**NEUROMUSCULAR BLOCKING AGENTS AND MUSCLE RELAXANTS**

Drugs that affect skeletal muscle function:

1. Neuromuscular blockers - used in surgical procedures to cause muscle paralysis
2. Centrally acting muscle relaxants - reduce spasticity in neurologic conditions

**NEUROMUSCULAR BLOCKING DRUGS**

*General concept*

They interfere with transmission at the motoric end-plate and act postsynaptically by one of the two mechanisms:

1. **Nondepolarizing blocking agents** - competition with Ach for the end-plate receptor
2. **Depolarizing blocking agents** - initial depolarisation followed by desensitization

**BOTH GROUPS ACT ON NICOTINIC RECEPTOR!**

Muscular relaxation and paralysis may occur from interruption of function at:

- the CNS level
- myelinated somatic nerves
- unmyelinated motor terminals
- the Ach receptor
- the motor end-plate
- the muscle membrane or contractile apparatus

**NOTE:** Skeletal muscle relaxation can be achieved by:

- Centrally acting drugs - antianxiety drugs: mephenesin, meprobamate, diazepam primary effect on the CNS
- Direct effect on skeletal muscle - dantrolene
- Some antibiotics (aminoglycosides, polymyxins) interfere with normal neuromuscular function
**Motor end-plate** (sensitive for Ach but not for electrical stimulation)
Transmitter: acetylcholine (= Ach; Dale and Feldberg)
Receptor: nicotinic
MEPP = miniature end-plate potential
EPP = end-plate potential  
- it is not propagated
- it is directly related to the amount of the released Ach
- it has no refractory period
- it is not an “all or nothing” response

- **Inhibition of the neuromuscular transmission**
  
  **A: Presynaptic**
  
  a. Inhibition of Ach synthesis
     - Hemicholinium
  
  b. Inhibition of Ach release
     - Butulin toxin, Mg$^{2+}$ excess, Ca$^{2+}$ deficiency, Streptomycin, Neomycin
  
  c. Inhibition of conduction
     - Local anaesthetics, tetrodotoxin
  
  **B: Postsynaptic**
  
  a. Competitive inhibitors of Ach
     - non-depolarizing muscle relaxants (CURARE, GALLAMINE, etc)
  
  b. Depolarizing inhibitors
     - SUCCINYLCYLCHOLINE (SUCH)
Basic pharmacology of neuromuscular blocking drugs

History
16th century - arrow poison (South America, Amazon Basin) - produced death by skeletal muscle paralysis
19th century - Magendie and Claude Bernard - pharmacological effects and mechanism of action of the active principle of Chondodendron tomentosum roots - d tubocurarine (it does not prevent the muscle from responding to direct stimulation, it fails to block conduction in the nerve but it blocks transmission at the junction of the nerve and muscle).
20th century - isolation and structure analysis - large molecule, two quaternary ammonium structures separated by an estimated distance of 14 A.

1. Chemistry
   Structural similarity to Ach
   A: Depolarizing drugs: linear structure (two Ach molecules linked end to end), e.g. SUCH
   B: Non depolarizing drugs - 'double Ach' structure with rigid ring system

2. Mechanism of action
   A: Non-depolarizing blocking drugs
      TUBOCURARINE, METOCURINE, TOXIFERINE (from curare), PANCURONIUM, GALLAMINE, VECURONIUM, ATACURUM
      • In low doses - act predominantly on the nicotinic receptor - competition with Ach
      • In higher doses - enter into the ion channel (Na⁺) - channel blockade
      • Blockade of the prejunctional Na⁺ channels (but not Ca²⁺ channels or interference with Ach release)
      • The nature of the blockade - reversible - tetanic stimulation/ChE inhibitors can relief the block

B: Depolarizing drugs
   SUCCINYLCHOLINE, DECAMETHONIUM

a.) Phase I block (depolarization)
The effects of SUCH are almost identical to those of Ach but they last longer (SUCH reacts with the receptor, opens the channel and depolarizes the end-plate). Depolarization spreads to and depolarizes adjacent membranes → generalized, disorganized contraction of muscle motor unit.
SUCH is metabolised slower than Ach → the depolarized membrane remains unresponsive to additional stimuli (e.g. Ach) → flaccid paralysis
This phase of the blockade is potentiated, not reversed by ChE inhibitors

b.) Phase II block (desensitization)
Continuous exposure to SUCH → the initial depolarization decreases, the membrane becomes repolarised but it remains still unresponsive to Ach until SUCH is present → desensitization block
The mechanism is unknown (in the presence of SUCH, a non-excitable area develops around the motor end-plate which impedes the centrifugal spread of impulses initiated by Ach)
Phase II block can be reversed by tetanic stimulus (excess release of Ach) and by ChE inhibitors
COMPARISON OF TUBOCURARINE AND SUCCINYLCHOLINE

<table>
<thead>
<tr>
<th></th>
<th>dTC</th>
<th>SUCH</th>
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<tbody>
<tr>
<td>dTC</td>
<td>antagonistic</td>
<td>activates</td>
</tr>
<tr>
<td>SUCH</td>
<td>activate</td>
<td>antagonistic</td>
</tr>
<tr>
<td>Initial excitation</td>
<td>none</td>
<td>fasciculation</td>
</tr>
<tr>
<td>Response to tetanic stimulus</td>
<td>unsustained</td>
<td>sustained</td>
</tr>
<tr>
<td>Rate of recovery</td>
<td>30-40 min</td>
<td>10 sec</td>
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</table>

3. Clinical pharmacology of neuromuscular blocking drugs
Aim: To achieve adequate skeletal muscle relaxation (paralysis) during surgical intervention without depressant effects of deep anaesthesia

A: Non-depolarizing drugs
- During anaesthesia dTC (0.12-0.4 mg/kg, i.v.) causes motor weakness and then flaccid paralysis
- The order of muscle paralysis: jaw, eye, neck muscles, limbs, trunk, intercostal muscles, diaphragm (curarization)
- The order of recovery: reversed - the diaphragm regaining function first (de-curarization)
- The effect of dTC lasts 30-60 min but paralysis may still present for another hour (re-curarization)
a.) Isoquinoline derivatives

**d-TUBOCURARINE (TUBARINE)**
- Tubocurarine chloride - 3 mg/kg solution for injection
- Onset: within 1 min, duration: 25-60 min
- One third of dTC is excreted unchanged in the urine, the rest is metabolically altered

**DIMETHYL-TUBOCURARINE CHLORIDE (MECOSTRIN) and DIMETHYL-TUBOCURARINE IODIDE (METUBINE IODIDE)**
- Three-times more potent than dTC

**ALCURONIUM CHLORIDE (ALLOFERIN)**
- Weak histamine releasing effect

**Other isoquinolines:** ATRACURIUM (TACRINUM), DOXACURIUM, MIVACURIUM

b.) Steroid derivatives

**PANCURONIUM (PAVULON)**
- Its potency is 6-times greater than dTC
- Lack of histamine releasing and ganglion blocking effect
- 2 mg of Pancuronium produces the same effect as 10-15 mg of dTC

**GALLAMINE (FLAXEDIL) and BENZOQUINONIUM (MYTOLON)**
- Its action similar to dTC but it is less potent. It has a shorter duration of action
- It has no histamine releasing effect
- It has an “atropine-like” effect on the cardiac branch of the vagus nerve. The vagolytic and the catecholamine-releasing effect may produce tachycardia

**PIPECURONIUM (ARDURAN), ROCURONIUM, VECCURONIUM (NORCURON)**
- Their action is similar to dTC, but they have a shorter duration of action
- They have no histamine releasing, ganglion blocking and vagolytic effects

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**B: Depolarizing drugs**

**SUCCINYLCHOLINE (ANECTINE)**
- SUCH (0.5-1.0 mg/kg; i.v.) → transient muscle contractions (fasciculations due to Phase I block) occur (cheeks, abdomen) several seconds before paralysis develops.
- The order of muscle paralysis: arm, neck, legs, facial muscles, respiratory muscles.
- The onset of blockade: 1 min. The muscles remain paralysed for about 5 min and then resume their function in another 5 min (rapid hydrolysis by plasma pseudo-ChE to succinylmonocholine and then to succinic acid and choline)
- Neostigmine is not an antidote, it may aggravate muscle paralysis
- In some patients SUCH may cause prolonged apnoe (genetic abnormality in ChE formation)
- It is valuable for producing short periods of muscular relaxation
- Artificial respiration is required

**DECAMETHONIUM (SYNCURINE)**
- A methonium compound but it is largely replaced by SUCH.

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**4. Metabolism of neuromuscular blocking agents**

- Metabolism of gallamine, dTC and decamethonium is negligible
- Pancuronium is deacetylated, its metabolite can be active
- SUCH is rapidly metabolised
- Atracurium is inactivated by enzymatic ester hydrolysis in the plasma
5. Cardiovascular effects of neuromuscular blocking agents

All of the used muscular relaxants cause cardiovascular effects.

### Autonomic effects of neuromuscular blocking drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>AUTONOMIC EFFECTS</th>
<th>CARDIAC M2 EFFECTS</th>
<th>HISTAMINE RELEASE</th>
</tr>
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<tbody>
<tr>
<td>SUCH</td>
<td>stimulates</td>
<td>stimulates</td>
<td>slight</td>
</tr>
<tr>
<td>dTC</td>
<td>blocks</td>
<td>none</td>
<td>moderate</td>
</tr>
<tr>
<td>Metocurine</td>
<td>blocks</td>
<td>none</td>
<td>slight</td>
</tr>
<tr>
<td>Gallamine</td>
<td>none</td>
<td>blocks</td>
<td>none</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>none</td>
<td>blocks</td>
<td>none</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Atracurium</td>
<td>none</td>
<td>none</td>
<td>slight</td>
</tr>
</tbody>
</table>

TUBOCURINE and METOCURINE produce hypotension (histamine liberation + ganglion blockade) and bronchoconstriction (histamine release). These histamine-induced effects can be prevented by premedication with Promazine (antihistamine).

PANCURONIUM produces a moderate increase in heart rate and in cardiac output (vagolytic action + CA release + inhibition of NE uptake).

GALLAMINE increases heart rate (vagolytic + sympathetic stimulatory effect).

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SUCCINYLCHOLINE induced cardiac arrhythmias are many and varied.

- It stimulates all autonomic cholinoreceptors (nicotinic receptors in both sympathetic and parasympathetic ganglia, muscarinic receptors in the sinus node).
- In low doses: negative inotropic and chronotropic effects (can be blocked by atropine).
- In large doses: positive inotropic and chronotropic effects (sympathetic ganglion stimulation).
- After repeated doses: bradycardia may occur (cardiac muscarinic receptor stimulation + ggl. stimulation). This bradycardia can be prevented by Thiopental, Atropine, ggl. blockers and non-depolarizing muscle relaxants.

6. Therapeutic uses

- As surgical adjuvant to anaesthesia for promoting skeletal muscle relaxation and for facilitating endotracheal intubation.
- With electroconvulsant shock therapy to prevent trauma.
- In the diagnosis of myasthenia gravis (dTC) - potentially hazardous provocative test.
- Atracurium may be used in patient with renal failure (it is not excreted by the kidney).
7. Untoward effects
For all neuromuscular blocking drugs:

- They do not affect sensorial (despite paralysis), patients remain conscious and feel pain.
- Prolonged apnoea may occur.

A: Non-depolarizing muscle relaxants

- TUBOCURARINE
  - Dose dependent fall in blood pressure (ggl. blockade + histamine release)
  - Bronchospasm (histamine release)
- GALLAMINE and PANCURONIUM
  - Increases in heart rate and blood pressure (vagolytic and tyramine-like effects)

B: Depolarizing muscle relaxants

- Fasciculations can cause muscle pain, increase in gastric pressure (risk of aspiration) and in intraocular pressure. These effects can be prevented by the prior administration of a small dose of competitive antagonist.
- SUCH stimulates autonomic ganglia and muscarinic receptors → bradycardia, increased bronchial secretion
- With repeated i.v. injections cardiac arrest can occur (mainly in children)
- In some genetically predisposed individuals the combination of SUCH and Halothane can cause malignant hyperthermia
- SUCH can result in an increased release of K⁺ → cardiac arrest may occur. Patients with burns, nerve damage, renal failure are especially susceptible.

8. Factors influencing the action of neuromuscular blocking agents

- Serum ChE is determined genetically. The normally transient effect of SUCH will be greatly prolonged in individuals with deficient serum ChE.
- Serum ChE is synthesized in the liver; hepatic disease prolongs the action of SUCH.
- ChE inhibitors, used in the treatment of glaucoma, prolongs the effect of SUCH.
- Patients with myasthenia gravis are highly sensitive to competitive blockers.

Following administration of depolarizing drugs the Phase II block develops sooner.
- Patient with Eaton-Lambert syndrome (small cell or oat cell carcinoma of the lung) have an increased sensitivity to both types of neuromuscular blockers.
- Depolarizing blockers increase serum K⁺; this is exacerbated in conditions of hyperkalemia, such as burns.
- Aminoglycoside antibiotics potentiate the effect of neuromuscular blocking agents.
- All inhaled anaesthetics increase the effect of neuromuscular blocking agents.
  - Depression at sites proximal to the neuromuscular junction, i.e. CNS
  - Increased muscle blood flow - larger fraction of the neuromuscular blockers reaches the neuromuscular junction
  - Decreased sensitivity of the postjunctional membrane to depolarization
- Local anaesthetics and antiarrhythmic drugs enhance the blockade.
9. Reversal of neuromuscular blockade

1. Competitive neuromuscular blockers can be antagonised by ChE inhibitors, e.g. EDROPHONIUM, NEOSTIGMINE, PYRIDOSTIGMINE

2. No antagonist currently exists for depolarizing blockers
   • Controlled ventilation is required until spontaneous recovery occurs
   • Anti-cholinesterase aggravates Phase I block but may reverse Phase II block
SMOOTH MUSCLE RELAXANTS
(Spasmodytics)

Definition: They solve painful spasms of the smooth muscle by acting directly on the smooth muscle or influence its innervations.

Characteristic of smooth muscle: slow and prolonged reaction, autonomic innervations, myogenic automacy.

Classification of smooth muscles: according to responses to the autonomic stimulation and mediators.

1. Respond to cholinergic stimulants by contraction and to α and β stimulants by relaxation e.g. bronchial smooth muscles, m. detrusor vesicae urinariae, m. sphincter pupillae.

2. Respond to cholinergic stimulants and to α stimulants by contraction e.g. Sphincters of GIT, m. dilator pupillae, ductus coledochus and sphincter Oddi, sphincter of bladder, urethra, vesicula seminalis, ductus deferens.

3. Respond to α stimulants by contraction and cholinergic stimulants by relaxation e.g. Smooth muscle of the peripheral arteries.

Modulation of smooth muscle function

1. Effect on the neural components
   a.) ganglion
   b.) sympathetic nerve ending
   c.) parasympathetic nerve ending

2. Direct effect on the smooth muscle
   (Examination under in vitro condition in isolated smooth muscle preparations; aorta ring, ileum streps).

Spontaneous movement

- atropine
- adrenaline (α and β receptor blockers do not reverse this effect)
- Ach (smooth muscle relaxation)
- papaverine (smooth muscle contraction)
- BaCl₂ (smooth muscle contraction)

Examination under in vitro condition in isolated smooth muscle preparations; aorta ring, ileum streps.
**Indication**

1. (a) gastro-intestinal spastic conditions
   (b) gall bladder
   (c) ulcer
2. Dysmenorrhea
3. Bladder tenesmus, calculus
4. Adjuvant therapy  
   (a) vessel spasms
   (b) bronchial asthma
   (c) angina pectoris

**Preparations**

**PAPAVERINE**
Opiate alkaloid without central effects. Directly act on the smooth muscle, in particular in spastic states. In case of colic pain together with morphine is effective.
Dose: 0.05-0.2 g parenteral or rectal administration (rapid effect), i.v. in slow injection because the cardiovascular side effects: (+) inotropic, (-) dromotropic effects, BP ↓, peripheral circulatory abnormalities)

**Note:** The spastic condition of muscles, which react with contraction to both sympathetic and parasympathetic stimulation is difficult to influence by spasmolytics. To relieve spasm and pain is important, but some spasmolytics can enhance pain, e.g. in gall bladder, kidney stone cholera, whereas on the sphincters (e.g.: Oddi, bladder, pupil) morphine causes spasm. Large doses of ALGOPYRIN (25 g i.v.) would relieve spasm and pain. In pulmonary embolism PAPAVERINE is effective (vasodilatation).

**ETHAVERINE** (Perparin) stronger than Papaverine. Dose: 0.04-0.25 g

**No-Spa** (Drotaverine hydrochloride) Stronger than Papaverine, (well absorbed after oral administration) Dose: 0.04-0.08 g (i.v.) + 3 x 0.08 g p.o.

**HALIDOR** (Bencyclan, Fludial) Strong vasodilator (coronary, brain and peripheral vessels spasms). Dose: 50 mg i.v.

**SIDE EFFECTS:** dry mouth, weakness, dizziness, nausea, arrhythmia

**HIDRALAZINS**
Directly effecting vasodilators – antihypertensive

**SIDE EFFECTS:** headache, dizziness, reflex tachycardia, orthostatic collapse

**DIAZOXID** Arteriolar vasodilator – RR ↓, less effective on other smooth muscle types

**SIDE EFFECTS:** salt and water retention, uric acid ↑, hyperglycaemia

**OTHER SPASMOLYTICS**

Nitrates and nitrates – Angina pectoris

Adenosine – vasodilator

Nicotinic acid – dilates skin vessels

Parasympatholytics: **ATROPINE, NOVATROPINE**

**COMBINATIONS:**

**TROPARIN** (Papaverine + Novatropine)

**NEOTROPARIN** (No-Spa + Novatropine)

**BISPAN** (No-Spa + Isopropamid)

**TRIOSPAN** (No-Spa + Isopropamid + Phenobarbital)

Relaxants with dual effect (neural + direct)

**TRANSENTIN, SYNTROPAN, GASTROPIN, NEOPEPULSAN,**

**GASTRIXON, GAPONA**

**RELAXANT DRUGS:** Plant active ingredients can relieve smooth muscle spasm

Anise, cumin, chamomile, mint (tee)
DRUGS ACTING ON THE ADRENERGIC NEURON

GENERAL CONCEPT
Drugs can influence sympathetic function by affecting the storage and release of catecholamines (CA).

Application: antihypertensive agents, and in the field of psychopharmacology

History: Discovery of reserpine (Rauwolfia alkaloid) → release of serotonin (5HT), NE and DA → decreased sympathetic functions (hypotension, bradycardia).

MECHANISM OF CATECHOLAMINE RELEASE
1. Interference with the granular storage mechanism
   - RESERPINE
   - GUANETHIDINE

2. Displacement of catecholamines
   - TYRAMINE, AMPHETAMINE
   - METARAMINOL
   - METHYLDOPA

Indirect sympathomimetics

metabolised

COCAIN IMIPRAMINE

reuptake

GUANETHIDIN RESERPIN

NA

COMT

MAO

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MAO

NA

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NA

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**Catecholamine release can be modified:**

1. **MAO inhibitors** - protect the intraneuronally released CAs from inactivation
2. **BRETYLIUM** - prevents CA release to nerve stimulation and inhibits the action of indirectly acting amines (eg. TYRAMINE)
3. **COCAINE, TRICYCLIC ANTIDEPRESSANTS**
   - they block the action of TYRAMINE
   - they block the neuronal uptake of NE
4. Drugs acting on presynaptic α2 and β2 receptors modulate CA release.
   - (α2 inhibits, β2 facilitates NE release)

**Basic difference between the actions of RESERPINE and GUANETHIDINE**

Both drugs deplete CA content of the vesicles by interfering with the granular storage mechanism, **BUT**

GUANETHIDINE has additional effects, such as:
- Tyrarmine-like effect (transient increase in BP) - blocked by COCAINE
  - Bretylium-like effect (early effect), inhibition of NE release after nerve stimulation
  - It has no effect on the CNS

Mechanism of decreased sympathetic activity induced by CA depletion
- CA content of a nerve is below 50 % → lessened response
- The rate of depletion depends on
  - the dose of reserpine
  - the turnover of amines

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**RESERPINE**

Rauwolfia alkaloid which acts - via CA depletion

- inhibits the uptake of NE into the vesicles
  - (NE released into the axoplasm and attacked by MAO)

1. **Mechanism and site of action**

   It blocks the ability of vesicles to take up and store biogenic amines by interfering with an uptake mechanism that depends on Mg²⁺ and ATP.
   The result is depletion of NE, DA, 5HT in both central and peripheral neurons. Its effect appears reversible.

2. **Pharmacologic effect**

   - Large doses may cause a transient sympathomimetic effect (fast release of NE and the uptake is inhibited)
   - Blood pressure decreases, both in supine and in standing patients. Reflex tachycardia occurs followed by bradycardia (stores are depleted)
   - Depletion of CAs and 5HT in the brain results in sedation, mental depression and Parkinsonism.

3. **Pharmacokinetics and dosage**

   Reserpine disappears rapidly from the circulation but its effect persists much longer (irreversible inactivation of CA stores). Dose: less than 1 mg/day orally.
4. **Therapeutic uses**
   - Mild hypertension. In higher doses it is used in endogenous psychoses.

5. **Untoward effects**
   - Sedation, psychic depression (often results suicide), abdominal cramps and diarrhea, GIT ulceration, increased incidence of breast carcinoma

6. **Toxicity**
   - Postural hypotension (low doses), sedation, nightmares, mental depression, Parkinson disease (DA depletion in the corpus striatum), mild diarrhea, increased gastric acid secretion.

**GUANETHIDINE (ISMELIN)**

- It decreases sympathetic activity by a dual mechanism:
  - Depletes NE at peripheral nerve endings (like Reserpine)
  - Causes early sympathetic neuronal blockade (like Bretylium)

1. **Mechanism and sites of action**
   - 1. G blocks physiologic release of NE
   - 2. G displaces NE from granule stores
   - 3. Cocaine, tricyclic antidepressants block membrane transport of G.
   - 4. Tyramine, amphetamine, reserpine release G from granules
**Result:** profound sympathoplegia which results from
(i) gradual depletion of the NE stores (guanethidine is taken up by the vesicle)
(ii) inhibition of NE release (local blockade of membrane electrical activity in the nerve ending)

BUT • after rapid iv. administration, sudden NE release \[\rightarrow\] transient hypertension
• supersensitivity of effector smooth muscle cells (chemical sympathectomy) occur (the neuronal uptake of exogenously administered sympathomimetics is inhibited)
• the hypotensive effect is associated with reduced CO (due to bradycardia and relaxation of capacitance vessels). Later CO returns normal (reduction of blood flow in renal beds \[\rightarrow\] Na\(^+\) and water retention \[\rightarrow\] blood volume expansion)

After guanethidine the fall in BP is more intense in erect than supine patients

3. Pharmacokinetics and dosage
   • Its bioavailability is variable (3-50 %); 50 % cleared by the kidney. Gradual sympathoplegia can develop within 1-2 weeks
   • Therapy is usually initiated at a low dose 10 mg/day

4. Therapeutic use
   Potent, long acting ANTIHYPERTENSIVE agent

5. Untoward effects and toxicity
   • Postural hypertension
   • Syncope (especially with exercise)
   • Diarrhea, increased GIT motility (increased parasympathetic tone)
   • Decreased blood flow to the heart and brain \[\rightarrow\] overt shock
   • Delayed or retrograde ejaculation
   CONTRAINDIATED with MAO inhibitors. In pheochromocitoma patients guanethidine can cause hypertensive crisis.

GUANDAREL
• It is similar to guanethidine in its mode of action and indications but it has a shorter duration of action
• Guandarel causes less morning hypotension and diarrhea than guanethidine
• It is also contraindicated in patients taking MAO inhibitors
• It causes water retention

DEBRISOQUINE
   Structure analogue of Guanethidine but it produces adrenergic neuronal blockade by the same mechanism as Bretylium. Potent antihypertensive drug.

BRETYLIUM
   It produces a selective block on the peripheral sympathetic nervous system.

1. Pharmacological effects
   • It is taken up by adrenergic nerve terminals \[\rightarrow\] blocks of the release of NE
   • It also inhibits the reuptake of NE into the nerve terminal
   • Initially it produces sympathomimetic effect

2. Therapeutic uses
   It is no longer available as an antihypertensive drug.
   In some cases it can be used as an antiarrythmic agent

3. Untoward effects
   a.) cardiac stimulation
   b.) strong hypotension
   c.) muscle weakness
   d.) mental confusion
METHYLDOPA
In the treatment of mild and moderately severe hypertension. It lowers blood pressure by reducing TPR without a considerable change in HR and in CO.

1. Mode of action
• As a dyhydroxyphenylalanine analogue competes with the NE precursors for the decarboxylase enzyme. It is metabolised to \( \alpha \)-methyl-NE which can replace NE and acts as a "FALSE TRANSMITTER"

\[
\text{METHYLDOPA} \rightarrow \alpha\text{-METHYL-DOPAMINE} \rightarrow \alpha\text{-METHYL- NE}
\]
• Methyldopa antihypertensive actions appear to be due to stimulation of central \( \alpha \) adrenoeceptors by \( \alpha \)-methyl-NE or \( \alpha \)-methyl dopamine

2. Pharmacokinetics and dosage
Bioavailability is low (25 %). Its half life about 2 h. 75 % cleared by renal excretion. Oral administration: maximal effect within 4-6 h, and it persists about 24 h.
Usual therapeutic dose: 1-2 g/day

MAO INHIBITORS
• Antidepressants. Undesired effects: orthostatic hypotension
• They elevate the levels of NE and 5-HT in the brain, ganglia, other peripheral tissues.
• They can prevent many of the actions of Reserpine
• Hypertensive crisis may occur after consuming tyramine rich food

PARGYLINE Lower blood pressure by increasing the concentration of an ineffective fals transmitter. TYRAMINE (in food) \( \rightarrow \) OCTOPAMINE (fals transmitter) (if MAO is inhibited in gastrointestinal mucosa)