A double-blind randomized control trial of diazepam

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SUMMARY. A double-blind randomized controlled trial of diazepam against placebo in the management of minor conditions seen in general practice demonstrated that administration of either diazepam or placebo was associated with a substantial reduction in symptomatology three weeks later. There was no demonstrable difference between diazepam and placebo.

Introduction

DESPITE the widespread use of benzodiazepines in general practice, very little has been published. Salkind and his colleagues[1] reported a double-blind randomized control trial of clobazam, a 1,5-benzodiazepine, against diazepam and placebo. The patients were selected on the basis of persistent rather than transient anxiety and the results were interpreted as showing more benefit from the benzodiazepines than from the placebo. There was some evidence that diazepam in a dose of 15 mg or more daily impaired performance. This study is difficult to interpret because the patients in the placebo group improved more during a pretreatment of 14 days of management with ascorbic acid. The evidence that diazepam is superior to placebo is not convincing. This is the only randomized double-blind control trial that has, as far as we are aware, been carried out in general practice.

Aims and method

This study set out to assess the value of diazepam, as compared with placebo, in the management of minor conditions in general practice. It specifically excluded conditions such as epilepsy in which its use might be obligatory.

The method used was a double-blind randomized control trial. Tablets, both active and placebo, in 2 and 5 mg strengths were made available. They were numerically coded using random numbers, thus the number, whether odd or even, did not determine the nature of the pill. The co-ordinator retained the master code but each participating doctor received a sealed envelope which could be opened in the event of an overdose.

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Doctors were invited to participate in the trial by circulating the protocol to approximately 150 Fellows, Members and Associates of the Royal College of General Practitioners. Twenty doctors expressed interest and received tablets and data collection sheets. Eight doctors eventually returned completed forms. The reasons for this low response rate were not investigated but may include: many doctors now seldom use diazepam; difficulty about informed consent; reluctance, particularly in a fee for item-of-service framework, to suggest giving a placebo.

Having decided that their usual management of presenting symptoms would be diazepam in a three times daily dose, doctors were obliged to obtain informed consent from the patient before entering them into the trial. The nature of the informed consent created problems and to some extent this had to be left to the discretion of individual doctors. The final sample may be biased because: there is no record of the number of patients who were judged unlikely to give consent or who refused consent; there was no obligation to enlist every patient for whom diazepam was to be prescribed.

A data sheet was completed for each patient entered which recorded baseline data and scored symptoms on a scale of 0 to 6—0 indicating absence and 6 severe intensity. The following symptoms, based upon a pilot study carried out in the University of Dublin Teaching Practice, were offered and had to be scored (there was an opportunity to add other symptoms): anxiety, palpitations, shakiness/tremor, fear of going out, other fears, sweating, depression, loss of appetite, loss of libido, sleep difficulty, headache, muscle tension and lightheadedness. Patients were reviewed at three weeks, when remaining tablets were counted and symptoms rescored in the same way. There was an opportunity to record side effects. Other drugs being used were also recorded.

Results

Forty-seven completed protocols were returned; 22 of the 47 either failed to record the number of remaining pills or the patient failed to complete the course. This is not surprising if therapy is effective and therefore these incomplete protocols have been included in the results but analysed separately. Eight patients did not return for review; this may be an underestimate.

In each instance the change in symptom score is expressed both numerically and as a percentage. Use of a percentage makes allowance for individual doctor's idiosyncracy in symptom grading.

The characteristics of the two groups of patients, placebo and diazepam, and the main results are shown in Table 1. Both showed a substantial reduction in symptom score.

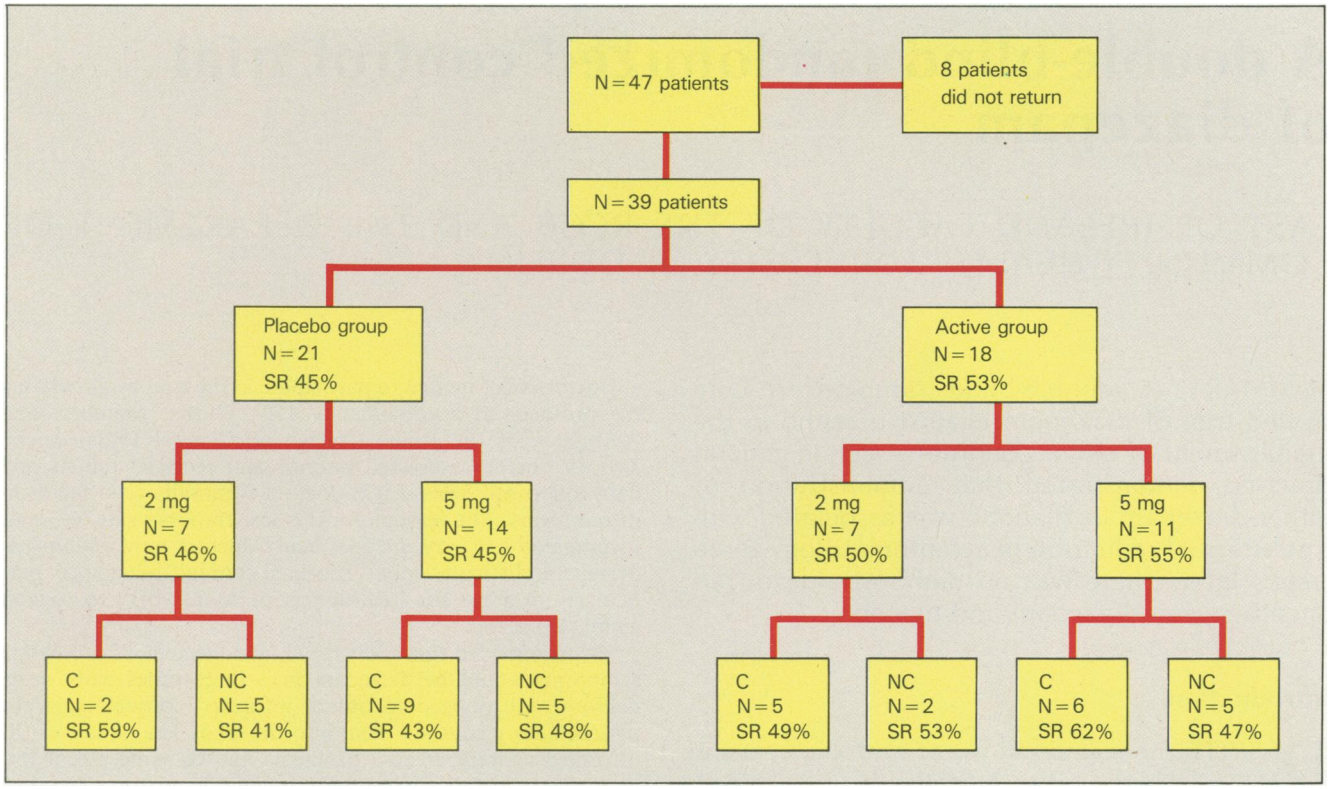

Figure 1. *Summary of results.* (*N* = number, C = compliant, NC = non-compliant, SR = percentage reduction in symptom score.)

Table 1. Results of treatment in the patient groups.

	Placebo group	Active group
Number of patients	21	18
Male/female	7/14	5/13
Age (years)		
Median	49	45
Mean	47	47
Range	22–75	28–74
Mean score		
Before	26 ± 12.8	27.5 ± 10.7 NS
After	14.9 ± 9.5 $P<0.001$	12.6 ± 9.4 NS $P<0.001$
Percentage reduction	*45*	*53*

A more detailed summary is provided in Figure 1. This suggests that the results were independent of dose or of full compliance.

Recorded side effects were minimal: one patient on 15 mg of diazepam complained of drowsiness.

Discussion

Because of the difficulties of carrying out randomized double-blind controlled trials in general practice, the number of patients in this study is small and those entered may be a biased sample of those for whom treatment with diazepam is usually recommended.

The study does not address the possibility that the natural history of such symptoms is towards marked improvement within three weeks.

The association of placebo administration and marked improvement is of theoretical interest in that there may be naturally occurring benzodiazepine receptors.[2] This suggests an analogy with the placebo affect on pain which may be blocked by morphine antagonists.

Administration of diazepam or placebo is associated with a reduction in symptoms after three weeks. This is independent of dose, up to 15 mg diazepam daily in divided doses, or full compliance. There was no demonstrable difference between diazepam and placebo.

References

1. Salkind MR, Hanks GW, Silverstone JT. Evaluation of the effects of clobazam, a 1,5-benzodiazepine, on mood and psychomotor performance in clinically anxious patients in general practice. *Br J Clin Pharmacol* 1979; **7**: 113S-118S.
2. Haefely W, Mohler H. Mechanisms of action of the benzodiazepines. *Roche Research Report*. Basel: Roche Products, 1980.

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