SUMMARY

Entamoeba histolytica is important in terms of frequency as a cause of dysentery in Cape Town children attending a large outpatient department. In patients from 2 to 12 years old it is a more commonly identified pathogen than salmonellae and shigellae taken together. Under outpatient conditions, a 5-day course of metronidazole (Flagyl) gave better results in the treatment of intestinal amoebiasis than the combined regimen of tetracycline, chloroquin and dihydroxyquinoline formerly used, and has now become the treatment of choice.

ANMINOREX FUMARATE: A DOUBLE-BLIND TRIAL AND EXAMINATION FOR SIGNS OF PULMONARY ARTERIAL HYPERTENSION*

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Aminorex (2-amino-5-phenyl-2-oxazoline) fumarate† is an appetite suppressant which differs from other drugs of this sort both in chemical structure and in profile of action.5 Its structural formula is shown in Fig. 1. It is not an amphetamine and produces minimal stimulation of the central nervous system. Although the drug has been on the European market since the end of 1965 and is widely used in these countries, few controlled trials have been reported. For this reason a double-blind cross-over trial comparing aminorex fumarate with placebo was commenced early in 1968.

Shortly before the conclusion of the trial, a further justification for the study became apparent. During recent years a group of Swiss cardiologists has observed a striking increase in the number of cases of 'primary' pulmonary arterial hypertension.6 In seeking an explanation for this observation they noted that a large portion of their patients, particularly aminorex. The opportunity was therefore taken to look specifically for clinical, electrocardiographic and radiological evidence of pulmonary arterial hypertension and its sequelae in the patients taking part in the trial.

MATERIAL AND METHODS

The trial was carried out in the obesity clinic of the Johannesburg Non-European Hospital. It was designed to include 40 patients but 20 failed to complete the course. These fell into 2 groups: those who failed to report back, usually after the first visit (12 patients), and those who proved to be unreliable in taking their tablets (8 patients) and were therefore withdrawn from the trial. This high 'drop-out' rate has been a feature of trials of this nature when carried out on Bantu patients. The failure to return for follow-up did not appear to be due to side-effects (9 of the subjects were receiving placebo, the remaining 3 aminorex). The patients were allocated to treatment at random. Of those who completed the course, 12 were in group I (aminorex for 120 days followed by placebo for 120 days) and 8 were in group II (placebo for 120 days followed by aminorex for 120 days). Eighteen were Bantu and 2 Coloureds. Sixteen were females and 4 males. Their ages ranged from 36 to 63 years, with a mean of 50. At the first visit, the subject's weight (in underclothes), height and triceps skinfold thickness were measured. The percentage by which each individual's weight exceeded the ideal was calculated from tables prepared by the Metropolitan Life Insurance Company (1960). The triceps skinfold thickness varied from 14 to 57 mm. with a mean of 32. The % overweight ranged from 21 to 142 with a mean of 60.6. The sex, age and race distribution, initial and ideal weights and triceps skinfold thickness in the 2 groups of subjects are shown in Table I. They were advised about a weight-reducing diet and given typewritten instructions to refer to. The patients received numbered bottles containing tablets of aminorex fumarate (10 mg. of base) or placebo which were identical in appearance and flavour. The key to the numbering of the bottles was made available to me only on completion of the trial. The patients were instructed to take one tablet before breakfast each morning and were then seen at 2-weekly intervals when their weights were recorded.

The subjects were examined clinically when first seen, after 120 days and at the end of the trial. At the initial examination, none was found to be somnolent, cyanosed or to show other signs of the Pickwickian syndrome. Carbon dioxide retention, as judged by measurement of the carbon dioxide content of the blood, was not observed. Apart from one patient who had suffered from attacks of bronchial asthma for 5 years, there was no history of chronic lung disease and none of the patients showed evidence of thoracic deformity, pulmonary disease or cor pulmonale. Three of the subjects had varicose veins but none gave a history of varicose veins or had previously had varicose veins. Four were known to have systemic hypertension, 3 diabetes and 1 pernicious anaemia, and in 2 there was a history of myocardial infarction. Electrocardiograms

REFERENCES


*Date received: 24 October 1969.
†Menocil; McNeil Laboratories and Cilag Chemie.
TABLE I. RELEVANT CLINICAL CHARACTERISTICS OF THE 20 SUBJECTS

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug sequence</th>
<th>No.</th>
<th>Age Range</th>
<th>Sex</th>
<th>Race</th>
<th>Ideal weight (lb.)</th>
<th>Actual weight (lb.)</th>
<th>Triceps skinfold thickness (mm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Aminorex</td>
<td>Placebo</td>
<td>12</td>
<td>49-2 34-63</td>
<td>0 12</td>
<td>11 1</td>
<td>212-3 108-134</td>
<td>209-9 157-295</td>
<td>35-55 25-57</td>
</tr>
<tr>
<td>II Placebo</td>
<td>Aminorex</td>
<td>8</td>
<td>51-1 37-62</td>
<td>4 4</td>
<td>7 1</td>
<td>130-9 117-145</td>
<td>182-1 153-222-5</td>
<td>26 19-41</td>
</tr>
</tbody>
</table>

TABLE II. WEIGHT CHANGE (BY GROUPS) DURING TREATMENT WITH AMINOREX FUMARATE

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean initial weight (lb.)</th>
<th>Weight change (lb.)</th>
<th>Frequency by type change in weight</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
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<td>-9.04</td>
<td>Decrease 10 Increase 1 No change 1</td>
<td>12</td>
</tr>
<tr>
<td>II</td>
<td>182-1</td>
<td>7.59</td>
<td>8 0 0</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>18 1 1</td>
<td>20</td>
</tr>
</tbody>
</table>

TABLE III. WEIGHT CHANGE (BY GROUPS) DURING TREATMENT WITH PLACEBO

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean initial weight (lb.)</th>
<th>Weight change (lb.)</th>
<th>Frequency by type change in weight</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>209-9</td>
<td>+3.12</td>
<td>Decrease 4 Increase 8 No change 0</td>
<td>12</td>
</tr>
<tr>
<td>II</td>
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<td>-6.19</td>
<td>6 2 0</td>
<td>8</td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td>10 10 0</td>
<td>20</td>
</tr>
</tbody>
</table>

...and chest X-rays were recorded at the end of the trial. Blood was taken for blood urea level and serum glutamic oxaloacetic transaminase, alkaline phosphatase and bilirubin levels as well as haematological examination before commencing, in the middle of, and at the end of the trial. Urinalysis was performed at these times.

RESULTS

Weight Loss

Weight change on aminorex varied from +3 to −32.3 lb. with a mean of −8.6 lb. (−2.15 lb. per month). Weight change on placebo ranged from +18 to −34 lb. with a mean of −1.1 lb. (−0.27 lb. per month). The difference is statistically highly significant (p<0.001). The results by groups are shown in Tables II and III.

During the first 120 days patients lost weight on both aminorex (−9.04 lb.) and placebo (−6.19 lb.) and the difference is not statistically significant. This illustrates the fact that patients entered into a trial of this sort will usually lose weight initially, even on placebo. By contrast, during the second half of the trial, patients on aminorex again lost weight (−7.59 lb.), whereas those on placebo gained weight (+3.12 lb.), and this difference is statistically highly significant (p<0.001). The hypothesis that no change in weight will occur during 120 days’ treatment with aminorex can be rejected at the p<0.01 level of confidence. However, the hypothesis that no change in weight will occur during the 120 days of placebo therapy cannot be rejected. Weight loss on aminorex continued throughout the 4 months without evidence of tolerance developing.

Side-Effects

None of the patients complained of dyspnoea, chest pain or swelling of the ankles. Clinical examination failed to reveal evidence of giant ‘a’ waves in the jugular venous pulse, an increase in the intensity of the pulmonary component of the second heart sound, narrow splitting of the second heart sound or a right atrial or ventricular sound. No ejection clicks or murmurs of pulmonary or tricuspid incompetence were heard. There were no clinical signs of right ventricular hypertrophy or failure. There was no electrocardiographic evidence of enlargement of the right atrium or ventricle, or of right axis deviation in the mean frontal plane QRS axis (a slight change in this axis may of course have been missed as electrocardiograms were not performed before the trials commenced). Chest X-rays revealed no prominence of the pulmonary artery segment, right atrial or ventricular hypertrophy or dilatation, and there was no obvious attenuation of the peripheral pulmonary vessels. One patient, an elderly diabetic, was admitted to hospital in hypoglycaemic precoma 4 months after finishing the trial. There was no clinical evidence of pulmonary arterial hypertension or cor pulmonale. Three days after admission, he collapsed suddenly and died. A presumptive diagnosis of myocardial infarction was made. Necropsy was not performed.

The patient who complained of mild insomnia, no significant stimulation of the central nervous system was detected. No abnormalities were observed in the urine or in the biochemical or haematological indices.

DISCUSSION

Aminorex fumarate has been found to be significantly more effective than placebo in the treatment of obesity. This appetite suppressant effect was achieved with minimal stimulation of the central nervous system and without the development of tolerance, the 2 effects which severely limit the usefulness of the amphetamines. Aminorex may therefore have proved to be a useful drug in the management of refractory obesity. However, following a report of an apparent association between ‘primary’ pulmonary...
arterial hypertension and appetite suppressants, particularly aminorex, the drug has been withdrawn from the market while proof of a cause-and-effect relationship is sought.

Gurtner and co-workers noticed a 10-fold increase in the incidence of 'primary vascular cor pulmonale' in their clinic in Berne since mid-1967. A retrospective analysis of the case records showed that many of their patients were overweight and had taken appetite suppressants. Most had received aminorex, the most widely used appetite suppressant in Switzerland at that time. In the entity of 'primary vascular cor pulmonale' Gurtner includes thrombo-embolic heart disease, and at least 3 of the 17 patients may have belonged in this category: one gave a history of recurrent pulmonary emboli, while varicose veins requiring surgery were present in another 2, one of whom was also receiving oral contraceptives. A further 7 subjects had had at least one pregnancy or abortion and in 4 the figure was 3 or more. The incidence of venous thrombosis in the legs and pulmonary emboli is known to be higher in obese individuals. Finally, gross obesity alone may be associated with pulmonary arterial hypertension, but only 2 of Gurtner's cases belonged in this category. Even after the exclusion of those cases in which an alternative explanation for the pulmonary arterial hypertension is possible, there remains a group of patients with no obvious cause for this grave condition, and it is in these that aminorex may be incriminated.

Pulmonary arterial hypertension was found in some of Gurtner's patients as long as 14 months after discontinuation of the drug, so that if a cause-and-effect relationship is established, it will mean that aminorex is capable of producing irreversible changes in the pulmonary vessels. This would be an unprecedented direct side-effect of a drug. The only association of this sort known at present is an indirect one: the increased tendency to venous thrombosis and pulmonary embolism in individuals taking oral contraceptives. Lung biopsies were performed in 4 of Gurtner's patients. No evidence of pulmonary emboli was found. The only changes were non-specific intimal thickening and fibrosis with hyalinization of the media, changes which may be seen in pulmonary arterial hypertension from a variety of causes. However, in 5 necropsies performed subsequently, Gurtner has found evidence of fresh or old pulmonary emboli. In only one of these were thrombotic changes detected in the venous system.

In the present study no clinical, electrocardiographic or radiological evidence of pulmonary arterial hypertension or its sequelae was found. It is possible that slight elevations of pulmonary pressure may have been missed and would only have been detected at cardiac catheterization. However, it was not felt justified or ethical to submit these subjects to this procedure, more especially as the diagnosis of significant degrees of pulmonary arterial hypertension can almost always be made on the criteria used in this study.

An investigation of this sort has obvious limitations. In spite of these, it was felt worth while to record our findings. An answer to the important question whether or not aminorex and other appetite suppressants may give rise to pulmonary arterial hypertension must await further case reports and the results of experimental studies.

**SUMMARY**

An apparent association between a new appetite suppressant, aminorex fumarate, and irreversible pulmonary arterial hypertension has recently been described. The opportunity was therefore taken to look for clinical, electrocardiographic and radiological evidence of this complication in 20 patients taking part in a nearly completed trial comparing aminorex with placebo. No evidence of pulmonary arterial hypertension or its sequelae was found. The trial showed aminorex to be significantly more effective than placebo in the treatment of obesity.

I wish to thank Dr. R. E. Bauling of Ethnor Laboratories, Johannesburg, for supplies of aminorex fumarate and placebo and also for secretarial assistance.

**REFERENCES**


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**A RANDOM TRIPLE-BLIND STUDY OF TABLETS PENICILLIN VK, INJECTION PENILENTE FORTE AND INJECTION BICILLIN L-A IN PROPHYLAXIS OF TONSILLITIS**

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This study was initiated and carried out at Coronation Hospital because of an overwhelming waiting list for tonsillectomy and the difficulty of resolving the list due to shortage of beds and operating time. It was therefore decided to run a triple-blind trial of an oral penicillin, a semi-long-acting penicillin by injection and a long-acting penicillin by injection.

With the assistance of Wyeth Laboratories, we investigated firstly the most efficacious method of dealing with recurrent tonsillitis, and secondly, while doing so, we hoped to cure, if possible, some of these cases and thus reduce the ever-lengthening waiting list.

**METHOD OF TRIAL**

The patients were chosen from those referred to the ear, nose and throat outpatient department because of recurring attacks of tonsillitis. They were all under the age of 12 years. Their selection depended upon their history and our criterion was more than 4 attacks of tonsillitis in any one year, with or without otitis media. Any child who

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