

DIPHENHYDRAMINE



“....And my intention is to show him Hell” (Dante) - Afflicted man; detail from the Isenheim Altarpiece, “The Temptation of St. Anthony”, inner right wing, oil on panel; 1510 - 1515. Matthias Grunewald; Musée d’Unterlinden, Colmar, France

*When we stood above the final cloister
of Malebolge and all of its lay brothers
became discernable to us,*

*strange arrows of lament, their shafts,
with pity at their tips, pierced me,
so that I pressed my hands against my ears,*

*If the contagion of every hospital
in Valdichiana, from July until September,
and in the Maremma and Sardeegna, were
amassed*

*in one malarial ditch, such suffering
was in that place. And from it rose
the stench of festering limbs.*

*We came down, always to our left, and reached
the last bank of the lengthy crag.
And then my eyes could have a better view*

*into the pit, there where the minister
of God on high, unerring justice, punishes
the counterfeiters whom she here records.*

*I think it could have been no greater sorrow
to see the people of Aegina stricken,
with such corruption in the very air*

*that every animal, even the smallest worm,
perished, and later, as the poets holds for
certain
these ancient people were restored to life,*

*hatched from the eggs of ants -
no greater sorrow, than in that somber valley
to see those spirits, heaped on one another,
languishing.*

*Some lay upon the bellies or the backs
of others, still others dragged themselves
on hands and knees along that gloomy path.*

*Step by step we went ahead in silence
looking and listening to the stricken spirits,
who could not raise their bodies from the
ground.*

*Two I saw seated propped against each other
as pans are propped to warm before the fire,
each of them blotched with scabs from head to
foot.*

*And never did I see a stable boy,
with his master waiting, nor youth whose chore
keeps him from sleep, ply his curry comb*

*more hurriedly than each one clawed his nails
across his skin because of that mad itch,
which knows no other remedy,*

*and their nails tore off scabs
as a knife strips scales from bream
or other fish with ever larger scales,*

*“You there, stripping off your coat of mail”,
began my leader, addressing one of them,
“and sometimes making pincers with your
fingers,*

*“tell us whether, among those gathered here,
any are Italian, so may your nails
last you in this task for all eternity”.*

*“We whom you see so blasted are Italian”,
answered one of them, through his tears,
“but who are you, that enquire of us?”*

*And my leader: “I am one who makes his way
down with this living man from ledge to ledge
And my intention is to show him Hell”.*

*They stopped propping one another up
and each one, trembling, turned in my
direction as others did who'd overheard those
words.*

**Dante Alighieri, *The Inferno*, XXIX 40 -98,
(1306-1317)**

Dante and Virgil have reached the Tenth and final Ditch of Malebolge in the Eighth and penultimate circle of Hell. This region is horrific beyond description, it holds the damned souls of the counterfeiters - those who in life not only debased the coin, but also gave false council in general for the purpose of their own gain. It is the only ditch in which Dante gives a physical dimension, 22 miles in circumference (The enormosity of the ditch was enthusiastically discussed by early Dante commentators. It seemed to them that there were not enough falsifiers to justify its huge size. Of course the reason has subsequently become apparent, in the vast numbers of 21st century advertising executives, telemarketers and investment advisors it would be required to accommodate).

In the ditch of the falsifiers, the shades of the dead are afflicted with unspeakable diseases of every description. Festering sores and weeping leprous lesions, infested with scabies, render them so weak and tormented that all they can do is lie propped up against each other "as pans are propped to warm before the fire" or crawl around on their hands and knees. It is as though all the malaria cases from the notorious regions for this disease, Maremma and Sardeegna, have been super-concentrated into one place. The first inkling Dante has of this place, virtually devoid of all light, is the pitiable laments of their torment. Dante is so distressed that he must cover his ears to block them out, "strange arrows of lament, their shafts, with pity at their tips, pierced me, so that I pressed my hands against my ears". Their skin lesions are putrid and irritating beyond measure, "each of them blotched with scabs from head to foot". Their only relief comes from furious scratching which only makes matters worse. They scratch as stable boys who curry horses, their nails have become like knives that scrape the scales off fishes, "and their nails tore off scabs as a knife strips scales from bream".

*Virgil, Dante's guide through Hell, sees that Dante, though horrified and barely coping with what he is seeing, seems to be eager to talk to some of the shades. He edges closer to the ditch and calls out to them, enquiring if any are Italian and so may converse with him, "tell us whether, among those gathered here, any are Italian" A few look up, and through their tears give answer, "We whom you see so blasted are Italian...but who are you, that enquire of us?" Virgil explains that he is escorting a **living** soul who wishes to speak to them. His chilling purpose is to "show him Hell !" For a brief moment, the tormented souls forget their suffering, so astonished are they to see a living man; "...They stopped propping one another up and each one, trembling, turned in my direction as others did who'd overheard those words".*

It is generally considered sound medical advice that when prescribing antihistamines, those of the newer generation, non-sedating type are best. In the tenth ditch of Malebolge in the Eighth circle of Hell, however a first generation sedating agent, will be much preferred!

DIPHENHYDRAMINE

Introduction

Diphenhydramine (trade name “Benadryl”, among others) is a first generation **sedating antihistamine**.

It has *significant* sedating effects.

Diphenhydramine is used therapeutically as both an **antihistamine** and a **sedative agent**.

See also separate document on **Sedating Antihistamine Overdose (in Toxicology folder)**.

History

Diphenhydramine was developed in 1943 by the American chemist **George Rieveschl**.

In 1946, it became the first prescription antihistamine approved by the U.S. FDA.

In the 1960s it was found to inhibit the reuptake of the neurotransmitter serotonin, a discovery which led to a search for new antidepressants that helped culminate in the development of fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI).

Chemistry

Diphenhydramine is an **ethanolamine** antihistamine.

Physiology

Histamine Receptor	Physiological Effects
H1	<ul style="list-style-type: none">● Inflammation:<ul style="list-style-type: none">♥ Pruritis♥ Vascular smooth muscle relaxation♥ Capillary vasodilatation/ increased permeability● GIT smooth muscle contraction

	<ul style="list-style-type: none"> • Bronchial smooth muscle constriction (bronchoconstriction)
H2	<ul style="list-style-type: none"> • Stimulation of gastric acid secretion • Vascular smooth muscle relaxation
H3	<ul style="list-style-type: none"> • Presynaptic auto-receptors (mainly within the CNS) <p>An auto-receptor is a type of receptor located in the membranes of presynaptic nerve cells, that act as negative feedback controls i.e stimulation will result in an <i>inhibition</i> of further release of the transmitter.</p>
H4	<ul style="list-style-type: none"> • Mediates mast cell chemotaxis.

Classification

Antihistamines can be classified as follows:

1. **Histamine H1 receptor antagonists:**

First generation sedating antihistamines:

These agents are moderately to heavily sedating and possess some mild anticholinergic effects:

They include:

- Azatadine
- Chlorpheniramine
- Dexchlorpheniramine
- Cyclizine
- Cyproheptadine
- Pheniramine
- **Diphenhydramine**

- Doxylamine
- Promethazine
- Trimeprazine

Second generation non-sedating antihistamines:

These histamine H₁-receptor antagonists do not cross the blood - brain barrier appreciably when given in normal therapeutic doses.

They do not produce significant sedation and so have become known as the non (or less) sedating antihistamines.

In addition they possess only minimal, if any, anticholinergic activity (dry mouth, blurred vision, constipation and urinary retention).

They include:

- Loratadine
- Desloratadine
- Cetirizine
- Fexofenadine
- Levocetirizine

2. **Histamine H₂ receptor antagonists:**

These include

- Cimetidine
- Ranitidine
- Famotidine
- Nizatidine

Preparations

Diphenhydramine hydrochloride as:

Tablets:

- 50 mg

Capsules:

- 50 mg

Oral liquid:

- 2.5 mg/mL, in 120 mL bottle.

Mechanism of Action

Reduces the effects of histamine by binding to the **H₁ receptor** both centrally and peripherally and stabilizing it in an inactive form.

It also has an anticholinergic action.

Pharmacodynamics

Diphenhydramine is an antihistamine, but also has significant **sedating** effects.

The sedative effect appears to be maximal within 1 - 3 hours after administration.

Its effects appears to be positively correlated with plasma drug concentration.

Marked drowsiness and/or sleep occurs at plasma concentrations of 70 nanogram/mL or greater.

Pharmacokinetics

Absorption:

- Diphenhydramine is administered orally.

It is well absorbed following oral administration

The drug appearing in plasma within 15 minutes.

Peak plasma concentrations are achieved within 1 - 4 hours

- There is high first-pass metabolism in the liver that limits systemic availability to only 40 - 60 %

Distribution

- Diphenhydramine is widely distributed throughout the body including the CNS, as it crosses the blood - brain barrier.
- Protein binding is around 80 - 85 %
- Diphenhydramine crosses the placenta
- Diphenhydramine is distributed into breast milk although the extent has not been quantified.

Metabolism and excretion:

- Diphenhydramine is rapidly and almost completely metabolized.
- Only about 1% of a single dose is excreted unchanged in the urine.
- Half-life varies from 2.4 to 9.3 hours

Indications

1. Situations of excessive histamine effect:

- Allergic rhinitis, pruritus, urticaria

However **non-sedating** antihistamines have essentially replaced the older first generation agents for these indications.

Diphenhydramine may have some use in controlling **nocturnal symptoms** and so assist sleep or in others situations in which some sedation is desirable.

- Insect stings (**skin** reactions only):

Diphenhydramine may be used when a strong agent is required for a limited time period, and when sedation is not an issue, to control distressing skin symptoms of **hymenoptera** stings.

It should be *avoided* however in situations of **true anaphylaxis** or **angioedema**, caused by insect stings, (see below).

2. Nausea and vomiting, in general.

3. Motion sickness

4. Sedation (short term use for **insomnia**).

Contra-indications/precautions

These include:

1. Anaphylaxis (contraindicated):

Antihistamines have no role in treating respiratory or cardiovascular symptoms of anaphylaxis. ⁴

- Diphenhydramine is also strongly sedating and this is undesirable in a seriously unwell patient.

2. Angioedema of the upper airways (contraindicated):

- Diphenhydramine is strongly sedating and should never be given for any patient with an upper airway obstruction, as a reducing conscious state will further compromise an already compromised airway.

3. Diphenhydramine can strongly potentiate the actions of other CNS depressants in general, including alcohol.

4. Situations where anticholinergic effects would not be desirable:

- Closed-angle glaucoma, GIT obstruction, bladder outlet obstruction (e.g. prostatic hypertrophy), may be worsened by the anticholinergic effects of antihistamines.

5. Extremes of age:

- **Elderly:**
 - ♥ They are more susceptible to the adverse effects of diphenhydramine
- **Avoid in children < 2 years:**
 - ♥ Less sedating antihistamines are preferred for allergic conditions in this age group.

Pregnancy

Diphenhydramine is a class A drug with respect to pregnancy.

Category A drugs are those drugs which, have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Maternal use of diphenhydramine has not been associated with an increased risk of congenital malformations.

Diphenhydramine is safe to use during pregnancy at the lowest effective dose for the shortest duration possible.

Breast feeding

Reports describing the use of diphenhydramine during breastfeeding have not been located.

As diphenhydramine is excreted into breast milk, consider less sedating antihistamines such as loratadine during breastfeeding where possible.

If diphenhydramine is the medicine of choice, use the lowest effective dose for the shortest duration possible and observe the breastfed infant for potential adverse effects such as sedation and sleeping pattern changes.

Adverse Effects

The principle adverse effects include:

1. Sedation:

- Diphenhydramine is **strongly sedating**.

Patients should be warned of this side effect in particular, especially in regards to potentially hazardous activities such as driving or operating machinery.

2. Hypotension

3. Anticholinergic effects:

These can include:

- Confusion, blurred vision, mydriasis, dry eyes, constipation, dry mouth, urinary retention.

4. Can potentiate the effects of other CNS depressants, including alcohol.

Dosing²

Allergy

Adult, child >12 years:

- Oral 25 - 50 mg every 4 - 6 hours as required.

6 - 12 years:

- Oral 12.5 mg every 4 - 6 hours as required.

2 - 6 years:

- Oral 6.25 mg every 4 - 6 hours as required.

Avoid in children < 2 years of age.

Insomnia

Adult:

- Oral 50 mg at night.

References

1. eTG - July 2019.
2. Diphenhydramine in Australian Medicines Handbook, Accessed July 2019.
3. Diphenhydramine in MIMs 1 April 2011
4. Diphenhydramine in RWH Pregnancy & Breastfeeding Guidelines, 17 February 2016.

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