

SOFT-DFC Snapshot – Diphenhydramine

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SOFT-DFC Snapshots are short reports of critical information about the more common drugs associated with drug-facilitated crimes (DFCs). They are not complete literature reviews about the drug or drug class. One key aspect is their focus on the ability to detect a drug after a single-dose administration, as is often the situation in DFC investigations. As such, these summaries also point out instances in which available data is limited in the hopes that this will encourage further research studies. Finally, SOFT-DFC Snapshots point to the use of these drugs in actual DFC cases, as cited in the medical and open literature.

Diphenhydramine is indicated for use as an antihistamine, sedative, and antiemetic. It is available over the counter in several different preparations such as elixirs, tablets, capsules, and creams ranging in concentration from 12.5 to 100 mg. Its antihistaminic properties were first described in 1946, and it has been suspected or confirmed in numerous drug-facilitated crime (DFC) investigations. The elixir formulation is especially easy to use to spike a drink. A 2019 review of toxicological findings in urine from 1000 drug-facilitated sexual assault (DFSAs) cases from the United States found the prevalence of diphenhydramine to be 9% using a lower detection limit of 50 ng/mL¹. The Drug Facilitated Crimes Committee's recommended limit of detection in urine is 10 ng/mL²; therefore, the incidence of diphenhydramine in this study could be underreported.

Drug Class:	Antihistamine, antiemetic, sleep aid, sedative, CNS depressant.
Generic Name:	Diphenhydramine
Brand Name(s):	Benadryl®, Unisom® Sleepgels, Dytuss®, Dramamine®.
Dosage Forms:	Oral, injected, and topical forms are available as pills, liquids, or creams. As an antihistamine, the recommended dose for adults is 25-50 mg of diphenhydramine every 6-8 hours, not exceeding 50-100 mg every 4-6 hr. 12.5-25 mg three or four times daily is recommended for children. 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. ²
Pharmacodynamics:	Diphenhydramine is a first-generation antihistamine and is an H ₁ receptor antagonist. Antagonism is achieved by blocking the effect of histamine more than blocking its production or release. Diphenhydramine inhibits most smooth muscle responses to histamine and histamine's vasoconstrictor effects. The antagonism may also produce significant anticholinergic, antiemetic, and sedative side effects. First-generation H ₁ antagonists can stimulate and depress the central nervous system (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, and impaired cognitive and psychomotor performance may also be observed. Side effects may include 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 H₁ antagonists. The duration of effects is dose-dependent. Some tolerance may develop to the sedative effects of diphenhydramine with repeated oral dosing. No reported dependence or withdrawal effects were associated with the recommended doses. The co-ingestion of ethanol, MAOIs, benzodiazepines, hypnotics, sedatives, tranquilizers, and other CNS depressants increases the sedative effects of diphenhydramine. Ethanol enhances the effects of drowsiness, sedation, and decreased motor skills. These decrements are more pronounced in the elderly. Additionally, MAOI's prolong and intensify the anticholinergic effects of diphenhydramine.

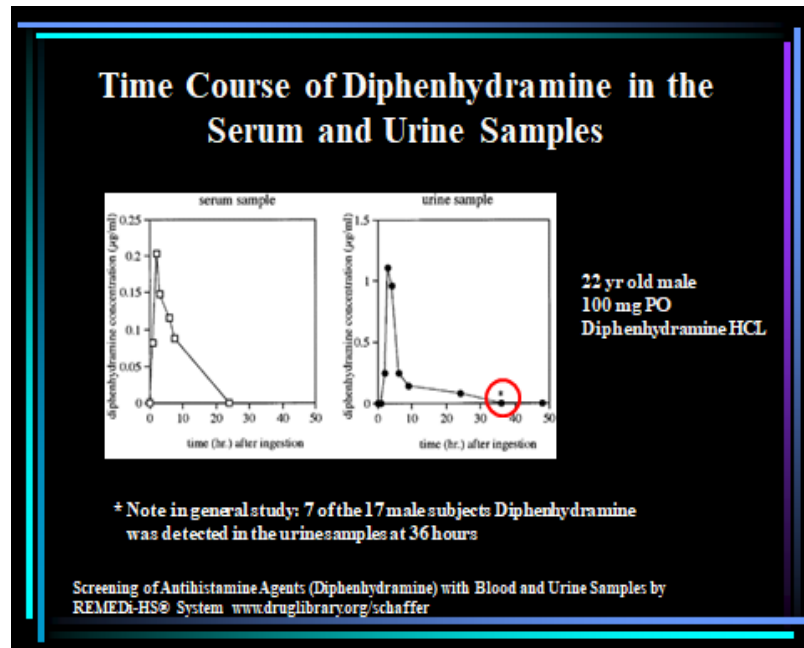
Metabolism/Elimination:

There is rapid absorption of diphenhydramine after oral administration, with effects starting within 15 to 30 minutes and fully developing within 2 to 3 hours and lasting from 3 to 6 hours.^{6,7} Diphenhydramine is widely distributed throughout the body and can pass through the blood-brain barrier. The oral bioavailability is 61%, and 78% is bound in plasma. Diphenhydramine is metabolized to nordiphenhydramine (active metabolite), dinordiphenhydramine, and diphenylmethoxyacetic acid. The plasma half-life is 8.5 ± 3.2 hr.; shorter and longer half-lives have been reported for children and elderly subjects, respectively. Urinary excretion of unchanged diphenhydramine is 1.9% in the 24-hour urine, while 11% is eliminated as the diphenhydramine glucuronide conjugate. Diphenhydramine is metabolized via cytochrome P450 2D6 (CYP2D6) isoenzyme. Potential inhibitors of CYP2D6 could decrease the rate of drug elimination if administered concurrently, while potential inducers could increase the rate of drug elimination.

Single Dose Studies *Urine*:

The SOFT DFC Committee² and the AAFS Standards Board⁴ have established the importance of testing urine samples from alleged victims of drug-facilitated crimes for diphenhydramine at a decision point concentration of 10 ng/mL or lower. Urine is easily collected, straightforward to analyze, and provides a longer window of detection of diphenhydramine ingestion compared to blood. There are limited single-dose studies of diphenhydramine with measurements made in urine over time. In one study of 17 male subjects, a 100 mg oral dose was detected

in urine for up to 36 hours in 7 subjects. The graph below shows one of the subjects' elimination kinetics in serum and urine.⁵



Blood/Plasma/Serum:

Blood, plasma, and serum specimens allow for more meaningful quantitative assessments of positive findings; however, diphenhydramine may no longer be detectable if these specimens are collected more than 8-12 hrs. after the alleged ingestion of a single dose. Conventional therapeutic doses will produce sedation in 50% of those treated. 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/mL³.

One study characterized diphenhydramine in 42 subjects following a single oral dose in children aged 2-17 yr. and using a weight and age-based dose. Plasma samples were collected for up to 48 hr. The maximum serum concentration ranged from 48-92 ng/mL, depending on the age and dose of the subject⁷.

Hair:

Hair allows for the longest window of detection for diphenhydramine. However, hair testing has the disadvantage of being more difficult to analyze, the requirement of methods is about 1,000-1,000,000 times more sensitive than what is needed for analyzing blood or urine, and the general inability to differentiate ingestions from one week to the next.

DFC Cases:

Reviewing case studies presentations demonstrates that diphenhydramine is reported in drug-facilitated toxicological findings. Scott-Ham published a summary finding of DFC cases, where 6 cases of diphenhydramine findings were published in association with this type of casework. Subsequently, two were determined as known administrations to facilitate sexual assault⁸.

Black Cab Rapist John Worboys was convicted in 2009 for attacking 12 victims, with law enforcement officers believing he may have been responsible for more than 100 victims in the UK. He would pick up his victims in his cab late in the evening. He would tell them he was celebrating winning a large amount of money at a casino or lottery. Mr. Worboys would show the victim a bag of money and ask them to join him in celebrating by drinking champagne; unbeknownst to them, he had spiked the champagne with a sedative drug, in some cases diphenhydramine. He would continue to drive around until the drug-alcohol mix took effect and then sexually assaulted them.⁹

One of the most high-profile cases involved an American actor and comedian, William (Bill) Cosby – who was accused of the drugging and sexual assault of a woman in 2004. In this case, Mr. Crosby had asked his victim to take three diphenhydramine pills to relax. In his own words, he knew the pills would put her to sleep. The victim described her symptoms as; feeling unusual, a “little spacy,” blurry vision, unable to focus or keep her eyes open, difficulty speaking, body incoordination, dry mouth, drowsiness, and sleeping with memory loss. Mr. Cosby was found guilty in April 2018 of three counts of aggravated indecent assault for drugging and sexually assaulting a woman in 2004 and was sentenced to 3 to 10 years in state prison. On 30 June 2021, Mr. Cosby’s conviction was vacated. The Pennsylvania Supreme Court justices found Cosby relied on a promise when he agreed to testify without invoking his Fifth Amendment right against self-incrimination in a lawsuit brought against him. The Court concluded that the prosecutor who later brought the charges was obligated to stick to the non-prosecution agreement. Thus, the conviction could not stand.¹⁰

Special Juice Predator: Commonwealth [PA] v Barry McOwen. Law enforcement investigating child pornography identified three young female victims ages 4 to 10 yrs. old being assaulted over five years. McOwen had committed the assault while babysitting the girls. McOwen would talk about “sleep assaulting” the girls in online chats. During the first day of the trial, testimony revealed he drugged the girls with Benadryl [diphenhydramine], referring to the drug as “half a roofie” and “my special juice.” On the second day of the trial, McOwen took the stand and confessed to the crimes. He then accepted a plea agreement and was sentenced to 50.5 to 101 years in jail.¹¹

References:

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