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Original Article

A randomized, open-label, standard controlled, parallel group study of efficacy and safety of baclofen, and chlordiazepoxide in uncomplicated alcohol withdrawal syndrome

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ABSTRACT

Background: Alcohol withdrawal syndrome (AWS) is a distressing condition, generally controlled by benzodiazepines (BZD's). Baclofen, a gamma-aminobutyric acid-B ($GABA_B$) agonist, has also shown promising results in controlling AWS. As there are few studies comparing the efficacy and tolerability of chlordiazepoxide with baclofen, the present study was taken up. The objective of this study was to compare efficacy and tolerability of baclofen with chlordiazepoxide in uncomplicated AWS.

Methods: Sixty subjects with uncomplicated AWS were randomized into two groups of 30 each, to receive baclofen (30 mg) or chlordiazepoxide (75 mg) in decremented fixed dose regime for 9 days. Clinical efficacy was assessed by Clinical Institute Withdrawal Assessment for Alcohol-Revised Scale (CIWA-Ar) and tolerability by the nature and severity of adverse events. Lorazepam was used as rescue medication. Secondary efficacy parameters were Clinical Global Impression scores, symptom-free days, and subject satisfaction as assessed by visual analog scale. This study was registered with Clinical Trial Registry-India (CTRI/2013/04/003588), also subsequently registered with WHO's ICTRP clinical trial portal.

Results: Both baclofen and chlordiazepoxide showed a consistent reduction in the total CIWA-Ar scores. However, chlordiazepoxide showed a faster and a more effective control of anxiety and agitation requiring lesser lorazepam supplementation, and also showed a better subject satisfaction compared to baclofen. Both the drugs showed good tolerability with mild self-limiting adverse events.

Conclusion: The present study demonstrates that baclofen is not as good as chlordiazepoxide in the treatment of uncomplicated AWS. However, baclofen might be considered as an alternative.

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At a glance commentary

Scientific background on the subject

The pathophysiology of alcohol withdrawal syndrome (AWS) has been largely implicated toward gamma-aminobutyric acid-B ($GABA_B$) disturbance among other neurotransmitters, which is also presently targeted in the pharmacological intervention of AWS management. Chlordiazepoxide and other benzodiazepines (BZDs) which are allosteric agonists of $GABA_A$ are equally efficacious in controlling the AWS, also provides smoother withdrawal; however has the risk of over-sedation and abuse liability. Baclofen a $GABA_B$ receptor agonist has demonstrated the ability to rapidly control the manifestations of AWS without producing significant side effects such as over-sedation, euphoria, abuse liability, systemic toxicity, and are safe in hepatic dysfunction.

What this study adds to the field

The baclofen in a dose of 30 mg/day is inferior to chlordiazepoxide in controlling the AWS, However baclofen may be considered as an alternative option when BZD's cannot be used, which necessitates further studies.

Alcohol dependence is a major and a multifaceted problem throughout the world, the incidence and prevalence of which varies from country to country, and alcohol consumption is the third largest risk factor for disease and disability in the world, especially with a greater risk in middle-income countries. It accounts for about 4% of all deaths worldwide [1]. In developing countries like India, which has seen a tremendous rise in alcohol consumption among younger generation which is aided by swift sprouting of nightclubs, lately the people are quickly detaching from the inhibitions about alcohol as a lifestyle choice.

It is estimated that 10–15% of the alcohol users in India, develop dependence and become chronic alcoholics who are accounted as one million [2]. The ideal objective in the management of alcohol dependence is to achieve complete abstinence which may not always be practicable, can be accomplished by various behavioral and pharmacological approaches.

Treatment of alcoholism starts only when the alcoholic is motivated; it includes detoxification, rehabilitation, and maintenance of abstinence. Abrupt discontinuation of alcohol in alcohol dependents may result in withdrawal symptoms referred to as alcohol withdrawal syndrome (AWS), a distressing and life-threatening condition, where it is estimated that about 8% of hospitalizations are due to the alcohol withdrawal manifestations. The manifestations of AWS includes mild to moderate symptoms characterized by anxiety, depression, tremors, restlessness, insomnia, sweating, vivid dreams, diarrhea, tachycardia, and headache, which are mostly self-limiting and resolve spontaneously within a day or two and medical intervention is necessitated only if symptoms persist. Severe withdrawal symptoms are characterized by seizures, hallucinations (auditory, visual, and tactile), agitation, tremulousness, and delirium tremens, where prompt pharmacological interventions are necessary to control the symptoms and prevent complications. The long-term consumption of alcohol causes increase in brain gamma-aminobutyric acid (GABA) levels and decrease in N-methyl-D-aspartate levels, which on abrupt withdrawal of alcohol, unmasks the adapted defense responses to persistent chronic alcoholism, resulting in nervous system hyperactivity, producing AWS, and hence treatment is aimed at enhancing the GABA activity by GABA receptor agonists or sensitizers [3].

The withdrawal manifestations are well controlled by benzodiazepines (BZDs) like chlordiazepoxide, and all BZDs are equally efficacious in controlling the signs and symptoms of alcohol withdrawal and aids in smoother withdrawal of alcohol, however with the risk of over-sedation and abuse liability, hence it must be used with care [4].

Baclofen a $GABA_B$ receptor agonist has demonstrated the ability to rapidly control the manifestations of AWS without producing significant side effects such as over-sedation, euphoria, abuse liability, systemic toxicity, and are safe in hepatic dysfunction. Baclofen is considered as an off-label agent in the management of AWS and as there are few studies with inconsistent data and presently there is no data regarding the usefulness of baclofen in Indian population for AWS. Moreover, there are no studies on the comparative efficacy and tolerability with that of BZDs, the present study was taken up [5,6].

Methods

Study subjects

Inclusion criteria

1. Subjects of either gender aged between 18 and 65 years
2. Subjects who fulfill Diagnostic and Statistical Manual of Mental Disorders IV Revised Criteria for AWS and or alcohol dependence
3. Last alcohol intake within 24–48 h preceding the initiation of therapy
4. Willingness to give written informed consent.

Exclusion criteria

1. Subjects with complicated AWS comprising any one or all of the following delirium tremens, withdrawal seizures, and cognitive impairment (Wernicke–Korsakoff syndrome)
2. Subjects with known psychiatric disorders
3. Subjects with multi-drug abuse (except nicotine)
4. Subjects with advanced hepatic, renal, and cardiovascular diseases
5. Subjects with known allergy to any of the study medications
6. Subjects with recent use of drugs which lower the seizure threshold
7. Subjects with conditions which can mask or affect the clinical parameters of AWS such as use of β-blockers (propranolol), thyrotoxicosis, meningitis, and hemorrhage/head injury.