

# STRYCHNINE

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## Introduction and History of Strychnine

Strychnine is classified as an extremely potent, naturally occurring alkaloid, renowned primarily for its profound toxicity and historical use as a central nervous system stimulant and, more commonly, as a lethal poison. Derived primarily from the seeds of the ***Strychnos nux-vomica*** tree, native to Southeast Asia and Australia, this compound has captivated chemists, physicians, and toxicologists for centuries due to its rapid onset of action and dramatic physiological effects. The history of strychnine utilization stretches back into antiquity, where extracts containing the alkaloid were used in folk medicine, often incorrectly prescribed as tonics or purported treatments for various ailments, though the extreme danger associated with dosage made these applications highly perilous and unreliable.

The formal isolation of strychnine marked a significant milestone in pharmacological history. It was first successfully isolated in 1818 by the French chemists Pierre Joseph Pelletier and Joseph Bienaimé Caventou, shortly after their isolation of quinine. This achievement allowed for precise study and, unfortunately, precise deployment of the pure compound, ushering in an era where strychnine became a favored tool in both intentional poisoning and rodenticide applications. Throughout the 19th and early 20th centuries, despite growing knowledge regarding its lethality, small doses of strychnine were sometimes included in prescription tonics and elixirs, based on the belief that its stimulating properties could enhance vitality or improve athletic performance, a practice now entirely abandoned due to the narrow therapeutic index and the overwhelming risk of catastrophic neurotoxicity.

Understanding strychnine requires recognizing its fundamental action not as a neurotransmitter itself, but as a critical disruptor of crucial inhibitory pathways within the nervous system. The original, simplified descriptions often label it merely as a **central nervous system (CNS) stimulant**; however, this stimulation is non-specific and pathologically uncontrolled, resulting directly from the removal of necessary physiological braking mechanisms. Unlike many other neurotoxins that interfere with uptake or release, strychnine acts specifically at the post-synaptic receptor level, leading to the highly characteristic clinical syndrome of tetanic convulsions that define strychnine poisoning.

## Chemical Structure and Source

Chemically, strychnine is classified as an indole alkaloid, characterized by a complex, rigid molecular structure that includes six ring systems. Its chemical formula is  $C_{21}H_{22}N_2O_2$ , and it presents physically as a colorless, crystalline solid. One of the most defining characteristics of strychnine, apart from its toxicity, is its intensely bitter taste, detectable even at extremely low concentrations. This bitterness is a natural defense mechanism for the plant source, the *\*Strychnos nux-vomica\** tree, which also contains related, highly toxic compounds such as brucine,

often found alongside strychnine in the raw seed extract. The high toxicity and rapid systemic distribution necessitate extreme caution in any setting where this compound is handled, particularly given its use in historical toxicology.

The primary biological source, the **Nux Vomica tree**, is a medium-sized deciduous species found predominantly across the Indian subcontinent and Southeast Asia. The seeds, often referred to as "vomit buttons" due to their shape and emetic properties at sub-lethal doses, contain the highest concentration of strychnine and brucine. The traditional preparation of the seeds involves drying and grinding to produce the raw poison. The specific chemical configuration of strychnine is what allows it to interact with such high affinity and specificity with the glycine receptor, distinguishing its mechanism of action from that of other CNS convulsants. The rigidity of the molecule is key to its competitive binding site interaction, preventing the natural inhibitory signal from terminating neuronal excitation.

The synthesis and structural elucidation of strychnine were monumental achievements in organic chemistry, demonstrating the complex architecture found in natural products. Its structure was largely determined by Sir Robert Robinson in the mid-20th century, and the total synthesis was famously achieved by Robert Burns Woodward in 1954, solidifying its place as a benchmark molecule in chemical synthesis due to its complexity. This chemical stability and complexity contribute to its persistence in the environment and its potent action within the biological system, allowing it to remain intact long enough to cross the blood-brain barrier efficiently and exert its primary neurotoxic effect centrally.

### Mechanism of Action: Glycine Antagonism

The primary and most critical mechanism by which strychnine exerts its deadly effect is through the potent, competitive antagonism of the receptor for the amino acid neurotransmitter, **glycine**. Glycine functions as the major inhibitory neurotransmitter in the spinal cord and the caudal brainstem, mediating critical inhibitory processes that regulate motor control, reflex arcs, and general neuronal excitability. When an inhibitory signal is sent via glycine, it binds to its post-synaptic receptor (a ligand-gated chloride channel), causing an influx of chloride ions that hyperpolarizes the neuron, thereby making it less likely to fire or propagate an excitatory signal. This process is essential for coordinating antagonistic muscle groups, ensuring that when the flexor muscle contracts, the opposing extensor muscle relaxes, and vice versa.

Strychnine mimics the shape of the glycine molecule enough to bind effectively to the same receptor site (specifically, the alpha subunit of the Glycine Receptor, GlyR), but it acts as a non-activating antagonist. By occupying the receptor site, **strychnine prevents glycine from binding** and initiating the chloride influx. This blockade effectively removes the "brakes" from the central nervous system circuitry. Without this crucial post-synaptic inhibition, normally balanced excitatory

signals become unopposed, leading to a state of massive, uncontrollable, and simultaneous activation of both excitatory and inhibitory motor pathways.

The resultant loss of coordination manifests as the classic sign of strychnine poisoning: **tetanic convulsions**. These seizures are characterized by the simultaneous contraction of antagonistic muscles, leading to rigidity and the severe arching of the back known as opisthotonus. Crucially, the effects are concentrated in the spinal cord, where glycine inhibition is most prominent, leading to exaggerated reflex responses and muscle spasms triggered by minimal sensory input, such as a slight noise, a touch, or a sudden change in light. The original mischaracterization of strychnine as an "inhibitory neurotransmitter" is thus fundamentally inaccurate; rather, it is a highly effective pharmacological tool for removing the primary inhibitory control mechanisms of the motor system, resulting in profound CNS hyperexcitation.

## Pharmacology and Toxicology

The pharmacological profile of strychnine is defined by its rapid absorption, efficient distribution, and relatively narrow metabolic pathway, contributing significantly to its high toxicity. Strychnine is readily absorbed through all mucosal surfaces, including the gastrointestinal tract, and can also be absorbed through inhalation or broken skin. Due to its lipophilic nature, it quickly crosses the blood-brain barrier, reaching its target sites in the spinal cord and brainstem rapidly. Onset of symptoms is often extremely fast, sometimes occurring within five to thirty minutes of ingestion, depending on the dose and the presence of food in the stomach. The speed of onset is critical in toxicology, as it often limits the timeframe available for effective decontamination procedures.

Toxicology studies indicate that the lethal dose (LD50) in humans is highly variable but generally estimated to be between 50 and 100 milligrams for an average adult, although fatalities have been reported with doses as low as 30 milligrams. The severity of poisoning is directly related to the dose absorbed and the time elapsed until intervention. Metabolism of strychnine occurs primarily in the liver, mediated by microsomal enzymes, leading to inactive metabolites. However, the rate of hepatic metabolism is relatively slow compared to the rate of absorption and the rapidity of its toxic effect. This slow clearance means that the active compound remains in circulation long enough to cause severe, protracted poisoning unless immediate medical intervention is provided to control the seizures and support vital functions.

A key toxicological principle confirmed by historical observation and referenced in the source material is that **strychnine acts as a poison if repeatedly exposed**. While acute exposure to a high dose is immediately lethal, chronic, low-level exposure can lead to cumulative neurological effects, or perhaps more commonly, the cumulative damage and sensitization of the nervous system pathways, making the individual progressively more susceptible to severe toxicity upon subsequent exposure. Given the absence of any established therapeutic use, any exposure to

strychnine, whether acute or chronic, is considered a significant medical emergency due to the high risk of rapid respiratory failure resulting from sustained muscular contractions and exhaustion.

## Clinical Manifestations of Poisoning

The clinical syndrome of strychnine poisoning is one of the most dramatic presentations in toxicology, characterized by a rapid progression from minor irritability to severe, life-threatening convulsions. The initial symptoms often include generalized muscle stiffness, neck rigidity, and heightened sensory awareness, known as hyperesthesia. Patients may report extreme anxiety and fear, recognizing the rapid deterioration of their physical state. The heightened sensory input--even minor stimuli like a draft, a loud noise, or a light touch--acts as a trigger for the generalized muscular spasms.

As the poisoning progresses, the patient experiences powerful, generalized convulsions, which are distinct from typical epileptic seizures. These are **tetanic seizures**, marked by simultaneous, maximal contraction of all voluntary muscles, including the flexors and extensors. This leads to the characteristic posture of opisthotonus, where the back is severely arched, the head and heels are bent backward, and the limbs are rigidly extended. The facial muscles are often affected, resulting in the fixed, painful grin known as *risus sardonicus*. These convulsions are excruciatingly painful for the patient.

A particularly distressing aspect of strychnine toxicity, and one that contributes significantly to the psychological trauma, is that **consciousness is typically preserved throughout the tetanic episodes**. The poisoned individual is fully aware of the intense pain, the inability to control their body, and the struggle for breath. Death usually ensues rapidly, often within one to three hours of ingestion, due to respiratory arrest caused by the sustained contraction (tetany) of the diaphragm and other respiratory muscles, leading to asphyxia. Even if respiration is temporarily maintained, the intense metabolic demands, coupled with rhabdomyolysis (muscle breakdown) and hyperthermia induced by the sustained muscle activity, rapidly lead to systemic failure.

## Historical and Current Applications

Historically, strychnine has held a dual reputation--as a powerful tool for nefarious purposes and a misunderstood agent in early pharmacology. During the 19th century, before its mechanism was fully understood and while clinical pharmacology was nascent, minute doses were sometimes incorporated into various patent medicines. These preparations were marketed as general tonics, circulatory stimulants, or even performance-enhancing compounds for athletes, leveraging the compound's potent effect on the CNS. However, these applications were highly dangerous, lacked genuine therapeutic efficacy, and were quickly abandoned by modern medicine due to the extreme toxicity and the availability of safer, more effective treatments. **There are currently no clinical**

**applications for strychnine** recognized or approved by major regulatory bodies globally.

Despite the cessation of medicinal use, strychnine retains a significant, though highly regulated, commercial application: its use as a **rodenticide** and general pest control agent. Its high toxicity, rapid action, and ability to cause death quickly made it an effective agent for controlling populations of rodents, moles, and certain predatory animals. This use continues today, particularly in agricultural settings where rapid elimination of pests is deemed necessary. However, the use of strychnine-based poisons is heavily restricted in many jurisdictions due to the high risk of secondary poisoning to non-target species, including domestic pets, wildlife, and accidental human exposure.

The regulation surrounding strychnine is stringent. Its classification as a restricted-use pesticide means that its purchase, possession, and application are strictly controlled, often requiring specialized licensing. The continued existence of strychnine in the environment, primarily through its use in pest control, ensures that accidental poisoning remains a relevant toxicological concern, necessitating specialized knowledge regarding its diagnosis and treatment in emergency medical settings. Its history serves as a stark reminder of the transition in pharmacology from natural, potent, but often dangerous compounds to modern, targeted, and safer synthetic drugs.

## Treatment and Management of Toxicity

The management of strychnine poisoning is centered entirely on aggressive supportive care and pharmacological control of the life-threatening convulsions, as there is no specific antidote that reverses the binding of strychnine to the glycine receptor. The overriding priority in the emergency room is the immediate control of muscle spasms to prevent asphyxiation, hyperthermia, and exhaustion.

The standard approach involves heavy sedation using drugs that enhance the activity of the other major inhibitory neurotransmitter in the brain, **gamma-aminobutyric acid (GABA)**. The drugs of choice are high doses of benzodiazepines (such as diazepam or lorazepam), which potentiate GABAergic inhibition, helping to dampen the uncontrolled excitatory firing caused by the lack of glycine inhibition. If benzodiazepines alone are insufficient to control the seizures, barbiturates may be utilized.

A critical component of treatment is respiratory support. Since the convulsions often paralyze the respiratory muscles, mechanical ventilation is frequently required.

**Seizure Control:** Administration of intravenous benzodiazepines to counteract hyperexcitation.

**Airway Management:** Endotracheal intubation and mechanical ventilation to manage respiratory failure caused by tetany.

**Decontamination:** If the patient presents within a very short window after oral ingestion (typically less than one hour) and the airway is protected, activated charcoal may be administered to reduce further absorption.

**Supportive Care:** Monitoring and correction of metabolic acidosis, hyperthermia, and management of rhabdomyolysis and renal failure resulting from severe, sustained muscle contraction.

## Psychological and Behavioral Effects

While the primary effects of strychnine are physiological, the psychological and behavioral consequences, both during the acute phase and long-term, are profound. During the acute intoxication, the maintenance of consciousness throughout the agonizing tetanic convulsions induces a state of extreme psychological terror and panic. The patient experiences unimaginable pain and the sensation of suffocation while being completely cognizant of their fate and their lack of physical control. This unique combination of preserved awareness and systemic failure results in acute psychological distress that is highly traumatic.

The behavioral component is inextricably linked to the neurophysiological effect of strychnine on the sensory system. The heightened sensory perception (hyperesthesia) means that the patient becomes hypersensitive to external stimuli.

**Auditory Triggers:** Even minor sounds, such as footsteps or the closing of a door, can trigger a full-body seizure.

**Visual Triggers:** Sudden changes in light intensity or movement in the peripheral vision can initiate spasms.

**Tactile Triggers:** The slightest touch on the skin or movement of the bedclothes can induce severe tetany.

These factors necessitate placing the patient in an extremely quiet, darkened, and carefully controlled environment during treatment to minimize triggers. For survivors of strychnine poisoning, the psychological sequelae can be long-lasting. The memory of the conscious experience of near-fatal, agonizing physical torture often leads to symptoms consistent with **Post-Traumatic Stress Disorder (PTSD)**, requiring specialized psychological intervention long after the physical toxicity has been resolved. The behavioral fear and anxiety associated with sudden noises or physical touch may persist as conditioned responses to the acute trauma.