Effects of Clorazepate on Breathlessness and Exercise Tolerance in Patients With Chronic Airflow Obstruction

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Five patients with severe chronic lung disease were given placebo or 7.5 mg of clorazepate, a benzodiazepine, at bedtime for two weeks using a double-blind cross-over study design. Exercise tolerance, arterial blood gases, pulmonary function tests, self-rated breathlessness, and self-administered depression and anxiety scores were similar during drug treatment, placebo treatment, and washout periods. Higher doses of clorazepate were not tolerated by three of five patients. Nonanxious patients with chronic lung disease seem not to benefit subjectively or objectively from a low-dose benzodiazepine regimen.

The use of sedatives and other central nervous system depressants in patients with chronic obstructive pulmonary disease (COPD) has been generally discouraged.[1] Some investigators have reported improvement in exercise tolerance with diazepam,[2,3] dihydrocodeine,[4-5] and promethazine [6];others showed no improvement with caffeine,[4] theophylline,[7] or diazepam.[6] Despite such conflicting and overall negative data, breathless patients commonly receive sedatives as part of their therapy, even when anxiety, per se, is not one of their complaints. The purpose of this study was to determine whether consistent benefit could be achieved with clorazepate, a benzodiazepine, in nonanxious breathless patients with COPD and, if so, whether the effect is related to the patient's emotional state.

Methods

Patients were recruited for the study from the family medicine and internal medicine clinics at the Moses H. Cone Memorial Hospital, a 489-bed community teaching hospital. The charts of 56 patients with a diagnosis of debilitating COPD (dyspnea grades 3 to 5 of the Medical Research Council) were reviewed. Patients excluded from

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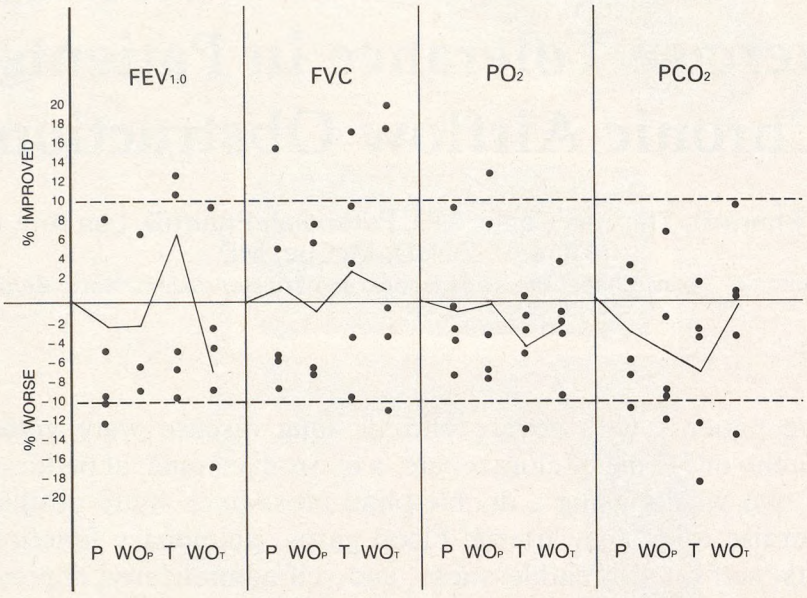

Figure 1. Percentage of change from baseline values for forced expiratory volume at one second ($FEV_{1.0}$), forced vital capacity (FVC), PO_2 and PCO_2 during treatment with placebo (P), washout from placebo (WO_P), treatment with clorazepate (T), and washout from clorazepate (WO_T). Treatment and placebo values reflect the average of two weeks for each patient and the line connects the mean value for each study interval

the study included those with (1) any concurrent illness that limited exercise, (2) known psychiatric illness, (3) arterial PCO_2 above 50 mmHg or pH below 7.35, or (4) concurrent use of any psychotropics, benzodiazepines, narcotics, beta-blocking agents, or alcohol. Informed consent was obtained from all subjects.

Patients were assigned in a randomized double-blind manner to three, two-week treatment regimens with a one-week washout between treatments. The treatment regimens studied were (1) three placebo capsules at bedtime, (2) one 7.5-mg clorazepate capsule and two placebo capsules at bedtime, and (3) three 7.5-mg clorazepate capsules at bedtime. With the third regimen three of the five patients experienced intolerable side effects requiring termination of this treatment phase and exclusion of these data from this analysis.

Tests, performed at the same time each week, included pulmonary functions (ie, forced expiratory volume at one second [$FEV_{1.0}$], peak expiratory flow rate [PEFR], forced vital capacity [FVC]), emotional ratings (Zung Depression Questionnaire and the Spielberger "State-Trait" Anxiety Inventory), exercise tolerance (two 12-minute walks,[8] oxygen cost diagram,[9] arterial blood gases, compliance (pill count and urine drug screening), other drug use (serum tricyclic antidepressant drug screening and blood alcohol concentrations), and a drug adverse effects questionnaire. Patients were also asked to keep a daily self-rated breathlessness calendar graded from 1 (little breathlessness) to 6 (extreme breathlessness).

An examination by one physician (T.C.) was performed on each patient at the end of each treatment course. Paired two-tailed *t* tests were used to compare the statistical significance of differences among the regimens.

Pulmonary functions were assessed as the best of three efforts using a CPI 5100 (Cardiopulmonary Instruments). Blood gas measurements ob-

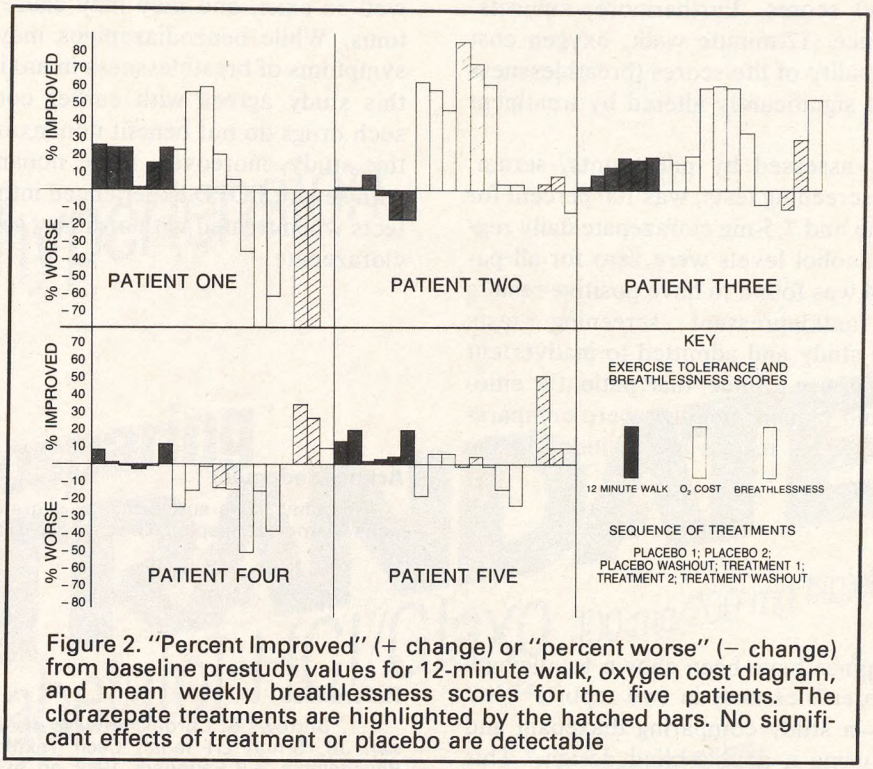

Figure 2. "Percent Improved" (+ change) or "percent worse" (− change) from baseline prestudy values for 12-minute walk, oxygen cost diagram, and mean weekly breathlessness scores for the five patients. The clorazepate treatments are highlighted by the hatched bars. No significant effects of treatment or placebo are detectable

tained from a radial artery puncture were determined using an IL303 Blood Gas Analyzer and an IL282 co-oximeter (Instrumentation Laboratory). Urine drug screening tests were performed by thin-layer chromatography in a local commercial laboratory. Positive findings for urine benzodiazepines and screening for serum tricyclic antidepressants were confirmed using enzyme immunoassay (EMIT-Syva). Blood alcohol concentrations were measured by a modification of the alcohol dehydrogenase procedure (DuPont Automatic Clinical Analyzer).

Results

Five patients (four male, one female) aged 51 to 68 years completed treatments with clorazepate and placebo. All five had severe COPD based on FVC, $FEV_{1.0}$, and PEFR <50 percent predicted.[10] Drug treatment did not significantly alter arterial blood gases or pulmonary function tests (Figure 1). Mean FVC for baseline, placebo, and clorazepate treatment were 2.55 L (±.848 L), 2.57 L (±.976 L), and 2.62 L (±.90 L), respectively. Mean partial pressures for oxygen and carbon dioxide were 65.36 mmHg (±11.23 mmHg) and 41.58 mmHg (±5.64 mmHg) for baseline, 64.43 mmHg (±10.73 mmHg) and 42.96 mmHg (±6.42 mmHg) during placebo, and 62.62 mmHg (±6.86 mmHg) and 44.7 mmHg (±8.61 mmHg) during clorazepate therapy.

Figure 2 shows the percentage change from baseline to placebo and treatment in the breathlessness scale, oxygen cost diagram, and 12-minute walk. Although some correlations are apparent for individual subjects, no consistent patterns were detected. Student's *t* tests ($P < .05$) revealed no significant differences between placebo and treatment on any parameters including anxiety and depression. During the entire course of the study, no patient fell outside the normal population values for the Zung (depression) and Spiel-

berger (anxiety) scores. Furthermore, subjects' exercise tolerance (12-minute walk, oxygen cost diagram) and quality of life scores (breathlessness scale) were not significantly altered by treatment or placebo.

Compliance, assessed by pill counts, serum, and urine drug screening tests, was 100 percent for both the placebo and 7.5-mg clorazepate daily regimens. Blood alcohol levels were zero for all patients. Patient 4 was found to have positive results on tricyclic antidepressant screening tests throughout the study and admitted to inadvertent chronic doxepin use. Since this patient's emotional scores and clinical findings were comparable to the others, his results are included in the analysis.

Discussion

Benzodiazepines have been shown to alleviate symptoms of breathlessness in two reports[2,3] but not in a third—a study comparing diazepam and promethazine using a double-blind design.[6] This study, strictly controlled and double blinded, also failed to demonstrate that placebo or clorazepate (a benzodiazepine) consistently relieved breathlessness in nonanxious patients with severe COPD. Moreover, there were no associations noted among weekly anxiety or depression scores and concurrent self-rated breathlessness.

Mitchell-Heggs et al[2] and Woodcock et al[6] used a higher dose of benzodizepine, 25 mg of diazepam (equivalent to 37.5 mg of clorazepate daily). However, on a clorazepate dose of 22.5 mg daily, three of five patients refused to continue their treatment regimen. Some study parameters, in fact, deteriorated even when patients were taking the lower dose of clorazepate. Particularly concerning was the observation that some patients had worsening of pCO_2 even during the daily 7.5-mg clorazepate regimen. This response contradicts an earlier report that 10 mg of diazepam given four times daily did not cause deterioration in blood gases of COPD patients with hypercapnia.[11]

This study suggests that patients with severe COPD and symptoms of breathlessness should be assessed carefully for anxiety before anxiolytic sedatives are prescribed. COPD and anxiety may well co-exist, and they may cause similar symptoms. While benzodiazepines may relieve some symptoms of breathlessness in anxious patients,[2,3] this study agrees with earlier conclusions[6] that such drugs do not benefit nonanxious patients. In this study, moreover, some nonanxious patients with severe COPD experienced intolerable side effects when treated with ordinary sedative doses of clorazepate.

Acknowledgment

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