Chapter 7

Cholinoceptor-blocking drugs
Objectives

- Classification, structure in relation to ADME
- The mechanism of drug action
- The major pharmacological effects and therapeutic applications
Classification of drugs

Anticholinergic Drugs

M-cholinergic receptor blockers (Muscarinic antagonist)
- atropine-like alkaloids
- synthetic and semisynthetic substitutes for belladonna alkaloids

N-cholinergic receptor blockers (antinicotinic)
- ganglionic blocking drugs
- neuromuscular blocking drugs

Very rare used in clinical practice
Pharmacokinetics

Absorption:
Natural alkaloid and tertiary antimuscarinic--- well absorbed
Quaternary antimuscarinic--<30% absorption

Distribution:
Atropine and tertiary antimuscarinic– widely distribution including CNS
Quaternary antimuscarinic-poorly in CNS

Metabolism and Excretion:
Disappeared quickly.
M-receptor blocking drugs (antimuscarinic drugs)

I. Atropine-like alkaloids

atropine, scopolamine, anisodamine
A. atropine

1. Mechanism of action

Competitively antagonize M-R- mediated effects of Ach. High selective drug for M receptors

Antagonize $N_1$-R in peripheral ganglia at very high doses.
a. Eye

① Mydriasis
block M₃-R → lead to contraction of the iris dilator muscle and dilator of the pupil

② cycloplegia:
eyes can not focus for near vision because the weak contraction of ciliary muscle

Useful in ophthalmology, but with caution in acute glaucoma
③ Cycloplegia (调节麻痹)

mechanism: block M₃-cholinergic receptor

↓

ciliary muscle relaxation

↓

zonule drawn tight

↓

lens fixed for far vision, blurring of near objects

These effects of atropine on eye are able to be antagonized by pilocarpine.
Fig. 7-1  Schematic diagram of the anatomic structures of eyes and regulation effects by antagonists (showing in upside), and agonists (showing in downside) of muscarinic receptor
b. Heart

① Heart rate (HR) → tachycardia (moderate to high dose)

   Clinical dose (0.4-0.6 mg) → HR reduction

② Atrioventricular (AV) conduction

   Atropine may accelerate the AV conduction.

③ Blood pressure:

   Normal dose, no significant effect.
c. Relaxation of visceral smooth muscles

block M-cholinergic receptor

① Gastrointestinal smooth muscle spasm is inhibited and amplitude and frequency of intestinal peristalsis are reduced

② To reduce the normal tone and amplitude of ureter and bladder

③ less effective in biliary and renal colic

④ less effective in uterine smooth muscle
d. Glands—be able to inhibit secretion of glands

The secretion of sweat and salivary glands is particularly sensitive (0.5 mg)

Used prior to inhalant anesthetics to reduce the secretion of lacrymal and tracheobronchial glands

Able to reduce the secretion of gastric gland at high doses
e. **Respiratory system**

Smooth muscle: bronchodilation

Secretory gland: reduced secretion

(used frequently before administration of inhalant anesthetics)

f. **Central nervous system (CNS)**—exciting effect

0.5-1.0 mg --- mild vagal excitation

toxic doses--restlessness, irritability, disorientation

larger doses---depression, paralysis, coma, circulatory collapse, respiratory failure.
B. Anisodamine

[Compared to atropine]

1. Less effective in inhibiting gland

2. The selectivity for vascular and visceral smooth muscle is relatively higher than that of atropine.
Therapeutic applications

a. Relief for smooth muscle spasm

① intestinal colic and abdominal cramps

② biliary and renal colic:

    atropine + opioid analgesics

b. Inhibition of gland secretion

① Before anaesthetics, atropine can be used to prevent aspiration pneumonia induced by salivary and tracheobronchial secretions.

② For night sweating and salivation
c. CNS diseases

Parkinson’s disease: adjunctive therapy
Motion sickness: scopolamine
d. Application in ophthalmology

Iridocyclitis: it may relax the iris and ciliary muscles, and prevent the adhesions.

Ciliary paralysis for the measurement of the refractive error

e. Bradyarrhythmias

bradycardia, sinoatrial or atrioventricular conduction blockade.

f. Organophosphate poisoning

discussed in detail in chapter 11
g. Cholinergic poisoning

insecticides: cholinesterase inhibitor-excess acetylcholine
tertiary antimuscarnic drug (atropine) must be used, not quaternary, why?

Mushroom poisoning:
4. Adverse reactions and toxicity

a. Common adverse reactions:

- dryness of mouth
- blurring of near vision
- tachycardia
- dilation of the pupil (mydriasis)
- skin flushed.

Overdose may cause rapid and weak pulse, rapid and deep respiration, eclampsia, excitement, coma, and respiration failure.
b. The management of atropine poisoning
   ① gastric lavage
   ② physostigmine iv, diazepam
   ③ symptomatic treatment
   [contraindication]
      glaucoma, prostate hypertrophy
C. Scopolamine

1. peripheral effects:
   similar to those of atropine, but more effective in mydriasis, cycloplegia and inhibition of gland secretion, less effective on heart and vessels.
2. CNS effects:

(1) CNS depression (blocking $M_{1-R} > M_{2-R}$):

Drowsiness, amnesia, fatigue, dreamless sleep with a decrease in rapid eye movement sleep.

(2) Prophylactic agent for motion sickness which causes nausea and vomiting. (via inhibiting the gastrointestinal smooth muscle motion.)

(3) Parkinsonism treatment discussed in detail in chapter 19
II. Synthetic and semisynthetic substitutes for belladonna (beautiful lady) alkaloids

1. Synthetic mydriatics
2. Synthetic spasmodylant
3. Selective M-cholinergic receptor blockers
1. Synthetic mydriatics

<table>
<thead>
<tr>
<th>drugs</th>
<th>concentration (%)</th>
<th>mydriasis maximum action (min)</th>
<th>mydriasis duration (day)</th>
<th>cycloplegia maximum action (h)</th>
<th>cycloplegia duration (day)</th>
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<tbody>
<tr>
<td>atropine</td>
<td>1.0</td>
<td>30 ~ 40</td>
<td>7 ~ 10</td>
<td>1 ~ 3</td>
<td>7 ~ 12</td>
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<tr>
<td>homatropine</td>
<td>1.0 ~ 2.0</td>
<td>40 ~ 60</td>
<td>1 ~ 2</td>
<td>0.5 ~ 1.0</td>
<td>1 ~ 2</td>
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<tr>
<td>tropicamide</td>
<td>0.5 ~ 1.0</td>
<td>20 ~ 40</td>
<td>0.25</td>
<td>0.5</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>cyclopentolate</td>
<td>0.5</td>
<td>30 ~ 50</td>
<td>1.0</td>
<td>1.0</td>
<td>0.25 ~ 1.0</td>
</tr>
<tr>
<td>eucatropine</td>
<td>2.0 ~ 5.0</td>
<td>30</td>
<td>1/12 ~ 1/4</td>
<td>no effect</td>
<td>—</td>
</tr>
</tbody>
</table>
2. Synthetic spasmolysant

(1) Quarternary ammonium

a. Ipratropium bromide belongs to nonselective M-R blocker.

b. Tiotropium bromide is a selective $M_1/M_3$-R blocker.

They can selectively act on the bronchia, leading to bronchodilatation and reduction of respiratory tract secretion.

Clinical applications: chronic obstructive pulmonary disease (COPD), not asthma.
c. Propantheline bromide

Strong and long lasting effects on relaxation of visceral smooth muscle spasm, and to reduce the secretion of gastric gland, no CNS side effects.

Application:
Gastric and duodenal ulcer, gastro-intestinal smooth muscle spasm, night sweats, vomiting during pregnancy.

Adverse reactions:
Similar to those of atropine.
(2) **Tertiary amines**

a. Synthetic mydriatics: such as homatropine, tropicamide, cyclopentolate, eucatropine.

b. Drugs used in treatment of Parkinsonism: such as benzatropine mesylate, trihexyphenidyl hydrochloride.

c. Antispasmodic drugs: such as dicyclomine hydrochloride, flavoxate hydrochloride, oxybutynin chloride

Relaxation of smooth muscle spasm
3. Selective M-cholinergic receptor blockers

Pirenzepine belongs to mixture of $M_1/M_4$ –R blockers; telenzepine is highly selective for $M_1$-R.
Both of drugs can inhibit secretion of gastric acid and pepsin.

Applications: --- treatment of peptic ulcer and chronic obstructive bronchitis.

There is relatively low incidence of dry mouse and blurred vision.
N-cholinergic receptor blocking drugs
I. Ganglionic blocking drugs ($N_1$-R blockers)

They block both sympathetic and parasympathetic autonomic ganglia. They cause many and severe side effects due to lack of selectivity.

Mecamylamine
2. Nuromuscular blocking drugs(skeletal muscle relaxants, N$_2$-R blockers)

Drugs with N$_2$-R antagonistic activity block the action of Ach, leading to skeletal muscle relaxation.

Classification

a. Depolarizing muscular relaxants

b. Nondepolarizing muscular relaxants
A. Depolarizing muscular relaxants

**Drugs** produce the lasting depolarization which causes no reaction of N$_2$-R at the postjunctional membrane of nerve-muscle to Ach, and results in skeletal muscle relaxation.
Some points to make:

① There is an initially transient muscle fasciculation.

② The repetitive use of this class of drugs results in rapid tolerance.

③ Cholinesterase-inhibiting drugs cannot reverse the effect induced by depolarizing muscular relaxants.

④ There is no ganglionic blocking effect in therapeutic doses.
Representative: suxamethonium (scoline, succinylcholine)

Feature:

- iv injection, rapidly action (1 min)
- Muscle fasciculation → muscle relaxation (5 min)

Degree of muscle relaxation:

- Neck, limb > face, tongue, throat
- Less effective in respiratory paralysis
Clinical applications:

1. iv for bronchoscopy and esophagoscopy

2. iv adjuvant in surgical anesthesia
[adverse reactions and application]

1 Choke
   rescue : artificial respiration

2 Muscle fasciculation
3 Hyperkalemia
4 Others
   (increase secretion of glands and release of histamine)
B. Nondepolarizing muscular relaxants
(competitive muscular relaxants)
B. Nondepolarizing muscular relaxants
(competitive muscular relaxants)

- **ACh** activates *N*_2 receptor

- Depolarizing muscular relaxants activate last depolarization

- Nondepolarizing muscular relaxants block *N*_2 receptor

- Lasting depolarization leads to relaxation

- Contract

- Relaxation
<table>
<thead>
<tr>
<th>Drug</th>
<th>Time of Onset (min)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d- Tubocurarine</td>
<td>4-6</td>
<td>80</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>4-6</td>
<td>120-180</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>4-6</td>
<td>90-120</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>2-4</td>
<td>80-100</td>
</tr>
<tr>
<td>Intermediate duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocuronium</td>
<td>1-2</td>
<td>30-40</td>
</tr>
<tr>
<td>Vecuronium bromide</td>
<td>2-4</td>
<td>30-40</td>
</tr>
<tr>
<td>Atracurium</td>
<td>2-4</td>
<td>30-40</td>
</tr>
<tr>
<td>Short duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mivacurium</td>
<td>2-4</td>
<td>12-18</td>
</tr>
</tbody>
</table>
Representative drugs: d-tubocurarine

[Feature]

1. iv injection for 3-6 min → skeletal muscle relaxation

2. Prone to respiratory paralysis

3. Increasing the release of histamine, blocking ganglia and resulting in the decline of blood pressure
THANKS!