NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATIO

Drugs and Human Performance Fact Sheets



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**Biographical Sketches of Lead** Authors and Main Contributors

## Diphenhydramine

Diphenhydramine is a white, crystalline powder. Available primarily in tablet, capsule and liquid form.

**Synonyms:** 2-(diphenylmethoxy)-N.N-dimethylethylamine hydrochloride: diphenhydramine hydrochloride; Benadryl®, Unisom® Sleepgels, Dytuss®, Dramamine®.

Source: Available in capsules, tablets, chewable tablets, syrups, elixirs, topical, and injectable forms in a variety of prescription and over-thecounter medications. Products contain diphenhydramine alone or in combination with other drugs such as pseudoephedrine and acetaminophen. Diphenhydramine is also an ingredient in several Tylenol® (i.e., acetaminophen) preparations. Dimenhydrinate (Dramamine®) is a combination of diphenhydramine and 8chlorotheophylline in equal molecular proportions.

Drug Class: Antihistamine, antiemetic, sleep aid, sedative, CNS depressant.

Medical and Recreational Uses: Used as an antihistamine for the temporary relief of seasonal and perennial allergy symptoms. Diphenhydramine is also used as a sleep aid and a cough suppressant, and has been used as a centrally acting antitussive although the mechanism for this action is unclear. Dramamine is used as a prophylaxis against and for the treatment of motion sickness.

Potency, Purity and Dose: As an antihistamine, recommended doses for adults is 25-50 mg diphenhydramine every 6-8 hours, not to exceed 50-Methylenedioxymethamphetamine 100 mg every 4-6 hours. For children, 12.5-25 mg three or four times daily is recommended. As a sleep aid the dose is 50 mg at bedtime. Adults can be given 10-50 mg intravenously or intramuscularly, up to a maximum daily dose of 400 mg.

Route of Administration: Oral, injected, and topical applications.

Pharmacodynamics: Diphenhydramine is a first generation antihistamine and is a H 1 receptor antagonist. Antagonism is achieved through blocking the effect of histamine more than blocking its production or release. Diphenhydramine inhibits most responses of smooth muscle to histamine and the vasoconstrictor effects of histamine. The antagonism may also produce anticholinergic effects, antiemetic effects, and significant sedative side effects.

Pharmacokinetics: Following oral administration diphenhydramine is well absorbed from the gastrointestinal tract, is widely distributed throughout

the body, and is able to pass though the blood-brain barrier. The oral availability is 61%, and 78% is bound in plasma. Peak plasma concentrations are reached in 2-3 hours. Diphenhydramine is metabolized to nordiphenhydramine (active metabolite), dinordiphenhydramine, and diphenylmethoxyacetic acid. The plasma half-life is 8.5±3.2 hours; shorter and longer half-lives have been reported for children and elderly subjects, respectively. Urinary excretion of unchanged diphenhydramine is 1.9%.

*Molecular Interactions / Receptor Chemistry:* Diphenhydramine is metabolized via cytochrome P450 2D6 isoenzyme. Potential inhibitors of P450 2D6 could decrease the rate of drug elimination if administered concurrently, while potential inducers could increase the rate of drug elimination.

Blood to Plasma Concentration Ratio: 0.77 and 0.82 reported.

*Interpretation of Blood Concentrations:* Following a single oral dose of 50 mg, average peak plasma concentrations of 83 ng/mL diphenhydramine were detected at 3 hours, declining to 9 ng/mL by 24 hours. A single oral 100 mg dose resulted in average peak plasma concentrations of 112 ng/mL at 2 hours post dose. Effective antihistamine concentrations are greater than 25 ng/mL, drowsiness can be observed at 30-40 ng/mL, and mental impairment may be observed with concentrations above 60 ng/mL.

*Interpretation of Urine Test Results:* Less than 2% of an oral dose is excreted in the 24 hour urine as unchanged parent drug, while approximately 11% is eliminated as its glucuronide conjugate.

*Effects:* First generation H 1 antagonists can both stimulate and depress the CNS. Stimulation results in restlessness, nervousness and inability to sleep, while depressive effects include diminished alertness, slowed reaction time and somnolence. Diphenhydramine is particularly prone to cause marked sedation. Drowsiness, reduced wakefulness, altered mood, impaired cognitive and psychomotor performance may also be observed.

*Side Effect Profile:* Includes agitation, anticholinergic side effects such as dry mouth, confusion, dizziness, drowsiness, fatigue, disturbed coordination, irritability, paresthesia, blurred vision, and depression. In overdose, symptoms may include excitement, ataxia, tremor, sinus tachycardia, fever, hallucination, athetosis, convulsions or seizures, hypotension, deep coma, cardiorespiratory collapse, and death. Fixed and dilated pupils are also observed. Gastrointestinal symptoms are less with diphenhydramine than with other H 1 antagonists.

*Duration of Effects:* Dose-dependent, however, following oral administration of therapeutic doses, peak plasma concentrations are reached in 2-3 hours and effects usually last 4-6 hours.

**Tolerance, Dependence and Withdrawal Effects:** Some tolerance may develop to the sedative effects of diphenhydramine with repeated oral dosing. No reported dependence or withdrawal effects with doses recommended.

**Drug Interactions:** Effects of diphenhydramine are increased by the presence of alcohol, MAOI's, diazepam, hypnotics, sedatives, tranquilizers, and other CNS depressants. Alcohol enhances such effects as drowsiness, sedation and decreased motor skills. These decrements in effect are more pronounced in the elderly.

MAOI's prolong and intensify the anticholinergic effects of diphenhydramine.

**Performance Effects:** All first generation antihistamines, including diphenhydramine, have been demonstrated to diminish cognitive and psychomotor performance in healthy volunteers. Impairment might even be of greater clinical significance in patients when the allergic disorder per se adversely affects CNS function, as suggested in studies in which a reduction in cognitive functioning in patients was exacerbated by diphenhydramine . Laboratory studies have shown diphenhydramine to decrease alertness, decrease reaction time, induce somnolence, impair concentration, impair time estimation, impair tracking, decrease learning ability, and impair attention and memory within the first 2-3 hours post dose. Significant adverse effects on vigilance, divided attention, working memory, and psychomotor performance have been demonstrated. It is important to note that impairment has been shown to occur even in the absence of self-reported sleepiness or sedation. Concurrent use of diazepam and diphenhydramine caused significant performance decrements at 2 hours, and to some degree up to 4 hours.

*Effects on Driving*: The drug manufacturer states that p atients should be warned about engaging in activities requiring mental alertness such as driving a car. Diphenhydramine has repeatedly been shown to severely impair tracking and reaction time performance in actual on-the-road driving tests. Single doses of 50 mg have been shown to cause significant impairment during a 90 km highway test (measuring vehicle following, constant speed and lateral position). In contrast, single 25-100 mg doses caused no significant driving effects during a short 15 minute driving test. Using the Iowa Driving Simulator, Weiler et al, 2000 compared the effects of a single oral dose of 50 mg diphenhydramine to the effects corresponding to a blood alcohol concentration of 0.1 g/100 mL. Diphenhydramine caused significantly less coherence (ability to maintain a constant distance) and impaired lane keeping (steering instability and crossing center line) compared to alcohol. Overall driving performance was the poorest after taking diphenhydramine, and participants were most drowsy after taking diphenhydramine (before and after testing). The authors concluded that diphenhydramine clearly impairs driving performance, and may have an even greater impact than does alcohol on the complex task of operating a motor vehicle.

## DEC Category: CNS depressant

**DEC Profile:** Data not available; however, the profile for a CNS depressant is: horizontal gaze nystagmus present; vertical gaze nystagmus present at high doses; lack of convergence present; pupil size normal; reaction to light slow; pulse rate normal; blood pressure normal; body temperature normal. Diphenhydramine may produce dilated pupils.

**Panel's Assessment of Driving Risks:** Single therapeutic doses of diphenhydramine have been shown to significantly impair psychomotor performance during the first 4 hours, and may have a greater impact on driving performance than alcohol.

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