

Cholinergics and Anti-cholinergics

PHL-358-PHARMACOLOGY AND THERAPEUTICS-I

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Cholinergic Drugs

- Parasympathomimetics or cholinomimetics
- Stimulate parasympathetic nervous system in same manner as does acetylcholine
- May stimulate cholinergic receptors directly or slow acetylcholine metabolism at synapses (affect the enzyme acetylcholinesterase)

Cholinergic Drugs

- Useful in treating Alzheimer's Disease, Myasthenia gravis and to tx atony of the smooth muscle of the GI system or urinary system

Cholinergic Drugs

- Normal neuromuscular function, acetylcholine binds to nicotinic receptors on cell membranes of muscle cells to cause contraction
- *Myasthenia gravis* autoantibodies presumably destroy nicotinic receptors; thus, acetylcholine less able to stimulate muscle contraction. Results in severe muscle weakness.

Cholinergic Drugs

- Acetylcholine important neurotransmitter affecting cognitive functioning, memory storage and retrieval
- In *Alzheimer's disease (AD)*, abnormalities of the cholinergic, serotonergic, noradrenergic, and glutaminergic neurotransmission systems
- In cholinergic system, patient with AD found to have loss of neurons that secrete acetylcholine

Cholinergic Drugs—GI effects

- Acetylcholine stimulates cholinergic receptors in the gut to promote normal secretory and motor activity
- Cholinergic activity in the gut will increase peristalsis and facilitates movement of flatus and feces
- The secretory functions of the salivary and gastric glands also stimulated

Cholinergic Drugs—GU effects

- Acetylcholine stimulates cholinergic receptors in the urinary system to promote urination
- Results in contraction of the detrusor muscle and relaxation of the urinary sphincter to facilitate emptying of the urinary bladder

Acetylcholine

- One of the main neurotransmitters of the ANS is acetylcholine
- Acetylcholine is released at preganglionic fibers of both the sympathetic and parasympathetic nervous system
- Also released from postganglionic sympathetic neurons that innervate the sweat glands and from motor neurons that innervate the skeletal muscles

Acetylcholine

- Sympathetic and parasympathetic divisions of the ANS are antagonistic to each other
- When acetylcholine acts on body cells that respond to parasympathetic stimulation, it interacts with two types of cholinergic receptors: *nicotinic* and *muscarinic*

Acetylcholine

- *Nicotinic* receptors are located in motor nerves and skeletal muscle
- Stimulation results in muscle contraction

Acetylcholine

- *Muscarinic* receptors are located in most internal organs. This includes the cardiovascular, respiratory, gastrointestinal, and genitourinary. Stimulation of the muscarinic receptors may result in either excitation or inhibition, depending on the organ involved.

Mechanisms of Action—

Direct Acting

Cholinergics

- *Direct acting cholinergics* are lipid insoluble
- Do not readily enter the CNS so effects are peripheral
- Resistant to metabolism by acetylcholinesterase
- Effects are longer acting than with acetylcholine

Direct Acting Cholinergic Drugs cont.

- Widespread systemic effects when they combine with muscarinic receptors in cardiac muscle, smooth muscle, exocrine glands and the eye

Direct-acting Cholinergic Drugs Effects

- Decreased heart rate, vasodilation, variable BP effects
- Increased tone and contractility in GI smooth muscle, relaxation of sphincters, increased salivary gland and GI secretions
- Increased tone and contractility of smooth muscle in urinary bladder and relaxation of the sphincter

Direct Acting Cholinergic Drugs cont.

- Increased tone and contractility of bronchial smooth muscle
- Increased respiratory secretions
- Constriction of pupils (miosis) and contraction of ciliary muscle

Direct Acting Cholinergics

- Bethanecol (Urecholine)—given orally. Not given IM or IV.
- Used to treat urinary retention due to bladder atony and for postoperative abdominal distention due to paralytic ileus

Indirect-Acting Cholinergic Drugs

- Action is by decreasing the inactivation of acetylcholine in the synapse by the enzyme acetylcholinesterase
- Accumulation of acetylcholine then occurs which enhances the activation of the nicotinic and muscarinic receptors

Indirect-Acting or Anticholinesterase Drugs cont.

- Anticholinesterase drugs are either reversible or irreversible inhibitors of acetylcholinesterase
- Reversible agents are such drugs as: edrophonium (Tensilon). Used to diagnose myasthenia gravis and for reversal of non-depolarizing neuromuscular blockers

Indirect-acting agents cont.

- Neostigmine (Prostigmine)—prototype anticholinesterase agent. Used for long-term tx of myasthenia gravis and as an antidote for tubocurarine and other non-depolarizing agents in surgery.
- Poorly absorbed orally so requires larger doses than when given parenterally.
- Can develop resistance to its action over time

Indirect Acting Agents

- Pyridostigmine (Mestinon) is the maintenance drug of choice for patients with Myasthenia gravis. Slow release.

Indirect Acting— Reversible cont.

- Physostigmine (Antilirium)—only anticholinesterase capable of crossing the blood brain barrier. Is more lipid soluble. Used as an antidote for overdose of anticholinergics such as: atropine, antihistamines, TCA, phenothiazines. May also be used in tx of glaucoma.

Indirect Acting Agents used to treat Alzheimer's disease

- Donepezil (Aricept)—said to delay progression of the disease by up to 55 weeks. Does not cause liver toxicity.
- Galantamine (Reminyl)—newest kid on the block
- Rivastigmine (Exelon) long acting. Twice a day dosing.
- Tacrine (Cognex)—hepatotoxic. Elevated liver enzymes usu. Within 18 wks. > in women.

Specific Conditions

- Distinction between cholinergic crisis and a myasthenic crisis
- Difficult to ascertain as both are characterized by respiratory difficulty or failure
- Need to distinguish as require opposite treatment measures

Specific Conditions—Cholinergic vs. Myasthenic Crisis

- Myasthenic crisis requires more anticholinesterase drug whereas cholinergic crisis requires discontinuation of the anticholinesterase drugs
- Diagnosis can be made by evaluating patient response to their medication (s/s one hour after medication often is cholinergic crisis, s/s 3 or more hours after medication often is myasthenic crisis)

Myasthenia Gravis

- If s/s not clearly indicative of the problem, may have to intubate patient, inject dose of IV edrophonium. If dramatic improvement in breathing, diagnosis is myasthenic crisis. If edrophonium makes s/s worse, the diagnosis is cholinergic crisis. *Patient must be intubated and assisted with mechanical ventilation to perform this test.*

Toxicity of Cholinergic Drugs

- Atropine is the specific antidote to cholinergic agents
- Atropine reverses only the muscarinic effects of cholinergic drugs; heart, smooth muscle, and glands.
- Atropine cannot reverse the nicotinic effects of skeletal muscle weakness or paralysis due to overdose of indirect cholinergic drugs.

Toxicity of Irreversible Anticholinesterase Agents

- These agents are lipid soluble
- Can enter the body by the eye, skin, respiratory system and GI tract.
- Case in point, organophosphate insecticides (malathion, parathion) or nerve gases (sarin, tabun, soman)
- These agents cause excessive cholinergic stimulation (muscarinic) and neuromuscular blockade

Anticholinergics

- Also called cholinergic blocking agents or parasympatholytics
- Again, focus is on the parasympathetic nervous system
- Parasympathetic system acts as a resting and reparative function
- Functions include digestion, excretion, cardiac deceleration, anabolism and near vision

Parasympathetic Nervous System

- 75% of all parasympathetic nerve fibers are in the vagus nerves
- These nerves supply the thoracic and abdominal organs, which innervate the heart, lungs, esophagus, stomach, small intestine, proximal half of the colon, liver , gallbladder, pancreas and upper portions of the ureters

Parasympathetic Nervous System

- Also supply the muscles of the eyes, lacrimal, nasal, submaxillary, and parotid glands; descending colon and rectum; lower portions of the ureters, bladder and genitalia
- All are regulated by acetylcholine—exerts excitatory effects at nerve synapses and neuromuscular junctions; and inhibitory effects at peripheral sites e.g. heart

Anticholinergics

- Most anticholinergic drugs interact with the muscarinic receptors in the brain, secretory glands, heart, and smooth muscle
- A few can also affect the nicotinic receptors. Glycopyrrolate (Robinul) is an example

Mechanism of Action and Effects

- Act by occupying receptor sites at parasympathetic nerve endings, thereby leaving fewer receptor sites free to respond to acetylcholine
- Distribution of receptors is broad so effects of anticholinergics will be diffuse.

Effects on Body Tissues

1. CNS stimulation followed by depression, can result in coma and death (atropine, antiparkinson's)
2. Decreased cardiovascular response to vagal stimulation resulting in tachycardia. Increases vagal tone. Ex. Atropine.
3. Bronchodilation and decreased respiratory tract secretions.

Effects on Body Tissues

- Antispasmodics of GI tract due to decreased tone and motility.
- Mydriasis and cyclopegia. Normally do not increase IOP but caution as can precipitate acute glaucoma.
- Can cause decreased oral secretions, decreased sweating, relaxation of urinary bladder

Indications for Use

- Uses include GI, GU, ophthalmic and respiratory disorders, bradycardia and in Parkinson's disease.
- Used preoperatively

Use In GI Disorders

- Helpful in treating irritable colon or colitis
- Useful in gastritis, pylorospasm and ulcerative colitis as they slow motility

Use in GU disorders

- Antispasmodic effects seen in overactive bladder and in urinary incontinence

Ophthalmology

- Mydriatic and cycloplegia for examinations and surgery

Respiratory

- In bronchospasm whether related to asthma or COPD
- Atrovent very useful for its bronchodilating effects

Cardiology

- Atropine is used to increase heart rate in symptomatic bradycardias and higher blocks

Parkinson's Disease

- Useful in those with minimal side effects
- Those who cannot take Levodopa
- Helpful in decreasing salivation, spasticity and tremors

Preop

- Help prevent vagal stimulation and potential bradycardia
- Reduce respiratory secretions as well

Contraindications

- BPH
- Myasthenia gravis
- Hyperthyroidism
- Glaucoma
- Tachydysrhythmias
- Not in situations whereby delaying of gastric emptying is a concern

Individual Anticholinergic Drugs

- Atropine—prototype. Antidote. Belladonna alkaloid.
- Ipratropium (Atrovent). Useful in rhinorrhea. Also excellent bronchodilator.
- Scopolamine, similar to atropine. Depresses CNS and causes amnesia, drowsiness, euphoria, relaxation and sleep. Also good for motion sickness. Given parenterally, orally and transdermally.

Centrally Acting Anticholinergics

- Benztropine (Cogentin)—temporary use in Parkinson’s disease. Useful for dystonic reactions caused by antipsychotics.
- Trihexyphenidyl (Trihexy)—also used for txing EPS by some antipsychotics. Contraindicated in glaucoma.

Urinary Antispasmodics

- Flavoxate (Urispas)—relieves dysuria, urgency, frequency, and pain with GU infections
- Oxybutynin (Ditropan) has direct antispasmodic effects on smooth muscle and anticholinergic effects. Decreases frequency of voiding.
- Tolterodine (Detrol) is competitive, antimuscuranic anticholinergic that inhibits contraction. More selective for this area than elsewhere in the body.

Toxicity of Anticholinergics

- Anticholinergic overdose syndrome is characterized by: Hyperthermia, delirium, dry mouth, tachycardia, ileus, urinary retention. Seizures, coma and respiratory arrest may occur.
- Tx—activated charcoal, Atropine, cooling agents (ice bags, cooling blankets, tepid baths).