Prevention and Treatment of Alcohol-Withdrawal Phenomena

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A review of the literature reveals deficiencies of adrenal corticoids, Pyridoxine (vitamin B_6) and magnesium are importantly involved in alcohol-withdrawal phenomena. Each deficiency can cause delirium or grand mal seizures. Unexpected death may occur if these deficiencies are not promptly corrected.

Whenever there is a decreased ratio of extracellular sodium to intracellular sodium ($\frac{E\ Na}{I\ Na}$), brain cell exciteability is increased.[1] Evidence indicates the alcohol-withdrawal state is characterized by a depletion of adrenal corticoids and decreased plasma sodium.

Smith[2] showed that the alcohol-withdrawal state is characterized by an increase in plasma potassium and nitrogen, a decrease in plasma sodium and chloride, he-moconcentration, acidosis and frequently a low blood sugar. He demonstrated that adrenal steroid replacement therapy relieved alcohol-withdrawal symptoms.

Autopsy studies of alcoholics who died in the alcohol-withdrawal state revealed almost universal adrenal cortex thinning, 50% of which was judged severe on microscopic examination.[3] Cerebral edema or congestion were present in 18% of the cases. The clinical course was characterized by grand mal seizure, rising fever, vascular collapse and sudden death.

Travis and Sayers[4] reviewed evidence that glucosteroids are specific in preventing or rapidly alleviating cerebral edema. If animal studies are pertinent, cerebral edema in the alcoholic caused by glucosteroid deficiency may be complicated by pyri-doxine deficiency.

Eisenstein[5] found depressed gluconeogenic activity of adrenal corticoids in

pyridoxine-deficient rats. Slater[6] reported impaired release of adrenal steroids from the adrenal cortex or rapid peripheral utilization in pyridoxine- and riboflavin-deficient rats.

Corticosteroid Replacement

Correction of the alcoholic's corticosteroid deficiencies is best accomplished by giving 5 ml. to 10 ml. of adrenal cortex extract (ACE) intramuscularly every six hours for three days. Use of a single steroid may cause complications and may be ineffective in correcting cerebral edema or in normalizing the $\frac{E\ Na}{I\ Na}$ ratio.[4] Adrenocorticotropic hormone should not be used as the adrenal cortex may be depleted.

Fluid extract of glycyrrhiza (licorice), which powerfully potentiates existing adrenal corticoids,[7] should be given 10 ml. four times a day for seven days, then decreased 5 ml. daily. Licorice decreases the amount of ACE required. However, ACE is required for three days as licorice does not exert an effect until the third day.

Administration of licorice for seven days gives the adrenal cortex a rest and allows replenishment of adrenal steroids in the adrenal cortex. Gradual reduction of licorice is necessary to prevent a sudden state of hypoadrenocorticism or aggressive behavior secondary to a rebound phenomenon.[7]

Adrenalectomized animals can be kept alive and their EEGs normalized by administering an 0.9% sodium chloride solution. Considering this fact and the alcoholic's sodium deficit, sodium chloride, 2 gm. with a glass of water, should be given four times daily for two or three days. The paradoxical hypertension frequently seen in delirium tremens need not be feared as it is caused by excessive aldesterone secretion which is primarily stimulated by sodium deficiency.[4] Blood pressure rapidly normalizes when adrenal corticoid and sodium deficiencies are corrected. Licorice and sodium chloride may be contraindicated if severe heart or kidney disease is present.

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Pyridoxine Deficiency

Pyridoxine deficiency occurs in alcoholics who have withdrawal seizures.[8] Administration of Pyridoxine in large amounts significantly decreases the incidence of withdrawal seizures.[9] Pyridoxine is thought to be a part of the brain cell membrane, and is also a coenzyme necessary for the production of gamma aminobutyric acid (GABA), one of the important brain cell depressants.[10]

Pyridoxine deficiency may be the most important factor in alcohol-withdrawal seizures. This possibility is suggested by Es-sig,[11] who successfully protected barbiturate-withdrawn dogs by administering ami-no-oxyacetic acid which increases GABA by blocking its breakdown. Pyridoxine and diphenylhydantoin failed to protect the dogs from seizures.

Essig's hypothesis is that barbiturate addiction causes a compensatory decrease in GABA. On withdrawal of barbiturates, the regulatory mechanisms producing GABA slowly normalize over a period of several weeks. Barbiturate addicts abruptly withdrawn may suffer seizures or delirium tremens as long as three weeks after withdrawal.

Prevention of seizures in alcoholics by the use of Pyridoxine suggests a relatively small decrease of GABA by the direct depressant effect of alcohol, and a large decrease of GABA because of Pyridoxine deficiency.

Asada and Mitsumori[12] showed the production of serum pyridoxal phosphate (PLP), the active biological from of Pyridoxine, is depressed in patients with liver damage. This fact may explain why alcoholics eventually develop withdrawal symptoms after very brief drinking bouts. Depressed PLP production may also account for poor treatment response in those alcoholics with liver damage.

French[13] has reported cardiac necrosis in pyridoxine-deficient rats. This possibility should be considered in alcoholics. Impaired immune response in Pyridoxine deficiency is well documented[14] and probably accounts for the alcoholic's notoriously poor resistance to infection. The Pyridoxine deficiency can be corrected by giving 100 mg. of Pyridoxine intramuscularly every six hours for two or three days.

Magnesium Deficiency

Fishman[15] reviewed the literature on magnesium deficiency and concluded that magnesium deficiency can cause delirium and grand mal seizures. Although Fishman acknowledged moderate to slight magnesium deficiency in alcoholics, he did not believe magnesium deficiency was importantly involved in alcohol-withdrawal phenomena.

However, alcoholics who have gross twitching of muscles and extremities are promptly relieved by giving 4 ml. of a 50% solution of magnesium sulfate intramuscularly four times a day for two or three days. Solutions of magnesium sulfate and Pyridoxine may be safely combined in one syringe. Caution should be exercised in administering magnesium sulfate to patients with kidney disease.

Treatment Errors

Nonbarbiturate addicting drugs (mepro-bamate, glutethimide, methyprylon, eth-chlorvynol, chlordiazepoxide hydrochloride, diazepam and ethinamate), phenothia-zines and barbiturates should not be used to treat alcohol-withdrawal phenomena.[16] They do not correct the deficiencies which, if severe, may cause death. Phenothiazines, known to activate epileptogenic discharges[17] may increase the EEG abnormality which develops about 18 hours after withdrawal.[18]

However, barbiturates should be given to alcoholics who seek treatment more than 14 hours after withdrawal as their EEGs may be developing abnormalities. Alcoholics may learn to use these drugs and later die from their potentiating effect on alcohol. My estimate, based on 10 years practice in a small town, is that probably in this country 30,000 alcoholics a year die suddenly of the combined effects of alcohol and one or more of the drugs mentioned previously.

Lest the physician inadvertently administer a lethal dose of medication, every intoxicated alcoholic should be considered to have one or more alcohol-potentiating drugs in his system. Alcoholics may become addicted to these drugs or use them in an attempt to manage their alcohol-withdrawal symptoms. They may suffer seizures or delirium when the drug is abruptly discontinued.

Diphenylhydantoin is a poor anticonvulsant for alcohol-withdrawal seizures as it exerts its effect by changing the ratio.[1] Diphenylhydantoin does not have a direct brain cell depressant effect which could counter the increased brain cell exciteability caused by a decrease in GABA. Essig[16] does not consider diphenylhydantoin effective against sedative-withdrawal convulsions.

In 1952 I began using ACE to treat

alcohol-withdrawal symptoms. Magnesium sulfate was added in 1958, and Pyridoxine and sodium chloride were added in 1963. Since 1952 I have treated approximately 3,000 alcoholics without a fatality.

In my experience, approximately 20% of male alcoholics and 50% of female alcoholics entering alcoholic rehabilitation programs may be addicted to barbiturates or one of the newer sedative-type drugs. Since most alcoholics addicted to drugs deny they are taking drugs, this complication will make meaningful double blind controlled studies of alcohol-withdrawal treatment regimens very difficult or impossible.

Summary

Routine prompt replacement of adrenal corticoids, Pyridoxine, magnesium and sodium chloride deficiencies will safely prevent or rapidly alleviate alcohol-withdrawal phenomena. The rare exception is the alcoholic who has liver damage so severe he can not manufacture sufficient pyridoxal phosphate. For each deficiency the mechanisms causing delirium and seizures are known and have been documented.

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