

Discussion

These results show, firstly, that each of the three components of the standard treatment for IBS—that is, the tranquilliser, anticholinergic, and bland bulk-provider—is more effective as treatment than the corresponding placebo; secondly, a combination of two agents tends to be more helpful than a single agent; and, thirdly, the use of all three agents together is better than any two.

The apparent therapeutic value of placebo in some controlled studies of treatment of IBS is largely inversely proportional to the duration of the trial. Over a short period, as in the three-week trial by McHardy *et al*¹ of chlordiazepoxide with clidinium bromide, up to 35% of patients may be relieved by a placebo. This is comparable with the improvement shown in the present study after four weeks by three of the 12 patients who received the dummy preparations (abf). In a trial lasting two or three months it is not unreasonable for no patients to improve with placebo, as Kleckner² found in his evaluation of mepenzolate bromide, though this prompted Ivey³ to reject his findings without further consideration. Rhodes *et al*,⁴ testing phenobarbitone, belladonna, and placebo, found only one patient out of 15 who showed a preference for placebo compared with seven for each of the two active drugs. All the evidence thus suggests that patients with IBS derive little benefit from placebo treatment.

Although results of conventional medical treatment are better than those of placebo treatment, they are far from perfect. Even the most effective combination tested in the present study—namely, lorazepam, hyoscine butylbromide, and ispaghula husk

—resulted in improvement in only seven out of 12 patients receiving it. Some other combination of therapeutic agents, however, might possibly be much more effective. For example, it is not only scientifically but also economically important to find out whether ordinary wheat bran is an effective substitute for ispaghula husk. Mebeverine may be better than an anticholinergic drug, and an antidepressive better than a tranquilliser. These and other combinations of therapeutic agents need to be tested in IBS, and we intend to set up further trials for this purpose.

Meanwhile we conclude that a combination of a tranquilliser, antispasmodic, and bland bulk-provider is more effective in treating IBS than any single agent or pair of agents. A physician should be prepared to try various alternatives within these three types of therapeutic agents if a patient does not show a good symptomatic response to the first combination.

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Mianserin and agranulocytosis

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Summary and conclusions

An alcoholic woman who was admitted to hospital for detoxification was prescribed thyroxine because of hypothyroidism and mianserin to alleviate severe depression. After several weeks' treatment she became unwell and was readmitted to hospital. Haematological examination indicated agranulocytosis. Further extensive investigations elicited no cause for this other than the mianserin, since no such disturbance has been reported for thyroxine after years of use.

Thus mianserin is probably implicated in this case of agranulocytosis. Although the response may have been idiosyncratic, it highlights the need to monitor new drugs during the early phases of widespread use.

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Introduction

We report a case of agranulocytosis associated with treatment with the antidepressant mianserin. We believe that this is the first case to be described.

Case report

A 49-year-old alcoholic woman was admitted to hospital in December 1977 for detoxification. She was found to have hypothyroidism and was prescribed thyroxine 0.1 mg daily before discharge two weeks later. She was readmitted on 14 February 1978 for further detoxification and psychiatric assessment of her depressive state and suicidal ideation. A blood picture was normal. She remained severely depressed, however, and mianserin 20 mg three times daily was started on 23 February. She made an excellent recovery and was free of all depressive symptoms three weeks later.

On 28 March, during the fifth week of mianserin treatment, she returned to hospital from weekend leave to report that she felt generally unwell and had a sore throat. On examination she was pyrexial (temperature 38.2°C), her throat was inflamed, and she had cervical lymphadenopathy. Her only medication had been the thyroxine and mianserin at the prescribed doses. Two full blood pictures obtained on that same day showed a complete absence of neutrophils. She was transferred to a medical ward, the mianserin was stopped, and she was managed with reverse-barrier nursing, gut sterilisation, and systemic antibiotics. A sternal marrow biopsy on 31 March disclosed an L:E ratio of 1:1. Erythropoiesis was active and normoblastic.

Leucopoiesis was depressed: mature granulocytes were virtually absent but some myelocytes were present, with a few in mitosis. Plasma cells and lymphocytes were slightly increased. There were ample megakaryocytes. The appearances were consistent with drug-induced agranulocytosis. Spontaneous recovery appeared likely.

On the above regimen her sore throat improved. Extensive medical investigations did not elicit any other cause for the agranulocytosis. Serial blood counts steadily improved, and by 7 April she had a neutrophil count of $1.287 \times 10^9/l$ ($1287/mm^3$) and was considered to be fit for discharge. She was subsequently referred to the Hammer-smith Hospital for marrow culture and dose-response tests with mianserin. Unfortunately, technical difficulties invalidated the first results and repeat testing proved impossible because the patient had resumed her drinking and refused to co-operate further.

Discussion

Mianserin is one of the newer antidepressant drugs, and its pharmacology and clinical effectiveness have been reviewed by Bridges and Barnes.¹ Double-blind trials have shown it to be as effective as imipramine² and amitriptyline^{3,4} but with fewer unwanted effects. Crome and Newman⁵ reported 19 cases of self-poisoning with mianserin, in which the more serious symptoms associated with tricyclic and maprotiline poisoning did not occur. The combination of therapeutic potency with low toxicity has probably accounted for the drug's increasing popularity.

The manufacturers encountered no haematological disturbances in the preliminary studies performed on animals and man during the drug's development. The present case is the only one to have been reported to them so far. The Committee on

Safety of Medicines has received four adverse reports of blood dyscrasias in relation to treatment with mianserin.⁶ Pancytopenia, vitamin B₁₂ deficiency, and fatal agranulocytosis were associated with nine, five, and 15 other drugs respectively. A patient with neutropenia recovered spontaneously within 10 days after stopping mianserin. Unfortunately, details of the blood counts were not supplied, but as the patient was not receiving any other drugs at the time it would seem reasonable to conclude that mianserin may have been responsible.

This is the first case of agranulocytosis to be described in a patient receiving mianserin. The only other possible cause was the thyroxine, but after years of use no such disturbance has been reported. The marrow biopsy and rapid spontaneous recovery were typical of a drug reaction, and it was unfortunate that further testing of cultures of the patient's marrow proved impossible.

Thus mianserin is probably implicated in this case, and, while the response may have been idiosyncratic, it highlights the need to monitor all new drugs, especially during the early phases of widespread use.

References

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SHORT REPORTS

Glossopharyngeal neuralgia with cardiac arrhythmia: a rare but treatable cause of syncope

Glossopharyngeal neuralgia, like trigeminal neuralgia, usually occurs without structural abnormality but is occasionally seen with lesions of the cerebellopontine angle, base of skull, and carotid artery. It differs from trigeminal neuralgia in its association with syncopal attacks. We describe two patients in whom both pain and syncope responded to carbamazepine.

Case 1

A 50-year-old man had experienced a severe pain on swallowing in the region of the right fauces, lasting about one second. This increased in frequency and severity over 10 days. He then developed episodes of unconsciousness each preceded by the severe pain, sometimes without the stimulus of swallowing.

He was a fit man with vesicles on soft palate and fauces; his pulse was 60 beats/min and regular; and blood pressure 115/70 mm Hg. An electrocardiogram (ECG) recorded during an attack when he became pulseless showed sinus bradycardia followed by asystole for five seconds. A similar effect followed right carotid sinus massage. Between attacks the ECG was normal. Antibody titres to herpes viruses were negative.

Demand pacing was started and was required often during episodes of pain. Carbamazepine 200 mg twice daily at once abolished his pain and he could eat normally; he did not again require the pacemaker. A day after beginning treatment sinus massage failed to produce asystole. Carbamazepine was continued for one week and he remained pain free. The pacemaker was removed and he was discharged. He remained well two years later.

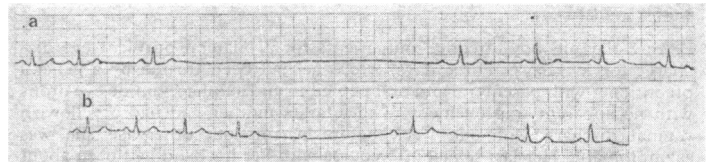
Case 2

A 66-year-old housewife had a three-year history of paroxysms of lancinating pain deep in the right ear. The attacks of pain were sometimes provoked

by swallowing. On six other occasions she collapsed while standing without preceding pain. She lost consciousness for only a few seconds.

She was very still during attacks of pain, unable to talk or swallow. During and between paroxysms her pulse was regular at 76 beats/min, and blood pressure was 160/110 mm Hg. The fauces were not inflamed and had normal sensation. A resting ECG was normal; sinus rhythm was 75 beats/min. Right carotid sinus massage produced asystole for four seconds (see figure, a).

Carbamazepine 50 mg three times a day and isoprenaline 30 mg four times a day were given. One month later both pain and syncope had stopped and isoprenaline was withdrawn. Sinus massage showed atrioventricular dissociation for three seconds (see figure, b). The patient remained well one year later taking carbamazepine 150 mg/day.



Case 2. (a) Right carotid sinus massage before treatment; (b) right carotid sinus massage after treatment.

Comment

The concurrence of glossopharyngeal neuralgia and syncope was clearly established in the first patient; in the second patient a close connection was suggested by the fact that carbamazepine abolished both symptoms, although pain and syncope occurred at different times.

Glossopharyngeal neuralgia may be confused with Stokes-Adams attacks or carotid sinus syndrome, but in neither of these does pain occur. In carotid syncope sinus massage will reproduce the symptoms. This is said to be ineffective in glossopharyngeal neuralgia,¹ but it occurred in both our patients.

Treatment aims at controlling pain and abolishing arrhythmia.