Original Article

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Pharmacology Section

A Comparative Study of the Clinical Efficacy and Safety of Lorazepam and Chlordiazepoxide in Alcohol Dependence Syndrome

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ABSTRACT

Background: Currently, benzodiazepines are the preferred drugs in the management of alcohol withdrawal symptoms. Chlordiazepoxide and diazepam, the most frequently used drugs have a long duration of action and are converted to active metabolites in the liver, while lorazepam is shorter acting, with no active metabolites.

Objective: To compare and evaluate the safety and efficacy of lorazepam and chlordiazepoxide in patients with alcohol dependence syndrome with symptoms of alcohol withdrawal.

Materials and Methods: This was a prospective, randomized, double-blind, study carried out at a teaching hospital in Bangalore. Sixty patients aged ≥18 y with alcohol dependence syndrome with mild-to-moderate withdrawal symptoms were allocated at a ratio of 1:1 to either lorazepam or chlordiazepoxide, by means of a computer-generated randomization chart. Thirty patients each were started with lorazepam tablets 8 mg/day and chlordiazepoxide 80 mg/day. For both treatment groups, the dose was tapered and at the end of 8 days, the patients were drug-free. The severity of alcohol dependence was assessed using the Severity of Alcohol Dependence Questionnaire (SADQ). The CIWA-Ar was used for quantification of withdrawal symptoms. Liver function tests were performed at baseline and at the end of the study.

Results: Of the 60 patients included in the study, 15 patients each had mild and moderate withdrawal symptoms in the chlordiazepoxide group and 17 and 13 patients respectively in the lorazepam group, based on the SADQ score. At baseline, the mean CIWA-Ar scores were similar in both the treatment groups: 24.77±5.98 in the chlordiazepoxide group and 24.90±6.12 in the lorazepam group. There was a significant intragroup decrease in the CIWA-Ar scores measured from baseline to the end of 8 days ($p<0.0001$) and 12 days ($p<0.0001$) in both treatment groups; however, there was no significant difference between the two groups. There was no significant difference observed in the liver function tests done at baseline and at the end of study period.

Conclusion: Lorazepam is noninferior to chlordiazepoxide in reducing alcohol withdrawal symptoms.

Keywords: Alcohol de-addiction, Benzodiazepines, Half-life, Withdrawal

INTRODUCTION

Alcohol is an important risk factor for morbidity and mortality, worldwide. It is estimated that globally, around two billion people consume alcoholic beverages, of whom nearly 76.3 million are likely to suffer from at least one alcohol use disorder [1]. Alcohol is responsible for almost 3.2% of all deaths and loss of 4% of total Disability adjusted life years (DALYs) [2]. Research has shown that countries where the alcohol consumption was initially low are showing a significant increase in the consumption trends [1]. Further, according to World Health Organization (WHO) estimates, in South East Asian countries up to one third of male population consume alcohol [3], and there is also a rise in the number of women who also do [4].

In India, the estimated number of alcohol users in 2005 were 62.5 million, with 17.4% of them (10.6 million) being dependant users [5] and 20–30% of them hospitalized for alcohol-related problems [5].

Alcohol dependence was recognized as a separate disorder in the 1960s [6]. In the 1970s, Edwards described the "alcohol dependence syndrome" that included the cognitive, behavioral, and physiological changes associated with alcohol use [7]. Individuals with alcohol dependence syndrome can develop alcohol withdrawal symptoms, which include physical and psychological symptoms that they experience on sudden reduction of quantity of alcohol consumed.

Clinical assessment of alcohol use includes various aspects including proper history taking include the type and quantity of drink consumed, the impact of alcohol on the normal activities, and the physiological and psychological effects of consumption as well as cessation of alcohol [8].

Considering the magnitude of the problem of alcohol consumption and dependence, the management of individuals with symptoms of alcohol withdrawal is important to help individuals in alcohol de-addiction. Currently, benzodiazepines like chlordiazepoxide, diazepam and lorazepam are the preferred drugs in the management of alcohol withdrawal symptoms. While the first two drugs are long-acting with half-lives of 24–48 h and 20–50 h, respectively, lorazepam is intermediate-acting with a shorter half-life of 10–20 h [9]. Both chlordiazepoxide and diazepam are time-tested choices to treat alcohol withdrawal. However, they are metabolized by the hepatic enzymes, and also form active metabolites that accumulate in the liver. As a result of this, these drugs can complicate withdrawal, and also increase the risk of hepatic encephalopathy. On the contrary, lorazepam is less likely to accumulate in the liver, because it is metabolized by conjugation, a pathway that is less affected than the hepatic microsomal pathways in liver dysfunction. Additionally, lorazepam has no active metabolites. However, because of its relatively short half-life, there can be fluctuations in blood levels over the course of the day resulting in poorer protection against

alcohol-withdrawal seizures [10], and discontinuation may be more problematic [11]. Despite these issues, lorazepam is preferred in the management of alcohol withdrawal, especially in those with alcoholic liver disease [9].

Currently, there are very few head-to-head trials comparing chlordiazepoxide/ diazepam with lorazepam [9,12-16]. Therefore, the current study was undertaken to compare the safety and efficacy of chlordiazepoxide and lorazepam in individuals with alcohol dependence syndrome having withdrawal symptoms. We conducted the current study to compare and evaluate the safety and efficacy of lorazepam and chlordiazepoxide in patients of alcohol dependence syndrome with mild-to-moderate withdrawal symptoms.

MATERIALS AND METHODS

Study Population

Patients above the age of 18 y with alcohol dependence syndrome with mild-to-moderate alcohol withdrawal symptoms admitted to in-patient wards, Departments of Psychiatry and Medicine at a Teaching hospital in Bangalore between November 2011 and October 2012 were included in the study. Informed consent was obtained from all the patients. Ethical clearance was obtained from the Institutional Ethics Committee.

Inclusion criteria: (i) Age ≥18 y, (ii) meet criteria for alcohol dependence (DSM-IV) and mild-to-moderate alcohol dependence, (iii) were medically stable, (iv) had a clinical withdrawal assessment prior to study, and (v) not on any psychotropic medication.

Exclusion criteria: (i) dependent on any substance other than nicotine, (ii) had a history of alcohol withdrawal seizures, epilepsy or delirium tremens, (iii) had a history of hepatic encephalopathy, ascites, diabetes, or renal disease, (iv) taken any drug known to lower the seizure threshold during the past 14 days, (v) received any drug which alter the clinical presentation of alcohol withdrawal or the outcome assessments, (vi) any comorbid illness, (vii) had contraindications for the use of either of the study drugs, and (vii) pregnant or nursing females.

Methodology

This was a prospective, randomized, double-blind, interventional study. Sixty patients with alcohol dependence syndrome with mild-to-moderate withdrawal symptoms were allocated to receive either lorazepam or chlordiazepoxide, by means of a computer-generated random sequence using a concealed envelop at a ratio of 1:1. The study drugs were powdered and filled in opaque, empty capsules of the same size and color and the required number of capsules were administered to the patients according to the randomization number mentioned in the envelop, by the pharmacist in our department. All the participants and the outcome assessor were unaware of the treatment allocation.

Thirty patients were treated with lorazepam tablets 8 mg/day (2 mg in the morning, 2 mg in the afternoon, 4 mg in the night). The dose was reduced by 2 mg per day every 2 days, and at the end of 8 days of treatment, the patient was drug free. Another thirty patients were treated with chlordiazepoxide 80 mg/day (20 mg in the morning, 20 mg in the afternoon and 40 mg in the night). The dose was reduced by 20 mg per day every two days, and at the end of eight days of treatment, the patient was drug free. This dose titration schedule was fixed. All patients received a multivitamin injection daily, because malnutrition from dietary deficiency and vitamin deficiencies due to malabsorption are common in alcoholism; additionally, malabsorption of water-soluble vitamins is especially severe.

The severity of alcohol dependence was assessed using the Severity of Alcohol Dependence Questionnaire (SADQ) [17]. Those with mild-to-moderate dependence were included (Scores 4-19 and 20-30 respectively). The CIWA-Ar [18] was used for quantification of withdrawal symptoms. The maximum score is 67 and those with a score less than 10 do not require additional medications for withdrawal [17]. Liver function tests were performed at baseline and at the end of the study.

STATISTICAL ANALYSIS

The data collected was tabulated and analyzed using descriptive statistical tool, mean, standard deviation, and comparison between the groups using student t-test. Complete analysis was carried out using SPSS package (version 19).

RESULTS

A total of 60 patients were randomized equally to receive either chlordiazepoxide or lorazepam. In our study most patients were in the age-group of 28–47 y (18 and 17 patients each in the Chlordiazepoxide and Lorazepam groups respectively). Most patients were male (Male: Female=9:1). The last drink consumed was <12 h ago in majority of patients (Chlordiazepoxide group: 21 patients and Lorazepam group: 23 patients). Most patients had been consuming alcohol for a duration of 6-20 y (Chlordiazepoxide group: 25 patients and Lorazepam group: 24 patients). The average quantity of alcohol consumed was 534.37 mL (Range 180–1540 mL) and 444 mL (Range 180–1080 mL) in the Chlordiazepoxide and Lorazepam groups respectively. Whisky was the commonest drink in the Chlordiazepoxide group (n=15) and brandy in the Lorazepam group (n=11). Eighteen in the Chlordiazepoxide group and fifteen in the Lorazepam group were smokers.

At baseline, the severity of dependence was assessed using the SADQ. In the chlordiazepoxide group, 15 patients each had mild and moderate dependence. In the lorazepam group, 13 patients had mild-, while 17 had moderate dependence.

The CIWA-Ar scores (mean ± standard deviation) at baseline were similar in both the treatment groups: 24.77±5.98 in the chlordiazepoxide group and 24.90±6.12 in the lorazepam group.

At the end of 8 days and 12 days, the scores (mean ± standard deviation) were 4.30±2.77 and 3.73±2.56; and 1.27±1.34 and 1.43±1.36 in the chlordiazepoxide and lorazepam groups, respectively [Table/Fig-1]. There was significant intragroup difference in the CIWA-Ar scores measured at baseline and at the end of 8 days ($p<0.0001$) and that at the end of 12 days ($p<0.0001$) in both groups. However, there was no significant difference between the two groups in terms of the CIWA-Ar scores [Table/Fig-1].

Liver function tests were done at baseline and at the end of the study to assess the safety of the drugs. However, we did not find any significant change in any of the parameters [Table/Fig-2].

DISCUSSION

The current study was conducted to compare the efficacy and safety of Chlordiazepoxide vs. Lorazepam in the management of alcohol withdrawal symptoms in patients who had alcohol dependence syndrome. Based on the SADQ, it was observed that 15 patients each had mild and moderate withdrawal symptoms in the Chlordiazepoxide group and 17 and 13 patients respectively in the Lorazepam group.

In our study, the CIWA-Ar scale was used to assess the withdrawal symptoms. At baseline, the mean CIWA-Ar scores were similar in both the treatment groups: 24.77±5.98 in the chlordiazepoxide group and 24.90±6.12 in the lorazepam group. There was a significant intragroup decrease in the CIWA-Ar scores measured from baseline to the end of 8 days ($p<0.0001$) and 12 days ($p<0.0001$) in both treatment groups; however, there was no significant difference between the two groups [Table/Fig-1].

Dependence occurs because of progressive pharmacological adaptation to alcohol resulting in tolerance. When alcohol is abruptly

Day of assessment	Chlordiazepoxide group			Lorazepam group			p-value**
	CIWA-Ar Score	Difference in CIWA-Ar from baseline	p-value*	CIWA-Ar Score	Difference in CIWA-Ar from baseline	p-value*	
Baseline	24.77±5.98	-	-	24.90±6.12	-	-	-
Day 1	24.93±6.87	0.17±7.9	0.91	24.73±5.10	-0.17±7.67	0.91	0.899
Day 2	21.30±7.46	-3.47±7.51	0.02	21.00±5.16	-3.90±7.13	.006	0.857
Day 3	17.90±5.65	-6.87±6.61	<0.0001	18.13±4.80	-6.77±6.89	<0.0001	0.864
Day 4	15.20±5.77	-9.57±6.64	<0.0001	14.57±4.08	-10.33±6.67	<0.0001	0.626
Day 5	11.73±5.19	-13.03±5.89	<0.0001	11.77±4.32	-13.13±6.45	<0.0001	0.979
Day 6	9.33±3.38	-15.433±5.66	<0.0001	8.33±2.75	-16.57±6.26	<0.0001	0.213
Day 7	6.70±2.94	-18.07±5.63	<0.0001	5.57±2.54	-19.33±6.20	<0.0001	0.116
Day 8	4.30±2.77	-20.47±5.78	<0.0001	3.73±2.56	-21.17±6.48	<0.0001	0.414
Day 9	3.67±4.20	-21.10±6.02	<0.0001	2.63±3.10	-22.27±6.54	<0.0001	0.283
Day 10	2.27±2.42	-22.50±5.74	<0.0001	1.70±1.98	-23.20±6.38	<0.0001	0.326
Day 11	0.97±1.38	-23.80±5.92	<0.0001	1.13±1.33	-23.77±6.43	<0.0001	0.636
Day 12	1.27±1.34	-23.50±5.91	<0.0001	1.43±1.36	-23.47±6.38	<0.0001	0.634

[Table/Fig-1]: Change in the CIWA-Ar scores from baseline to the end of study.
*p value of change in CIWA-Ar score within each treatment group (intragroup)
**p value of change in CIWA-Ar score between both treatment groups (intergroup)

Parameter	Chlordiazepoxide group				Lorazepam group			
	End of study value	Baseline value	Difference	p-value	End of study value	Baseline value	Difference	p-value
Total bilirubin (mg/dL)	1.03±0.50	1.04±0.49	0.01±0.98	0.46	0.87±0.57	0.86±0.55	0.01±0.12	0.67
Direct bilirubin (mg/dL)	0.26±0.13	0.26±0.11	0.00±0.59	1.00	0.28±0.23	0.27±0.23	0.01±0.07	0.62
Total protein	6.81±0.63	6.80±0.61	0.01±0.11	0.73	6.80±0.59	6.80±0.58	0.01±0.06	0.57
Serum Albumin	4.06±0.37	4.08±0.33	0.02±0.16	0.57	4.0±0.47	4.02±0.47	0.01±0.13	0.59
Serum Globulin	2.59±0.39	2.60±0.38	0.01±0.76	0.47	2.74±0.45	2.71±0.45	0.03±0.10	0.12
SGOT	41.13±42.17	41.60±42.90	0.04±1.79	0.16	54.23±41.32	55.00±41.24	0.77±1.90	0.04
SGPT	45.53±35.34	46.60±35.24	1.07±1.93	0.005	67.77±68.44	68.10±68.67	0.33±1.72	0.30
Alkaline Phosphatise	67.57±21.85	66.67±22.20	0.90±4.19	0.25	78.00±11.74	78.50±10.84	0.50±2.25	0.23

[Table/Fig-2]: Liver function test results at baseline and end of study

stopped, a withdrawal syndrome, with symptoms opposite to the original effects of alcohol ensues, where the adaptive responses are unopposed by it [19]. The pharmacological management of alcohol withdrawal most commonly involves the use of drugs that are cross-tolerant with alcohol. Giving enough of a CNS depressant on the first day to diminish symptoms, tapering the dose over the next few days, and then stopping the drug offers most patients optimal relief and minimizes the possibility that a severe withdrawal will develop. Any depressant, including alcohol, barbiturates, or benzodiazepines is effective, but most clinicians choose benzodiazepines for their relative safety and have therefore been used for decades in alcohol detoxification programs [20,21].

Long-acting benzodiazepines are the drugs of choice for alcohol detoxification or treatment of alcohol withdrawal symptoms, because their blood levels are relatively stable and therefore, the risk of withdrawal symptoms including seizures is minimised [7]. As discussed previously, there are important pharmacokinetic reasons to prefer lorazepam (less likely to accumulate in the liver, because it is metabolized by conjugation, which is less affected than the hepatic microsomal pathways in liver dysfunction; no active metabolites and therefore, preferred especially in those with alcohol liver disease) over the time-tested benzodiazepines diazepam and chlordiazepoxide for the medical management of alcohol withdrawal in patients with impaired liver function. However, on literature search, we could identify only six randomized, controlled studies comparing lorazepam with other benzodiazepines.

In the study by Kumar et al., [9], the CIWA-Ar scores in the two treatment groups were virtually identical (Chlordiazepoxide group: Baseline score of 12.0±5.6 and day 12 score 0.3±0.9; Lorazepam group: Baseline score of 11.7±4.6 and day 12 score 0.3±1.6) across the first 12 days of withdrawal as seen in our study [Table/Fig-1]. Patients with a CIWA-Ar score less than 10 usually do not require treatment for withdrawal [18]. In our study, by day 6, in both treatment groups, the CIWA-Ar scores were <10. However, since we were tapering the dosage of the drugs, we continued to treat the patients for the remaining two days, before stopping therapy. In another recently published study by Rajmohan et al., [16]. lorazepam was better than chlordiazepoxide in the management of alcohol withdrawal, both in terms of time to improvement of symptoms, as well as duration of total withdrawal. There was a significant difference in the rate of improvement over 48 h in the lorazepam group vs. chlordiazepoxide group (70.4% vs. 54.8%; p<0.0001). The total duration of withdrawal was 5.6 days with lorazepam vs. 6.7 days with chlordiazepoxide (p=0.001). The treatment schedule we used in our study is the same as that in the study by Kumar et al.,[9], in which there was no difference between the two groups (Chlordiazepoxide and lorazepam treated groups) in terms of developing any withdrawal symptoms during the treatment period. Unlike previous studies (see following text), they found that withdrawal with lorazepam was as smooth and uneventful as that with chlordiazepoxide. Additionally, it should be noted that patients received lorazepam or chlordiazepoxide only during the first 8 days. Therefore, if symptoms of benzodiazepine withdrawal had to develop, they would have been identified during the last 4 days of the study, as would have been the case with symptoms of alcohol withdrawal. However, there were virtually no symptoms recorded during the last 4 days, nor were there impairing adverse events reported during this period. Similarly in our study, we did not observe any adverse events either during the study or after stopping the medications.

This difference observed is probably because different doses of the study drugs were used in previous studies, especially with that of lorazepam being lower than that used in the study by Kumar et al [9], and our study. In the study by Solomon et al., [15], lorazepam and chlordiazepoxide were started at a dose of 6 and 150 mg/day, which were tapered to 2 and 50 mg/day over a period of 4 days. Two patients in the lorazepam group had withdrawal seizures, but none in the chlordiazepoxide group. Additionally, none of the subjects withdrew from the study due to adverse events.

In the study by O'Brien et al., [13] lorazepam was compared with diazepam. The lorazepam regimen was the same as in the study by Solomon et al., [15], while diazepam was started at a dose of 30 mg/day and tapered to 10 mg/day over 4 days. One patient in the lorazepam group experienced confusion, but no other adverse events were reported.

In the study by Miller and McCurdy [12], the dosing with lorazepam and diazepam was the same as that used by O'Brien et al., [13], except that some patients received an additional dose of medication on the first day. Two patients receiving lorazepam developed delirium tremens.

In a study by Ritson and Chick [14], lorazepam and diazepam was initiated at 6 mg per day and reduced by 1 mg per day, and treatment was stopped at Day 6. Similarly, diazepam was started at 30 mg per day, reduced by 5 mg per day, and treatment was stopped at Day 6. Patients on lorazepam reported more anxiety and depression. One patient on lorazepam experienced withdrawal seizures.

Liver function tests were done for all patients at baseline as well as at the end of the study period to assess the safety of the two study drugs. However, there was no significant difference in the various parameters [Table/Fig-2]. This is probably because it takes about three months to observe any significant change in the liver function tests. Chlordiazepoxide is metabolized predominantly in the liver into active metabolites, and therefore has a longer duration of action. Because chronic alcoholism is known to cause liver dysfunction, the metabolism of Chlordiazepoxide is impaired. In these patients, lorazepam may be a preferred option.

CONCLUSION

According to our study, lorazepam is not inferior to chlordiazepoxide in reducing alcohol withdrawal symptoms. Furthermore, the lack of significant difference in the liver function tests between the two groups was probably because the interval between the two assessments is not long enough to cause derangement in the liver function tests. Lorazepam may prove to be beneficial in these patients, based on follow-up and LFT assessment for longer durations. Additionally, the sample size in our study is small, and therefore including a larger sample, might be helpful in discerning the beneficial effects of shorter acting benzodiazepines like lorapezam over longer acting ones like chlordiazepoxide. To conclude, considering that in most alcohol dependent patients liver function is compromised, drugs like lorazepam which do not undergo biotransformation in the liver should be preferred in the management of acute withdrawal symptoms.

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