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Schizophrenia and Dimenhydrinate Abuse

INTRODUCTION

Reports that dimenhydrinate (DMH), an over the counter antihistamine that is available under the brand names of Gravol® and Dramamine® has abuse potential date as far back as 1968.

One of the first Case Reports was published in 1988 in which two female patients, ages 26 and 25 years old developed dependency and tolerance. In the first case a 26 year old female with a history of psychological problems started taking DMH for it's anorexic and sedative effects. To maintain these effects she gradually increased the dose over a period of 6 months to 2500 mg daily.

The second case, a 25 year old female patient had been taking DMH since 1981 for severe vertigo, the cause of which was unknown. This patient increased the daily dose up to 600 mg and at this dose level and found the sedative effect pleasurable.

The purpose of this early report was to alert physicians that abuse of dimenhydrinate, due to the availability and low cost properties may be more common than is realized.

At recommended doses DMH is used most commonly as an anti-emetic, an effect that is associated with antagonism at the H₁ receptor. In 1997, a series of case studies describing DMH abuse by adolescents who administered the drug for its hallucinatory and euphoric properties was published.

In doses more than four times the recommended dose, DMH produces a "high" characterized by hallucinations, excitement, incoordination and disorientation.

A 1968 article on drug use among Canadian youth cited DMH as being one of the drugs abused by adolescents. Doses in the 400 mg per day range were being ingested to obtain a "high". Case reports followed cited abuse in doses of up to 750 mg per day. Teenagers who abused it to get "high" reported that it was cheap and easily obtained in pharmacies.

PHARMACOLOGY

Dimenhydrinate is a combination of the antihistamine, diphenhydramine (DP) (or Benadryl®) and the methylxanthine, 8-chlorotheophylline, in equimolar ratios. Many researchers suggest that DP, the antihistaminergic component of DMH, is responsible for the reinforcing effect of the drug. This antihistamine influences neurotransmitter systems either directly, by acting on receptors or transporters, or indirectly, by modulating their influence.

The effectiveness of dimenhydrinate as an anti-emetic was first reported in 1949 when it was found to aid in the prevention of both seasickness and airsickness.

The anti-emetic properties of DMH are thought to be the result of antagonism of H₁ histamine receptors in the vestibular system. There may

also be a synergistic effect with the addition of 8-chlorotheophylline.

Diphenhydramine (DP), often identified as the active component of DMH, is a competitive antagonist at the H₁ histamine receptor. Histamine exists in both the peripheral and central nervous systems (CNS). Antagonism of CNS H₁ receptors account for its sedative properties.

There have been reports of anxiolytic effects in psychiatric patients due to the abuse of doses of DMH as high as 5000 mg daily. This suggests that the pharmacological effects of these agents may not be limited to the histamine system. There is evidence that anti-histamines can interact with acetylcholine, serotonin, norepinephrine, dopamine and opioid systems and this may explain their effects on depression and anxiety.

TOXICITY, DEPENDENCE AND TOLERANCE

The concerns with dimenhydrinate abuse involve two possible clinical situations: acute and chronic abuse. The acute presentation is primarily one of anticholinergic and central nervous system (CNS) symptoms. Seizures, hallucinations, toxic psychosis and extrapyramidal movements can occur. Cardiac arrhythmias, potentially resulting in death, have been reported in DMH overdose. Prolongation of the QT interval may be the antecedent electrocardiographic event. The treatment is supportive and symptomatic as there are no specific antidotes for this class of drugs. Dependence and tolerance occur with chronic abuse.

Daytime drowsiness, psychomotor impairment and learning impairment are known to occur with chronic abuse of DP. More recently, reports have emerged of DMH abuse masquerading as psychiatric disorders

(primarily depression, often resistant to treatment) among adolescents.

ACUTE AND CHRONIC ABUSE

Acute Intoxication: DMH intoxication occurs when an individual ingests anywhere from 750 mg (15 tablets) to 1250 mg (25 tablets) on a single occasion. At doses close to 800 mg, patients reported hallucinations, pleasant and euphoric tactile and visual sensations and excitement; at larger doses (1250 mg) some patients become confused and violent. DMH intoxication can be seen when someone with a history of using illicit drugs, especially marijuana or LSD wants a "cheap high".

Chronic Use: When DMH is abused chronically, tolerance to the subjective effects of the drug develops. Some patients report taking up to 5000 mg of DMH daily, more than 12 times the recommended daily dose of 400 mg. During periods of abstinence, patients exhibit withdrawal symptoms including depressed affect, lethargy, irritability, and loss of appetite and amnesia. In more severe cases of withdrawal, abusers experience agitation, hostility, clumsiness and nausea.

Craving between doses also occurs. A history of psychiatric problems is often evident in individuals who chronically abuse DMH. Many of the reported case studies involve patients with clinical diagnoses of schizophrenia, depression, panic attacks, personality disorders or substance abuse. There are no known case studies describing abuse of 8-chlorotheophylline, suggesting that the abuse potential of DMH is dependent on the anti-histamine component of the drug.

On the other hand, the methylxanthine may interact synergistically with DP to produce a greater reinforcing effect, which could explain anecdotal evidence suggesting that patients have

a tendency to abuse dimenhydrinate instead of diphenhydramine.

SUBJECTIVE EXPERIENCES WITH DMH

While there are reports of anti-histamines having stimulant effects in animal subjects, DMH is described as a depressant by human participants. One sign of this action is lethargy reported by participants in self assessment reports. At the recommended therapeutic dose (100 mg), DMH increases ratings of drowsiness, sluggishness, silence and depression. Participants in this study also felt less energetic, effective, decisive and confident. Thus at the recommended doses, DMH appears to produce psychomotor depressant effects in humans.

High dose DP (400 mg) increases subjective ratings on scales associated with drug abuse, such as "drug liking" and "willingness to take the drug again" in patients with a history of barbiturate abuse. At the same time, however, self-ratings of negative side effects of DP administration, including "difficulty concentrating", "light-headed/dizzy" and the "bad effects" also increased.

ABUSE IN PSYCHIATRIC PATIENTS

Individuals with a history of a psychiatric disorders, such as schizophrenia, depression, substance abuse and personality disorders may repeatedly administer DMH. In such cases, tolerance to the acute effects of the drug and symptoms of drug withdrawal can occur. Chronic consumption of DMH may be difficult to identify because symptoms of the dependence resemble the symptoms of some psychiatric disorders such as major depression.

Schizophrenic patients may be particularly susceptible to DMH abuse because of its ability to relieve the extrapyramidal (EPS) symptoms that are caused by anti-psychotic drugs. EPS is

often treated with anticholinergic medications and DMH has anticholinergic properties.

NEUROCHEMISTRY OF ABUSE

The abuse potential of DMH may be related to an interaction with the dopamine systems, which has been implicated in the reinforcing value of most drugs of abuse. For example, the reinforcing effects of amphetamine and cocaine depend critically on the dopamine release in the nucleus accumbens. Neurochemical evidence, such as the H₁ antagonist-induced increase in dopamine levels in the nucleus accumbens and the inhibition of the re-uptake of dopamine in the striatum support this theory. Although DMH has a diverse range of physiological and behavioral effects, abuse potential of this drug may be related to the reinforcing effects produced by its interaction with the mesolimbic dopamine system.

CONCLUSIONS

This review targets the abuse potential of anti-histamines and in particular DMH and DP. Psychiatric patients and street drug users are the most common abusers of anti-histamines. Psychiatric patients may be particularly susceptible to the abuse potential of anti-histamines, including DMH and DP, because these agents have anxiolytic, antidepressant and anti-cholinergic properties. At the same time, both DMH and DP are readily available as street drugs.

In the drug subculture, 16 tablets, equivalent to 800 mg of DMH, is understood to be the standard dose for a "high". Both DMH and DP have the potential to become accessible substitutes for illegal drugs such as marijuana or LSD.

The methylxanthine theophylline appears to have stimulatory effects similar to those created by caffeine. It has been theorized that the abuse

potential of drugs is related to an agent's psychomotor stimulant properties. Therefore, anti-histamines such as DMH that include a methylxanthine component like 8-chlorotheophylline may have a greater stimulatory effect than the anti-histamine alone in humans and may have a greater abuse liability.

The actions of DMH on dopamine systems may be a key factor in the drug's reinforcing effects and the development of dependence. Attempts to pinpoint a single mechanism of DMH abuse liability are complicated because there is an interaction of each component of DMH with the

brain's neurotransmitter systems and there may be an interaction between those components. A real concern in a major psychiatric setting such as Riverview Hospital is that DMH abuse may be identified as a worsening of a patient's symptoms instead of a drug related problem, which could result in inappropriate psychiatric treatment. Further research on the neurotransmitters and the abuse liability of histamine antagonists would be beneficial for our understanding of the reinforcing qualities of DMH and the behavioral consequences of its abuse.

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