MIANSERIN AND DOXEPIN IN THE TREATMENT OF OUTPATIENT DEPRESSION WITH ANXIETY

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- 1 A double-blind group comparative trial was performed comparing mianserin (Bolvidon—Organon) and doxepin (Sinequan—Pfizer) in the treatment of depression with anxiety.
- 2 Sixty outpatients from two centres were divided into 'high' and 'low' severity groups, based on initial HRS scores, and treated for four weeks.
- 3 Standard rating scales for depression and anxiety demonstrated a substantial improvement with both drugs. However, no consistent difference in efficacy was found although the 'low severity' group appeared to respond better to mianserin.
- 4 There was a greater incidence of drug-related side-effects with doxepin treatment.

Introduction

The presentation of patients suffering from manifestations of both depression and anxiety is much more common than classical depressive disorders (Roth *et al.*, 1972) and causes the dual problem of correct diagnosis and treatment. This is particularly true in general practice where the majority of mild psychiatric disease is treated. The choice of appropriate therapy in the absence of a definitive diagnosis has led to the development of a variety of combinations of antidepressant and anxiolytic compounds. However, since it is generally preferable to prescribe a single compound there has been substantial research to establish whether antidepressants can also adequately treat symptoms of anxiety. It has been shown that doxepin is superior to amitriptyline and equivalent to commonly available combination products in the treatment of depression with associated anxiety (Querol, 1970; Ebie, 1974). Mianserin has been shown to be an effective antidepressant which is less cardiotoxic and safer in overdose than standard tricyclics (Burgess *et al.*, 1978; Crome *et al.*, 1978; Smith *et al.*, 1978). We have also previously reported its efficacy and relative lack of side-effects (Bennie, 1978; Khan & Moslehuddin, 1980). The anxiolytic activity of mianserin has been shown in the treatment of pure anxiety (Murphy, 1978; Conti & Pinder, 1979) and in anxiety associated with depression (Russell *et al.*, 1978).

Methods

Outpatients presenting with a primary depressive illness with a pronounced anxiety component and

scoring a minimum total of 15 on the Hamilton Rating Scale (Hamilton, 1967), including a minimum combined score of four on items 10 and 11 of this scale (anxiety somatic and anxiety psychic), were recruited to the trial. Patients were excluded if they suffered with concomitant physical illness, organic brain disease, mental subnormality, alcoholism, pregnancy, drug dependency or if they had received an adequate course of either the two trial preparations or ECT during the previous six months. Informed consent was obtained and patients were free to withdraw from the trial at any time.

After selection for the trial, each patient was randomly allocated to either mianserin or doxepin treatment for the following four weeks. Patients who had been receiving psychotropic medication were subject to a 4–7 day treatment-free period before entry to the trial. In addition to a detailed patient history, assessments were performed at baseline and after one, two and four weeks on the Hamilton Rating Scale, Leeds Self-rating Specific Scales for depression and anxiety (Snaith *et al.*, 1976), Clinical Global Impression and a Treatment Emergent Symptoms Scale. Assessments were in all cases completed by one of the authors and inter-rater reliability was improved by a session of dual rating at the beginning of the study. A careful record of patient compliance was kept, and the reason for any withdrawal from the trial was reported.

Safety monitoring consisted of measurements of blood pressure, ECGs, routine biochemistry and haematology, including differential white cell count, which were all performed at baseline and after four weeks treatment.

Patients received identical capsules containing

either 10 mg mianserin or 25 mg doxepin. Appropriate dissolution tests confirmed that the bioavailability was comparable to the normal tablet presentation of the two compounds. An initial dosage of one capsule t.i.d. was doubled after the first week. Apart from 5 mg nitrazepam, no concurrent psychotropic medication was permitted during the trial period.

Results

Sixty patients (15 male and 45 female) were recruited at the two hospital outpatient centres over a period of 12 months. The patient populations from each centre were compatible with reference to severity of illness and numbers per treatment group. Distribution of patients between treatment groups was well balanced with respect to age, sex and severity of illness (Table 1). Eight patients dropped

Table 1 Patient population (number of patients in parentheses)

	<i>Mianserin</i>	<i>Doxepin</i>
Sex		
M	6	9
F	24	21
Age		
Mean	40.7	41.5
Range	(20–58)	(20–64)
Mean HRS at LS group	22.2(15)	22.4(15)
Baseline HS group	29.7(15)	29.8(15)

LS low severity, HS high severity

out from the study during the first two weeks and were discarded from the statistical analysis which was therefore based on 52 patients. A further six patients dropped out during the second half of the trial and their data were included. For the purpose of the analysis patients were retrospectively divided into 'high' and 'low' severity groups according to whether they scored >25 or 15–25 on the Hamilton Rating Scale on entry to the trial. There was a reduction in HRS scores in both the mianserin and the doxepin treated groups in patients with moderate to severe illness with most of the reduction occurring in the first week of treatment (Figures 1 and 2). However, no significant difference between the mianserin and doxepin groups could be demonstrated for the sum score of items 1–17 of the HRS or the patients' own assessment of symptoms of anxiety and depression as rated on the Leeds Specific Self-rating Scales. Substantial improvement was recorded for anxiety (Figure 3) and depression self-ratings in both

Figure 1 Comparison of the change in mean Hamilton scores in the 'low' severity group. — Mianserin. --- doxepin.

Figure 2 Comparison of the change in mean Hamilton scores in the 'high' severity group. Symbols as in Figure 1.

Figure 3 Amelioration in Leeds Specific Anxiety scores. Symbols as in Figure 1.

treatment groups. For the Clinical Global Impression, when the severity groups were combined, no difference between treatments was found. However, a statistically significant difference (Yates test, $P=0.02$) in favour of mianserin could be demonstrated for the 'low' severity group (Figures 4 and 5).

Figure 4 Clinical Global Impression, 'low' severity group. Symbols as in Figure 1.

Figure 5 Clinical Global Impression, 'high' severity group. Symbols as in Figure 1.

Treatment emergent symptoms were corrected for baseline scores to reveal drug-related side-effects and by means of the Yates test no differences could then be found between the two treatment groups comparing individual side-effects. However, patients on doxepin experienced a significantly greater number of different side-effects (Figure 6). The most common of these were headache and dry mouth. One-third of all patients complained of insomnia at baseline but in every case this was absent by the end of the first treatment week. A total of 14 patients withdrew from the trial during the treatment period—these are detailed in Table 2.

Figure 6 Mean number of treatment emergent symptoms reported per patient. □ Mianserin, ▨ doxepin.

Table 2 Drop-outs

	Mianserin	Doxepin
Improved	1	
Worse	1	1
Overdose	1	
Side-effects	1	5
DNA/non-compliance	2	2
Total	6	8

It would appear that there were more treatment-related drop-outs in the doxepin group. No abnormalities of clinical relevance were reported for ECGs, blood pressure, haematology or biochemistry.

Discussion

Research into classification of anxiety and depressive states has clearly shown that many symptoms are common to both disorders. It has been reported that 95% of depressive patients complain of psychological symptoms of anxiety and 85% have somatic symptoms of anxiety (Roth *et al.*, 1972). Although the approach to treatment is often quite different in these disorders, there are distinct advantages in a single compound which is demonstrably effective in relieving symptoms of both anxiety and depression.

Both mianserin and doxepin fulfil these requirements and have been shown in this study to be effective therapies for the psychiatric outpatient presenting with symptoms of depression and anxiety. We would not anticipate demonstrating major differences in efficacy between two proven antidepressants in a trial of this size. However it is interesting that the low severity group appeared to

have a better response to mianserin. The pressures on psychiatric services in most parts of this country at the present time necessitate quite severely depressed patients being treated within the community and, therefore, antidepressant therapy should ideally have a rapid onset of action, a minimum of side-effects and a beneficial effect on sleep.

Both treatments displayed a substantial therapeutic effect within the first week of the trial period. However, the incidence of drug-induced side-effects varied considerably between the two treatment groups. This is an important consideration when managing large numbers of outpatients on antidepressant therapy.

Sleep disturbance is a common problem and both treatments appeared to improve sleep from the first week. This is in agreement with previous findings (Goldberg *et al.*, 1974; Smith *et al.*, 1978; Nicholson & Stone, 1982).

The advantages of a single night time dose for improved compliance is well established and studies have demonstrated the benefits of giving 60 mg mianserin in a single night time dose

(Montgomery *et al.*, 1978; Magnus, 1979). The equivalent dose of doxepin is only recommended in divided doses (maximum single dose is 100 mg) and therefore this regimen was employed in the trial. Certainly with regard to patient compliance we have found a single night time dose to be a considerable advantage when treating depressive outpatients, particularly in a semi-rural area where regular patient supervision is rarely feasible.

Conclusion

Although doxepin has a reputation as the treatment of choice in mixed depression and anxiety, in this study mianserin has been shown to be at least as effective and may have advantages in respect to side-effects.

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