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Studies on the effectiveness, safety and tolerability of two doses of Anti Hangover Drink in Reducing Alcohol Induced Hangover Symptoms in Adult Male Social Drinkers

Sreeraj Gopi[1]*, Robin Georgea, Roshin U Thankachen[1], V.T.Sriraam[2], and Shakthi Abirami[2]

[1]R&D Centre, Aurea Biolabs (P) Ltd – A Plantlipids Company, Cochin, India
[2]Aurous HealthCare Research and Development India Private Limited, Chennai, India
**Corresponding author*

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Anti Hangover Drink, Hangover Symptoms, Oh!K

A B S T R A C T

An alcohol hangover is associated with a variety of symptoms that may include drowsiness, concentration problems, dry mouth, dizziness, gastrointestinal complaints, sweating, nausea, hyper-excitability, anxiety and a feeling of general discomfort that may last more than 24 hours. Alcohol hangover symptoms develop when blood alcohol concentration falls considerably and peaks when it returns to almost zero. Several pathophysiological changes may give rise to the alcohol hangover including increased levels of acetaldehyde, hormonal alterations of the cytokine pathways and decrease of the availability of glucose. A natural spice blend was develepoed, branded as Oh!K and evaluated clinically for its efficacy. Alcohol induced hangover symptoms such as tremor, headache nausea were observed and experienced by the subjects on the day following the consumption of alcohol. This was shown to be significantly reduced in the volunteers who had consumed Oh!K Anti Hangover drink (25ml or 50 ml) after consuming alcohol. The hangover symptom of tremor was significantly reduced only in the subjects who has consumed 50ml – high dose of Oh!k Anti Hangover Drink.

Introduction

There is no consensus definition of Hangover. Most descriptive and experimental studies have identified a set of common symptoms: headache, diarrhea, anorexia, tremulousness, fatigue, and nausea. Objective criteria have focused on decreased occupational, cognitive, or visual spatial skill performance or on alterations in hemodynamic and hormonal measurements. Although tachycardia, tremor, orthostasis, cognitive impairment, and visual spatial impairment are frequently observed they do not capture the overall experience for the patient. This remains subjective, varying from person to person and from episode to episode. Hangover is defined as the presence of at least two of the symptoms in occurring after the consumption and full

metabolism of alcohol with sufficient severity to disrupt the performance of daily tasks and responsibilities.

Alcohol metabolism

After ingestion and absorption alcohol is metabolized. First, the enzymes alcohol dehydrogenase (ADH), cytochrome P450 (CYP2E1), and catalase convert alcohol into acetaldehyde. Acetaldehyde is then further metabolized by aldehyde dehydrogenase (ALDH) to acetate. Most people rapidly metabolize acetaldehyde, which means that it is only present in the blood in low concentration and disappears completely during the hangover phase. Acetaldehyde is highly reactive and can cause tissue damage due to its toxic effects, which may lead to hangover like symptoms such as nausea, sweating, rapid pulse and headache. It has been suggested that the rise in acetaldehyde concentration and its persistent effects eventually leads to the appearance of hangover symptoms.

Pathophysiology

Alcohol withdrawal is secondary to the development of physiological alcohol dependence over the course of many drinking episodes, whereas the hangover occurs after one night of drinking and does not require alcohol dependence. Another possibility is that that a hangover may be the result of the direct effects of last night's extracurricular activities. That is, a hangover may be the lasting effects of electrolyte imbalances, hypoglycemia, and dehydration, which persist longer than the ethanol itself. Unfortunately, studies have shown little correlation between hangover symptoms and serum electrolytes, blood glucose, or markers of dehydration such as antidiuretic hormone and renin. A similar argument has been made for acetaldehyde, a metabolic breakdown product of ethanol that has vasodilatory and gastrointestinal effects on the body. Again, limited evidence has been found linking acetaldehyde levels with hangover severity. Perhaps understanding the effect of alcohol consumption on the immune system will elucidate the underlying cause of the hangover.

A number of studies have shown that following a night of heavy drinking there is an up regulation of cytokines and prostaglandins. Specifically, increased plasma levels of interleukin-10, interleukin-12, and interferon-gamma were measured in individuals suffering from hangover symptoms long after their last drink. Prostaglandin E2, thromboxane B2, and C-reactive protein were similarly increased. Most importantly, the serum levels of these inflammatory markers were directly related to the degree of hangover symptoms. This association has been supported by evidence that treatment with cyclooxygenase inhibitors leads to a decrease in these inflammatory factors and a subsequent decrease in hangover symptoms.

Materials and methods

The drink was formulated using the spice extracts such as green ginger, turmeric , pepper, and green tea extract, along with salt, citric and ascorbic acid. Fructose was used as the carrier.

Clinical methodology

The purpose of the study was to evaluate the effectiveness, safety and tolerability of Oh!K (in two doses) in reducing the alcohol induced hangover symptoms in adult male social drinkers.The clinical study was planned, designed, conducted and reported as per applicable ethical and regulatory guidelines – ICH Tripartite Guidelines –

E6(R1)- Good Clinical Practice, Indian Council of Medical Research's (ICMR) Ethical Guideline for Biomedical Research on Human Participants. Prior to conduction, the clinical study was reviewed and approved by an Ethics Committee. The study was also registered with ICMR's Clinical Trial Registry India and World Health Organisation (WHO) – International Clinical Trial Registry Platform. Volunteers were prescreened at hotels, bars, pubs and other alcohol selling outlets. 36 such volunteers who were identified as occasional consumers of alcohol (social drinkers) were further screened as per the norms of the approved study protocol.

The Screening Questionnaires such as Short Michigan Alcohol Screening Test (SMAST) and Modified Suicide Behaviors Questionnaire (m-SBQ) were answered by participants. The drinking pattern of participants in past 12 months was assessed through Subjective Questionnaire Short Michigan Alcohol Screening Test (SMAST). The suicidal behaviors of study participants were assessed by the principal investigator through Objective Questionnaire Modified Suicide Behaviors Questionnaire (m-SBQ).

The volunteers were randomised into three treatment arms, categorised as per their body weight.

- Treatment Arm I: High Dose of Anti Hangover Drink (50 ml)
- Treatment Arm II: Low Dose of Anti Hangover Drink (25 ml)
- Treatment Arm III: Control Group – No IP given.

For baseline metrics, objective and subjective measurements using CIWA – A (Clinical Institute Withdrawal Assessment - Alcohol) and m-AHSS (Alcohol Hangover Severity Scale) for alcohol induced hangover symptoms such as tremors, headache, nausea, cognitive, auditory and visual impairment etc were assessed.

Objective assessment – CIWA-A Questionnaire was measured by Social Scientist/Psychologist or by Principal Investigator and the subjective assessment was measured using m-AHSS on Day 1 (enrollment and before consumption of alcohol) and Day 2 (hangover day) to assess the hangover symptoms.

Metered dose of alcohol was calculated as per the body weight category and provided to each subject along with dietician approved food. Post consumption, the alcohol concentration was measured using an Alcohol Breath Analyzer. Oh!K Anti Hangover Drink was then provided to the subjects based on the randomization schedule. The subjects were allowed to sleep for a period of 10 hours. Upon waking up, a sleep inertia time of 30 minutes was allowed. The objective and subjective questionnaires CIWA-A and m-AHSS were assessed and data was recorded.

The volunteers were constantly monitored by an attending physician and the entire study was conducted by checking in the subject in the research facility. This negates any external influences of food/drug or uncontrolled consumption of alcohol that may have influenced the study. Safety investigations such as Complete Blood Count and Serum Biochemistry and recording of vital signs such as body temperature, blood pressure, respiratory rate and pulse rate were also measure on day 1 and day 2 to ensure safety of the subjects. The subjects were also constantly monitored during Day 1 and Day 2 of Visit 1 for adverse events. None of the subjects were reported/observed any adverse Events.

Mechanism of action

After being ingested, ethanol is first converted to acetaldehyde by the enzyme alcohol dehydrogenase and then to acetic acid by oxidation process. These reactions also convert Nicotinamide adenine dinucleotide (NAD^+) to its reduced form NADH in a redox reaction. By causing an imbalance of the NAD^+/NADH redox system, alcoholic beverages make normal bodily functions more difficult. Consequences of the alcohol induced redox changes in the human body include increased triglyceride production, increased amino acid catabolism, inhibition of the citric acid cycle, lactic acidosis, ketoacidosis, hyperuricemia, disturbance in cortisol and androgen metabolism and increased fibrogenesis. The metabolism of glucose and insulin are also influenced.

However, recent studies showed no significant correlation between hangover severity and the concentrations of various hormones, electrolytes, free fatty acids, triglycerides, lactate, ketone bodies, cortisol, and glucose in blood and urine samples.

Alcohol also induces the CYP2E1 enzyme, which metabolizes ethanol and other substances into more reactive toxins. In particular, in binge drinking the enzyme is activated and plays a role in creating a harmful condition known as oxidative stress which can lead to cell death.

The Spice drink is a rich source of anti oxidants, which neutralise the free radicals formed during the alcohol metabolism. The free radicals will attack the internal organs especially the liver, causing internal inflammation which is one of the root cause for the hangover symptoms. The drink contain curcumin and gingerols, which are very good anti inflammatory agent, thus preventing inflammation. This natural drink also contains nutrients, thus rehydrate the body. Curcumin significantly reversed the alcohol-induced inhibition of the alcohol dehydrogenase, aldehyde dehydrogenase 2 and antioxidant enzyme activities as well as the activation of cytochrome P4502E1 and promotion of lipid peroxidation ($p<0.05$). Curcumin significantly increased the hepatic total AMPK protein level and concomitantly suppressed the fatty acid synthase and phosphatidate phosphohydrolase activities.

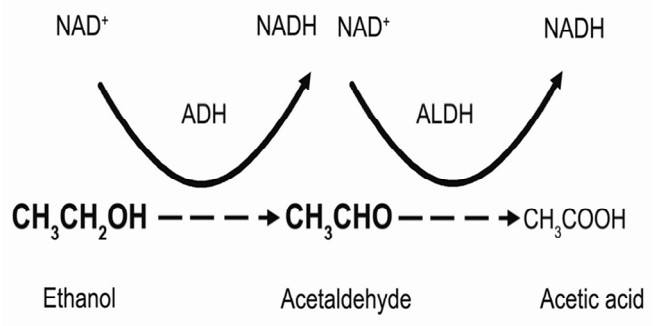


Figure.1 Metabolism of Alcohol

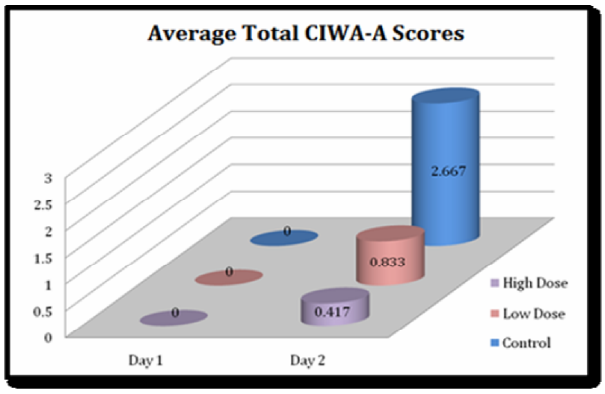
Results and Discussion

Inter Group Analysis

Clinical Institute Withdrawal Assessment – Alcohol (CIWA-A):

Mean (SD) Total Score of CIWA- A questionnaire for all the treatment groups on Day 2 is given below:

Low Dose (25 ml) of Anti Hangover Drink	:	0.833 (0.718)
High Dose (50 ml) of Anti Hangover Drink	:	0.417 (0.515)
Control	:	2.677 (1.67)



Hence the Primary Endpoint is achieved for Low Dose, High Dose and Control Group. However, from the statistical analysis of the results of all the treatment groups, the following results are concluded.

- The difference between the Total Score of Control and Low dose group is statistically significant. ($Z = -2.63$, $p=0.0084 < 0.05$)
- The difference between the Total Score of Control and High dose group is statistically significant. ($Z = -3.12$, $p=0.0018 < 0.05$)
- The difference between the Total Score of Low dose and High dose group is not statistically significant. ($Z = 1.44$, $p=0.1485 > 0.05$)
- This clearly indicates that the Hangover symptoms on next day morning of alcohol consumption are relatively reduced in Low Dose and High Dose group than Control group.

In particular of the symptoms, the result confirms that

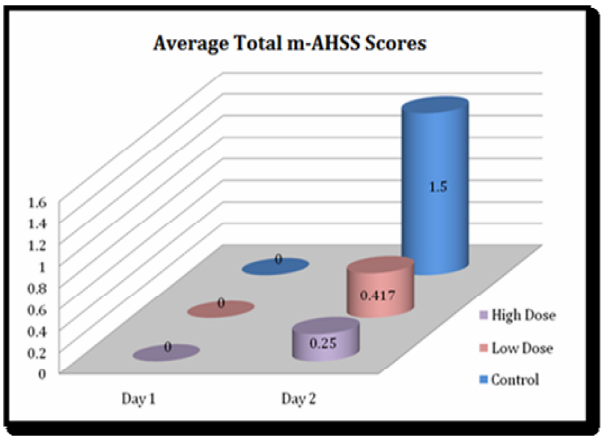
- There is significant difference between Control and High Dose group with respect to the hangover symptom of Tremor ($Z = -2.19$, $p=0.0287 < 0.05$).
- There is significant difference between Control and Low Dose group with respect to the hangover symptom of Headache ($Z = -3.01$, $p=0.0026 < 0.05$).
- There is significant difference between Control and High Dose group with respect to the hangover symptom of Headache ($Z = -3.01$, $p=0.0026 < 0.05$).

This clearly indicates that the Hangover Symptom Headache is reduced in subjects who had taken Low Dose and High Dose of Anti Hangover Drink than the subjects who had not taken Anti Hangover Drink. The Hangover Symptom Tremor is reduced only in subjects who had taken High Dose of Anti Hangover Drink than Low dose and Control group.

Modified Alcohol Hangover Severity Scale (m-AHSS):

Mean (SD) Total Score of m-AHSS questionnaire for all the treatment groups on Day 2 is given below:

Low Dose (25 ml) of Anti Hangover Drink	:	0.417 (0.515)
High Dose (50 ml) of Anti Hangover Drink	:	0.25 (0.452)
Control	:	1.50 (1.17)



Hence the Primary Endpoint is achieved for Low Dose, High Dose Group.

The statistical analysis confirmed that

- The difference between the Total Score of Control and Low dose group is statistically significant. *(Z = –2.51, p=0.0120 < 0.05)*
- The difference between the Total Score of Control and High dose group is statistically significant. *(Z = –2.88, p=0.0040 < 0.05)*
- The difference between the Total Score of Low dose and High dose group is not statistically significant. *(Z =0.81, p=0.4165 > 0.05)*

This clearly indicates that the Hangover symptoms on next day morning of alcohol consumption are relatively reduced in Low Dose and High Dose group than Control group.

Intra Group Analysis

- There is significant difference between Control and High Dose group with respect to the change in the scores of Tremor (*Z = 2.19, p=0.0287 < 0.05*).
- There is significant difference between Control and High Dose group and Control and Low Dose with respect to the change in the scores of Headache (*Z = 3.01, p=0.0026 < 0.05*)
- There is significant difference between Control and High Dose group in Total Score of CIWA-A from Day1 to Day2 (*Z = 3.12, p=0.0018 < 0.05*).
- There is significant difference between Control and Low Dose group in Total Score of CIWA-A from Day1 to Day2 (*Z = 2.63, p=0.0084 < 0.05*).
- The difference between Low dose and High dose group (Z = -1.44, p = 0.1485 > 0.05) was found to be not statistically significant for the change in "Total Scores of CIWA-A" from Day1 to Day 2.

This shows that the average increase in Hangover Symptoms Tremor, Headache from Day 1 to Day 2 is relatively high in Control group than the Low Dose or High Dose group which means that the symptoms were reduced in subjects who have taken Anti Hangover drink after alcohol consumption.

- The difference between Control and Low dose group (Z = 2.51, p = 0.0120 < 0.05) was found to be statistically significant for the change in "Total Scores of mAHSS" from Day1 to Day2.
- The difference between Control and High dose group (Z = 2.88, p = 0.0040 < 0.05) was found to be statistically significant for the change in "Total Scores of mAHSS" from Day1 to Day 2.
- The difference between Low dose and High dose group (Z = -0.81, p = 0.4165 > 0.05) was found to be not statistically significant for the change in "Total Scores of mAHSS" from Day1 to Day 2.

This shows that the average increase in Hangover Symptoms from Day 1 to Day 2 is relatively high in Control group than the Low Dose or High Dose group which means that the symptoms were reduced in subjects who have taken Anti Hangover drink after alcohol consumption.

Conclusion

Alcohol induced hangover symptoms such as tremor, headache nausea were observed and experienced by the subjects on the day following the consumption of alcohol. This was shown to be significantly reduced in the volunteers who had consumed Oh!K Anti Hangover drink (25ml or 50 ml) after consuming alcohol. The hangover symptom

of tremor was significantly reduced only in the subjects who has consumed 50ml – high dose of Oh!k Anti Hangover Drink.

Overall, there is no significant difference between Low Dose and High Dose of Anti Hangover Drink in reducing Hangover symptoms on next day morning of alcohol consumption. Hence it is recommended that either Low Dose (25 ml) of Anti Hangover Drink or High Dose (50 ml) of Anti Hangover Drink can be taken after consumption of alcohol to reduce next day Alcohol Hangover Effects.

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