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Medical Information

Vulnerability to Disulfiram Psychosis

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ABBREVIATIONS USED IN TEXT

DA = dopamine
DBH = dopamine-beta-hydroxylase
NE = norepinephrine

DISULFIRAM (Antabuse) is a drug commonly used in the management of impulsive drinking in patients addicted to alcohol. Besides the severe cardiovasular effects it produces with alcohol intake (by increasing circulating acetaldehyde levels through inhibition of the enzyme aldehyde dehydrogenase), disulfiram has various adverse effects when used alone. These effects include drowsiness, fatigue, impotence, headaches, skin eruptions and polyneuritis, as well as, most seriously, neurological toxicity and psychosis. Disulfiram delirium is probably mediated by toxic metabolites, such as carbon disulfide (CS_2).[1] Nontoxic psychosis produced by disulfiram is frequently missed in clinical practice, as evidenced by the continued use of disulfiram in affected patients, or a diagnosis of psychosis that disregards the role of disulfiram in its precipitation.

In this paper, a hypothesis of vulnerability to disulfiram psychosis is proposed, based on the current lines of evidence for the biological mechanisms involved in the psychoses.

The Dopamine Hypothesis

The dopamine (DA) hypothesis of schizophrenia[2] states that an increase in DA activity in certain brain areas (probably the mesolimbic and mesocortical tracts) is associated with psychotic symptoms in schizophrenic patients. According to this hypothesis, drugs that increase DA activity (that is, DA agonists) would worsen the symptoms of schizophrenia, and this has been confirmed with controlled studies using amphetamine and methylphenidate (DA agonists) as well as L-dopa (a DA precursor). These drugs cause relapses in schizophrenic patients in doses much lower than those needed to produce psychosis in normal persons. On the other hand, DA antagonists such as neuroleptics (DA receptor blockers) produce a pronounced improvement or remission of schizophrenic symptoms, and alpha-methyl-para-tyrosine (a DA synthesis blocker) has been reported to potentiate the clinical efficacy of neuroleptics.

Disulfiram Is a DA Agonist

Disulfiram is an inhibitor of dopamine-beta-hydroxylase (DBH), an enzyme that catalyzes the metabolism of DA to norepinephrine (NE).[3] By inhibiting the metabolic pathway from DA to NE in the central nervous system, disulfiram results in an increase of DA concentrations. Therefore, disulfiram is a DA agonist, and is likely to exacerbate preexisting or latent psychosis, similar to amphetamine, methylphenidate and L-dopa.

DA and Affective Psychosis

Increased brain DA is highly correlated with psychomotor activity in animals, and L-dopa has been shown to produce episodes of hypomania and mania in most patients with bipolar affective psychosis.[4] It is possible, therefore, that disulfiram can uncover a preexisting or latent hypomania or mania.

Alcoholism, Affective Psychosis and Schizophrenia

Alcoholism was shown to occur more frequently in the first degree relatives of patients with manic-depressive psychosis, schizophrenia and al-

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coholism.[5] Schizophrenia and affective illness have also been shown to have a strong genetic component.[6,7] Therefore, alcohol addicts with family history of psychosis are likely to be more vulnerable to precipitants of psychosis than alcohol addicts without such history or than the general population.

DBH and Psychosis

Hartmann,[8] who proposes that a DBH deficit is the underlying mechanism of schizophrenia, describes in an experiment on himself how fusaric acid, a DBH inhibitor like disulfiram, did not have any effects on him except for some headache and stuffy nose. L-dopa alone had little effect on him as well. However, the combination of the two drugs produced in him a depersonalization syndrome, racing thoughts, unspecified fear bordering on terror and difficulty in sleeping. He suggests that the dopaminergic effects of L-dopa, in combination with DBH inhibiting effects of fusaric acid, recreate the biochemical disturbance in schizophrenia. Some evidence also is accumulating that certain subtypes of schizophrenia may have a DBH deficit while other subtypes do not.

A low activity of DBH in schizophrenia was also postulated by Wise and Stein,[9] who reported a deficit of this enzyme in the postmortem examinations of brains of schizophrenic patients. This finding was not replicated by Wyatt and coworkers[10] and measurements of DBH in serum of remitted or relapsed schizophrenic patients did not differ significantly from nonschizophrenic controls.[11] It is conceivable, however, that although DBH activity is not low in schizophrenic patients, a biochemical challenge with DBH inhibitors or DA agonists could induce a psychotic state.

In one study of the effects of disulfiram on serum DBH in 30 normal volunteers[12] one subject became psychotic while receiving 250 mg per day. He was found to have the lowest DBH activity in the group, and further history showed that he did have a schizophrenic episode a year before, which he had lied about.

DBH is also known to increase with stress,[13] apparently a physiological response necessary for the increased turnover of NE during stress. It is possible that DBH inhibition with disulfiram can compromise this adaptive response to stress, and increase the susceptibility to the increased DA activity that results from DBH inhibition.

The Literature on Disulfiram-Induced Psychosis

For many years after disulfiram was introduced in 1948, it was used in much higher doses (up to 2,000 mg per day) than it is now (125 to 500 mg per day). That resulted in many reports of toxicity, delirium and psychosis. Liddon and Satran[14] reviewed the literature on disulfiram psychosis and concluded that of 52 case reports in the literature, all but five were actually toxic delirium. Of these five patients, four had manic or hypomanic symptoms, and one had symptoms of paranoid schizophrenia. Many patients suffered from severe depression as well (which, according to the catecholamine hypothesis of depression, could be due to the blockage of NE synthesis by disulfiram's inhibition of DBH).

Heath and associates[15] reported that schizophrenic patients became worse and control subjects became toxic with the ingestion of large doses of disulfiram (1,500 mg per day for several days). There are no reported studies of the effects of low doses of disulfiram (125 to 250 mg per day) on schizophrenic symptoms.

Other reports in the literature indicate that patients with depression, schizoid personalities or borderline schizophrenia do poorly on regimens of disulfiram.[16,17]

Vulnerability to Disulfiram Psychosis

The following hypothesis is derived from the preceding discussion:

- Disulfiram, like amphetamine, L-dopa and and other DA agonists, can induce or exacerbate preexisting psychoses.
- Alcohol addicts with a history of drug-induced schizophrenic or affective psychosis are probably more vulnerable to disulfiram-induced psychosis than addicts with no such history.
- Alcohol addicts with a family history of psychosis (in parents, siblings or offspring) are probably more vulnerable than the general population to disulfiram-induced psychosis because of the assumed higher genetic predisposition to the biochemical correlates of psychosis, which may be uncovered by a disulfiram challenge.

The implications for the above are clear. Disulfiram should not be given indiscriminately to alcohol addicts, but only to those with no personal or family history of psychosis. For those with such history, disulfiram could induce or exacerbate a psychosis even at relatively low doses (250 to

500 mg per day). The author's clinical experience is compatible with this hypothesis but controlled studies to validate it are needed.

Conclusion

Disulfiram can produce psychosis, probably via its DBH inhibiting effects, which lead to an increase in DA activity. Because such an increase is associated with exacerbation of schizophrenic and affective psychosis (as with other DA agonists like amphetamine, L-dopa and methylphenidate) it is important to avoid using it in the management of alcohol addicts with a personal or family history of schizophrenia or manic-depressive psychosis.

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