

## The Source-Synthesis- History and Use of Atropine

### Source and Synthesis

The species name "belladonna" ("beautiful woman" in Italian) comes from the original use of deadly nightshade to dilate the pupils of the eyes for cosmetic effect. Atropine and the genus name for deadly nightshade derive from Atropos, one of the three Fates who, according to Greek mythology, chose how a person was to die. Atropine is found in many members of the Solanaceae family. The most commonly found sources are *Atropa belladonna*, *Datura innoxia*, *D. metel*, and *D. stramonium*. Other sources include members of the *Brugmansia* and *Hyoscyamus* genera (1). Atropine can be synthesized by the reaction of tropine with tropic acid in the presence of hydrochloric acid. The biosynthesis of atropine starting from L-Phenylalanine first undergoes a transamination forming phenylpyruvic acid which is then reduced to phenyl-lactic acid (2). Coenzyme A then couples phenyl-lactic acid with tropine forming littorine, which then undergoes a radical rearrangement initiated with a P450 enzyme forming hyoscyamine aldehyde (2). A dehydrogenase then reduces the aldehyde to a primary alcohol making (-)-hyoscamine, which upon racemization forms atropine (1).

### History

The naturally occurring muscarinic receptor antagonists atropine and scopolamine are alkaloids of the belladonna (*Solanaceae*) plants. Preparations of belladonna were known to the ancient Hindus and have long been used by physicians. During the time of the Roman Empire and in the Middle Ages, the deadly nightshade shrub was frequently used to produce an obscure and often prolonged poisoning, prompting Linnaeus to name the shrub *Atropa belladonna*, after Atropos, the oldest of the three Fates, who cuts the thread of life. The name belladonna derives from the alleged use of this preparation by Italian women to dilate their pupils; modern-day fashion models are known to use this same device for visual appeal. Atropine (d,l-hyoscyamine) also is found in *Datura stramonium* (Jamestown or jimson weed). Scopolamine (l-hyoscyne) is found chiefly in *Hyoscyamus niger* (henbane). In India, the root and leaves of jimson weed were burned and the smoke inhaled to treat asthma. British colonists observed this ritual and introduced the belladonna alkaloids into west-

ern medicine in the early 1800s. Atropine extracts from the Egyptian henbane were used by Cleopatra in the last century B.C. to dilate her pupils, in the hope that she would appear more alluring. In the Renaissance, women used the juice of the berries of *Atropa belladonna* to enlarge the pupils of their eyes, for cosmetic reasons. This practice resumed briefly in the late nineteenth- and early twentieth-century in Paris (1).

The mydriatic effects of atropine were studied among others by the German chemist Friedlieb Ferdinand Runge (1795-1867). In 1831, the German pharmacist Heinrich F. G. Mein (1799-1864) (3). Succeeded in preparing atropine in pure crystalline form (4). The substance was first synthesized by German chemist Richard Willstätter in 1901 (5). Bezold and Bloebaum (1867) showed that atropine blocked the cardiac effects of vagal stimulation, and Heidenhain (1872) found that it prevented salivary secretion produced by stimulation of the chorda tympani (1). Many semisynthetic congeners of the belladonna alkaloids and a large number of synthetic muscarinic receptor antagonists have been prepared, primarily with the objective of altering GI or bladder activity without causing dry mouth or pupillary dilation (1).

### Medical Uses

Atropine is a competitive antagonist for the muscarinic acetylcholine receptor types M1, M2, M3, M4 and M5 (6). It is classified as an anticholinergic drug (parasympatholytic). Working as a nonselective muscarinic acetylcholinergic antagonist, atropine increases firing of the sinoatrial node (SA) and conduction through the atrioventricular node (AV) of the heart, opposes the actions of the vagus nerve, blocks acetylcholine receptor sites, and decreases bronchial secretions.

### Ophthalmic Use

Topical atropine is used as a cycloplegic, to temporarily paralyze the accommodation reflex, and as a mydriatic, to dilate the pupils. Atropine degrades slowly, typically wearing off in 7 to 14 days, so it is generally used as a therapeutic mydriatic, whereas tropicamide (a shorter-acting cholinergic antagonist) or phenylephrine (an  $\alpha$ -adrenergic agonist) is preferred as an aid to ophthalmic examination.



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Atropine induces mydriasis by blocking contraction of the circular pupillary sphincter muscle, which is normally stimulated by acetylcholine release, thereby allowing the radial pupillary dilator muscle to contract and dilate the pupil. Atropine induces cycloplegia by paralyzing the ciliary muscles, whose action inhibits accommodation to allow accurate refraction in children, helps to relieve pain associated with iridocyclitis, and treats ciliary block (malignant) glaucoma. Atropine is contraindicated in patients pre-disposed to narrow angle glaucoma. Atropine can be given to patients who have direct globe trauma (7).

## Resuscitation

Injections of atropine are used in the treatment of bradycardia (an extremely low heart rate). Atropine blocks the action of the vagus nerve, a part of the parasympathetic system of the heart whose main action is to decrease heart rate. Therefore, its primary function in this circumstance is to increase the heart rate. Atropine was previously included in international resuscitation guidelines for use in cardiac arrest associated with asystole and PEA, but was removed from these guidelines in 2010 due to a lack of evidence (8). For symptomatic bradycardia, the usual dosage is 0.5 to 1 mg IV push, may repeat every 3 to 5 minutes up to a total dose of 3 mg (maximum 0.04 mg/kg) (9). Atropine is also useful in treating second-degree heart block Mobitz Type 1 (Wenckebach block), and also third-degree heart block with a high Purkinje or AV-nodal escape rhythm. It is usually not effective in second-degree heart block Mobitz type 2, and in third-degree heart block with a low Purkinje or ventricular escape rhythm. One of the main actions of the parasympathetic nervous system is to stimulate the  $M_2$  muscarinic receptor in the heart, but atropine inhibits this action.

## Secretions and Bronchoconstriction

Atropine's actions on the parasympathetic nervous system inhibit salivary and mucus glands. The drug may also inhibit sweating via the sympathetic nervous system. This can be useful in treating hyperhidrosis, and can prevent the death rattle of dying patients. Even though atropine has not been officially indicated for either of these purposes by the FDA, it has been used by physicians for these purposes (10).

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