Research Note

Improvement of Inpatient Treatment of the Alcoholic as a Function of Neurotransmitter Restoration: A Pilot Study

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Abstract

We report results of a double-blind evaluation of the nutritional supplement SAAVE for facilitating improvement in a 30-day inpatient alcohol and drug rehabilitation center. SAAVE is uniquely designed to elevate levels of enkephalin(s), serotonin, catecholamines, and GABA, which are believed to be functionally deficient in alcoholics. Twenty-two patients were studied. The SAAVE patients, as compared to the...
control group (a) had a lower BUD (building up to drink) score, 1 vs.
2; (b) required no PRN benzodiazepines, 0% vs 94%; (c) ceased tremor-
ing at 72 h, as compared to 96 h; and (d) had no severe depression on
the MMPI, in contrast to 24% of control group. These preliminary data
suggest that SAAYE is a valuable adjunct to therapy by aiding the
patient’s physical adjustment to a detoxified state while facilitating a
more positive response to behavioral therapy.

INTRODUCTION

The causes of alcoholism are still unknown. Pharmacological treatment of
this neuropsychogenetic disease is limited to the utilization of anti-anxiety
agents during detoxification (1), as well as aldehyde dehydrogenase inhibitors
(e.g., Antabuse®) (2) alone or in combination with known antidepressants on
the assumption that alcoholism is secondary to depression (3). There is increasing
evidence that alcoholism is a primary disease which may or may not have
secondary affective disorder of psychotics associated with it (4). It is well-
established that long-term abuse of alcohol produces marked alterations in the
synthesis, release, and degradation of brain neurotransmitters. In genetically
alcohol-prefering strains of mice, for example, brain enkephalin levels are
dramatically depressed (5). Additionally, in genetically predisposed rats, brain sero-
tonin is similarly depressed relative to non-alcohol-prefering animals (6). Fur-
ther, thiamine deficiency impairs the functioning of the opiate peptides (7),
serotonin (8, 9), GABA (10), dopamine, and norepinephrine (7, 11). Deficiencies in
certain of these neurotransmitters have been linked to impairments of the re-
ward system (12), anxiety (13), insomnia (14), and craving (15). Finally, differences in platelet enzyme activities of monoamine oxidase and adenylyl cyclase
following ethanol challenge between alcoholics and non-alcoholics has been
reported (16).

PRELIMINARY DOUBLE-BLIND, NON-PLACEBO-
CONTROLLED STUDY

Of 22 patients admitted, 2 were given SAAYE (2 capsules, t.i.d.) upon ad-
mission and throughout their 28-day program. Experimental subjects were
selected at random by the medication nurse and pharmacist. Neither the medical
director (J.C.R.) nor the staff knew which of the patients received SAAYE.
Characteristics of the patient populations are shown in Table 1. Blood alcohol
levels (BAU) taken on entry are not meaningful measures as persons enter treatment facilities often after having abstained for a period of time.

*The following are registered trademarks: Antabuse, Benzacon, SAAYE, Theogran-M.
Table 1

<table>
<thead>
<tr>
<th></th>
<th>SAAVE group</th>
<th>Control group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>56.0</td>
<td>50.7</td>
<td>56.0</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M/F</td>
<td>M/F</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>68%</td>
<td>72%</td>
</tr>
<tr>
<td>Race</td>
<td>5W</td>
<td>19W</td>
<td>24W</td>
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<tr>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>BAL (mg/dL)</td>
<td>.013</td>
<td>.043</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>19</td>
<td>20</td>
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All alcoholic subjects were interviewed by a psychiatrist and were found to fulfill the criteria for alcoholism described in the Diagnostic and Statistical Manual of Mental Disorders (3rd ed.) (DSM). None exhibited psychiatric signs. All subjects were included in the study after providing informed consent.

Medication was administered individually so there is little occasion for one patient to observe another taking medications. Detoxification medication (Doxapram), and in several patients phenytoin (promet phenytoin sodium), was given with full explanation of what these capsules were. SAAVE was put in with routine vitamins (i.e., Thromatrim-M, thiamine, and Berocca) which were given daily with the explanation that this medication cup was “full of vitamins.” In addition, each patient received 1 mg vitamin B-12 intramuscularly weekly with no other explanations offered.

All patients were observed in the primary care unit from 24 to 72 h, depending on rapidity of detoxification, for evidence of delirium tremens, possible seizures, and any other symptoms which might impede progress to the rehabilitation treatment program. After this period of observation, during which time a complete physical evaluation was achieved (history, physical exam, CBC, EKG, etc.) the patient was transferred to the residential living area and was introduced to a 10-h per day treatment program.

The BUD Response

In this investigation the BUD (building up to drink) response was evaluated as a subjective measure of patient response. The assigned score of 1 to 3 relates to alcohol craving, which is defined as follows:

1. Mild somatic complaints, that is, pain, sinusitis, mild insomnia, complaints of old injury, etc.
2. Move verbal and frequent complaints, that is, requests for the attending physician along with more extreme complaints: for example, too early an hour to rise and start the program (7 a.m.), food was poor, program was inappropriate, lack of freedom, temporary insomnia, cost of program, etc. These are fairly easy to placate with occasional PRN benzodiazepines for the first few days after routine detoxification when medications were discontinued.

3. Open hostility to the hospital or facility. The patient feels kidnapped and the subject has many somatic complaints. The patient demands PRN medications, especially hypnotics. There is severe insomnia as well as threats to leave AMA (against medical advice) and leaving AMA in certain cases.

To assess the craving of an individual the BUD response was noted by nurses, counselors, and the medical director during Days 3 to 10 and evaluated for all patients.

RESULTS

The mean BUD response rating for the SAAVE patients was 1 (mild insomnia) while it was 2 for the non-SAAVE patients. The BUD response criteria, while subjective in nature, are believed to fairly represent the craving of the individual toward alcohol and are observed commonly by alcohol counselors in

![Graph](image)

Fig. 1. Frequency of occurrence of depression measured by the MMPI, tremor at 72 hr, and use of tranquilizers for experimental (SAAVE) and control (non-SAAVE) groups.
programs of all types. Other observations such as tremulousness, requirement of PRN antianxiety agents, and MMPI evaluation data are depicted in Figure 1.

The patients on SAAVE had only mild tremulousness after the first 24 h which had disappeared by 72 h. Nine of the 17 non-SAAVE patients had noticeable tremors at 96 h. All 20 patients were able to hold a coffee cup with one hand and drink from it without a spill 5 days following detoxification, in spite of the fact that most of the patients used two hands for the first 24-48 h.

It is noteworthy that all of the SAAVE patients differed from the non-SAAVE group in that the former group did not require any PRN benzodiazepines throughout the 28-day program after detoxification was completed, while almost all the non-SAAVE patients required at least one PRN dose during 10 days of observation.

All patients were administered an MMPI on the fifth or sixth day of admission. All of the non-SAAVE patients showed some degree of depression, 4 out of the 17 subjects exhibiting severe depression with suicidal ideation. However, the 3 SAAVE patients showed less depression and no significant suicidal ideation.

**DISCUSSION**

The exact role and interrelatedness of each of the neuropeptides and neurotransmitters in the process of alcoholism is unclear. However, there are sufficient data in both animals and humans to suggest that deficiencies in these central chemicals may, in part, mediate sequelae observed in alcoholic patients. Thus it was reasonable to investigate, in a preliminary, blinded fashion, the potential effectiveness of an amino acid combination, SAAVE, consisting of 51.5 mg total weight of DL-phenylalanine, L-glutamine, L-tryptophan, and pyridoxal-5-phosphate per capsule, in subjects being treated for severe alcoholism. The ingredients in SAAVE are specific amino acids and vitamins in particular ratios and amounts, with very low toxicity and a high therapeutically index (18).

That the patients receiving SAAVE exhibited a reduced BUD response, required no PRN benzodiazepine medication throughout the 28-day stay, demonstrated less depression without observable suicidal ideation as measured by the MMPI, and exhibited only mild tremulousness during the first 24 h following detoxification suggests a significant improvement of the alcoholic during the 28-day inpatient treatment period. While it is premature to advance a full explanation of these results, we would speculate that a major benefit of precursor amino acid loading and enkephalinase inhibition is to enhance the functioning and content of various neurotransmitters such as enkephalins, dopamine, norepinephrine, GABA, and serotonin, which, as previously mentioned, are altered in alcoholism. We have postulated an endorphinergic and norepinephrine deficiency as an important determinant in craving, anxiety, depression, insomnia, and tremulous-
ness associated with alcohol abstinence (19, 20). These results support and expand on our animal data with carboxypeptidase A inhibitors. Animal studies show a significant reduction in alcohol intake during both forced and voluntary alcohol intake by administration of D-phenylalanine and hydroxyctamine acid, known “enkephalnin inhibitors” (20). Other researchers found that prolonged alcohol consumption leads to modification in the activity of the enzymes of enkephalin metabolism, in particular enkephalinase (21). Further, support for opioid peptide involvement in alcohol actions includes alterations of delta receptor expression (22), neurosynaptic processing differences in inbred strains of mice with variable sensitivities to ethanol (23) and differences in response to pharmacologic benzeorphin following acute ethanol challenge between individuals with a family history of alcoholism (24). Other work in our laboratory further supports these initial findings (25). Currently, we are extending this research in both inpatient and outpatient settings. Research on outpatients will include a systematic evaluation of total alcohol intake over a 12-month period. In addition, we will determine the number of days abstinent as well as relapse rate.

SUMMARY

In this pilot double-blind non-placebo-controlled study, it is too early to fully describe the observable differences in craving between SAAVE and non-SAAVE patients solely to the restoration of enkephalins and other neurotransmitters. However, as mentioned earlier, additional studies reveal (submitted elsewhere) that SAAVE is of significant value in patients hospitalization during detoxification from alcohol and other drugs of abuse (25). In one placebo-controlled double-blind study consisting of over 60 patients, significant differences occurred between SAAVE and placebo in skin conductance level, physical assessment scores, and the BIS/BIS (Behavioral Emotional Spiritual Social) values. Through elevation of neurotransmitter content and functionality by inhibition of degradative enzymes and concurrent precursor amino acid loading, novel anti-alcohol-craving agents may be developed. SAAVE may be a useful adjunct in psychotherapy in achieving sobriety, not only in an inpatient setting but as a crucial element for continued recovery. Other research in our laboratory and others should provide additional information regarding the potential usefulness of this novel modality in both prevention and treatment of chemical dependency for inpatients, outpatients, and aftercare modalities.

ACKNOWLEDGMENTS

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REFERENCES


