Double blind trial of clonidine in the treatment of migraine in a general practice

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SUMMARY. The value of clonidine ('Dixarit') for the prophylaxis of migraine has been assessed by a double blind cross-over trial. A dose of up to 0·15 mg daily was used. No effect on the frequency of the headaches could be detected over and above the 60 per cent reduction observed with a placebo. Severity, assessed subjectively by the patient, when it varied between placebo and clonidine, was less with clonidine ($p<0·01$). There was also some evidence that headaches lasting more than 12 hours were less common during treatment with the drug.

Introduction

IT was suggested, on pharmacological grounds, that clonidine should be given a trial in the treatment of migraine by Zaimis and Hannington (1969) and "encouraging results" of a preliminary trial were reported by Wilkinson (1969). To a large measure these have been supported by subsequent reports (Wilkinson *et al.*, 1971; Shafar *et al.*, 1972) but a more recent controlled trial failed to demonstrate any benefit from the use of clonidine in the management of migraine (Ryan *et al.*, 1975). The controlled trials have usually been conducted over a period of eight weeks but benefit has been reported up to 12 months after starting treatment (Shafar *et al.*, 1972) and in the experience of Wall and Wilkinson (1973) a response to clonidine might continue after the drug is withdrawn. It was also noted by Wilkinson and her colleagues (1971) that some patients complained that their headaches were made worse by the treatment.

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In our study, patients were treated with clonidine for six months and with placebo for six months. Since the response to the drug may persist after withdrawal, the order in which treatments are administered can influence response to the placebo control, and so a cross-over design was selected. Carry-over effects were not avoided by inclusion of a prolonged no-treatment phase as this would have been unacceptable to many patients.

Method

Patients with 'migraine' were recruited from an NHS general practice of approximately 7,500 patients in the north Edinburgh area. They were accepted into the study if they had suffered from paroxysmal headaches at least once a month for a period of three months or more which were accompanied or preceded by visual or gastrointestinal disturbances. In all instances the patients were symptom-free between headaches and no other abnormality could be found on clinical examination and investigation. After acceptance the patients were seen by one of four doctors.

Ninety-six patients, of whom 81 (84 per cent) were female, entered the trial over a period of two years. It is well recognized that men are less likely to consult doctors because of migraine and this probably contributes to the large number of women included in the trial.

Design of the trial

The drug was given prophylactically and patients were assigned by simple randomization to one of two treatment groups:

Group one: Patients treated by clonidine during the first six months of study and by placebo control during the second six months.

Group two: Patients treated by placebo control during the first six months of study and by clonidine during the second six months.

Throughout the trial neither the doctors nor the patients were aware of the group to which patients had been assigned.

Table 1. Information given at the initial visit for the total sample of 70 patients.

Severity/ duration	Headaches always require treatment		Headaches do not always require treatment	
Frequency	⩽ 12 hrs	More than 12 hrs	⩽ 12 hrs	More than 12 hrs
⩽ 3 headaches per 3 months	9(10)	11(9)	3(3)	1(3)
More than 3 headaches per 3 months	17(19)	17(17)	8(6)	4(5)

In brackets are shown the number of patients expected in each cell when severity, duration, and frequency are independent characteristics for headache. The results are compatible with independence. $\chi^2_{(4)} = 3.20$.

The initial dosage for each treatment was one tablet (0·025 mg) three times a day but this could be increased at subsequent visits to a maximum of two tablets three times a day.

Patients visited the clinic for assessment after one, two, three, and six months of treatment. At the six-month visit patients crossed over to the alternative treatment and were again assessed after intervals of one, two, three, and six months.

At the initial visit information was recorded on sex, age, menopausal status (if applicable), family history of recurrent headache or migraine, number of years during which the patient suffered migraine, specific precipitating factors, and previous therapy to ensure that patients randomized to group one and group two did not differ markedly in respect of these characteristics. In all respects the two groups were comparable.

At the initial visit, pre-trial frequency (per three months) and duration of headaches were recorded for all patients. Severity was assessed by the patient's response to the following questions:

1. Do your headaches require treatment?
2. Do your headaches prevent you from working?

The answers were recorded as: always, usually, sometimes, never. In a subsequent comparison of patients randomly assigned to the two groups, this information was used to ensure that there was no marked disparity in severity (Table 1).

During the trial, each patient kept a diary to record the time of onset and duration of each headache. The patient also noted any treatment and whether he or she was able to carry on with work. With the aid of this diary and discussion with the patient, the doctor decided at each visit whether the headaches since the last visit had been less severe, equally severe or more severe than before the trial began, and accordingly coded them as −1, 0, or +1 respectively. (The accuracy in this

Table 2. Reasons for failure to complete the trial by 26 patients.

Patient number	Group	Reason for withdrawal
10	2	Patient felt headaches were worse (after withdrawal from trial it was noted that the headaches had become progressively more severe whilst on placebo and clonidine).
12	2	Nausea, vomiting, flatulence, skin irritation. These symptoms occurred while on placebo.
15	1	Non-attendance beyond 3 months.
16	1	Did not meet criteria for admission to trial when reviewed at second visit.
20	1	Non-attendance after 6 months.
26	2	Non-attendance after first visit.
30	2	Non-attendance after 1 month.
33	2	Non-attendance after 9 months.
34	1	Non-attendance after 1 month.
37	2	Non-attendance after 7 months.
40	1	Non-attendance after 1 month.
51	2	Palpitations and dyspnoea. Symptoms occurred within 1 month of changing from placebo to clonidine.
58	1	Nausea, epigastric discomfort, abdominal distension. Symptoms occurred within 1 month of starting treatment with clonidine.
62	2	Non-attendance after 9 months.
63	2	Non-attendance after 6 months.
66	2	Non-attendance after 3 months.
67	2	Pregnancy.
69	1	Non-attendance after 2 months.
71	1	Non-attendance after 9 months.
77	2	Non-attendance after 6 months.
79	2	Non-attendance after 1 month.
82	2	Non-attendance after 9 months.
85	1	Re-diagnosed as tension headaches following first visit.
91	1	Non-attendance after 6 months.
94	1	Non-attendance after 3 months.
95	2	Did not meet the criteria of the trial on review following first visit.

assessment may be time-dependent.) The frequency of headaches per three months and their mean severity were also derived at each visit.

Results

Seventy (73 per cent) of the 96 patients completed the trial. One of these (in group one) missed two visits. Table 2 lists the reasons for which the 26 patients dropped out of the study. The analyses are based on the 70 patients who were treated for one year. The mean age of the 38 patients (30 female, eight male) randomized to group one who completed the study was 40 years (range 11–67 years) and of the 32 patients (29 female, three male) randomized to group two who completed the study was 35 years (range 16–56 years).

Three patients were withdrawn from the trial owing to side effects. Two of the three patients were under treatment by clonidine, the third by placebo control. The nature of the side effects is described in Table 2.

Statistical analysis

The response variables on which long-term efficacy of clonidine was assessed were frequency, severity, and duration of headaches at the final visit in each treatment phase (visits five and nine).

In group one there were four patients at both final visits who reported no headache during the last three months of the treatment phase; in group two there were six and eight patients at visits five and nine respectively. The median frequency of headaches for all 70 patients fell from nine headaches per three months (interquartile range three to 24 per three months) pre-trial, to three per three months (interquartile range one to nine per three months) at both final-phase visits.

On completion of the study response to clonidine was compared with response to placebo for each patient. Accordingly the differences—response on clonidine minus response on placebo (where response is response at visit five or nine)—were calculated for the 70 patients and are referred to as frequency difference, severity difference, and duration difference. Since severity and duration were coded, these differences are differences in coded severity and coded duration. The severity code was incompletely specified, as no code was assigned for the severity of headaches which "do not occur". Assignment after data collection may be biased and so analysis of severity difference is based on group one patients and group two patients for whom the difference does not depend on the code assigned to headaches which "do not occur".

The duration code was defined as follows:

0 no headache
1 0 hrs < mean duration < 1 hr
2 1 hr ⩽ mean duration < 3 hrs
3 3 hrs ⩽ mean duration < 12 hrs
4 12 hrs ⩽ mean duration

Table 3. Distribution of severity difference.*

Severity difference	Group 1 Number of patients	Group 2 Number of patients
−2	4	2
−1	12	10
0	13	11
1	3	0
2	0	1

*Severity difference = coded severity on clonidine minus coded severity on placebo.

If the difference for a patient is less than zero, the patient has responded better to clonidine; if the difference for a patient is less than or equal to zero, the patient has responded at least as well to clonidine as to placebo. Throughout this section the sample median difference is compared with zero—the expected difference if clonidine and placebo are equally good therapies. A symmetrical distribution of differences is assumed in the absence of treatment effect.

Frequency difference

In neither group one nor group two is there evidence that clonidine reduces frequency of headaches more than placebo. The median frequency differences and interquartile ranges are:

0, (−3, 1) for group 1
0, (−1.5, 0.5) for group 2

Severity difference

Table 3 is based on the 32 group one and 24 group two patients for whom difference in coded severity does not depend on the code selected for the severity of non-existent headaches, and shows the distribution of severity difference. A 95 per cent confidence interval for the probability that severity is less on clonidine than on placebo in the combined sample of 56 patients is 0.37 to 0.63.

The results do not suggest that severity is strictly less on clonidine than on placebo as 24 patients have a difference of zero, but the probability is estimated as 0.93 (combined sample) that severity is certainly no worse on clonidine. However, if clonidine and placebo have comparable effect, the 32 patients who show a non-zero severity difference should be equally divided between those experiencing headaches on clonidine of diminished and increased severity relative to placebo. But 28 experienced headaches that were less severe, which is significantly more ($p<0.01$) than expected (16).

This is evidence that clonidine is more effective than placebo in diminishing the severity of headaches for patients who respond differently to the two treatments.

Table 4. Distribution of duration difference.*

Duration difference	Group 1 Number of patients	Group 2 Number of patients
$\leqslant -3$	3	5
$-2, -1$	7	5
0	18	18
1, 2	8	1
$\geqslant 3$	2	3
Total	38	32
Median	0	0
q_1 (lower quartile)	−1	−1
q_3 (upper quartile)	2	0

*Duration difference = coded duration of clonidine minus coded duration on placebo.

Duration difference

The distribution of duration difference is presented in Table 4 for groups one and two. Ten patients (26 per cent) in group one reported shortened duration of headaches whilst on clonidine; 10 group one patients also benefited from placebo. In group two, 10 patients (31 per cent) benefited from clonidine compared with only four favouring the placebo. The results do not point to a remarkable benefit from clonidine even in group two patients but the chance is estimated as 0.88 (28/32) that group two patients fare as well or better on clonidine than on placebo. Group one patients show less favourable response to clonidine and so the duration of headaches at visit five was compared between groups one and two, as this comparison does not involve a possible carry-over effect on duration from previous treatment by clonidine. Six of the 38 group one patients (16 per cent) endured headaches whose mean duration exceeded 12 hours in the final three months of phase one treatment compared with 15 of the 32 group two patients (47 per cent).

Thus significantly fewer patients during the last three months of phase one clonidine therapy suffered headaches lasting more than 12 hours than patients on placebo ($\chi^2_{(1)\ \text{corrected}} = 6{\cdot}58$; $0{\cdot}01 < p < 0{\cdot}03$). The corresponding comparison at visit nine showed no difference in the proportion of group one (29 per cent) and group two (31 per cent) patients whose mean duration of headaches in the previous three months exceeded 12 hours.

Single variable within-patient comparisons of frequency, severity, and duration, although unlikely to be independent assessments, nevertheless throw light on the action of clonidine.

Discussion

During the trial the frequency of headaches fell by about 60 per cent but, in the dose used, clonidine was no more effective than a placebo in bringing about this reduction. It is an improvement rate which has been described in other trials of therapy for migraine (Blau, 1971). There was no evidence that clonidine increased the frequency of headaches. There was evidence that clonidine reduced severity and that this benefit was experienced by about 50 per cent of the patients.

The order in which drug and placebo had been administered made no difference to severity so that in this respect there did not appear to be a carry-over effect after stopping clonidine. On the other hand the change in duration of headaches indicated some continuing effect of the drug, since if clonidine was administered following a six-month period of placebo, the headaches were equal in duration to those experienced by control patients who had taken clonidine in the previous six months. This would suggest that the control patients were still benefiting from the clonidine. An effect persisting for six months after the drug is discontinued is consistent with the findings of Wall and Wilkinson (1973).

Conclusion

The conclusions that can be drawn from the trial are that clonidine in a dose of 0·15 mg daily, although it does not reduce the frequency of headaches, does significantly reduce severity of headaches in some patients and appears to reduce duration. The trial produced convincing evidence that in no respect were patients worse on clonidine than on placebo. There was also some suggestion that an effect of the drug persists after it has been withdrawn.

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