College of pharmacy

3rd year stage, pharmacology lecture.

Cholinergic Antagonists

The cholinergic antagonists (also called cholinergic blockers, parasympatholytics or anticholinergic drugs) bind to cholinoceptors, but they do not trigger the usual receptor-mediated intracellular effects. The most useful of these agents selectively block muscarinic synapses of the parasympathetic nerves. The effects of parasympathetic innervation are thus interrupted, and the actions of sympathetic stimulation are left unopposed.

A second group of drugs, the ganglionic blockers, show a preference for the nicotinic receptors of the sympathetic and parasympathetic ganglia. Clinically, they are the least important of the anticholinergic drugs.

A third family of compounds, the neuromuscular blocking agents, interfere with transmission of efferent impulses to skeletal muscles. These agent are used as adjuvants in anesthesia during surgery.

Antimuscarinic Agents

Commonly known as antimuscarinics, these agents (for example, **atropine and scopolamine**) block muscarinic receptors , causing inhibition of all muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating salivary and sweat glands. In contrast to the cholinergic agonists, which have limited usefulness therapeutically, the cholinergic blockers are beneficial in a variety of clinical situations. Because they do not block nicotinic receptors, the antimuscarinic drugs have little or no action at skeletal neuromuscular junctions or autonomic ganglia. [Note: A number of antihistaminic and antidepressant drugs also have antimuscarinic activity.]

*Atropine

Atropine , a tertiary amine belladonna alkaloid, has a high affinity for muscarinic receptors, where it binds competitively, preventing acetylcholine from binding to those sites . Atropine acts both centrally and peripherally. Its general actions last about 4 hours except when placed topically in the eye, where the action may last for days.

Actions:

Eye: Atropine blocks all cholinergic activity on the eye, resulting in persistent mydriasis (dilation of the pupil, unresponsiveness to light, and cycloplegia (inability to focus for near vision). In patients with narrow-angle glaucoma, intraocular pressure may rise dangerously. Shorter-acting agents, such as the antimuscarinic tropicamide, or an α-adrenergic drug, like phenylephrine, are generally favored for producing mydriasis in ophthalmic examinations.

Gastrointestinal (GI): Atropine can be used as an antispasmodic to reduce activity of the GI tract. Atropine and scopolamine are probably the most potent drugs available that produce this effect. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, the drug is not effective in promoting healing of peptic ulcer. [Note: Pirenzepine , an M_1-muscarinic antagonist, does reduce gastric acid secretion at doses that do not antagonize other systems.]

Urinary system: Atropine is also employed to reduce hypermotility states of the urinary bladder. It is still occasionally used in enuresis (involuntary voiding of urine) among children, but α-adrenergic agonists with fewer side effects may be more effective.

Cardiovascular: Atropine produces divergent effects on the cardiovascular system, depending on the dose. At low doses, the predominant effect is a decreased cardiac rate (bradycardia). Originally thought to be due to central activation of vagal efferent outflow, the effect is now known to result from blockade of the M_1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased acetylcholine release. With higher doses of atropine, the M_2 receptors on the sinoatrial node are blocked, and the cardiac rate increases modestly. This generally requires at least 1 mg of atropine, which is a higher dose than ordinarily given. Arterial blood pressure is unaffected, but at toxic levels, atropine will dilate the cutaneous vasculature.

Secretions: Atropine blocks the salivary glands, producing a drying effect on the oral mucous membranes (xerostomia). The salivary glands are exquisitely sensitive to atropine. Sweat and lacrimal glands are also affected. [Note: Inhibition of secretions by sweat glands can cause elevated body temperature.]

Therapeutic uses:
Ophthalmic: In the eye, topical atropine exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye. [Note: Phenylephrine or similar α-adrenergic drugs are preferred for pupillary dilation if cycloplegia is not required. Shorter-acting antimuscarinics (cyclopentolante and tropicamide) have largely replaced atropine due to prolonged mydriasis observed with atropine (7-14 days versus 6-24 hours with other agents). Atropine may induce an acute attack of eye pain due to sudden increases in eye pressure in individuals with narrow-angle glaucoma.

Antispasmodic: Atropine is used as an antispasmodic agent to relax the GI tract and bladder.

Antidote for cholinergic agonists: Atropine is used for the treatment of overdoses of cholinesterase inhibitor insecticides and some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases). Massive doses of the antagonist may be required over a long period of time to counteract the poisons. The ability of atropine to enter the central nervous system (CNS) is of particular importance. The drug also blocks the effects of excess acetylcholine resulting from acetylcholinesterase inhibitors, such as physostigmine.

Antisecretory: The drug is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.

Pharmacokinetics: Atropine is readily absorbed, partially metabolized by the liver, and eliminated primarily in the urine. It has a half-life of about 4 hours.

Adverse effects: Depending on the dose, atropine may cause dry mouth, blurred vision, tachycardia, and constipation.

Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death.

Low doses of cholinesterase inhibitors such as physostigmine may be used to overcome atropine toxicity. In older individuals, the use of atropine to induce mydriasis and cycloplegia is considered to be too risky, because it may exacerbate an attack of glaucoma in someone with a latent condition. In other older individuals, atropine may induce urinary retention that is troublesome. Children are

sensitive to effects of atropine-in particular, the rapid increases in body temperature that it may elicit. This may be dangerous in children.

*Scopolamine

Scopolamine, another tertiary amine belladonna alkaloid, produces peripheral effects similar to those of atropine. However, scopolamine has greater action on the CNS (unlike with atropine, CNS effects are observed at therapeutic doses) and a longer duration of action in comparison to those of atropine. It has some special actions as indicated below.

Actions: Scopolamine is one of the most effective anti-motion sickness drugs available. Scopolamine also has the unusual effect of blocking short-term memory. In contrast to atropine, scopolamine produces sedation, but at higher doses it can produce excitement instead. Scopolamine may produce euphoria and is subject to abuse.

Therapeutic uses: Although similar to atropine, therapeutic use of scopolamine is limited to prevention of motion sickness (for which it is particularly effective) and to blocking short-term memory. [Note: As with all such drugs used for motion sickness, it is much more effective prophylactically than for treating motion sickness once it occurs. The amnesic action of scopolamine makes it an important adjunct drug in anesthetic procedures.]

*Ipratropium

Inhaled ipratropium , a quaternary derivative of atropine, is useful in treating asthma in patients who are unable to take adrenergic agonists. Ipratropium is also beneficial in the management of chronic obstructive pulmonary disease. It is

inhaled for these conditions. Because of its positive charge, it does not enter the systemic circulation or the CNS, isolating its effects to the pulmonary system.

*Tropicamide and cyclopentolate

These agents are used as ophthalmic solutions for similar conditions as atropine (mydriasis and cyclopegia). Their duration of action is shorter than that of atropine; tropicamide produces mydriasis for 6 hours and cyclopentolate for 24 hours.

Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium chloride

These synthetic atropine-like drugs are used to treat overactive bladder.
By blocking muscarinic receptors in the bladder, intravesical pressure
is lowered, bladder capacity is increased, and the frequency of
bladder contractions is reduced. Side effects include dry mouth, constipation,
and blurred vision, which limit tolerability of these agents if
used continually. Oxybutynin is available as a transdermal
system (topical patch), which is better tolerated because it
causes less dry mouth than oral formulations. The overall efficacies of
these antimuscarinic drugs are similar.

Ganglionic Blockers

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous

system at the nicotinic receptor. Except for nicotine, the other drugs mentioned in this category are nondepolarizing, competitive antagonists. The responses observed are complex and unpredictable, making it impossible to achieve selective actions. Therefore, ganglionic blockade is rarely used therapeutically. However, ganglionic blockers often serve as tools in experimental pharmacology.

* **Nicotine**

A component of cigarette smoke, nicotine is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health. [Note: Nicotine is available as patches, lozenges, gums, and other forms. Patches are available for application to the skin. The drug is absorbed and is effective in reducing the craving for nicotine in people who wish to stop smoking.] Depending on the dose, nicotine depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia. The stimulatory effects are complex due to effects on both sympathetic and parasympathetic ganglia. The effects include increased blood pressure and cardiac rate (due to release of transmitter from adrenergic terminals and from the adrenal medulla) and increased peristalsis and secretions. At higher doses, the blood pressure falls because of ganglionic blockade, and activity both in the GI tract and bladder musculature ceases.

* **Mecamylamine**

Mecamylamine produces a competitive nicotinic blockade of the ganglia. The duration of action is about 10 hours after a single administration. The uptake of the drug via oral absorption is good, in contrast to that of **trimethaphan**. As with trimethaphan, it is primarily used to lower blood pressure in emergency situations.

Neuromuscular Blocking Drugs

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular end plate of skeletal muscle . These neuromuscular blockers are structural analogs of acetylcholine, and they act either as antagonists (nondepolarizing type) or agonists (depolarizing type) at the receptors on the end plate of the neuromuscular junction. Neuromuscular blockers are clinically useful during surgery for producing complete muscle relaxation, without having to employ higher anesthetic doses to achieve comparable muscular relaxation. Agents are also useful in facilitating intubation as well.

A second group of muscle relaxants, the central muscle relaxants, are used to control spastic muscle tone. These drugs include diazepam, which binds at γ-aminobutyric acid (GABA) receptors; dantrolene, which acts directly on muscles by interfering with the release of calcium from the sarcoplasmic reticulum; and baclofen, which probably acts at GABA receptors in the CNS.

A. Nondepolarizing (competitive) blockers

The first drug that was found to be capable of blocking the skeletal neuromuscular junction was curare, which the native hunters of the Amazon in South America used to paralyze game. The drug tubocurarine was ultimately purified and introduced into clinical practice in the early 1940s. Although tubocurarine is considered to be the prototype agent in this class, it has been largely replaced by other agents due to side effects. The neuromuscular blocking agents have significantly increased the safety of anesthesia, because less anesthetic is required to produce muscle relaxation, allowing patients to recover quickly and completely after surgery. Note: Higher doses of anesthesia may produce respiratory paralysis and cardiac depression, increasing recovery time after surgery.

Mechanism of action:

At low doses: Nondepolarizing neuromuscular blocking drugs interact with the nicotinic receptors to prevent the binding of acetylcholine . These drugs thus prevent depolarization of the muscle cell membrane and inhibit muscular contraction. Because these agents compete with acetylcholine at the receptor without stimulating the receptor, they are called competitive blockers. Their action can be overcome by increasing the concentration of acetylcholine in the synaptic gap-for example, by administration of cholinesterase inhibitors, such as neostigmine, pyridostigmine, or edrophonium. Anesthesiologists often employ this strategy to shorten the duration of the neuromuscular blockade.

At high doses: Nondepolarizing blockers can block the ion channels of the end plate. This leads to further weakening of neuromuscular transmission, and it reduces the ability of acetylcholinesterase inhibitors to reverse the actions of nondepolarizing muscle relaxants.

Actions: Not all muscles are equally sensitive to blockade by competitive blockers. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers. Thereafter, the limbs, neck, and trunk muscles are paralyzed. Then the intercostal muscles are affected, and lastly, the diaphragm muscles are paralyzed. Those agents (for example, **tubocurarine, mivacurium,** and **atracurium**), which release histamine, can produce a fall in blood pressure, flushing, and bronchoconstriction.

Therapeutic uses: These blockers are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscle. These agents are also used to facilitate intubation as well as during orthopedic surgery.

Pharmacokinetics: All neuromuscular blocking agents are injected intravenously, because their uptake via oral absorption is minimal. These agents possess two or more quaternary amines in their bulky ring structure, making them orally ineffective. They penetrate membranes very poorly and do not enter cells or cross the blood-brain barrier. Many of the drugs are not metabolized; their actions are terminated by redistribution. For example, **tubocurarine, pancuronium, mivacurium, metocurine,** and **doxacurium** are excreted in the urine unchanged. **Atracurium** is degraded spontaneously in the plasma and by ester hydrolysis. [Note: Atracurium has been replaced by its isomer, **cisatracurium**. Atracurium releases histamine and is metabolized to laudanosine, which can provoke seizures. Cisatracurium, which has the same pharmacokinetic properties as atracurium, is less likely to have these effects.] The aminosteroid drugs (**vecuronium and rocuronium**) are deacetylated in the liver, and their clearance may be prolonged in patients with hepatic disease. These drugs are also excreted unchanged in the bile. The choice of an agent will depend on how quickly muscle relaxation is needed and on the duration of the muscle relaxation.

Adverse effects: In general, agents are safe with minimal side effects.

Drug interactions:

Cholinesterase inhibitors: Drugs such as neostigmine, physostigmine, pyridostigmine, and edrophonium can overcome the action of nondepolarizing neuromuscular blockers, but with increased dosage, cholinesterase inhibitors can cause a depolarizing block as a result of elevated acetylcholine concentrations at the end-plate membrane. If the neuromuscular blocker has entered the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade.

Halogenated hydrocarbon anesthetics: Drugs such as halothane act to enhance neuromuscular blockade by exerting a stabilizing action at the neuromuscular junction. These agents sensitize the neuromusclular junction to the effects of neuromuscular blockers.

Aminoglycoside antibiotics: Drugs such as gentamicin or tobramycin inhibit acetylcholine release from cholinergic nerves by competing with calcium ions. They synergize with tubocurarine and other competitive blockers, enhancing the blockade.

Calcium-channel blockers: These agents may increase the neuromuscular block of tubocurarine and other competitive blockers as well as depolarizing blockers.

B. Depolarizing agents

Mechanism of action: The depolarizing neuromuscular blocking drug **succinylcholine** attaches to the nicotinic receptor and acts like acetylcholine to depolarize the junction. Unlike acetylcholine, which is instantly destroyed by acetylcholinesterase, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and providing a constant stimulation of the receptor. [Note: The duration of action of succinylcholine is dependent on diffusion from the motor end plate and hydrolysis by plasma cholinesterase.] The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptors, which results in depolarization of the receptor (Phase I). This leads to a transient twitching of the muscle (fasciculations). Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or

is blocked. This causes a resistance to depolarization (Phase II) and a flaccid paralysis.

Actions: Succinylcholine initially produces short-lasting muscle fasciculations, followed within a few minutes by paralysis. The drug does not produce a ganglionic block except at high doses, but it does have weak histamine-releasing action. Normally, the duration of action of succinylcholine is extremely short, because this drug is rapidly broken down by plasma cholinesterase. However, succinylcholine that gets to the neuromusclular junction is not metabolized by acetylcholinesterase, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes). [Note: Genetic variants in which plasma cholinesterase levels are low or absent leads to prolonged neuromuscular paralysis.]

Therapeutic uses: Because of its rapid onset and short duration of action, succinylcholine is useful when rapid endotracheal intubation is required during the induction of anesthesia (a rapid action is essential if aspiration of gastric contents is to be avoided during intubation

Pharmacokinetics: Succinylcholine is injected intravenously. Its brief duration of action (several minutes) results from redistribution and rapid hydrolysis by plasma cholinesterase. It therefore is usually given by continuous infusion.

Adverse effects:
Hyperthermia: When halothane is used as an anesthetic, administration of succinylcholine has occasionally caused malignant hyperthermia (with muscular rigidity and hyperpyrexia) in genetically susceptible people . This is treated by rapidly cooling the patient and by administration of dantrolene, which blocks

release of Ca^{2+} from the sarcoplasmic reticulum of muscle cells, thus reducing heat production and relaxing muscle tone.

Apnea: Administration of succinylcholine to a patient who is genetically deficient in plasma cholinesterase or has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm.