A case of zolpidem-induced hepatic encephalopathy in a patient with major depression

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Introduction:

This is a case report of a 49 year old man admitted to a psychiatric inpatient unit with symptoms of severe depression, who developed hepatic encephalopathy after being started on zolpidem.

Zolpidem is an imidazopyridine that is reported to have similar sedative properties to the benzodiazepines but minimal effects as an anxiolytic, muscle relaxant or anticonvulsant. It has a rapid onset, short duration of action and is metabolized in liver through CYP450 system. Zolpidem is extensively used as a hypnotic in short term management of insomnia. There have been reports of hepatic encephalopathy induced by this medication.

Hepatic encephalopathy is characterized by confusion, altered level of consciousness and potentially coma and death. It results from liver failure and the accumulation of toxic substances in the blood stream such as nitrogenous waste products, of which ammonia is the most commonly measured. There is increased activity of the inhibitory gamma amino butyric acid (GABA) system and the energy supply to other brain cells is decreased. The diagnosis of hepatic encephalopathy is a clinical one and serum ammonia levels are elevated in 90% of patients.

Zolpidem has shown great utility as a sleep aid in patients with major depressive disorder, but must be approached with caution due to increasing concerns for adverse effects on mental status. The presenting case is a report of hepatic encephalopathy in a patient treated with zolpidem.

Case Report:

The patient is a 49 year old Hispanic man brought to the emergency department by his wife and daughters with a chief complaint of depressed mood and suicidal ideation. The patient presented with neurovegetative symptoms such as poor appetite, insomnia, and decrease in psychomotor activity, fatigue, decreased level of energy, anhedonia and passive suicidal ideation. The patient had been having recurrent thoughts of cutting his wrists. Evidence of psychosis or mania was absent. The patient's history was significant for alcohol dependence, major depressive disorder with a suicide attempt by overdose of acetaminophen several months prior to this admission. The patient also has a past medical history of hepatitis C, with cirrhosis, HIV, asthma, hypertension and stroke.

Upon admission to the inpatient psychiatric unit, the patient was started on sertraline 50mg daily which was not tolerated due to the emergence of gastrointestinal side effects. The patient was then placed on bupropion 150mg oral daily which was titrated to 300mg oral daily with considerable improvement in mood. However the patient continued to have poor sleep for which he was started on zolpidem at a dose of up to ten milligrams. After the initiation of zolpidem, the patient became progressively more isolative and refused to eat or take his medications. He became increasingly paranoid, irritable and then his mental status worsened revealing confusion and disorientation that exacerbated to the point of being unable to recognize his family members.

Zolpidem was discontinued. His ammonia level on admission was 49mg/dl. After initiation of zolpidem, his ammonia level increased up to 141mg/dl and then decreased back to 36mg/dl four days after the discontinuation of zolpidem with improvement of patient's symptoms.

Discussion:

In this case, there is evidence of worsening of mental status in a 49 year old man after treatment with zolpidem. In a small number of previous reports, the encephalopathy is caused directly by acute liver failure. More commonly, especially in chronic liver disease, hepatic encephalopathy is caused or aggravated by additional causes (excessive nitrogen load, electrolyte or metabolic disturbances, infections, drugs and medications like benzodiazepines and alcohol). Identifying these causes can be important to treat the episode effectively. Benzodiazepines are generally avoided in patients with advanced liver disease because they mediate GABAergic neurotransmission. Although zolpidem in theory has the same propensity to induce hepatic encephalopathy, its shorter half- life has made it a reasonable choice for subjects with chronic liver disease. However, increasing evidence of encephalopathy induced by zolpidem has been reported, (1, 2). In some cases, Flumazenil has been used to reverse the excessive confusion in such patients who were given zolpidem and good results were seen, (1).

Zolpidem is metabolized hepatically and excreted as a metabolite in urine, bile and feces. Plasma protein binding of zolpidem is markedly decreased in the presence of hepatic impairment and exacerbated by concomitant use of other medications that may displace zolpidem from carrier proteins. Therefore we recommend that clinicians should cautiously prescribe zolpidem keeping such factors in mind so as to minimize its side effects.

References:

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