2) as well as oral administration (7). This could be explained by the peripheral vasodilating properties of the drug, which were shown in a resorption study in healthy volunteers (3). This decrease could also be due to reduced sympathetic tonus, secondary to improvement of the disease. Before the terbutaline treatment most of the patients were regularly treated with ephedrine, which stimulates the α -receptors as well as the β -receptors and thereby might have caused higher peripheral resistance.

The observed slight mean increases of SGOT and SGPT-values were moderate and were probably not due to terbutaline. We could not find anything in the literature to indicate that agents with similar chemical configuration would have a toxic effect on the liver, nor could such effect be found in three months toxicity study of rats and dogs after high doses of terbutaline (1). The serum enzyme values fluctuated considerably in the individual patient. This may perhaps be due to changes in the disease (6) and connected medication.

There was no changes in the metabolic variables from the initial values. In acute experiments in healthy volunteers, terbutaline injections caused an increase in FFA, glycerol, and blood sugar (5). No similar tests with terbutaline in asthmatic patients have as yet been made. However, in this respect, asthmatics may respond less than healthy volunteers to sympathomimetics (8, 9).

The catechocholamines act through an enzyme, cyclic 3', 5'-AMP, which also mediates the glycogenolysis and the

lipolysis (4, 10, 12). According to the hypothesis by Szentivanyi regarding partial β -receptor blockade as pathogenic cause of asthma (11), there might also be a difference in the reaction pattern of these metabolic mechanisms.

The β -receptor blockade theory as a pathogenetic factor in asthma is supported by many authors and based on reliable studies. Therefore it seems justifiable to consider agents with selective β -stimulating properties as specifically acting drugs in asthma therapy.

SUMMARY

48 patients with chronic intrinsic asthma were treated with a new selective β -receptor stimulating agent, terbutaline. The therapeutic and side effects were checked monthly during six months. 5 mg terbutaline was given orally three times a day and replaced previously regularly used oral bronchodilating drugs.

Careful control of blood picture, liver function, blood lipids, blood sugar, and of cardiovascular effects could not reveal any side effects of importance. The subjective side effects were fewer and less than those experienced with previously used oral sympathomimetic drugs. In 96 per cent of the cases, the therapeutic effect was as good as or better than the other drugs previously used. The study shows that terbutaline has the necessary properties of a drug for long-term treatment of asthma, good therapeutic effect, no toxic effects, and only slight dose-depending side effects.

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