Viloxazine: assessment of potential rapid antidepressant action

Viloxazine (Vivalan) is a bicyclic compound with atypical pharmacological properties.[1] Preliminary evidence suggested that it might have a rapid antidepressant effect.[2] The following placebo-controlled trial was therefore carried out.

Method and results

The trial was undertaken in 34 moderately to severely depressed patients (nine inpatients, 25 outpatients), whose ages ranged from 18 to 64. The criteria for inclusion and methods adopted have been described elsewhere.[3] Patients were given either 100 mg of viloxazine or identical placebo tablets three times a day for a week. Statistically significant differences at the 5% level or less will be reported unless otherwise specified.

Five patients did not adhere to treatment because of alleged unwanted effects. All of them were taking viloxazine. Of those who completed their treatment, 12 received viloxazine and 17 placebo. The age range for the viloxazine group was 18 to 61 (mean 39·5); that for the placebo group was 22 to 57 (mean 43·8). Five men and 12 women received viloxazine; seven men and 10 women received placebo. Of the viloxazine group, five were inpatients and 12 were outpatients; for placebo the figures were four and 13, respectively. Of the patients receiving viloxazine, five had been ill for less than three months, 10 for three months to two years, and two for longer than two years, the corresponding figures for placebo being five, six, and six, respectively.

Hamilton rating scale for depression—The mean total scores during the baseline were 24·4 and 20·1 for the viloxazine and placebo groups, respectively. The difference between these was not significant. The two populations therefore were matched for severity of depression on this scale. The mean scores following treatment were 23·7 and 14·4 respectively. The decrease in the score was significant ($P<0.01$) for the placebo group, but not for the viloxazine group. The difference between the mean reduction in scores for the two groups was not significant. An analysis of the sum of the scores of the first three items on the Hamilton Scale, carried out for the purpose of comparison with reported results,[1] showed a significant fall in the placebo group, but not in the viloxazine group.

Wakefield self-assessment depression scale—The mean total scores during the baseline were 26·9 and 24·2 for the viloxazine and placebo groups, respectively. The difference between these was not significant. The two populations therefore were matched for severity of depression on this scale also. The mean scores after treatment were 27·2 and 18·4 respectively. The reduction in scores from before to after treatment with placebo was significant, and also significantly greater than the change that occured in the viloxazine group.

Global assessments—The differences in the global assessments of the severity of depression from before to after treatment, although showing a trend in favour of placebo, were not significant. The global assessments of change in condition shown in the table suggest that patients on placebo progressed better than those on viloxazine.

Unwanted effects—As expected when using a check-list, many symptoms identical to unwanted effects were elicited during the baseline and after treatment with placebo. It was therefore impossible to attribute any of the reported "side effects" to viloxazine with the possible exception of nausea and vomiting, which were more severe in the viloxazine group. There was no difference in the frequency of occurrence of drowsiness or anticholinergic effects. One patient receiving viloxazine had a grand mal seizure (*BMJ*, 9 July, p 96). No relevant laboratory abnormalities were found.

Conclusions

These results suggest that viloxazine, 100 mg given three times a day for a week, is not as effective as placebo. If this is a true and not a chance finding we have to consider the possibility of a "negative" effect, such as drug-induced, ill-defined feeling of dysphoria. In not showing advantages over placebo the findings also suggest that the results of those trials[5] that point towards viloxazine in a similar dosage having a rapid action—within one week—could be placebo responses.

Global assessment of change in condition

Change in condition	Viloxazine	Placebo
Very much improved		4
Much improved	1	1
Moderately improved		1
Slightly improved	3	2
No change	2	7
Slightly worse	3	1
Much worse	3	1
Total	12	17

I thank ICI Ltd, for providing the tablets for this trial; the pharmacy staff at Knowle Hospital; the pathology staff at Southampton University Hospitals and St Mary's Hospital, Portsmouth; Mr J A Lewis for his statistical and computer help; and Mrs Lynne Hitchins for her secretarial help.

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[5] International Vivalan Symposium: *Journal of International Medical Research*, 1975, **3**, Suppl No 3.

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A tumour inducing iron overload

Ferritin may be isolated from normal tissues, hepatic metastases, and primary neoplastic tissues.[1] We describe a patient with a primary bronchial carcinoma containing an abnormal ferritin that was thought to cause excess iron deposition in the liver and spleen.

Case report

A previously fit 72-year-old plumber gave a two-month history of anorexia, weight loss, and stabbing epigastric pain. He smoked 10 cigarettes and drank four pints of beer a day. He had a one-week course of iron tablets before admission. There was no family history of liver disease or haemochromatosis. He looked cachexic and unwell. There was hepatomegaly and coarse crepitations over both lung fields but no other clinical abnormality was present. Routine haematological and biochemical tests with chest radiography, barium meal, and intravenous cholangiography all gave normal results. Sputum cytology showed no malignant cells. Diagnostic laparotomy was carried out, and a granular, uniformly enlarged liver and spleen and cholelithiasis were found. Cholecystectomy, splenectomy, and liver biopsy were performed. Histology confirmed chronic cholecystitis and heavy iron deposition in the liver and spleen. Iron was present in the hepatocytes and Kupffer cells, and cirrhosis was absent. The patient made an uneventful recovery but was urgently re-admitted one month later with a Pancoast's tumour, subsequently confirmed at necropsy. After his abnormal histological findings at laparotomy, special investigations of the patient's iron metabolism were performed to determine the nature of his iron storage disease.

Serum collected before death was used in the study of iron binding proteins. Portions of liver and bronchial carcinoma were obtained within 12 hours of death, and kept at −20 C until studied. Polyacrylamide gel electrophoresis (PGE) of ^{59}Fe-labelled patient's serum disclosed two iron-binding proteins, subsequently proved by immunoprecipitation to be ferritin and transferrin. A 70 000 g supernatant of tumour homogenate was labelled with $^{59}Fe^{2}$ and on PGE was shown to contain ferritin with an isoelectric point of 4·9-5·0. Hepatic tissue similarly treated showed a different ferritin with an isoelectric point of 5·6, which is consistent with hepatic isoferritin. Serum showed serum iron 54 μmol/l (14-32 μmol/l) (302 μg/100 ml (78-178 μg/100 ml)); total iron binding capacity 77 μmol/l (54-81 μmol/l) (430 μg/100 ml (302-452 μg/100 ml)); ferritin 3800 μg/l (360 μg/l); and transferrin 1·8 g/l (2-3 g/l). Tumour ferritin showed isoelectric point 4·9-5·0 and concentration of 93 μg/g of tumour protein. Hepatic ferritin showed an isoelectric point 5·6.

Comment

Necropsy studies confirmed that the iron overload in this patient was confined to the hepatic and splenic tissues. The localisation of iron in the Kupffer cells and hepatocytes is not typical of early primary haemochromatosis, and this prompted the search for another explanation for the patient's iron overload.

We have shown the presence of ferritin within the primary lung tumour. The isoelectric point differs from that of hepatic isoferritin, thereby distinguishing the two proteins and showing that the ferritin isolated from the tumour did not represent contamination but was in fact tumour derived. The high normal total iron binding capacity in