Ganglionic Blockers

Ganglion-blocking agents competitively block the action of acetylcholine and similar agonists at nicotinic (Nn) receptors of both parasympathetic and sympathetic autonomic ganglia. Some members of the group also block the ion channel that is gated by the nicotinic choloceptor. 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. The responses of the non-depolarizing blockers are complex, and nearly all the physiological responses to these agents can be predicted by knowledge of the predominant tone of a given organ system. For example, the predominant tone in the arterioles is sympathetic. In the presence of a non-depolarizing, this system is affected the most, leading to vasodilation. The parasympathetic nervous system is the predominant tone in many organ systems. Thus, the presence of a ganglionic blocker will also produce atony of the bladder and the GI tract, cycloplegia, xerostomia, and tachycardia. The ganglion-blocking drugs are important and used in pharmacologic and physiologic research because they can block all autonomic outflow. However, their lack of selectivity confers such a broad range of undesirable effects that they have limited clinical use.
Chemistry and Pharmacokinetics

All ganglion-blocking drugs of interest are synthetic amines. Tetraethylammonium (TEA), the first to be recognized as having this action, has a very short duration of action. Hexamethonium ("C6") was developed and was introduced clinically as the first drug effective for management of hypertension. As shown in the figure below, there is an obvious relationship between the structure of the agonist acetylcholine and the nicotinic antagonist tetraethylammonium and hexamethonium. Decamethonium, the "C10" analog of hexamethonium, is a depolarizing neuromuscular blocking agent.

Mecamylamine, a secondary amine, was developed to improve the degree and extent of absorption from the gastrointestinal tract because the quaternary amine ganglion-blocking compounds were poorly and erratically absorbed after oral administration. Trimethaphan, a short-acting ganglion blocker, is inactive orally and is given by intravenous infusion.

Pharmacodynamics

A. Mechanism of Action

Ganglionic nicotinic receptors, like those of the skeletal muscle neuromuscular junction, are subject to both depolarizing (agonist) and non-depolarizing (antagonist) blockade. Nicotine itself and even acetylcholine (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block. Drugs now used as ganglion blockers are classified as non-depolarizing competitive antagonists. However, hexamethonium actually produces most of its blockade by occupying sites in or on the nicotinic ion channel, not by occupying the cholinoreceptor itself. In contrast, trimethaphan appears to block the nicotinic receptor, not the channel pore. Blockade can be surmounted by increasing the concentration of an agonist, e.g. acetylcholine.

B. Organ System Effects

1. Central nervous system

Mecamylamine, unlike the quaternary amine agents and trimethaphan, crosses the blood-brain barrier and readily enters the CNS. Sedation, tremor,
choreiform movements (usually associated with Parkinson’s disease), and mental aberrations have been reported as effects of mecamylamine.

2. 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. The effect on the pupil is not easily predicted, since the iris receives both sympathetic innervation (mediating pupillary dilation) and parasympathetic innervation (mediating pupillary constriction). Ganglionic blockade often causes moderate dilation of the pupil because parasympathetic tone usually dominates this tissue.

3. 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. The blood pressure may fall precipitously because both peripheral vascular resistance and venous return are decreased. Hypotension is especially marked in the upright position (orthostatic or postural hypotension). Cardiac effects include diminished contractility and, because the
Sino-atrial node is usually dominated by the parasympathetic nervous system, a moderate tachycardia.

4. Gastrointestinal tract

Secretion is reduced, although not enough to effectively treat peptic ulcer. Motility is profoundly inhibited, and constipation can be marked.

5. Other Systems

Genitourinary smooth muscle is partially dependent on autonomic innervation for normal function. 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. However, hyperthermia is not a problem except in very warm environments, because cutaneous vasodilation is usually sufficient to maintain a normal body temperature

6. Response to autonomic drugs

Patients receiving ganglion-blocking drugs are fully responsive to autonomic drugs acting on muscarinic, alpha, and beta-adrenergic receptors
because these effector cell receptors are not blocked. In fact, responses may be exaggerated or even reversed (e.g. intravenously administered norepinephrine may cause tachycardia rather than bradycardia), because homeostatic reflexes, which normally moderate autonomic responses, are absent.

**Clinical Applications and toxicity**

Ganglion blockers are used infrequently because more selective autonomic blocking agents are available. **Mecamylamine** blocks central nicotinic receptors and has been advocated as a possible adjunct with the transdermal nicotine patch to reduce nicotine craving in patients attempting to quit smoking. **Trimethaphan** is occasionally used in the treatment of hypertensive emergencies and “dissecting aortic aneurysm”; in producing hypotension, which can be of value in neurosurgery to reduce bleeding in the operative field. The toxicity of the ganglion-blocking drugs is widespread because of involvement of all the autonomic nervous system. For most patients, these effects are intolerable except for acute use.

An **aortic dissection** is a serious condition in which a tear develops in the inner layer of the aorta, the large blood vessel branching off the heart. Blood surges through this tear into the middle layer of the aorta, causing the inner and middle layers to separate (dissect). If the blood-filled channel ruptures through the outside aortic wall, aortic dissection is often fatal.
**Extra information:**

**Postsynaptic potential**

The postsynaptic potentials that are caused by neurotransmitter chemicals can be either depolarizing, often (but not always) resulting in an excitatory postsynaptic potential, or EPSP, or hyperpolarizing, resulting in an inhibitory postsynaptic potential, or IPSP. The postsynaptic potentials produced at most synapse are usually well below the threshold for generating postsynaptic action potentials. How, then, can synapses transmit information if their PSPs are sub-threshold? Suppose that two excitatory endings are activated, causing local depolarization of the cell body. Taken alone, neither would be sufficient to trigger an action potential, but when combined, the two depolarization sum to depolarize the membrane in the hillock region to threshold. When inhibitory synapses are also active, the membrane potential tends to be stabilized below threshold because they induce hyperpolarization or sub-threshold depolarization that cannot reach threshold. These postsynaptic effects also spread passively, dissipating as they travel. Because some potential's excite and others inhibit the hillock, these effects partially cancel out each other. Thus the net effect is the difference between the two; the neuron subtracts the IPSP from the EPSP. Postsynaptic potential last a few milliseconds before fading away. Only if the overall sum of all the potentials (both EPSP and IPSP) is sufficient to depolarize the cell to threshold at the axon hillock, is an action potential triggered.
Neuromuscular-blocking drugs

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular endplate of skeletal muscle. These neuromuscular blockers are structural analogs of Ach, and they act either as non-depolarizing or depolarizing type at the receptors of the endplate of the NMJ. Neuromuscular blockers are clinically useful during surgery for producing complete muscle relaxation, without having to use higher anesthetic doses to achieve comparable muscular relaxation. Decamethonium (Syncurine) is a depolarizing muscle relaxant or neuromuscular blocking agent, and is used in anesthesia to induce paralysis.

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