Drugs acting on the parasympathetic nervous system

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Reference: Katzung BG and Trevor AG.Basic and Clinical Pharmacology, McGraw-Hill, 13th edition, 2015

Learning objectives:

- Explain mechanism of action of parasympathomimetics and cholinergic antagonists.

- Describe organ system effects of parasympathomimetics and cholinergic antagonists.

- Name clinical indications of parasympathomimetics and cholinergic antagonists.

- Describe adverse effects of parasympathomimetics and cholinergic antagonists.

Drugs acting on the parasympathetic nervous system are divided into two main groups including cholinomimetic drugs and cholinergic antagonists. In the first part of this handout, the pharmacology of cholinomimetic drugs will be discussed. Cholinomimietic drugs are those that mimic the activity of parasympathetic nervous system, and are subdivided as direct acting drugs such as nicotinic and muscarinic agonists, and cholinesterase inhibitors.

Nicotinic agonists

Mechanism of action and organ system effects

Nicotinic agonists bind to and activate nicotinic receptors. The effects of these drugs occur mainly at two sites. At autonomic (sympathetic and parasympathetic) ganglia, these drugs cause excitation and depolarization of postganglionic nerves. At neuromuscular junction, they cause depolarization, excitation, and contraction of skeletal muscle. Prolonged agonist occupancy of the nicotinic receptor abolishes the effector response; that is, the postganglionic neuron stops firing (ganglionic effect), and the skeletal muscle cell relaxes (neuromuscular end plate effect). Furthermore, the continued presence of the nicotinic agonist prevents electrical recovery of the postjunctional membrane. Thus, a state of "depolarizing blockade" occurs initially during persistent agonist occupancy of the receptor. Continued agonist occupancy is associated with return of membrane voltage to the resting level. The receptor becomes desensitized to agonist, and this state is refractory to reversal by other agonists.

Muscarinic agonists

Mechanism of action Muscarinic agonists bind to and activate muscarinic receptors (M1, M2 and M3). These drugs act on a number of organ through the body, and such effects are predicted based on the function of parasympathetic nervous system in those organs.

Organ system effects

1. **Eye**- In the eye, muscarinic agonists have two effects, which are mediated by the activation of M3 receptors. They cause circular muscle contraction, and miosis. They also contract ciliary muscle, and cause accommodation. As a result, the iris is pulled away from the angle of the anterior chamber, and the trabecular meshwork at the base of the ciliary muscle is opened. Both effects facilitate aqueous humor outflow into the canal of Schlemm, which drains the anterior chamber.

2. ***Cardiovascular system***- Muscarinic agonists produce bradycardia and decrease trioventricular node conduction velocity, and reduce atrial contractility. Parasympathetic innervation of the ventricles is much less extensive than that of the atria; activation of ventricular muscarinic receptors causes much less physiologic effect than that seen in atria. Muscarinic agonists also cause peripheral vasodilation and reduction of blood pressure, which is believed to be medicated by the release of nitric oxide from endothelial cells. The cardiac effects are mediated by M2 receptors.

3. ***Respiratory system***—Muscarinic stimulants contract the smooth muscle of the bronchial tree. In addition, the glands of the tracheobronchial mucosa are stimulated to secrete. The respiratory effects of muscarinic agonists are medicated by M3 receptors.

5. ***Urinary tract***—Muscarinic agonists stimulate the detrusor muscle and relax the trigone and sphincter muscles of the bladder, thus promoting voiding. The effects of muscarinic agonists on urinary tract are medicated by M3 receptors.

6. ***Miscellaneous secretory glands***—Muscarinic agonists stimulate secretion by lacrimal, thermoregulatory sweat, and nasopharyngeal glands by activating M3 receptors.

4. ***Gastrointestinal tract—***Administration of muscarinic agonists, as in parasympathetic nervous system stimulation, increases the secretory and motor activity of the gut. The salivary and gastric glands are strongly stimulated; the pancreas and small intestinal glands are stimulated less so. Peristaltic activity is increased throughout the gut, and most sphincters are relaxed. These effects are mediated by M3 receptors.

Cholinestrase inhibitors

Mechanism of action

These drugs inhibit acetylcholinestrase to hydrolyze acetylcholine to acetic acid and choline. Thus these drugs amplify the effects of aceylcholine at autonomic ganglia, synapse of parasympathetic postganglionic fiber with organ, neuromuscular junctions, synapse of sympathetic postganglionic cholinergic with thermoregulatory sweat glands. Cholinestrase inhibitors are divided into two main types, reversible and irreversible. Reversible inhibitors are further subdivided into noncovalent and covalent enzyme inhibitors.

The mechanism involved in the hydrolysis of Ach explains the biochemical basis of the actions of ChE inhibitors (figure 1). The enzyme has an anionic and a catalytic domain. When ACh binds to ChE, the quaternary nitrogen of ACh binds to the anionic site, positioning the ester group near the catalytic site. The ester moiety undergoes as attack by the serine of the catalytic site, resulting in the cleavage of the ester bond on ACh and hydrolysis of Ach. The acetate group then binds to the serine of the catalytic domain, which results in the acetylation of the enzyme. The acetylated enzyme is rapidly hydrolyzed, the acetate group is liberated. This leads to regeneration of the free enzyme, which can attach another Ach molecule.

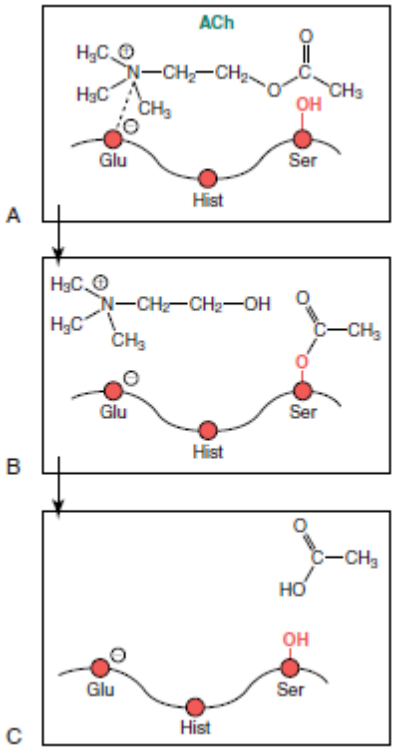

Figure 1. Hydrolysis of acetylcholine (ACh) by acetylcholinesterase (AChE). A major domain of the AChE enzyme contains an amino acid triad consisting of serine (ser), histidine (hist), and glutamate (glu). The (-) denotes the anionic region of the enzyme, and the ser-OH represents the catalytic region. (A) The quarternary (+) nitrogen of the choline portion of the Ach molecule is attracted to the anionic site positioning the ester portion of ACh in close proximity to the catalytic site; (B) the ester bond on ACh is cleaved, the enzyme is acetylated, and choline is released; (C) hydrolysis of the acetylated enzyme rapidly liberates the acetate, and the free enzyme can hydrolyze another ACh molecule.

Noncovalent inhibitors, such as edrophonium, bind noncovalently and reversibly to the anionic domain of AChE. The duration of action is determined in part by the way in which the inhibitor binds. The duration of this group of drugs is short (approximately 10 minutes for edrophonium). Tacrine and donepezil are also noncovalent ChE inhibitors used to treat Alzheimer's disease; they have higher affinities and partition into lipids, giving longer durations of action.

Covalent reversible ChE inhibitors, such as physostigmine and neostigmine, are sometimes referred to as carbamate inhibitors and are carbamic acid ester derivatives. The quarternary (+) nitrogen of carbamate inhibitors is attracted to the anionic site positioning the ester portion of the

molecule in close proximity to the catalytic site (figure 2). The ester bond on neostigmine is cleaved, the enzyme is carbamylated, which prevents the enzyme from interacting with ACh, and the remainder of the neostigmine molecule is released. Then, hydrolysis of carbamylated enzyme occurs slowly, causing reversible inhibition of the enzyme. Unlike the acetylated enzyme, which is deacetylated within seconds, the carbamylated enzyme takes 3 to 4 hours to decarbamylate, contributing to the moderate duration of action of these compounds in patients

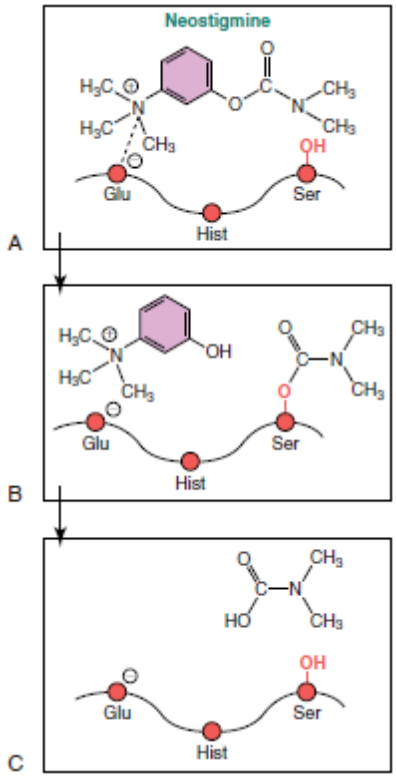

Figure 2. The interaction of a reversible acetylcholinesterase (AChE) antagonist, neostigmine, with the AChE enzyme. A major domain of AChE enzyme contains an amino acid triad that consists of serine (ser), histidine (hist), and glutamate (glu). The (-) denotes the anionic region of the enzyme, and the ser-OH represents the catalytic region. (A) The quarternary (+) nitrogen of neostigmine is attracted to the anionic site positioning the ester portion of the molecule in close proximity to the catalytic site; (B) the ester bond on neostigmine is cleaved, the enzyme is carbamylated, which prevents the enzyme from interacting with ACh, and the remainder of the neostigmine molecule is released; (C) hydrolysis of carbamylated enzyme occurs slowly, causing reversible inhibition of the enzyme.

Irreversible ChE inhibitors are termed organophosphorus ChE inhibitors. They include the toxic nerve gases sarin, soman, and tabun; the insecticides parathion and malathion; and the therapeutic agents echothiophate and isoflurophate. These compounds phosphorylate the serine in the active site of AChE (figure 3). Unlike acetylated or carbamylated enzyme, the phosphorylated enzyme formed with these compounds is extremely stable. Dephosphorylation usually does not occur, and if it occurs, it takes several hours. After that time, the phosphorylated enzyme undergoes a process termed ‘‘aging,’’ which apparently involves the breaking of one of the oxygen-phosphorus bonds of the inhibitor and further strengthens the phosphorus-enzyme bond.

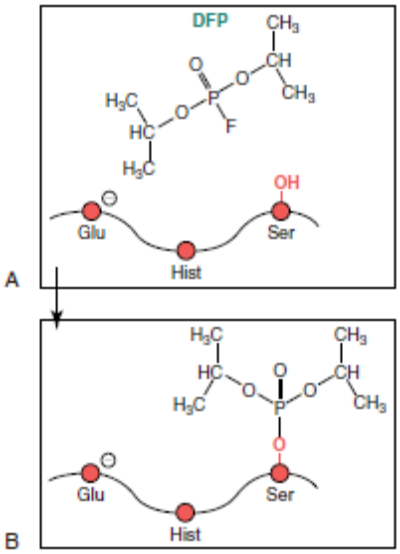

Figure 3. The interaction of an irreversible acetylcholinesterase (AChE) antagonist, isoflurophate (DFP or diisopropyl flurophosphate), with the AChE enzyme. A major domain of AChE enzyme contains an amino acid triad that consists of serine (ser), histidine (hist), and glutamate (glu). The (-) denotes the anionic region of the enzyme, and the ser-OH represents the catalytic region. (A) The phosphate portion of DFP aligns with the catalytic site of the enzyme; (B) the enzyme is phosphorylated, representing a very stable moiety. Enzyme inhibition is considered irreversible; dephosphorylation, if it occurs, takes hours. After that time the phosphorylated enzyme undergoes a process termed ‘‘aging,’’ which involves hydrolysis of one of the isopropyl groups of the inhibitor, rendering the complex unable to dissociate. Note: An oxime such as 2-PAM, if administered before aging occurs, can bind to and release the phosphate moiety attached to the enzyme; this process reverses the enzyme inhibition.

The rate of aging varies with the particular organophosphate compound. For example, aging occurs within 10 minutes with the chemical warfare agent soman, but as much as 48 hours later with the drug VX (nerve agent). Enzyme reactivation in clinical practice is achieved with oximes such as pralidoxime (2-PAM), which if administered before aging occurs, can bind to and release the phosphate moiety attached to the enzyme; this process reverses the enzyme inhibition.

Organ System Effects

1. ***Central nervous system*-** In low concentrations, the lipid-soluble cholinesterase inhibitors cause a subjective alerting response. In higher concentrations, they cause generalized convulsions, which may be followed by coma and respiratory arrest.

2. ***Eye, respiratory tract, gastrointestinal tract, urinary tract, and secretory glands*** - The effects of the cholinesterase inhibitors on these organ systems, all of which are well innervated by the parasympathetic nervous system, are qualitatively quite similar to the effects of the direct-acting cholinomimetics.

3. *Cardiovascular system*-The cholinesterase inhibitors can increase activity in both sympathetic and parasympathetic ganglia supplying the heart and at the acetylcholine receptors on neuroeffector cells (cardiac and vascular smooth muscles) that receive cholinergic innervation. In the heart, the effects on the parasympathetic limb predominate. Thus, cholinesterase inhibitors decrease heart rate, AV conduction, contractility, and cardiac output. The fall in cardiac output is attributable to bradycardia, decreased atrial contractility, and some reduction in ventricular contractility. The latter effect occurs as a result of prejunctional inhibition of norepinephrine release as well as inhibition of postjunctional cellular sympathetic effects. At moderate doses, cholinesterase inhibitors cause an increase in systemic vascular resistance and blood pressure

that is initiated at sympathetic ganglia in the case of quaternary nitrogen compounds and also at central sympathetic centers in the case of lipid-soluble agents.

The *net* cardiovascular effects of moderate doses of cholinesterase inhibitors therefore consist of modest bradycardia, a fall in cardiac output, and an increased vascular resistance that results in a rise in blood pressure. At high (toxic) doses of cholinesterase inhibitors, marked bradycardia occurs, cardiac output decreases significantly, and +

.

4. ***Neuromuscular junction*** Low (therapeutic) concentrations moderately prolong and intensify the actions of physiologically released acetylcholine. This increases the strength of contraction, for example, in muscle weakened by myasthenia gravis. At higher concentrations, the accumulation of acetylcholine may result in fibrillation of muscle fibers. With marked inhibition of acetylcholinesterase, depolarizing neuromuscular blockade occurs and that may be followed by a phase of nondepolarizing blockade as seen with succinylcholine. Some quaternary carbamate cholinesterase inhibitors, eg, neostigmine, have an additional *direct* nicotinic agonist effect at the neuromuscular junction.

Clinical uses of cholinomimetics

A. Glaucoma Muscarinic stimulants and cholinesterase inhibitors reduce intraocular pressure by causing contraction of the ciliary body so as to facilitate outflow of aqueous humor and perhaps also by diminishing the rate of its secretion. In the past, glaucoma was treated with either direct agonists (pilocarpine, methacholine, carbachol) or cholinesterase inhibitors (physostigmine, demecarium, echothiophate, isoflurophate). For chronic glaucoma, these drugs have been largely replaced by prostaglandin derivatives and topical β blockers. Acute angle-closure glaucoma is a

medical emergency that is frequently treated initially with drugs but usually requires surgery for permanent correction. Initial therapy often consists of a combination of a direct muscarinic agonist (eg, pilocarpine) and other drugs. Once the intraocular pressure is controlled and the danger of vision loss is diminished, the patient can be prepared for corrective surgery (laser iridotomy).

Postoperative ileus (atony or paralysis of the stomach or bowel following surgical manipulation) and congenital megacolon, urinary retention (postoperative, postpartum, or secondary to spinal cord injury or disease (neurogenic bladder)) are treated with neostigmine.

Myasthenia gravis is an autoimmune disease affecting skeletal muscle neuromuscular junctions. In the disease, antibodies are produced against nicotinic receptor in neuromuscular junction. Frequent findings are ptosis, diplopia, difficulty in speaking and swallowing, and extremity weakness. Severe disease may affect all the muscles, including those necessary for respiration. Cholinesterase inhibitors are extremely valuable as therapy for myasthenia. Edrophonium is sometimes used as a diagnostic test for myasthenia. A 2 mg dose is injected intravenously after baseline muscle strength has been measured. If no reaction occurs after 45 seconds, an additional 8 mg may be injected. If the patient has myasthenia gravis, an improvement in muscle strength that lasts about 5 minutes can usually be observed. Long-term therapy for myasthenia gravis is usually with pyridostigmine; neostigmine is an alternative. The doses are titrated to optimum levels based on changes in muscle strength. These drugs are relatively short-acting, and therefore require frequent dosing. Longer-acting cholinesterase inhibitors such as the organophosphate agents are not used, because the dose requirement in this disease changes too rapidly to permit smooth control of symptoms with long-acting drugs.

Reversal of effects of nondepolarizing neuromuscular relaxants- Neuromuscular blockade is frequently produced as an adjunct to surgical anesthesia, using such as pancuronium and newer agents. After surgery, it is usually desirable to reverse this pharmacologic paralysis promptly. This can be easily accomplished with cholinesterase inhibitors; neostigmine and edrophonium are the drugs of choice. They are given intravenously or intramuscularly for prompt effect.

Antimuscarinic drug intoxication Atropine intoxication is potentially lethal in children and may cause prolonged severe behavioral disturbances and arrhythmias in adults. The tricyclic antidepressants, when taken in overdosage (often with suicidal intent), also cause severe muscarinic blockade. Physostigmine has been used for this application because it enters the central nervous system and reverses the central as well as the peripheral signs of muscarinic blockade. However, as described below, physostigmine itself can produce dangerous central nervous system effects, and such therapy is therefore used only in patients with dangerous elevation of body temperature or very rapid supraventricular tachycardia.

Alzheimer's disease Tacrine was the first drug with anticholinesterase and other cholinomimetic actions used for the treatment of mild to moderate Alzheimer's disease. Tacrine's efficacy is modest, and hepatic toxicity is significant. Donepezil, galantamine, and rivastigmine are newer, more selective acetylcholinesterase inhibitors that appear to have the same modest clinical benefit as tacrine but with less toxicity in treatment of cognitive dysfunction in Alzheimer's patients.

Adverse effects

Direct-acting muscarinic stimulants Adverse effects of muscarinic agonists include nausea, vomiting, diarrhea, urinary urgency, salivation, sweating, cutaneous vasodilation, and bronchial constriction. The effects are all blocked competitively by atropine and its congeners.

Cholinesterase Inhibitors The major source of such intoxications is pesticide use in agriculture and in the home, and chemical warfare agents (soman, sarin, VX). The dominant initial signs are those of muscarinic excess: miosis, salivation, sweating, bronchial constriction, vomiting, and diarrhea. Central nervous system involvement (cognitive disturbances, convulsions, and coma) usually follows rapidly, accompanied by peripheral nicotinic effects, especially depolarizing neuromuscular blockade. Therapy always includes (1) maintenance of vital signs—respiration in particular may be impaired; (2) decontamination to prevent further absorption. This this may require removal of all clothing and washing of the skin in cases of exposure to dusts and sprays; and (3) atropine parenterally in large doses, given as often as required to control signs of muscarinic excess. Therapy often also includes treatment with pralidoxime, and administration of benzodiazepines for seizures.

Preventive therapy for cholinesterase inhibitors used as chemical warfare agents has been developed to protect soldiers and civilians. Personnel are given autoinjection syringes containing a carbamate (pyridostigmine), and atropine. Protection is provided by pyridostigmine, which, by prior binding to the enzyme, impedes binding of organophosphate agents and thereby prevents prolonged inhibition of cholinesterase. The protection is limited to the peripheral nervous system because pyridostigmine does not readily enter the central nervous system. Enzyme inhibition by pyridostigmine dissipates within hours; a duration of time that allows the clearance of organophosphate agent from the body.

Cholinergic antagonists

Cholinergic antagonists are divided into two groups including muscarinic antagonists and nicotinic antagonists.

Muscarinic antagonists They are also called parasympatholytic, because they block the effects of parasympathetic autonomic discharge, and antimuscarinic.

Mechanism of Action Muscarinic antagonists or antimuscarinic drugs competitively (surmountably) block muscarinic receptors, and thereby block muscarinic agonists actions at these receptors.

Organ System Effects

1. ***Central nervous system-*** Those, which can enter CNS (scopolamine), can produce drowsiness and amnesia in sensitive individuals. In toxic doses, scopolamine can cause excitement, agitation, hallucinations, and coma. The tremor of Parkinson's disease is reduced by centrally acting antimuscarinic drugs.

2. ***Eye-***Muscarinic antagonists block the pupillary constriction, and thereby cause mydriasis. The second important ocular effect of antimuscarinic drugs is to weaken contraction of the ciliary muscle, or cycloplegia. A third ocular effect of antimuscarinic drugs is to reduce lacrimal secretion.

3. ***Cardiovascular system*** Antimuscarinic drugs increase heart rate and AV conduction. The ventricles are less affected by antimuscarinic drugs at therapeutic levels because of a lesser degree of vagal control. There is also little effect on blood pressure.

4. ***Respiratory system-*** In normal individuals and patients with airway disease, these drugs cause bronchodilation, and reduce secretion.

5. ***Gastrointestinal tract-*** Antimuscarinic drugs decrease salivary secretion. Gastric secretion is blocked less effectively: the volume and amount of acid, pepsin, and mucin are all reduced, but large doses may be required. Basal secretion is blocked more effectively than that stimulated by

food, nicotine, or alcohol. Gastrointestinal smooth muscle motility is affected from the stomach to the colon. In general, antimuscarinic drugs diminish the tone and propulsive movements; the walls of the viscera are relaxed. Therefore, gastric emptying time is prolonged, and intestinal transit time is lengthened. Diarrhea due to overdosage with parasympathomimetic agents is readily stopped, and even diarrhea caused by nonautonomic agents can usually be temporarily controlled.

6. ***Urinary tract***-The antimuscarinic drugs relax smooth muscle of the bladder wall and slows voiding. This action is useful in the treatment of spasm induced by mild inflammation, surgery, and certain neurologic conditions, but it can precipitate urinary retention in men who have prostatic hyperplasia.

7. ***Sweat glands***-Atropine suppresses thermoregulatory sweating, and children are more sensitive than adults.

Clinical uses of antimuscarinic drugs

Central Nervous System Disorders

1. ***Parkinson's disease***

2. ***Motion sickness and sea sickness-*** Scopolamine is one of the oldest remedies for sea sickness and is as effective as any more recently introduced agent.

2- ***Amnesia***- Scopolamine produces significant amnesia for the events associated with surgery and obstetric delivery.

Ophthalmologic Disorders Accurate measurement of refractive error in uncooperative patients, eg, young children, requires ciliary paralysis. Also, mydriasis greatly facilitates ophthalmoscopic examination of the retina. Antimuscarinic drugs should never be used for mydriasis unless

cycloplegia or prolonged action is required. Alpha-adrenoceptor stimulant drugs, eg, phenylephrine, produce a short-lasting mydriasis that is usually sufficient for funduscopic examination.

Respiratory Disorders- Ipratropium bromide is synthetic analogs of atropine, are used as inhalational drug in asthma and COPD.

Cardiovascular Disorders Atropin is also used for bradycardia.

Gastrointestinal Disorders Antimuscarinic agents can provide some relief in the treatment of common traveler's diarrhea and other mild or self-limited conditions of hypermotility. They are often combined with an opioid antidiarrheal drug, an extremely effective therapy. In this combination, however, the very low dosage of the antimuscarinic drug functions primarily to discourage abuse of the opioid agent. The classic combination of atropine with diphenoxylate, a nonanalgesic congener of meperidine, is available.

Urinary Disorders Oxybutynin, which is somewhat selective for M3 receptors, is used to relieve bladder spasm after urologic surgery, eg, prostatectomy. It is also valuable in reducing involuntary voiding in patients with neurologic disease. Tolterodine, M3-selective antimuscarinics, is available for use in adults with urinary incontinence. Imipramine, a tricyclic antidepressant drug with strong antimuscarinic actions, has long been used to reduce incontinence.

Cholinergic Poisoning Atropine, because of its ability to penetrate CNS, is used for relieving muscarinic symptoms of muscarinic agonists and cholinesterase poisoning.

Adverse Effects

Mydriasis and cycloplegia, dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium, increase body temperature are the adverse effects of muscarinic antagonists. Overdoses of muscarinic antagonists are generally treated symptomatically. For those that can enter CNS, physostigmine is used to reverse the antimuscarinic symptoms. Poison control experts discourage the use of physostigmine or another cholinesterase inhibitor, because symptomatic management is more effective and less dangerous. When physostigmine is deemed necessary, *small* doses are given *slowly* intravenously. Symptomatic treatment may require temperature control with cooling blankets and seizure control with diazepam. For those antimuscarinic drugs that can not enter CNS, treatment can be carried out with a quaternary cholinesterase inhibitor such as neostigmine.

Contraindications

Antimuscarinic drugs are contraindicated in patients with glaucoma, especially angle-closure glaucoma. Even systemic use of moderate doses may precipitate angle closure (and acute glaucoma) in patients with shallow anterior chambers. In elderly men, antimuscarinic drugs should always be used with caution and should be avoided in those with a history of prostatic hyperplasia.

Nicotinic antagonists

Nicotinic antagonists are divided into two groups including neuromuscular blocking drugs and ganglionic blocking drugs. Neurmuscular blocking drugs block nicotinic receptors in the skeletal muscle neuromuscular junction. Therefore, they cause relaxation and paralysis of skeletal

muscle. These drugs are discussed in pharmacology 3. Ganlionic blocking drugs block nicotinic receptors located on the cell body of autonomic (sympathetic and parasympathetic) ganglia, and thereby inhibit the transmission of impulses from preganglionic fibers to postganglionic ones. Therefore, both sympathetic and parasympathetic nervous systems are blocked.

Organ System Effects of ganglionic blocking drugs

1. ***Eye***—The ganglion-blocking drugs cause a predictable cycloplegia with loss of accommodation because the ciliary muscle receives innervation primarily from the parasympathetic nervous system. Ganglionic blockade often causes moderate dilation of the pupil because parasympathetic tone usually dominates this tissue.

2. ***Cardiovascular system***—Blood vessels receive chiefly vasoconstrictor fibers from the sympathetic nervous system; therefore, ganglionic blockade causes a marked decrease in arteriolar and venomotor tone. Cardiac effects include diminished contractility and, because the sinoatrial node is usually dominated by the parasympathetic nervous system, a moderate tachycardia.

3. ***Gastrointestinal tract***—Secretion is reduced, although not enough to treat peptic disease effectively. Motility is profoundly inhibited, and constipation can be marked.

4. ***Other systems***—bladder wall is relaxed and blood sphincter is constricted, Therefore, ganglionic blockade causes hesitancy in urination and may precipitate urinary retention in men with prostatic hyperplasia. Sexual function is impaired in that both erection and ejaculation may be prevented by moderate doses. Thermoregulatory sweating is reduced by the ganglion blocking drugs.

Clinical uses Ganglionic blocker used to be indicated for hypertension. They are rarely used, because more selective autonomic blocking agents are available.

Sample questions

All of the followings are caused by muscarinic agonists except:
A) Bronchoconstriction
B) Miosis
C) Increased gastrointestinal motility
D) Skeletal muscle relaxation