REVIEW

Pharmacotherapy of Alcoholism: The American Current Status

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Abstract. This paper is a brief review which deals with research findings, clinical issues, and strategies in the pharmacotherapy of alcoholism. The pharmacotherapy is presented according to different clinical phases of the alcoholic process. The acute intoxicated patient receives supportive treatment, to be clinically observed to prevent severe respiratory depression, aspiration of vomitus, and severe alcohol withdrawal syndrome. Benzodiazepine therapy is the mainstay in treating alcohol withdrawal syndrome. Disulfiram is the only chemical used in the United States to deter the alcoholic patient from further alcohol drinking. Although there is not a specific agent for alcoholism *per se* during the sobriety state, the alcoholic patients' concurrent underlying psychiatric conditions (such as schizophrenia, anxiety, and depression) should be treated properly and adequately. (Keio J Med 40 (1): 9–12, March 1991)

Key words: benzodiazepines, disulfiram, alcohol intoxication, alcohol withdrawal

Introduction

This review article covers pharmacotherapy in different clinical phases of alcoholism. It is intended as a bird's eye view in the field and not intended to be a comprehensive review of the topic. This paper deals only important and updated relevant basic science data and clinical studies to familiarize the Japanese readers with state-of-the-art in pharmacological treatment of alcoholism in the United States.

Pharmacotherapy of Alcoholism in Different Clinical Phases

The following subtitles are designated to different phases of the alcoholic process. Some relevant basic research data are briefly described in order to better understand American pharmacological therapeutic practice. The readers who are interested in further details of the studies should consult with the references cited in this paper. Due to the space limitation of this article, the readers should refer elsewhere,^{1,2} for diagnosis and symptomatology description of alcoholism.

Agents in treating acute alcohol intoxication

Research in finding chemical agents to produce rapid sobering of acute alcohol intoxication have been focused

on hormones (thyroid hormones and glucagon), vitamins (A, B₆, B complex, C, E), stimulants (caffeine, strong coffee), sugar (glucose and fructose), pyruvate, amino acids (L-lysine, L-arginine, glycine, and L-ornithine, and L-dopa).³ Among them, fructose has been found most effective to increase alcohol metabolism rate of 10 percent or more.⁴ But the required dosage may add extra unwanted serious side effects in addition to the already existing sedative-hypnotic drug overdose produced by alcohol. Furthermore, the shortened intoxication time (for example, from 7 hours to 5 hours) does not give much clinical significance to make the "sobering pill" worthwhile.

Thus, the most important management for alcohol intoxication is the conservative and supportive treatment to let the alcohol-intoxicated patient take time to metabolize ethanol out of the system. Usually, a normal non-tolerant adult individual can metabolize 7–10 g of alcohol per hour^{5,6} — roughly the alcohol content of a 12 oz can of beer, a glass (4 oz) of wine or a fifth (1.5 oz) of 80 proof whisky. By this simple formula, most Japanese alcoholic beverages — sake, synthetic sake, shochu, mirin, beer, fruit wines, whisky, other spirits, cordials, and liquors,⁸ — can be easily converted into one of the above-described three categories to calculate the alcohol metabolism time.

The rate of ethanol oxidation follows zero-order kinetics, *i.e.*, it is independent of time and concentration of

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Fig. 1 Ligands of benzodiazepine-GABA_A-chloride ionophore protein complex.

ethanol.⁶ For instance, three cans of beer take about three hours, and five cans about five hours, to be metabolized in the liver for an individual adult. During the supportive treatment, the intoxicated patient is to be observed to prevent from severe respiratory depression, aspiration of vomitus, and severe alcohol withdrawal symptoms.

Agents in treating alcohol withdrawal syndrome

Alcohol withdrawal symptoms and signs can be minimized by tapering off the intake of alcohol gradually or by substituting the alcohol with an alcohol cross-dependent alcohol cross-tolerant agent which is reduced in dosage gradually. Theoretically, all the medications which mediate through gamma-aminobutylic acid (GABA), can be used to replace alcohol for the purpose of detoxification. Alcohol, barbiturates, and benzodiazepines all interact with GABA_A receptors.⁹ Alcohol and barbiturates, but not benzodiazepines depress the central nervous system (CNS) in a relatively nonselective, dose-dependent fashion.⁵ Figure 1 is an oversimplified presentation to show their pharmacodynamic differences between the GABA_A receptor protein complex (the benzodiazepine recognition site, GABA_A recognition site, and chloride ion channel) and ligands (both agonists and antagonists).⁹ Without affecting benzodiazepine receptor binding affinity, alcohol and barbiturates can directly open chloride ion channels.^{9,10} Physiologically, all the antagonists (RO-1788, bicuculine, and picrotoxin) in the figure produce anxiety and seizures through different sites of action in the benzodiazepine-GABA_A-chloride ionophore protein complex. Benzodiazepines enhance GABA_A receptor function only at GABAergic synapses. Thus, benzodiazepines are safe and are the drugs of choice to substitute for alcohol in treating alcohol withdrawal syndrome.

Table 1 is a list of benzodiazepines which are currently

available on the US market.¹¹ Most of the benzodiazepines biotransform among themselves in their metabolic pathways. Therefore, any benzodiazepine — including hypnotics (flurazepam, temazepam, and triazolam) and the antiepileptic (clonazepam)¹² should be effective in managing alcohol withdrawal syndrome if the dosage is appropriate.

Major objectives in treating alcohol withdrawal syndrome are to prevent seizures, delirium, and arrhythmias. The patient needs to be corrected for electrolyte imbalances (such as potassium, magnesium, and phosphate) and malnutrition (thiamine).¹³ After the patient's withdrawal syndrome is improved by an appropriate dosage of a benzodiazepine within the first 24 hours, the daily dosage of the drug can be reduced by about 20 to 25 percent per day over a course of four to seven days. Or, the benzodiazepine-treated patient can be left alone, without further reduction in dosage if a long-acting benzodiazepine (such as diazepam) is used.¹⁴ It is thought

Table 1 Benzodiazepines Which are Available in the US.

Alprazolam ^a
Chlordiazepoxide
Clonazepam ^b
Clorazepate
Diazepam
Flurazepam ^c
Lorazepam ^d
Oxazepam ^d
Prazepam
Temazepam ^{c,d}
Triazolam ^{a,c}

^aFused triazolo ring
^bMarketed as the antiepileptic agent
^cMarketed as hypnotic
^dNo need for oxidation step in biotransformation

Adapted from reference II

that the gradual biotransformation and excretion of diazepam gives the tapering-off effect by itself to cover the whole course of alcohol detoxification.

To contain the cost of medical care, most patients' employers and third party insurance payers in the US are advocating alcohol detoxification at outpatient settings. In the absence of severe physical conditions, seizures, and concomitant abuse of other substances, a physically uncomplicated patient can be detoxified safely as an outpatient if (s)he can be monitored for vital signs and observed or supervised daily by qualified medical staff during the course of withdrawal.

Agents to deter alcohol drinking

Disulfiram is the only agent used in the US to deter alcohol drinking. Cyanamide, which has been used in Japan since early the 1960's,^{15,16} is not available in America.

Disulfiram acts by inhibiting the activity of aldehyde dehydrogenase. Alcohol is metabolized as usual in the initial step of metabolic pathway, but acetaldehyde is not further converted to acetic acid in the following step and is accumulated.⁶ The symptoms resulting from disulfiram-ethanol reaction (DER) are typical for acetaldehyde toxicity.⁶ The DER produces redness of the face, throbbing in the head and neck, throbbing headache, breathing difficulties, stomach distress and urge to vomit, vomiting, sweating, thirst, chest pain, rapid action of the heart, labored breathing, excessive rapid breathing, fast heart beat, faintness, marked uneasiness, weakness, sensation of surrounding revolving, blurred vision, and confusion.¹⁷ The severe DER gives a decrease in breathing, shock, acute heart failure, unconsciousness, convulsion and death.¹⁷ Thus, 250 mg *per* day of disulfiram can give the "toxic placebo effect,"¹⁸ which is able to deter alcohol drinking for a period of time.^{18,19} In the US disulfiram has never been conceptualized as an "antialcoholic agent" (which is often classified in the Japanese pharmacologic literature), because of the lack to curb the desire to drink alcohol. The long-term (one year) disulfiram therapeutic effect is questionable.¹⁹

DER can occur from any alcohol exposure during disulfiram therapy, the patient is warned to avoid any alcohol in disguised form, *i.e.*, in sauces, vinegars, cough mixtures, mouthwash, aftershave lotions and back rubs.^{11,17} The patient is also warned that disulfiram may take 12–14 days to be excreted from the system completely.^{11,17}

Other drugs (*e.g.*, metronidazole, cephalosporins, hypoglycemic agents) have been found to have disulfiram-like effects on ethanol metabolism.^{17,20} Although the patients are routinely warned about the possible DER-like symptoms when metronidazole is prescribed. But these agents are not routinely prescribed although

some clinicians use them if the patients are allergic to disulfiram or having disulfiram side effects (such as neuropathy, sedation, or sensation of the metallic taste).

When a psychiatrist prescribes disulfiram, he or she should be confident and comfortable with this chemical. Otherwise, it may be communicated to the patients that disulfiram is useless. I believe that a serious non-authoritarian discussion about the pharmacologic mechanism of disulfiram, DER, and obtaining a signature on the consent form can improve the patient's trust in both the physician and the agent.

Agents used after acute intoxication-withdrawal phase

For primary alcoholism,^{2,21} there is no specific pharmacological agent in terms of curbing the patient's desire to drink. Lithium carbonate is reported to be able to alter the nature of alcohol intoxication by attenuating euphoria.²² It was thought to be beneficial to prevent the recovered alcoholics from relapses of excessive drinking alcohol. But in a recent double-blind study,²³ the alcoholics who received lithium do not show a longer period of sobriety as compared with the alcoholics who received only placebo. However, if alcoholism is secondary to a primary underlying psychiatric disorder, the primary psychiatric disorder should be treated properly and adequately.

Alcoholism is often co-existing with schizophrenia. Alcohol abusing schizophrenics were found to be 1.5–47 percent in the clinical population.^{24,25} Thus, sufficient acute and maintenance pharmacotherapy for underlying schizophrenia is important.^{26,27}

It may take months before the detoxified alcoholics can resume normal CNS functioning. The patients may complain of insomnia and nervousness after acute intoxication-withdrawal phase is over. Some psychiatrists may prescribe a benzodiazepine for temporary symptomatic relief, but some physicians are reluctant to give any habit-forming antianxiety agents. The complete abstinence from any chemical beyond the withdrawal phase is also advocated by many alcoholics anonymous groups. During this phase, the use of antianxiety medication for detoxified alcoholics remains controversial in the US. It is noteworthy that as compared with a benzodiazepine, an over-the-counter drug — mostly an antihistamine agent — is not as effective for insomnia and give more side effects in the following day.²⁸

The comorbidity issues between depression and alcoholism, and the treatment considerations are the subjects of a different article.²⁹ Antidepressants are indicated for acute depression in both primary and secondary depression,²⁹ but not indicated in the "withdrawal depression" which usually lasts several days or weeks after the sobriety from alcohol drinking.³⁰ Alcohol can enhance the liver oxidation capability through cyto-

chrome P-450 monooxygenases, the dosage level of an antidepressant needs to be increased to give the necessary antidepressant effect.³¹ For the maintenance and prophylactic pharmacotherapy of depression,³² antidepressants and lithium are used only if the alcoholic patients have diagnosable primary depression.

Concluding Remarks

After 20 years of steady increase in per capita alcohol consumption in the US, there has been a gradual but consistent downturn in alcohol consumption since 1970. In 1987, the apparent annual per capita consumption of alcohol in the US was 2.54 gallons of pure alcohol, which was used by more Americans than any other drug, including cigarette tobacco.³³ Alcohol abuse and dependence are serious problems that affect about 10 percent of adult Americans, and a minimum of 3 out of 100 deaths in the US can be attributed to alcohol-related causes.³³

Due to the magnitude of the problem in alcoholism, more knowledge in treatment — including pharmacotherapy — of alcoholism is urgently needed in the US.

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