A DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED TRIAL OF LOFEXIDINE IN ALCOHOL WITHDRAWAL: LOFEXIDINE IS NOT A USEFUL ADJUNCT TO CHLORDIAZEPOXIDE

FRANCIS KEANEY*, JOHN STRANG, MICHAEL GOSSOP, E. JANE MARSHALL, MICHAEL FARRELL, SARAH WELCH, BRITTA HAHN and ALEJANDRO GONZALEZ

National Addiction Centre (Institute of Psychiatry, King’s College London and The Maudsley Hospital), 4 Windsor Walk, London SE5 8AF, UK

(Received 18 August 2000; in revised form 5 March 2001; accepted 19 April 2001)

Abstract — Lofexidine is an alpha-adrenoceptor agonist which has proved useful in opiate withdrawal and which, through its attenuation of noradrenergic activity, might be a valuable adjunct in the management of alcohol withdrawal. The objective of this study was to compare the clinical effectiveness and patient retention with adjunctive lofexidine versus placebo in the treatment of alcohol withdrawal under chlordiazepoxide cover. This was done in a prospective double-blind randomized placebo-controlled trial with 72 alcohol-dependent adults referred and admitted for in-patient alcohol detoxification. The adjunctive lofexidine group experienced significantly more severe withdrawal symptoms, greater hypotensive problems, more adverse effects, and no better rates of retention in treatment. Lofexidine provides no discernible benefit as an adjunctive medication (to chlordiazepoxide) in alcohol detoxification and, on the basis of our study, appears to be contra-indicated.

INTRODUCTION

Alcohol withdrawal is hazardous and potentially life-threatening. A recent meta-analysis (Mayo-Smith, 1997) of pharmacological management recommended routine benzodiazepine cover. Withdrawal is associated with hyperactivity of noradrenergic cells, and alpha-adrenoceptor agonists (e.g. clonidine or lofexidine) may attenuate the noradrenergic storm (Brunning et al., 1986) and thereby reduce withdrawal distress. Lofexidine is an alpha-adrenoceptor agonist which is licensed for treatment of opioid withdrawal in the UK, with at least five randomized trials (Bearn et al., 1996; Kahn et al., 1997; Lin et al., 1997; Carnwath and Hardman, 1998; Buntwal et al., 2000) and which is not associated with the same degree of hypotensive problems as clonidine (Kahn et al., 1997; Lin et al., 1997; Carnwath and Hardman, 1998). In the alcohol field, an early double-blind study found lofexidine to be superior to placebo (Cushman et al., 1985) and, in an open trial of 28 in-patients, lofexidine treatment was associated with rapid relief of adrenergic symptoms (Brunning et al., 1986). However, further studies at that time were halted (Cook et al., 1988) when the pharmaceutical company withdrew lofexidine on commercial grounds following disappointing results for its main clinical indication (for hypertension). No further alcohol studies have been undertaken, to our knowledge. In the present paper, we report on a double-blind comparison of lofexidine versus placebo as adjunctive medication in alcohol withdrawal.

SUBJECTS AND METHODS

This research study follows ICHGCP guidelines and this paper is presented in accordance with the CONSORT guidelines.

Patients

The study sample consisted of 72 subjects (from an original 80; see below) who fulfilled DSM-IV criteria (American Psychiatric Association, 1994) and ICD 10 (World Health Organization, 1992) for alcohol dependence and who were referred for in-patient alcohol detoxification at our in-patient detoxification unit serving South London. Information was also collected on current and recent alcohol consumption, with haematological and biochemical investigation for markers of high alcohol consumption, and measures of alcohol in breath, saliva and urine. All subjects provided written informed consent, and underwent a full physical examination, including supine and standing blood pressure. Exclusion criteria included serious physical illness, other major psychiatric illness, pregnancy, use of psychotropic medication and a current other drug misuse/dependence.

The in-patient detoxification unit offers a 10-day in-patient stay with flexibility to allow negotiation of the discharge date between day 7 and day 10. All subjects undergo an initial 24-h assessment (extended to 48 h if needed) of objective and subjective alcohol-withdrawal symptoms. During this period, a flexible dosing regime is used to administer chlordiazepoxide as needed to attenuate withdrawal symptoms. The daily dose of chlordiazepoxide administered during the assessment period then becomes the starting dose for the subsequent detoxification schedule (20% dose reduction on each subsequent day for a total of 5 days). The chlordiazepoxide is given in four divided doses daily and all such medication ceases with the evening dose on day 6.

Study design

Study subjects were randomly assigned to receive the standard chlordiazepoxide regime with either adjunctive lofexidine tablets (0.2 mg) or placebo tablets on a double-blind basis. The patients were randomized, in blocks of four, to one of the groups. There was no stratification in this study. Patients were allocated in chronological order to their randomized treatment groups. Patients and staff were blind to the allocation sequence.
LOFEXIDINE IN ALCOHOL WITHDRAWAL 427

Only the pharmacist preparing the study medication was aware of the allocation. The adjunctive lofexidine tablets and placebo were indistinguishable, having the same physical characteristics (e.g. size, colour, appearance). The pharmacist held the code break for individual patients (in case it was clinically imperative for this information to be divulged): however, the code was not broken in this study. The evidence for successful masking among the patients themselves is reported in the Results section. All other clinical and research staff and data analysts were blinded until analysis had been completed. The study medication was given once on the evening of admission and then twice daily in divided doses for the next 5 days according to the schedule outlined below.

**Lofexidine schedule**

The dosing schedule for lofexidine was as follows. On the evening of admission, subjects randomized to lofexidine were given 1.2 mg of lofexidine (as six tablets of 0.2 mg each). Thereafter, they received lofexidine 1.2 mg twice daily (a.m. time/p.m. time) for 5 days. Subjects randomized to placebo received dummy tablets according to the same schedule.

In view of concerns about possible postural hypotension, pulse and blood pressure (supine and standing) were measured regularly prior to the administration of medication. A systolic reading of <80 mmHg, a diastolic reading of <55 mmHg or a standing pulse rate of <55 bpm prompted the omission of the next dose of lofexidine or placebo and no further doses were given until pulse and blood pressure had returned to within normal limits.

**Measures**

The Severity of Alcohol Dependence Questionnaire (SADQ) (Stockwell et al., 1983) was used as a measure of the severity of alcohol dependence. The Alcohol Problem Questionnaire (APQ) (Drummond, 1990) was used to measure alcohol-related problems.

The severity of the alcohol-withdrawal syndrome was measured using two scales, the objective Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) (Sullivan et al., 1989) scale and the self-report Alcohol Withdrawal Scale (AWS). The AWS is a 30-item scale which asks subjects to rate how they ‘have been feeling for the following conditions in the last 24 h’: ‘loss of appetite’, ‘nausea’, ‘tremor (the shakes)’, ‘sweating’, ‘itching’, ‘muscle pain’, ‘weak legs’, ‘sleep disturbance’, ‘nightmares’, ‘visual disturbance’, ‘ringing in the ears’, ‘feeling restless’, ‘feeling agitated’, ‘pins and needles’, ‘walking problems’, ‘feverishness’, ‘heart pounding’, ‘feeling confused’, ‘hearing things not really there’, ‘seeing things not really there’, ‘feeling things on your skin’, ‘smelling things not really there’, ‘unusual thoughts’, ‘feeling suspicious’, ‘feeling anxious’, ‘unnaturally sleepy/drowsy’, ‘miserable’, ‘problems with memory’, ‘feeling irritable’, ‘feeling depressed’. The severity of each symptom is rated on a 4-point scale: none (scored 0), mild (1), moderate (2), and severe (3). The item scores are summed to produce a total withdrawal severity score. The AWS scale properties, reliability and validity are under investigation. This was administered once daily during the treatment and post-treatment periods until discharge. Patients usually remained on the ward for 10 days, but could be discharged from day 7 onwards. The point considered to indicate completion of the in-patient treatment was, for the purpose of this study, therefore taken as 6 days.

The AWS was administered daily during the treatment and post-treatment periods until discharge. The State–Trait Anxiety Inventory (STAI; Spielberger, 1983) was used to assess severity of anxiety symptoms during withdrawal (on admission, days 2 and 4).

Supine and standing blood pressure and pulse rate were recorded before each administration of lofexidine or placebo. These recordings continued after medication ceased on day 6 until discharge, usually on day 10.

Data on retention rates between the groups were obtained. The extent of ‘blindness’ of the patients to the study allocation was examined at the end of the study, when patients were asked to guess the treatment group to which they had been assigned. Data on total dosage of chlor Diazepoxide between the groups were obtained.

**Statistical analysis**

Of the 80 patients who originally consented to the study, eight (five lofexidine; three placebo) withdrew prior to receiving any study medication (see Fig. 1). Those who withdrew after commencing study medication were included in the ‘intention-to-treat’ analysis.

The withdrawal scores and blood pressure were analysed as follows. The post-treatment mean (days 2–10) was compared between treatment groups using analysis of covariance, controlling for pre-treatment values (day 1). For each of systolic

![Flow diagram of study (the ‘R’ indicates randomization).](Image)
and diastolic blood pressure, the four values of morning, afternoon and supine, standing were averaged. For the STAI, change scores were computed for each subject, and the mean change was compared between treatment groups using independent sample t-tests.

The proportions of subjects completing the treatment to day 6 were compared between groups using a Pearson χ²-test. Fisher’s exact test was used to compare the proportion of patients correctly guessing their medication and also to compare the proportion of patients suffering adverse effects.

RESULTS

Seventy-two subjects commenced treatment according to the randomized double-blind design described above. No significant differences between subjects randomly assigned to the adjunctive lofexidine or placebo conditions were identified with regard to basic demographic data (age, sex, race), admission baseline observations (admission systolic and diastolic blood pressure and pulse rate) and alcohol histories (SADQ, APQ scores and haematological and liver function test values; data not shown).

There was no significant difference between the two groups in the dosage of chloridiazepoxide used. The mean ± SD dosage for the placebo group (n = 34) was 642 ± 287 mg, the mean dosage for the adjunctive lofexidine group (n = 39) was 570 ± 260 mg [t(14) = 0.96, P = 0.35].

Severity of the withdrawal syndrome

Severity of withdrawal symptoms for the active lofexidine group was higher throughout the treatment period (days 1–6), as measured by both the CIWA-Ar and the AWS. After adjusting for baseline differences, withdrawal severity scores with the CIWA-Ar were significant (more severe) for the active lofexidine group [F(1,64) = 5.52, P < 0.05, 95% confidence interval (CI) 1.8; range 0.3 to 3.3]. With the AWS, the difference was not significant, but there was a trend for a difference in the AWS scores in the same direction [F(1,62) = 3.24, P = 0.08, 95% CI 5.2; range −0.6 to 10.4] (see Fig. 2a and b).

The overall course of the severity of the alcohol-withdrawal syndrome was similar for both scales (the two scales were highly correlated: r = 0.57, P < 0.001). Peak symptom severity was on day 1 and thereafter on days 2 and 3 for both treatment groups with the adjunctive lofexidine subjects experiencing more withdrawal symptomatology.

There were no significant differences in STAI scores for stable patterns of anxiety-proneness (trait) or in the repeated measures of anxiety during detoxification (state) between the two treatment groups. The change in STAI did not differ significantly between the groups (t = 1.2, df = 42, P = 0.24), and the mean STAI did not differ significantly between the groups (t = 1.52, df = 64, P = 0.13).

Clinical complications and side-effects

Mean systolic and diastolic blood pressures are shown in Fig. 3. There was a progressively increasing hypotensive effect in the adjunctive lofexidine group with reductions in both systolic and diastolic pressures. For the placebo group, pressures remained broadly stable. The group differences were less marked after day 8, 2 days after the last dose of medication had been received. No rebound increase in blood pressure was observed on termination of the adjunctive lofexidine. Pressures for the adjunctive lofexidine group were significantly lower (compared with placebo) for both systolic and diastolic blood pressure [systolic: F(1,69) = 17.56, P < 0.001, 95% CI: 14.03, 7.35 to 20.7; diastolic: F(1,69) = 7.45, P < 0.005, 95% CI 7.94, 2.14 to 13.75].

Three serious adverse events were recorded. One subject in the adjunctive lofexidine group had a syncopal attack on the morning of day 2, prior to medication being administered. Two subjects in the placebo group suffered serious adverse events; one subject had a seizure on the morning of day 6. The second subject was a non-insulin-dependent diabetic who needed to be transferred to a general medical ward on day 5 for control of hyperglycaemia.

Thirty non-serious adverse events were recorded; 23 in the adjunctive lofexidine group and seven in the placebo group. The majority of these events took place on day 2 or day 3. Medication was omitted in the adjunctive lofexidine due to

Fig. 2. Symptom severity on the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) scale and the self-report Alcohol Withdrawal Scale (AWS).
Comparison of retention in treatment

The analyses have firstly been undertaken with reference to the 80 subjects (40 + 40) originally entered into the study; and then also for the 72 who were still in treatment at the commencement of the study medication.

Of the 40 patients in the placebo group, 31 (77.5%) completed the study, compared with 24 (60%) of the 40 patients in the adjunctive lofexidine group. The main reason in both treatment groups for lack of completion was self-discharge usually on day 2 or day 3 of the study. There was no significant difference in completion rates between the two groups \( \chi^2(1) = 2.85, P = 0.09 \).

If the analyses are re-calculated with reference to the 72 subjects who commenced receipt of the study medication (i.e. received at least the first dose of either adjunctive lofexidine or placebo), then 31 (84%) of the 37 subjects in the lofexidine group completed the treatment, compared with 24 (69%) of the 35 subjects in the placebo group: a difference which was not significant \( \chi^2(1) = 2.31, P < 0.05 \).

Testing the blinding

Patient self-report with respect to which medication they had taken revealed no significant difference between the two groups. In the placebo group, 85.7% had guessed that they were receiving the adjunctive lofexidine, compared with 95.2% in the adjunctive lofexidine group (Fisher’s exact test, \( P = 0.38 \)).

DISCUSSION

Patients who received the adjunctive lofexidine intervention had significantly more withdrawal symptomatology, hypotensive problems and adverse effects. No evidence of benefit was elicited. Patients who received active lofexidine had a significantly more severe alcohol-withdrawal syndrome than those who received placebo. This difference seems likely to be due to the active lofexidine treatment and not to benzodiazepine effects since the doses of chlordiazepoxide prescribed in the two study groups were virtually identical.

To be useful in the management of alcohol detoxification, a treatment would ideally not only relieve withdrawal distress, but would also be associated with good retention in treatment. Hence we were also interested in the possible impact of adjunctive lofexidine on retention in the treatment programme. A similar picture was seen — completion rates of 84% amongst those who received placebo compared with 69% amongst those who received the active lofexidine — although here the difference was not statistically significant.

Some consideration needs to be given to whether the lofexidine was being given at too high a dose, since some of the earlier alcohol studies (e.g. Brunning et al., 1986) used doses which, compared with clinical protocols in the opioid field in the 1990s (Bearn et al., 1996; Sheridan et al., 1999) were at a very low dose. The doses prescribed were higher than those which had been found to be effective in management of the alcohol-withdrawal syndrome (Brunning et al., 1986). This may relate to the findings that the active lofexidine group reported significantly more side-effects, including a more frequent reporting of postural hypotension, as well as a significant reduction across the whole lofexidine group of diastolic and especially systolic blood pressure, during all 6 days of lofexidine prescribing.

Some observations of interest can be made which have relevance to the clinical use of lofexidine for other indications (e.g. opiate detoxification). As observed by investigators in the opioid field in the UK, we found it feasible to induce the patients on to high doses of lofexidine according to a rapid induction schedule as increasingly used clinically in the UK (Bearn et al., 1998; Carnwath and Hardman, 1998; Sheridan et al., 1999), with such side-effects as occurring being adequately managed by dose adjustment. No evidence was seen of significant rebound hypertension on cessation of the lofexidine (as was mooted as a potential problem by Bearn et al., 1996).

We note a similar study in the opioid field that assessed clonidine as an adjunct to methadone detoxification and found no place for its use as adjunctive medication (Ghodse et al., 1994).

Lofexidine is not currently used for, or even licensed for, alcohol detoxification, although it is increasingly widely used for opiate detoxification, particularly in the UK where, since
its introduction in 1992, the extent of its use has rapidly increased up to an estimated 20,000 opiate detoxifications under lofexidine in 1999 (Strang et al., 1999). With regard to the alcohol field, despite the previous postulation of a theoretical basis and the encouraging results from earlier studies, no discernible benefit could be identified from adjunctive lofexidine during the management of the alcohol-withdrawal syndrome with standard tapering daily doses of chlor Diazepam. Indeed, on the basis of the findings of more severe withdrawal symptoms with the active lofexidine versus placebo, its use as adjunctive medication in the management of alcohol withdrawal may be specifically contra-indicated.

Acknowledgements — We are grateful to the staff and patients on The Acute Assessment Unit at the Maudsley Hospital and the Addictions Directorate Pharmacy Department. We would also like to thank Dr Fergus Law, Lesley Cartwright-Taylor and Dr Alun Morinan for helpful comments on an earlier draft, and to Britannia Pharmaceuticals for support.

REFERENCES


