Mean Total Sympton Scores before, during, and after Treatment with Mepiprazole and Placebo

	Agent	Group 1	Agent	Group 2
Pretreatment		11·17		13·67
After 2 weeks	Placebo	7·5	Mepiprazole	7·25
" 4 "		7·5		3·0
" 6 "	Mepiprazole	5·0	Placebo	2·75
" 8 "		3·5		6·5

active group continued to improve. In those who switched at four weeks from the active to the placebo group there was at first a "steady state" of symptoms. After further medication with placebo the total score for the target symptoms sharply increased (fig. 3). In those who switched from the placebo to the active group at four weeks there was a continuous drop in the score rating for target symptoms until the end of the trial (fig. 3). The difference between the placebo group and the active group was statistically significant ($P < 0.05$).

Discussion

The results of this trial of a tranquillizing agent alone in the treatment of the irritable bowel syndrome could lead to a different view of the aetiology of this disorder. When higher centres in the brain supersede the autonomic system in the regulation of the gut (Wolf, 1967) emotional disturbances may well affect the normal functioning of the lower bowel. Domestic or financial stress, occupational worries, and marital difficulties are common findings in the history of the syndrome (Chaudhary and Truelove, 1962). Treatment with a tranquillizer like mepiprazole which inhibits aggression and acts on certain monoaminergic systems might therefore be expected to be helpful (Fuxe, 1974). Nevertheless, tranquillizers do not abolish the cause of the stress and the patient should also be offered all possible support to try to overcome the psychosocial factors.

When gastroenterological symptoms are present disturbed autonomic function is clear-cut evidence of an extension of a primarily psychic irritation to the psychosomatic level. Thus the use of tranquillizing drugs seems to be justified. In the first two weeks of the present study the effect of the active drug did not differ significantly from that of the placebo. When considering the mean duration of the symptoms (seven years) and the psychic aetiology of the disorder a fairly good response to the placebo could be expected. Patients with the irritable bowel syndrome seem to respond to any drug at first, especially if they have confidence in their physician. After two weeks, however, our placebo group remained stationary whereas the group on the active substance continued to improve. After four weeks the difference in response was quite obvious.

The results after the cross-over at four weeks confirmed the findings in the first four weeks. The initial placebo group showed the same improvement as did the group which began with mepiprazole. That the symptoms of the patients who had received the active drug first did not start to get worse until after a fortnight could have been due to a carry-over effect. That their symptoms worsened in the second half of the placebo period is evidence that the placebo was ineffective compared with mepiprazole. It also indicates that the irritable bowel syndrome is a chronic condition which can be helped but not cured by treatment. Patients with the disorder require treatment over a long period.

In our opinion further studies are needed to evaluate the place of psychotropic drugs in the treatment of functional disorders of the gut. The present study shows that they relieve the symptoms of the irritable bowel syndrome.

We thank E. Merck, Darmstadt, who provided the capsules of mepiprazole and placebo.

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Prevention of Exercise-induced Asthma by Indoramin

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Summary

Indoramin, an alpha-adrenoceptor blocking drug, has been found to prevent the occurrence of exercise-induced bronchoconstriction. Evidence is provided in two cases that this was not due to the antihistamine properties of indoramin.

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Introduction

We have been interested in the possible application of alpha-adrenergic blocking drugs in the treatment of asthma after we found evidence of the existence of these receptors in the human bronchial tree (Prime *et al.*, 1972). We investigated the effects of a relatively new alpha-blocking drug, indoramin, on exercise-induced asthma in 11 patients who showed the typical phenomena of this disorder.

Indoramin is an alpha-adrenergic blocking agent (fig. 1). Its pharmacology has been reported in detail by Alps *et al.* (1970 a, b, c). Clinically, indoramin has been studied as an antihypertensive agent (Lewis *et al.*, 1973). One property of this drug which made it of particular interest for our studies in the treatment of asthma was the fact that it has been shown to be concentrated in the lung (Johnson, 1974). In addition to its alpha-blocking action it is also an antihistamine and antagonizes serotonin.

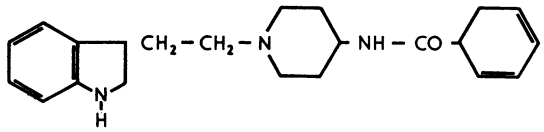

FIG. 1—Structure of indoramin.

Patients and Methods

Our choice of patients was confined to those who complained only of wheezing and undue breathlessness brought on by exercise and who at other times were apparently normal. Eleven patients were studied. Three were men ranging in age from 27 to 41 years and eight were women aged between 13 and 50 years. Measurements of forced expiratory volume in one second (FEV_1) at rest were lower than predicted in all the subjects except one (mean 83%, range 69%-104%), but none complained of symptoms except after vigorous exercise. Five of the patients were found to have positive skin reactions to an assortment of common antigens.

EXPERIMENTAL DESIGN AND PROCEDURE

The objects of the investigations were fully described to each patient before they were asked to take part, and all willingly consented. All drugs were stopped for a period of 12 hours before any trials were made. The patients came to the laboratory at about 9.30 a.m. and after a short rest measurements of airways resistance (Raw), thoracic gas volume (Vtg), functional residual capacity, and FEV_1 were made together with those of blood pressure and pulse rate. These measurements were repeated 90 minutes later. The patients then exercised on the bicycle ergometer for a time and at a load sufficient to induce bronchoconstriction. The amount of exercise required varied between patients both in rate and duration from 600 watts in six minutes to 1,050 watts in 10 minutes (table I). The severity of bronchoconstriction was assessed immediately after stopping the exercise by measuring Raw and Vtg followed by a recording of FEV_1. These measurements were repeated five and 10 minutes later as were measurements of blood pressures and pulse rate. On a second day baseline measurements were again made and then each patient was given a dose of indoramin varying between 20 mg and 70 mg by mouth. The dose given to each patient depended on his weight and age (Royds *et al.*, 1972). Ninety minutes later the resting measurements were repeated, then the patients exercised and subsequent observations were made as on the first day.

In two subjects the possibility that the effect of the drug observed was due to its antihistaminic properties rather than to its alpha-blocking effect was investigated. On a third day, after the first baseline measurements had been made, they were given 4 mg of chlorpheniramine (Piriton) by mouth instead of indoramin. A second set of resting measurements was made 90 minutes later before assessing the effects of exercise as described above.

In addition to these experiments one patient was given indoramin on two separate occasions; on the first the dose was 50 mg and on the second 60 mg.

TABLE I—*Amount of Exercise (Wattage by Time) needed to induce Bronchoconstriction in 11 Patients*

Case No.	
1	75 W × 5 min + 90 W × 2 min
2	75 W × 3 min + 90 W × 4 min + 100 W × 3 min
3	70 W × 5 min + 80 W × 2 min + 90 W × 2 min
4	60 W × 7 min
5	75 W × 2 min + 85 W × 2 min + 90 W × 2 min
6	70 W × 10 min
7	60 W × 5 min + 70 W × 2 min
8	75 W × 2 min + 100 W × 9 min
9 (50 mg)	75 W × 5 min + 85 W × 2 min + 100 W × 1 min
9 (60 mg)	75 W × 5 min + 85 W × 2 min + 100 W × 1 min
10	60 W × 3 min + 70 W × 2 min + 80 W × 2 min
11	65 W × 4 min + 75 W × 3 min

Results

In every subject indoramin caused some degree of bronchodilatation as observed by a rise in FEV_1 and fall in specific airway conductance (SGaw) measured 90 minutes after dosing. This is in keeping with the alpha-blocking action of the drug. The protective effects of indoramin on the exercise-induced bronchoconstriction are shown in tables II and III, which list the changes in SGaw. In some cases exercise caused a reduction in SGaw but in no case did this value fall below the control level. The effects of indoramin on the more familiar FEV_1 are shown averaged over all the subjects in fig. 2.

Chlorpheniramine did not prevent bronchoconstriction after exercise in either of the patients to whom it was given. The measurement most affected in both these patients was SGaw. On the control days SGaw fell from 0·088 $kPa^{-1}s^{-1}$ to a minimum of 0·17 in the case of the 13-year-old girl and from 0·5 $kPa^{-1}s^{-1}$ to 0·12 in the older woman. After giving 4 mg of chlorpheniramine SGaw fell from 0·93 $kPa^{-1}s^{-1}$ to 0·16 in the first case and from 1·15 $kPa^{-1}s^{-1}$ to 0·20 in the second. Indoramin had prevented these changes and the changes in FEV_1 in both patients.

The patient who was given two different doses of indoramin on two successive days (case 9) was not protected by the smaller dose of 50 mg but responded well to the second dose to 60 mg. It is unusual that such a small increase in dose should have produced such a striking change in therapeutic effect. The effect of diet and other factors on absorption may be an explanation.

TABLE II—*Specific Airway Conductance ($kPa^{-1}s^{-1}$) in 11 Patients at Rest and after Exercise*

Case No.	1	2	3	4	5	6	7	8	9	9	10	11
Baseline	0·94	0·90	3·70	1·25	0·62	0·70	0·75	0·79	0·53	0·75	0·88	0·50
After 90 min	0·79	0·50	3·75	1·25	0·40	0·70	0·75	0·10	0·82	0·72	0·88	0·62
Immediately after exercise	0·47	0·16	1·78	0·47	0·34	0·43	0·38	0·67	0·63	0·69	0·20	0·19
5 min after exercise	0·23	0·25	1·87	0·69	0·25	0·44	0·36	0·60	0·47	0·47	0·17	0·12
10 min after exercise	0·30	0·22	0·93	1·07	0·25	0·41	0·30	0·41	0·33	0·40	0·18	0·14

Note: The units for SGaw are S. 1. units and are 10 times the more familiar units.

TABLE III—*Specific Airway Conductance ($kPa^{-1}s^{-1}$) at Rest and after Exercise in 11 Patients given Indoramin*

Case No.	1	2	3	4	5	6	7	8	9	9	10	11
Baseline	0·44	0·32	1·67	1·00	0·19	0·42	1·00	0·58	0·56	0·83	1·25	0·47
Dose of indoramin (mg)	60	70	60	50	70	40	40	40	50	60	20	40
After 90 min	1·50	0·40	2·35	1·50	0·53	1·10	1·15	1·07	0·75	0·87	1·36	1·50
Immediately after exercise	1·00	0·25	1·88	1·87	0·19	1·00	2·50	1·36	0·29	1·25	0·93	0·83
5 min after exercise	1·50	0·29	1·50	1·87	0·21	0·75	1·15	1·20	0·23	0·94	0·42	0·62
10 min after exercise	1·50	0·30	2·15	1·87	0·30	0·65	1·29	1·07	0·28	0·75	0·83	0·78

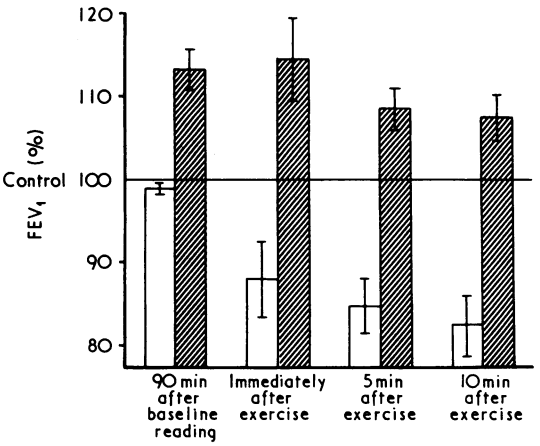

FIG. 2—Effect of indoramin on forced expiratory volume in one second (FEV_1) in 11 patients suffering from exercise-induced bronchoconstriction. Open columns show mean FEV_1 (±S.E.) before and after standard exercise sufficient to produce bronchoconstriction. Hatched columns show the mean FEV^1 values (± S.E.) after single oral doses of indoramin given next day under identical conditions.

The arterial blood pressures were not significantly or consistently affected from the beginning to the end of the experiments in any of the patients. The usual transient rise in systolic pressure was seen immediately after exercise. The same applied to the pulse rates.

Discussion

Our findings strongly suggest that alpha-adrenoceptors are involved in the mediation of exercise-induced bronchoconstriction, but it must be pointed out that all the alpha-blocking drugs have more or less powerful antihistaminic properties (Alps *et al.*, 1972). In the case of both thymoxamine and indoramin these properties are of the same order of potency as the alpha-blocking action (Birmingham and Szolcsanyi, 1965; Alps *et al.*, 1972). In the two subjects to whom we gave chlorpheniramine we were unable to show that this specifically antihistamine drug was effective in preventing the bronchoconstriction though both patients had responded to the protective effect of indoramin. The dosage of both chlorpheniramine and indoramin given was selected on the basis of the work of Hedges *et al.* (1971) and Royds *et al.* (1972) to be about equipotent in terms of their effects in preventing the occurrence of skin weals after an intradermal injection of histamine. This observation strengthens the hypothesis that the action of indoramin is primarily against alpha-adrenoceptor activity in exercise-induced bronchoconstriction.

The causes of exercise-induced airway obstruction are not yet clear. One possibility, supported by our results, is that it is an unusual response to endogenous catecholamine release during exercise (Gray and Beetham, 1957), which presupposes that alpha-receptors exist within the human bronchial tree which exert a constrictor effect upon the bronchi when stimulated by noradrenaline. The existence of such receptors can be shown easily enough even in some non-asthmatic subjects by giving phenylephrine after pretreating the subjects with the beta-receptor blocking drug propranolol (Prime *et al.*, 1973). In the case of patients who develop bronchoconstriction after exercise these alpha-receptors would have to be either more numerous or more sensitive than the bronchial beta-receptors, which might themselves be relatively refractory. Among the pharmacological agents which prevent or minimize this unusual response to exercise are isoprenaline (and other beta-adrenergic agonists) and sodium cromoglycate, and to these we would add alpha-receptor antagonists like indoramin. We have other experimental data which show that thymoxamine has a similar, though more evanescent, effect to indoramin in this condition. Exercise bronchoconstriction is not usually prevented by atropine or other anticholinergic drugs.

We thank the patients who voluntarily took part in the investigations and our colleagues who referred patients to us. John Wyeth and Brother Ltd. kindly defrayed the expenses of the investigation and supplied us with indoramin. Drs. E. S. Johnson and Peter Southgate of John Wyeth and Brother Ltd. were very helpful in giving us references on the pharmacology of the drug and commenting on the results of the investigation.

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