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Review

Mechanisms and abuse liability of the anti-histamine dimenhydrinate

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Abstract

The over-the-counter anti-emetic dimenhydrinate (DMH) (Gravol or Dramamine) has been reported to be abused for non-medicinal purposes. Street drug users abuse DMH for the acute effects of euphoric sensations and hallucinations, while psychiatric patients abuse DMH for its anxiolytic or anti-cholinergic effects. DMH is an H_1 histamine receptor antagonist, but it interacts either directly or indirectly with other neurotransimitter systems, including those using acetylcholine, serotonin, norepinephrine, dopamine, opioids or adenosine. Animal behavioural studies, such as self-administration, conditioned place preference, drug discrimination, and modulation of operant responding, show that anti-histamines have abuse potential. Further support comes from reports of acute and chronic abuse of DMH by humans. Collectively, results confirm the abuse liability of DMH. © 2002 Published by Elsevier Science Ltd.

Keywords: Dimenhydrinate; Diphenhydramine; 8-Chlorotheophylline; Drug abuse; Histamine; Anti-histamine; Review

Contents

1. Introduction

Over-the-counter (OTC) drugs are not always used for their intended purposes. Thus, anti-histamines may be administered for their reinforcing rather than their analphylactic effects. For example, heroin addicts will mix the narcotic analgesic pentazocine with the anti-histamine tripelennamine, a concoction known on the street as 'T's and Blues'. This drug combination creates a 'rush' that is indistinguishable from heroin [45]. Users of hallucinogens, such as lysergic acid diethylamide (LSD), or marijuana will substitute these drugs with large doses of OTC anti-histamines to achieve euphoric tactile, visual or auditory sensations [4,26]. These examples show that anti-histamines have abuse potential.

In recent years, a number of case study reports indicate that dimenhydrinate (DMH), an OTC anti-histamine with the trade name Gravol or Dramamine, has abuse potential. DMH is composed of the anti-histaminergic agent

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diphenhydramine (DP), sold under the trade name Benadryl, plus the methylxanthine, 8-chlorotheophylline, in equimolar ratios [18,20]. At recommended doses DMH is used most commonly as an anti-emetic, an effect that is attributed generally to it's antagonism at the H_1 receptor [23,55]. Both acute and chronic abuse of DMH have been reported.

In 1997, a series of case studies described DMH abuse by adolescents who administered the drug for its hallucinogenic and euphoric properties [41]. In large doses (more than four times the recommended dose), DMH produces a 'high' characterised by hallucinations, excitement, incoordination, and disorientation [2,4,9,18,26]. These cases of DMH abuse have been reported in individuals with a history of illicit drug use [4,26,41].

Individuals with a history of a psychiatric disorder, such as schizophrenia [2], depression, substance abuse, and personality disorders [9,18,35] may repeatedly administer DMH. In such cases, tolerance to the acute subjective 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 and dysthymia [18].

Many researchers suggest that DP, the anti-histaminergic component of DMH, is responsible for the reinforcing effect of the drug [27]. This anti-histamine influences neurotransmitter systems either directly, by acting on receptors or transporters, or indirectly, by modulating their influence. The neurotransmitter systems that have been implicated in the behavioural effects of DMH include those using dopamine [53], acetylcholine [9], serotonin [8], norepinephrine [22] and opioids [51]. The neural mechanisms underlying the abuse potential of DMH are not yet established, however, and evidence for the abuse potential of DMH in particular, and of anti-histamines in general, underscores the need to identify these mechanisms.

2. Behavioural and neurochemical effects of dimenhydrinate

2.1. Dimenhydrinate

The effectiveness of DMH as an anti-emetic was first reported in 1949, when it was found to aid in the prevention of both seasickness [19] and airsickness [50]. The anti-emetic properties of DMH are thought to be produced by antagonism of H_1 histamine receptors in the vestibular system [23,46,55]. For example, electrophysiological studies have shown that both DMH and DP can suppress vestibular neuronal firing that is enhanced by angular or linear acceleration motions [23]. This would suggest that the ability of DMH to reduce nausea is due to the DP component of the drug. There may also be a synergistic effect with the addition of 8-chlorotheophylline [10]. A cold microcaloric test on normal human subjects found that while DMH could alter vestibular functioning, neither DP nor 8-chlorotheophylline had the same effect [20].

2.2. Diphenhydramine

DP, often identified as the active component of DMH [27], is a competitive antagonist at the H_1 histamine receptor [1]. Histamine exists in both the peripheral and central nervous systems (CNS). In the CNS, it influences neuroendocrine system functions, ingestive behaviour, thermoregulation, cardiovascular regulation, and arousal [5,39]. The neurotransmitter also affects motor activity in both humans and laboratory animals. For example, histamine injections into the lateral ventricles of rats produced a biphasic motor response: decreased activity in the first 20 min after the injection, followed by a period of hyperactivity. Pretreatment with an H_1 receptor antagonist blocked both effects [24]. On the other hand, the anti-histamine DP has been reported to induce motor excitation in monkeys [14]. Whether these differences in motor activation are related to drug dose, route of administration, species, or some other experimental variable is not clear at present, and further studies are needed in this respect.

There is little disagreement that recommended doses of OTC anti-histamines, known to block the H_1 receptor, decrease activity levels in humans. For example, participants self-report significantly greater feelings of sleepiness after administration of DP than after placebo administration [32].

Anti-histamines also have been reported to act like anti-depressants in laboratory tests [39] or to have anxiolytic effects in psychiatric patients [18]. This suggests that the pharmacological effects of these agents may not be limited to the histamine system. Indeed, 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.

Acetylcholine: Histamine and acetylcholine have a number of similar characteristics: the regional distribution of the two neurotransmitters within the CNS is similar; both increase intra-cellular levels of cyclic guanasine monophosphate in the post-synaptic neuron; the long-term desensitisation profiles of histamine and acetylcholine are comparable [39]. Furthermore, anti-histamine drug administration produces effects that resemble those of anti-cholinergic drug administration, including thought disorder, hallucinations, amnesia and delirium [9], as well as analgesia [39]. This may be due to an excitatory effect on ACh release that is modulated by H_1 receptor activity [5]. Other classic anti-cholinergic effects, such as mydriasis, that are seen after anti-histamine administration may be the result of blockade of the muscarinic cholinergic receptor [34]. In line with these notions, schizophrenic patients may be particularly susceptible to DMH abuse because of its ability to relieve the extrapyramidal symptoms that are caused by anti-psychotic drugs and that are sensitive

to anti-cholinergic treatment [2]. Taken together, this evidence suggests that anti-histamines may directly affect cholinergic neurotransmission or that there may be a functional overlap between the cholinergic and histaminergic systems.

Serotonin: Animal studies show that anti-histamine drugs have the ability to block serotonin re-uptake [6], suggesting that they may possess anti-depressant properties [39]. In humans, 77% of reactive depressive patients showed an improvement in mood after chronic DP consumption, though this finding was not consistent [21].

Norepinephrine: Potential anti-depressant effects of anti-histamines also may be related to their ability to inhibit norepinephrine re-uptake [7]. Furthermore, the analgesic effects of anti-histamine drug administration may, at least partially, be explained by its interaction with the norepinephrine system [42], because increases in norepinephrine activity produce analgesia [17].

Dopamine: Central administration of histamine increases the activity of the mesolimbic, but not the nigrostriatal, dopamine system as measured by post-mortem analysis of dopamine metabolite levels, and this effect is blocked by H_1, but not H_2, receptor antagonists [16]. On the other hand, peripheral administration of anti-histamines increases in vivo release of striatal dopamine, particularly in the nucleus accumbens [13], and inhibits striatal dopamine uptake [8]. Behavioural studies have found that administration of the D_1-like dopamine receptor blocker SCH23390 abolishes the potentiating effect of anti-histamines on the conditioned place preference produced by the analgesic pentazocine [52,53]. This result implicates D_1 receptor activity in the reinforcing actions of anti-histamines. This apparent discrepancy, that both histamine agonists and antagonists potentiate DA activity in the nucleus accumbens, may be related to in vivo versus ex vivo measurements and/or central versus peripheral routes of administration. In any case, it is clear that histaminergic agents modulate dopaminergic activity. Histamine–dopamine interactions may be related to the abuse potential of DMH and these are discussed below.

Opioid: To explain the reinforcing effects of the T's and Blues street drug (a combination of the narcotic pentazocine and the anti-histamine tripelennamine), researchers have examined the drug interactions at the opioid receptor level. For example, Su [51] reported that it may be the high binding affinity of tripelennamine at these receptors that is responsible for potentiating the opioid-induced psychotomimetic effects. This suggests that anti-histamines may directly stimulate opioid receptors.

2.3. 8-Chlorotheophylline

8-Chlorotheophylline is a methylxathine drug related to caffeine and theophylline. It produces a number of effects, including nervousness, restlessness, insomnia, convulsions, anxiety, headaches, and nausea [36,44]. The behavioural effects of this agent are attributed primarily to its ability to block adenosine receptors [49]. Adenosine has a general inhibitory effect on neural firing, and 8-chlorotheophylline likely produces excitation by blockade of these receptors.

While 8-chlorotheophylline is generally not considered to be a contributor to the behavioural effects of DMH [23], psychomotor stimulant effects following administration of the methylxanthine have been reported in animal studies. Snyder et al. [48] found a correlation between potencies of methylxanthines at competing for adenosine receptors and the subsequent locomotor stimulation. For example, adenosine inhibits dopamine systems and reducing the influence of adenosine via receptor blockade would lead to an increase in dopamine neurotransmission and a consequent increase in motor activity. Antagonism at the adenosine A_2 receptor may be responsible for these stimulant effects of methylxanthines [49]. It has been suggested that the amount of 8-chlorotheophylline in a standard DMH tablet may have no significant stimulatory effect [7], however, the behavioural effects of high doses of this methylxanthine have not been examined.

In conclusion, DMH interacts with a variety of neurotransmitter systems, some of which are also influenced by 8-chlorotheophylline. It is therefore likely that some of these interactions may account for its diverse behavioural effects.

3. Evidence for abuse liability

3.1. Animal studies

Animal experiments provide researchers with a method of assessing abuse liability of drugs in controlled settings. To our knowledge, DMH itself has not been examined in these studies (except in our own recent and as yet unpublished work, see below), although a number of behavioural paradigms have been used to evaluate the reinforcing effect of the components of DMH, i.e., the anti-histamine DP and the methylxanthine 8-chlorotheophylline. These include drug self-administration, conditioned place preference, drug discrimination, and modulation of operant responding maintained by other reinforcers (Table 1).

i. *Self-administration*: In line with some theories of drug addiction [40,58], the anti-histamines that have psychomotor stimulant properties are likely to be self-administered [14]. For example, DP, which produces motor excitation in mice [6] and monkeys [14], will maintain self-injection in baboons and squirrel monkeys when substituted for cocaine [3,43]. Furthermore, both DP and another anti-histamine tripelennamine maintained rates of responding in a second-order fixed-interval schedule of i.v. drug injections similar to those maintained by cocaine and D-amphetamine under identical conditions [3]. These effects of DP may not be mediated solely through the histamine system: H_1 antagonists maintain self-administration at doses greater than those necessary to saturate H_1 receptors [3]. Whatever the mechanism of its action, DP clearly has rewarding effects in self-administration paradigms.

Table 1
Animal studies of the behavioural effects of DMH, DP or theophylline

Behavioural paradigm	Results	Reference
Self-administration	DP or tripelennamine maintained self-administration rates similar to those seen with cocaine or D-amphetamine when substituted for cocaine in monkeys	[3]
	DP maintained responding when substituted for self-injected cocaine in baboons	[43]
Conditioned place preference	Potentiation of pentazocin-induced place preference by tripelennamine	[53]
	Potentiation of morphine-induced place preference by histamine antagonists	[54]
	Injection of chlorpheniramine into nucleus basalis magnocellularis induced place preference	[38]
	Injection of chlorpheniramine into nucleus accumbens induced place preference	[60]
	Dose-dependent DMH-induced place preference in rats	Unpublished
Drug discrimination	Tripelleamine substituted for amphetamine in pigeons and monkeys	[14]
	Chloropheniramine but not DP substituted for cocaine in rats	[47]
	Theophylline was discriminated from saline; the behavioural effects were generalizable to caffeine	[7]
Modulation of operant responding	DP increased both suppressed and non-suppressed responding for food	[3]
	Responding for food or shock termination showed a dose-dependent increase after H1 antagonist administration	[28,29]
	Lesions to histamine system increase rates of self-stimulation	[56]
	Theophylline increased schedule-controlled operant responding	[49]
	Reinforcing effects of theophylline seen in operant responding are greater than those of caffeine	[30]
	Methylxanthines produce dose-dependent increases in reinforcement threshold in intra-cranial self-stimulation paradigms	[31]

ii. *Conditioned place preference*: Anti-histamines potentiate place preferences induced by the sigma receptor ligand pentazocine [53] and by morphine [54]. While Suzuki et al. [53] reported that the anti-histamine tripelannamine (2.5 mg/kg) did not produce a conditioned place preference, rats that were given the anti-histamine chlorpheniramine directly into the nucleus basalis magnocellularis [38] or into the nucleus accumbens [60] showed a significant preference for the drug-paired location. Recent as yet unpublished research from our own laboratory reveals a dose-dependent preference for a compartment paired with DMH (no effect with systemically administered 25 or 40 mg/kg of DMH, but significant preference with 50 and 60 mg/kg). Further experiments are being performed to determine the relative contributions of DP and 8-chlorotheophylline to this reinforcing effect. Results show that anti-histamines have rewarding effects in the place conditioning paradigms.

iii. *Drug discrimination*: Monkeys, but not pigeons, trained to discriminate amphetamine from saline, will not generalize the cue effect of DP from amphetamine when the anti-histamine is substituted for the psyhocomotor stimulant. Another anti-histamine, tripellenamine, completely substituted for amphetamine in both species [14]. When anti-histamines are substituted for cocaine in rats, chlorpheniramine mimicks the cocaine stimulus, while DP produces responses predominantly associated with the saline lever [47]. While DP appears discriminable from both cocaine and amphetamine, not all anti-histamines follow this pattern. This may suggest that anti-histamines have a roll in the neuronal reward system that is similar to the actions of psychomotor stimulants. Further studies are needed.

Rats can be trained to discriminate theophylline from saline. Furthermore, the responding is maintained when caffeine, another methylxanthine, is substituted for the theophylline [7]. The cue effect of theophylline experienced by rats appears to be similar to the cue effect of caffeine. As a methylxanthine, 8-chlorotheophylline appears to have behavioural effects similar to those of caffeine.

iv. *Modulation of operant responding*: Anti-histamines, including DP, increase responding for food on a second order schedule of reinforcement [3,28]. DP also increases the responding of squirrel monkeys that is suppressed by an aversive stimulus [3]. Responding for food or shock termination showed a dose-dependent increase when H_1 antagonists were administered prior to the test [28,29]. Results show that operant responding maintained by food reward is modulated by DP and other anti-histamines.

Placing lesions in parts of the histamine system will also enhance operant responding. Following destruction of the rostroventral part of the tuberomammillary nucleus, a hypothalamic region that is a source of brain histamine, rates of self-stimulation increased. Histamine may have an inhibitory roll in the neuronal reward system [56].

Theophylline increases schedule-controlled responding in operant conditioning experiments [49]. When McKim [30] compared the effects of theophylline with caffeine on the food-reinforced operant responding of mice, the response-rate enhancing effects of theophylline actually exceeded those of caffiene. On the other hand, methylxanthines, including 8-chlorotheophylline, produce dose-dependent increases in the reinforcement threshold in intra-cranial self-stimulation paradigms [31]. It is unclear whether the effects of anti-histamines and theophylline on operant responding are due to an influence on reinforcement systems or simply a consequence of their actions on the motor system.

3.2. Human studies

i. *DMH*: While there are reports of anti-histamines having stimulant effects in animal subjects [14], DMH is described as a depressant by human participants [27,33]. One sign of this action is lethargy reported by participants in self assessment reports [27]. At the recommended therapeutic dose (100 mg), DMH increases ratings of drowsiness, sluggishness, silence, and depression [57]. Participants in this study also felt less energetic, effective, decisive, and confident. Thus, at recommended doses, DMH appears to produce psychomotor depressant effects in humans.

ii. *DP*: A high dose of DP (400 mg) increased 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 barbituate abuse [37]. At the same time, however, self-ratings of negative side effects of DP administration, including 'difficulty concentrating', 'light-headed/dizzy', and 'bad effects', also increased. A later study reported that DP may serve as a reinforcer for individuals with a history of sedative abuse; the participants rated the direct measures of drug reinforcement, such as 'liking' and 'good effects', as well as the indirect measures of drug reinforcement, such as desire to take the drug again, estimates of the amount of money the drug would be worth on the street, and the amount of money participants would personally be willing to pay for the drug, higher for DP than for the placebo [32]. As in previous studies, DP use also resulted in significantly higher peak ratings of bad effects. These aversive side effects may deter potential abusers from using anti-histamines for a 'high' [32].

Although the data are limited, the studies cited above suggest that DP may be more reinforcing than DMH in humans. The problem with this interpretation is that DMH was administered in recommended doses, whereas the administered dose of DP was large enough to induce intoxication and aversive side effects. It is interesting to note that the quantity of DMH required to deliver 400 mg of DP is approximately 750 mg which is the amount of DMH reported to induce intoxication. Further studies are needed to compare the subjective effects of DP to DMH.

3.3. Case studies

i. *Acute intoxication*: DMH intoxication occurs when an individual ingests anywhere from 750 mg (15 tablets) to 1250 mg (25 tablets) on a single occasion [4,41]. At doses close to 800 mg, patients reported hallucinations, pleasant and euphoric tactile and visual sensations, and excitement [2,9,18]; at larger doses (i.e., 1250 mg), some patients became confused and violent [7]. DMH intoxication can be seen when someone with a history of using illicit drugs, especially marijuana or LSD [25,40], wants a 'cheap high' [18].

ii. *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 per day, more than 12 times the recommended daily dose of 400 mg [4]. During periods of abstinence, patients exhibit withdrawal symptoms including depressed affect, lethargy, irritability, loss of appetite and amnesia. In more severe cases of withdrawl, abusers experience agitation, hostility, clumsiness, and nausea [2,9]. Craving between doses also occurs [2]. 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 [2], depression, panic attacks, personality disorder or substance abuse [9,18,35].

DP may be recommended to patients with chronic illnesses to help alleviate some of the aversive effects of the illness. Dinndorf et al. [12] reported several cases of chronically ill children and adolescents exhibiting drug seeking behaviour after extended exposure to DP. Psychiatric patients, and in particular those with schizophrenia receiving neuroleptic treatment, may self-administer DP for its potential to reduce extrapyramidal symptoms caused by anti-psychotic medication [11].

We know of no 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 Gravol (DMH) instead of Benadryl (DP).

3.4. Neurochemistry of abuse

The abuse potential of DMH may be related to an interaction with the dopamine system, which has been implicated in the reinforcing value of most drugs of abuse [15,25,40,59]. For example, the reinforcing effects of amphetamine and cocaine depend critically on dopamine release in the nucleus accumbens [59] and some anti-histamines substitute for the psychomotor stimulants in the self-administration paradigm [3,43]. Neurochemical evidence, such as the H_1 antagonist-induced increase in dopamine levels in the nucleus accumbens [13], and the inhibition of re-uptake of dopamine in the striatum [8] support this notion. In addition, the dopamine D_1 receptor blocker SCH 23390 abolishes the potentiating effect of anti-histamines on the conditioned place preference produced by opioids [52,53]. Therefore, although DMH has a diverse range of physiological and behavioural effects, abuse potential of this drug may be related to the reinforcing effects produced by its interaction with the mesolimbic dopamine system.

4. Conclusions

This review emphasizes the abuse potential of anti-histamines, and in particular DMH and DP; anti-histamines

are reinforcing in animal paradigms, and humans report desirable subjective effects following the drugs' administration. Animal studies describe the ability of anti-histamines, and particularly DP, to produce reinforcing effects and to potentiate the reinforcing effect of other abused drugs. These studies also describe how administration of anti-histamines, such as DP, produces effects on operant responding that are similar to the effects produced by psychomotor stimulants. Taken together, this evidence confirms the abuse potential of DP [3].

In humans, psychiatric patients and street drug users are the most common abusers of anti-histamines. For example, psychiatric patients may be particularly susceptible to the potential abuse of anti-histamines, including DMH and DP, because these agents have anxiolytic, anti-depressant, and anti-cholinergic properites. 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' [18]. 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 [7,30]. It has been theorized that the abuse potential of drugs is related to an agent's psychomotor stimulant properties [40,58]. Therefore, anti-histamines such as DMH that includes 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.

Anti-histamines have a variety of diverse CNS effects. 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 also because there may be an interaction between those components.

DMH abuse may be identified as a psychiatric disorder instead of a drug related problem [9,18], which would result in inappropriate psychiatric treatment. Further research on the neural mechanisms and the abuse liability of histamine antagonists will be beneficial for our understanding of the reinforcing qualities of DMH and the behavioural consequences of its abuse.

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