A COMPARATIVE STUDY OF EFFICACY & TOLERABILITY OF LORAZEPAM AND GABAPENTIN IN THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME

Dr. Ashutosh Chourishi,* Dr. O.P. Raichandani, Dr. Sunita Chandraker***, Dr. Swati Chourishi******
* M.D. Assist. Prof., Deptt. Of Pharmacology, R.D. Gardi Medical College, Ujjain, India.
** M.D. DNB, Assist. Prof., Deptt. Of Psychiatry, NSCB Medical College, Jabalpur, India.
******* M.D. Asso. Prof., Deptt. Of Pharmacology, NSCB Medical College, Jabalpur, India.
******** Demonstrator, R.D. Gardi Medical College, Ujjain, India.
***Email:** dr_chourishi@yahoo.co.in

ABSTRACT

To compare the efficacy & tolerability of Lorazepam and Gabapentin in alcohol withdrawal syndrome. This was a 15 days, randomized, double blind and controlled study. Fourty-six in-patients with mean age 38.37 ± 8.00 years, with mild to moderate alcohol withdrawal syndrome were enrolled for study after obtaining informed written consent. Gabapentin 300 mg capsules and lorazepam 2 mg capsules were prescribed for 5 days. Primary variables were CIWA-Ar total score and CGI- scale. Other variables included global assessments of safety and tolerability. In both groups, from 2nd day all participants had achieved a clinically relevant improvement of their withdrawal symptoms on CIWA-Ar. There was drastic reduction on the scores of CIWA-Ar scale and CGI-S scale, and increment on CGI-I scale, from baseline to day 7 & day 15. These changes were statistically highly significant ($p < 0.001$), which shown that both drugs were efficacious in the treatment of acute mild to moderate alcohol withdrawal syndrome. But there were no statistically significant differences between the both treatment groups on day 7 & day 15 in all efficacy measures, so that the results obtained with these treatment schemes can be considered as equal. Side-effects were more common in the lorazepam group than in the gabapentin group. The most frequently reported side-effect of lorazepam was daytime sleepiness. From the present study it can be concluded that, gabapentin is equivalent in efficacy and better in tolerability to lorazepam in the treatment of alcohol withdrawal syndrome. Because gabapentin has less side-effects and less interaction with alcohol, therefore gabapentin may be used safely in alcohol withdrawal syndrome.

Keywords: Gabapentin, Lorazepam, Alcohol withdrawal syndrome.

INTRODUCTION

Alcoholism is a major public health problem, defined as a pattern of uncontrolled drinking leading to medical, legal and psychosocial adverse consequences. Alcohol withdrawal refers to symptoms that may occur when a person who has been drinking too much alcohol everyday, and suddenly stops or decreases drinking alcohol. Alcohol withdrawal syndrome usually occurs in adults, but it may happen in teenagers or children as well. The withdrawal usually occurs within 5-10 hours after the last drink, but it may occur up to 7-10 days later.

Withdrawal Symptoms:

The spectrum of withdrawal symptoms and the time range for the appearance of these symptoms after cessation of alcohol use are listed in Table 1. Generally, the symptoms of alcohol withdrawal relate proportionately to the amount of alcoholic intake and the duration of a patient's recent drinking habit. Most patients have a similar spectrum of symptoms with each episode of alcohol withdrawal.

Treatment:

The goals are to treat the immediate withdrawal symptoms, prevent complications and provide long-term preventive therapy.

Pharmacological treatment of alcohol withdrawal syndrome involves the use of medications that are cross-tolerant with alcohol. Benzodiazepines (lorazepam) have been shown to be safe and effective, particularly for preventing or treating seizures and delirium, and are the preferred agents for treating the symptoms of alcohol withdrawal syndrome.[1] Lorazepam is preferred over longer acting benzodiazepines such as diazepam and chlordiazepoxide for patients with liver disease and in the elderly.[2,3] Lorazepam can be given either orally or intravenously.

Though benzodiazepines are mainstay of treatment for mild-to-moderate alcohol withdrawal syndrome, but they can interact with alcohol, causes motor incoordination, or to be abused.

Gabapentin, a drug approved for use as adjunctive therapy in the treatment of partial seizures, has none of these BZD-type difficulties (drug interactions, abuse potential). Gabapentin which is structurally similar to GABA, has been effective in the treatment of alcohol withdrawal in some studies.[4,5] The low toxicity of gabapentin makes it a promising agent.

Alongwith treatment, a "drying-out" period should be appropriate. No alcohol is allowed during this time.

The study we report here compares gabapentin with lorazepam. Both drugs were evaluated for effects on acute withdrawal symptoms, craving for alcohol, and rebound phenomena after treatment discontinuation.

Table 1: Symptoms of Alcohol withdrawal Syndrome

Symptoms	Time of appearance after cessation of alcohol use
Minor withdrawal symptoms: insomnia, tremulousness, mild anxiety, gastrointestinal upset, headache, diaphoresis, palpitations, anorexia.	6 to 12 hours
Alcoholic hallucinosis: visual, auditory, or tactile hallucinations	12 to 24 hours
Withdrawal seizures: generalized tonic-clonic seizures	24 to 48 hours
Alcohol withdrawal delirium (delirium tremens): hallucinations (predominately visual), disorientation, tachycardia, hypertension, low-grade fever, agitation, diaphoresis	48 to 72 hours

OBJECTIVE OF TRIAL

Primary objective: To compare the efficacy & tolerability of Lorazepam and Gabapentin in the treatment of Alcohol withdrawal syndrome.

Secondary objective: To evaluate a safe and useful medication for Alcohol withdrawal syndrome.

MATERIALS AND METHODS

Study Design: The type of study was interventional. The study was 15 days, randomized, controlled, parallel-group, double blind clinical trial conducted at department of psychiatry in collaboration with department of pharmacology in NSCB Medical College Hospital, Jabalpur.

The study was approved by the Medical Ethical Committee of the NSCB Medical College Hospital Jabalpur and West Central Railway Hospital Jabalpur. The study was performed in accordance with Good Clinical Practice guidelines. All patients provided written informed consent prior to any study-related procedures.

Inclusion criterion:

- Meets criteria for alcohol dependence (DSM-IV-TR)[6] (American Psychiatric Association,1994) and mild-to-moderate alcohol withdrawal syndrome.
- Subjects must be medically stable (not likely to require Hospitalization for medical complication within 15 days.)
- Have a clinical withdrawal assessment prior to study.
- Subjects must be medically acceptable for study treatment. Considerations include no past or present physical disorder that is likely to deteriorate during participation.
- Not have any other psychiatric condition or psychotropic medication prior to entering the study.

Exclusion criterion:

- Current diagnosis of any other substance dependence syndrome other than alcohol dependence (excluding nicotine and caffeine dependence)
- Use of Pharmacological agents within the last 14 days that are known to lower the seizure threshold or augment or decrease the alcohol withdrawal syndrome.
- History of alcohol withdrawal seizures, epilepsy or delirium tremens.
- Diagnosis of schizophrenia, bipolar disorder or dementia.
- History of hepatic encephalopathy, jaundice, ascites, diabetes, or renal disease.
- Females who are pregnant or nursing.
- Subjects with known sensitivity of previous adverse reaction to gabapentin or lorazepam.

Study Population:

During the period of the study, 46 patients were registered to the psychiatry department for alcohol deaddiction who satisfied the inclusion and exclusion criteria and were asked for informed consent. They were all males in the age group of 18-60 years of age (mean age 38.37 ± 8.00 years). 35 patients were admitted consecutively between August 2004 and August 2005 for in-patient alcohol detoxification at our in-patient psychiatric detoxification unit at NSCB Medical College Jabalpur. 11 patients were taken from a alcohol deaddiction camp organized in West-Central Railway Hospital, Jabalpur from 8th june'05 to 15th june'05. The deaddiction camp was organized in collaboration of department of psychiatry, medical college Jabalpur. Total 11 railway employees have participated in this camp and were admitted in deaddiction ward at west-central Railway Hospital Jabalpur.

METHODOLOGY

Before admission of patients in deaddiction ward for this study a screening visit was required. During the screening visit, medical history was recorded, a neurological exam and brief physical exam were performed, and CAGE questionnaire was administered. Following this, each subject included in this study gave written informed consent relating to documentation of data on personal history and course of alcohol withdrawal for scientific purposes.

In this study only in-patients were taken. The in-patient detoxification unit offered a 10-day in-patient stay with flexibility to allow negotiation of the discharge date between day 7 and day 10.

A validated interview was carried out on admission. On the day of admission each patient was undergo detailed psychiatric, neurological and medical examinations. A detailed proforma was made to assess the patients on these points.

Randomization and blinding method:

After giving written informed consent, subjects who met all screening requirement were randomized to receive the either gabapentin (group-I) or lorazepam (Group-II) capsules on a double-blind basis. Patients were allocated in chronological order and randomized into two groups by even and odd method.

The lorazepam and gabapentin capsules were indistinguishable, having the same physical characteristics (e.g. size, colour, appearance). Study medications for both groups were dispensed in temper proof, packets that were similar in appearance. Label on the packets contained study code, patient's serial number, manufacturing date and expiry date and space for date of dispensing. Hence, neither the patient nor the investigator was aware of the medication received by the patients. Only the pharmacist preparing the study medication was aware of the allocation.

Interventions:

The study medication was given daily in divided doses for the next 5 days according to the schedule outlined below.

The patients were administered either Lorazepam or Gabapentin capsules at the dose of one capsule four times in 1st day, one capsule three times in 2nd & 3rd day, one capsule two times in 4th day and one capsule on 5th day. At admission and also during the study period, alcohol abstinence was checked by a Breathalyzer at least once every day.

Follow-up and assessment:

To quantify the severity of alcohol withdrawal syndrome, and to monitor and medicate patients going through withdrawal, CIWA-Ar (The revised Clinical Institute Withdrawal Assessment for Alcohol) scale is used, which is a validated 10-item clinical rating scale focusing on subjective and objective symptoms of withdrawal.[7,8,9] The withdrawal symptoms which included in this scale are – 1.Nausea & vomiting, 2.Tremor, 3.Paroxysmal sweats, 4.Anxiety, 5.Agitation, 6.Tactile disturbances, 7.Auditory disturbances, 8.Visual disturbances, 9.Headache, fullness in head, 10.Orientation and clouding of sensorium. In this scale each item rated of 0 to 7 (except orientation which is 0 to 4). The maximum score is 67. CIWA-Ar scores of 8 points or fewer correspond to mild withdrawal, scores of 9 to 15 points correspond to moderate withdrawal, and scores of greater than 15 points correspond to severe withdrawal symptoms. This scale adapted from Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Selleres EM [10].

CIWA-Ar scale was used to assess alcohol withdrawal symptoms on days 1 through 5 and post medication at days 7 and 15. Patients were evaluated every day for improvement of alcohol withdrawal symptoms and observed for any adverse events or relapse of symptoms. The assessment was also carried out on CGI-severity / improvement scales on days 1 through 5 and post medication at days 7 and 15.

Assessments of adverse events:

All adverse events reported or observed by patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication were predefined as "Unrelated", "Possible", and "Probable"

OUTCOME MEASURES

Efficacy and tolerability assessment:

The primary efficacy variable was reduction of the withdrawal syndrome on the CIWA-Ar compared to the individual baseline level, in the intention-to-treat (ITT) group. We were interested specifically in the main symptoms of physical withdrawal, such as anxiety, sweating and tremor. Efficacy was also assessed by total score of CGI-severity / improvement scales.

Both patient and investigators performed the global assessment on drug efficacy and tolerability, which was categorized into a five-point scale ('very good', 'good', 'fair', 'poor', 'very- -poor'), at each post-treatment visit.

Tolerability was continually evaluated by recording the frequency of adverse events (AEs) and serious adverse events (SAEs). A complete physical examination was performed at each visit.

Statistical analysis:

The demographic data of the two groups was compared by 'z- test'. Standard error of differences between two means $^{s}(X1-X2)$ test and the 'Z-test' were used in the statistical analysis to compare baseline demographics and the effects of both drugs at day 7 & day 15. The p-value > 0.05 ($Z < 2$) was required to declared not statistical significant at 5% level.

Chi-squared (x^2) test was used in the statistical analysis of the adverse and a p-value ≤ 0.05 was required to declare statistical significant at 5% level.

RESULTS

Study population:

The ITT group consisted of 46 participants. Twenty-three patients were randomized to each group. There were no significant differences between the treatment groups in terms of socio-demographic or clinical variables that were measured at baseline.

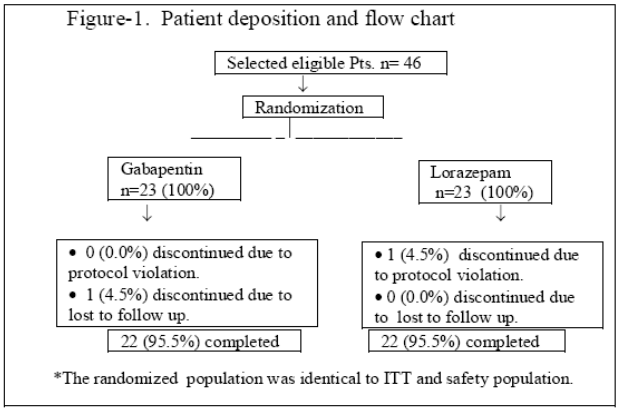
At baseline, all participants showed signs of mild to moderate withdrawal. At baseline, the participants showed a mean total score (sum of all items of the CIWA-Ar) of 12.57 ± 1.69 SD in gabapentin group and 12.52 ± 1.70 SD in lorazepam group. There were no significant differences between the both treatment groups in all baseline parameters.

Efficacy results:

In both groups, from 2nd day all participants had achieved a clinically relevant improvement of their withdrawal symptoms on CIWA-Ar. At the end of day 2, participants showed no more than one or two mild symptoms (such as tremor, sweating or restlessness). There was drastic

reduction on the scores of CIWA-Ar scale and CGI-S scale, and increment on CGI-I scale, from baseline to day 7 & day 15. These changes were statistically highly significant ($p < 0.001$), which shown that both drugs were efficacious in the treatment of acute mild to moderate alcohol withdrawal syndrome.

Figure-1. Patient deposition and flow chart



The *p*-value > 0.05, (Z < 2) was required to declared not statistical significant at 5% level.

All the "z" values were < 2, hence p value were > 0.05, so there were no statistical significant difference in the all the efficacy measures, between the both treatment groups at day 7 & day 15. So that the results obtained with these treatment schemes can be considered as equal.

Tolerability results:

No serious adverse events were reported in either groups. Side-effects were more common in the lorazepam group than in the gabapentin group ($x^2 = 4.058$, $p = <0.05$), in the form of drowsiness (0% and 17%, respectively), dizziness (4% and 13%, respectively), and confusion (0% and 9%, respectively). However insomnia (2% with gabapentin, 0% with lorazepam) was more common in the gabapentin group than in the lorazepam group (See Table). All these side-effects disappeared within 3 days of the start of the study.

Table 2: Comparison of CIWA-Ar, CGI-S and CGI-I scores from baseline values.

No.	Scale	Group	B.L.	Day 7	Z –value	Day 15	Z -value
1.	CIWA-Ar score	Group –1 (Gabapentin)	12.57 ± 1.69	2.22 ± 0.90	Z = 25.87	1.43 ± 0.66	Z = 29.31
		Group-2 (Lorazepam)	12.52 ± 1.70	2.74 ± 0.91	Z = 24.45	1.74 ± 0.75	Z = 27.92
2.	CGI- severity score	Group –1 (Gabapentin)	5.13 ± 0.50	1.35 ± 0.48	Z = 27	0.96 ± 0.36	Z = 33.36
		Group-2 (Lorazepam)	4.91 ± 0.66	1.52 ± 0.51	Z = 19.59	1.17 ± 0.57	Z = 20.66
3.	CGI-improvement score	Group –1 (Gabapentin)	1.09 ± 0.84	5.65 ± 0.48	Z = 22.80	6.04 ± 0.36	Z = 26.32
		Group-2 (Lorazepam)	1.13 ± 0.81	5.47 ± 0.51	Z = 21.91	5.83 ± 0.57	Z = 23.5

*z-values > 3, it means highly significant, p < 0.001

Table 3: Changes from baseline to day 7 and day 15 in CIWA-Ar Total score (mean ± SD).

Days	Group - 1 Gabapentin (n=23)	Group – 2 Lorazepam (n=23)	*P* - value
Day –7	-10.34 ± 1.36	-09.28 ± 1.53	*Z* = 1.30 *P* = > 0.10
Day- 15	-11.13 ± 1.29	-10.78 ± 1.66	*Z* = 0.79 *P* = > 0.10

Table 4: Changes from baseline to day 7 and day 15 in CGI-severity score (mean ± SD).

Days	Group - 1 Gabapentin (n=23)	Group – 2 Lorazepam (n=23)	*P* - value
Day –7	-3.78 ± 0.67	-3.39 ± 0.81	*Z* = 1.77 *P* = > 0.05
Day- 15	-4.17 ± 0.72	-3.74 ± 0.75	*Z* = 1.99 *P* = > 0.05

Table 5: Changes from baseline to day 7 and day 15 in CGI – improvement score (mean ± SD).

Days	Group - 1 Gabapentin (n=23)	Group – 2 Lorazepam (n=23)	*P* - value
Day –7	+4.56 ± 0.66	+4.34 ± 0.83	*Z* = 1.00 *P* = > 0.10
Day- 15	+4.96 ± 0.77	+4.70 ± 0.79	*Z* = 1.18 *P* = > 0.10

Table 6: Summary of safety and tolerability

	Gabapentin (n = 23) Group 1	Lorazepam (n = 23)Group- 2	p- value
Patients with SAEs, n (%)	0	0	
Patients with AEs, n (%)	3 (13)	9 (39)	p< 0.05
Discontinuations due to any AEs (including SAEs), n (%)	0	0 (0)	
Most frequent adverse events (≥ 2% for any group), n (%)			
Drowsiness	0	4 (17)	p< 0.05
Dizziness	1 (4)	3 (13)	p>0.05
Confusion	0	2 (9)	p>0.05
Insomnia	2 (9)	0	p>0.05

*SAE = serious adverse event; AE = adverse event;

DISCUSSION & CONCLUSION

Pharmacotherapy is only one part of the therapeutic strategy in the treatment of alcoholism. A short and effective management of withdrawal symptoms not only reduces the inconvenience for a patient, but also saves costs.

Lorazepam is a well-proven therapy for the treatment of mild to moderate alcohol withdrawal syndrome. This study was aimed to determine the efficacy and tolerability

of gabapentin compared to conventional lorazepam in the treatment of mild to moderate alcohol withdrawal syndrome. All participants included in our study had a mild to moderate alcohol withdrawal syndrome at baseline, with a CIWA-Ar score of ≥12 points. The observer bias has been taken care of by the double blind study design where the investigator and patient were kept unaware throughout the study period regarding the medication.

The ideal medication for the detoxification of alcohol-dependent patients would suppress withdrawal rapidly, suppress drinking behaviors, not interact with alcohol, cause little or no ataxia or incoordination, and have a low potential for abuse. Gabapentin fulfills some of these criteria. It has a mild adverse events profile, does not produce cognitive impairment, and has no abuse potential. Gabapentin does not induce hepatic metabolism and is excreted unchanged in the urine (Bonnet et al., 1999).

Preclinical experience with gabapentin indicates that it decreases withdrawal excitability in hippocample slices (Bailey et al., 1998). Also it has been shown to decrease both convulsions and anxiety in mice withdrawn from alcohol (Watson et al., 1997).

In both the treatment groups there was a significant reduction in withdrawal symptoms, although the difference between the two treatment groups was not found to be statistically significant.

In both treatment groups, the withdrawal syndrome did not last longer than 3 days. At the end of day 2, participants showed no more than one or two mild symptoms (such as tremor, sweating or restlessness). Therefore, we believe that acute withdrawal can be treated within 2 or 3 days with effective medication.

In terms of tolerability, the group treated with lorazepam experienced more side-effects (daytime sleepiness), but these were limited to the first 3 days of the study and did not influence the incidence of drop-outs from the study.

From the present study it can be concluded that, gabapentin is equivalent in efficacy to lorazepam in the treatment of alcohol withdrawal syndrome. Because gabapentin has less side-effects and less interaction with alcohol, therefore gabapentin may be used safely in alcohol withdrawal syndrome.

Additional studies are needed to ascertain gabapentin's utility as a treatment for preventing alcohol withdrawal or relapse to drinking after a period of abstinence.

Limitations of the Study:

1. Only male participants were included in the study.
2. Small population included in the study.

REFERENCES

1. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA 1997; 278:144-51.
2. CNS Spectrums 2000;5(2):22-32.
3. Pharmacotherapy 1996;16(1):49-57.
4. Myrick H, Malcolm R, Brady KT. Gabapentin treatment of alcohol withdrawal (Letter).Am J Psychiatry 1998;155:1632.
5. Bozikas V, Petrikis P, Gamvrula K,Savvidou I, Karavatos A. Treatment of alcohol withdrawal with gabapentin. Prog Neuropsychopharmacol Bio Psychiatry 2002; 26: 197-9.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. text version. Washington, D.C.:American Psychiatric Association,2000:216.
7. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol scale(CIWA-Ar).Br J Addict 1989;84:1353-7.
8. Reoux JP,Miller K.Routine hospital alcohol detoxification practice compared to symptom triggered management with an Objective Withdrawal Scale (CIWA-Ar). Am J Addict 2000; 9 : 135-44.
9. Stuppaeck CH, Barnas C, Falk M, et al. Assessment of the alcohol withdrawal syndrome - validity and reliability of the translated and modified clinical institute withdrawal assessment for alcohol scale (CIWA-A). Addiction. 1994; 89:1287-1292.
10. British Journal of Addiction. 1989;84:1353-1357

****