Microspheres as a drug carrier in Novel Drug Delivery System

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Abstract: The main goal of treatment should be to avoid serious hypertension complications such as heart attack, stroke, and heart failure. The microsphere has the properties of a free-flowing powder that contains proteins and synthetic or natural polymers. The advantages of advanced drug delivery systems over traditional multi-dose therapy are numerous. The drug delivery systems in the microsphere are suitable for delayed or sustained release formulations with low dose repeatability risk and short gastric habitation time. The current review delves into the therapeutic aspects of the microsphere drug delivery system, including the required area for micro particulate, the types of polymers used, the method of preparation, the types of microspheres in detail, microsphere parameters and targeting, and practical aspects of microspheres.

MICROSPHERE

To achieve optimum therapeutic efficacy, the chemical must be delivered to the target area in the correct amount and at the proper time, resulting in minimal toxicity and adverse effects**. [N. K. Jain]**

There are several methods for delivering a medicinal material to the target region in a regulated, sustained manner. One method is to use microspheres as medication carriers. One of the most exciting areas of research in pharmaceutical sciences is the development of novel delivery mechanisms for controlled medication release. A well-designed controlled drug delivery system can solve some of the drawbacks of traditional therapy while also improving a medicine's therapeutic efficacy.

It becomes required to maximize treatment efficacy. Deliver the agent to the target tissue in the right amount at the right time, resulting in minimal toxicity and side effects. There are several methods for delivering a medicinal material to the target region in a regulated, sustained manner. Attaching bioactive molecules to liposomes, bio erodible polymers, implants, monoclonal antibodies, and other particulates allows for site-specific targeting and administration with absolute accuracy.

One method is to use microspheres as medication carriers. Microspheres can be used to release medications, vaccines, antibiotics, and hormones in a regulated manner **[Chein YW.]**

The entrapped component is disseminated inside the microsphere's matrix in micrometrics, while the entrapped substance is clearly confined by the unique capsule wall in micro Capsules.

Micro matrices have trapped material that is scattered within the microsphere matrix, whereas microcapsules contain trapped material that is clearly confined by a defined capsule wall. The medication was disseminated or dissolved via the particle matrix, and the solid biodegradable microspheres have the potential to allow for regulated drug release. Microspheres are solid spherical particles that range in diameter from 1 to 1000m.They're biodegradable, spherical, free-flowing proteins or synthetic polymer particles.

Microspheres are divided into two categories:

- Microcapsules
- Micro matrices **[Inada A]**

Microspheres of various types

1. Biodegradable microspheres
2. Eye-catching microspheres
3. Microsphere skimming
4. Radioactive Microspheres
5. Demonstrative microspheres
6. Polymeric microspheres
    - Biodegradable polymeric microspheres
    - Synthetic polymeric microspheres **[Imran Abdul, Saravana Kumar K, Kataria Sahil]**

Advantages of microspheres

1. They provide safety before and after the administration of unstable drug.
2. They reduced drug centralization in locations other than the tissue or the target organ.
3. Diminished part and hazard
4. Molecule size reduction to improve dissolvability of poorly soluble medicines.
5. Provide a consistent and delayed corrective effect.
6. Reduces dose recurrence and, as a result, improves patient consistency.
7. Because of their spherical shape, they may be injected into the body.
8. Improved pharmaceutical use will increase bioavailability and reduce the occurrence or severity of adverse effects.
9. The shape of microspheres allows for controlled changes in corruption and pharmaceutical release.
10. Dosage form selection for intended drug delivery route

11. Drug release and distribution that is modified and tailored (even site-specific).
12. Pharmacokinetics with less intra- or inter-subject variability are more predictable.
13. A physiological environment with a more uniform distribution.
14. Drug combinations with stable fixed doses; - dosage titration and less dose-dumping
15. Patient centricity through improved compliance and adherence (e.g., patients with dysphagia).
16. Individual counselling (e.g., for pediatric or geriatric population)
17. Improving the medicinal formulations' stability.
18. Separating the elements to improve compatibility.
19. Patent protection for innovative items with a long life cycle **[Miléna Lengyel]**

LIMITATION

The following are some of the disadvantages discovered:

1. The formulas' changed release.
2. A range of circumstances, such as meals and the velocity of transit through the stomach, might affect the controlled release dosage form's release rate.
3. Variations in the rate of release from one dose to the next.
4. Because controlled release formulations often have a larger drug load, any degradation of the dosage form's release properties could result in toxicity.
5. These dosage forms should not be crushed or chewed.**[Vyas SP]**

MATERIALS USED IN MICROSPHERE PREPARETION

Polymers are commonly utilized as microspheres.

They are divided into two categories.

I. Synthetic Polymers
II. Natural Polymers

There are two types of **synthetic polymers**.

1) Non-biodegradable polymers
   - ✓ Poly methyl methacrylate (PMMA)
   - ✓ Acrolein
   - ✓ Glycidyl methacrylate
   - ✓ Epoxy Polymer
2) Biodegradable polymers**[P.M. Dandagi, Chinna Gangadhar B]**

   - ✓ Lactides, Glycolides & their co polymers
   - ✓ Poly alkyl cyano Acrylates
   - ✓ Poly anhydrides

Natural polymers derived from many sources such as proteins, carbohydrates, and chemically modified polysaccharides. **[Rana mazumder, Kavitha K]**

- **Proteins:**

✓ Albumin
✓ Gelatin9
✓ Collagen

- **Carbohydrates:**

✓ Agarose
✓ Carrageenan
✓ Chitosan10
✓ Starch

- **chemically modified carbohydrates:**

✓ Poly starch.
✓ Poly dextran11

Microspheres with bio adhesion

Adhesion is defined as the adhesion of a medication to a membrane by the use of water soluble polymers with adhesive properties. Bio adhesion is defined as the attachment of a drug delivery device to a mucosal membrane, such as the buccal, ocular, rectal, or nasal mucosa.

These microspheres have a longer residence duration at the application site, resulting in more intimate interaction with the absorption site and improved therapeutic activity.

Carrier technology is a smart approach to drug delivery that involves connecting the drug to a carrier particle, such as microspheres, Nano spheres, liposomes, nanoparticles, and so on, that controls the drug's release and absorption.

Because of their small size and high carrier capacity, microspheres are a significant component of particulate drug delivery systems. **[Meghna KS, Kumar A, Vikrant KN]**

Magnetic microspheres

This type of delivery method is critical since it targets the drug to the illness site.

A higher amount of freely circulating medicine can be substituted with a smaller amount of magnetically focused drug in this situation.

Magnetic carriers receive magnetic responses to a magnetic field from integrated components such as chitosan, dextran, and other materials utilized in magnetic microspheres.

Therapeutic magnetic microspheres and diagnostic magnetic microspheres are the two types. **[Gholap SB, Agusundaram M, Sudha MT]**

- **Therapeutic Magnetic Microspheres:**

It is utilized to deliver chemotherapy agents to a tumors in the liver.

This technique can also target drugs such as proteins and peptides.

- **Diagnostic Microspheres:**

By producing Nano size particles paramagnetic iron oxides, it can be used to image liver metastases as well as identify bowel loops from other abdominal structures.

Floating microspheres

The bulk density of floating kinds is lower than that of gastric fluid, therefore they float in the stomach without altering the rate of gastric emptying.

If the system is floating on stomach content, the drug is released slowly at the optimal rate, which enhances gastric residence and plasma concentration fluctuations.

It also minimizes the risk of striking and dose dumping, as well as providing a longer-lasting therapeutic benefit.

Another benefit is that it has a longer therapeutic impact and thus reduces dose frequency. **[Thanoo BC, Parmar H]**

Polymeric microspheres

Biodegradable polymeric microspheres and synthetic polymeric microspheres are the two forms of polymeric microspheres that can be categorized.

- **Biodegradable polymeric microspheres**

Natural polymers like starch are employed because they are biodegradable, biocompatible, and bio adhesive.

Because of their high degree of swelling in aqueous media, biodegradable polymers lengthen the residence period when in contact with mucous membranes, resulting in gel formation.

The rate and amount of medication release are controlled by the polymer concentration and the release pattern throughout time.

The fundamental disadvantage is that drug loading efficiency of biodegradable microspheres in clinical application is complex, making drug release difficult to control.

- **Synthetic polymeric microspheres**

Synthetic polymeric microspheres are widely employed in clinical applications as bulking agents, fillers, embolic particles, drug delivery vehicles, and other applications, and have been shown to be safe and biocompatible.

However, the fundamental disadvantage of these microspheres is that they tend to migrate away from the injection site, posing a danger of embolism and subsequent organ damage.

Radioactive microspheres

Radio embolization therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumor of interest. So these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are αemitters, β emitters, γ emitters.

Mucoadhesive microspheres

Mucoadhesive microspheres with a diameter of 1-1000 mm, made entirely of a mucoadhesive polymer or with an outer coating of it, and coupling mucoadhesive properties to microspheres have additional benefits, such as efficient drug absorption and increased bioavailability due to a high surface to volume ratio, a much more intimate contact with the mucus layer, and specific drug targeting to the absorption site achieved by anchoring plant lectin.

Mucoadhesive microspheres can be customized to stick to any mucosal tissue, including those found in the eye, nasal cavity, urinary tract, and gastrointestinal tract, allowing both localized and systemic controlled drug release.**[Kalyan S,]**

METHOD OF PREPARATION

1. Spray Drying
2. Solvent Evaporation
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technique
6. Spray drying and spray congealing
7. Solvent extraction
8. Quassi emulsion solvent diffusion

1. **Spray Drying**

The polymer is first dissolved in a suitably volatile organic solvent, such as dichloromethane or acetone, in the Spray Drying process.
With high-speed homogenization, the medication in solid form is spread in the polymer solution.
This dispersion is subsequently atomized using a hot air stream.
The atomization causes the development of minute droplets or fine mists, from which the solvent evaporates instantly, resulting in the formation of microspheres with sizes ranging from 1 to 100 micrometer's.
The cyclone separator separates the micro particles from the heated air, while vacuum drying removes any trace of solvent.
One of the most significant advantages of this method is its ability to operate under aseptic circumstances. **[Ramteke K.H]**

2. **Solvent Evaporation:**

This procedure takes place in a liquid production vehicle.The microcapsule coating is suspended in a volatile solvent that is incompatible with the liquid production vehicle.
In the coating polymer solution, a core material to be microencapsulated is dissolved or distributed.
To obtain the proper size microcapsule, the core material combination is distributed in the liquid production vehicle phase by agitation.
If necessary, the mixture is heated to evaporate the solvent so that the polymer of the core material can distribute in the polymer solution and shrink around the core.
Matrix-type microcapsules are generated when the core material is dissolved in the coated polymer solution.
Water soluble or water insoluble materials can be used as core materials. The creation of an emulsion between a polymer solution and an immiscible continuous phase, whether aqueous (o/w) or non-aqueous, occurs during solvent evaporation. **[Patel B, Ramteke K.H]**

3. **Single emulsion technique:**

Single emulsion approach is used to make micro particle carriers of natural polymers, such as proteins and carbohydrates.
Natural polymers are first dissolved or dispersed in an aqueous media, then distributed in a non-aqueous medium such as oil.
The dispersed globule is then cross linked in the following phase.
Heat or chemical cross linkers can be used to achieve cross linking.
Glutaraldehyde, formaldehyde, acid chloride, and other chemical crosslinking agents are used.
Thermolabile compounds are not appropriate for heat denaturation.
If introduced at the time of preparation and then centrifuged, washed, and separated, chemical cross linking has the problem of exposing the active substance to too many chemicals.
The size, size distribution, surface morphology, loading, drug release, and bio performance of the final multiparticulate product can all be influenced by the surfactants used to stabilize the emulsion phases **[Patel N. R].**

4. **Double emulsion technique:**

The development of several emulsions or a double emulsion of type w/o/w in the double emulsion method of microspheres preparation is best suited for water soluble medicines, peptides, proteins, and vaccines.
This approach is applicable to both natural and manmade polymers' lipophilic organic continuous phase disperses the aqueous protein solution. The active components may be present in this protein solution. The polymer solution that eventually wraps the protein contained in the scattered aqueous phase makes up the continuous phase. After that, the primary emulsion is homogenized or sonicated before being added to the poly vinyl alcohol aqueous solution (PVA).
A double emulsion is formed as a result of this.
The emulsion is then treated to either solvent evaporation or solvent extraction to remove the solvent.
The process of double emulsion solvent evaporation/ extraction has been used to successfully insert a variety of hydrophilic pharmaceuticals such as luteinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides, and conventional compounds into microspheres.**[Patel N. R]**

5. **Phase separation coacervation technique:**

This method works by lowering the polymer's solubility in the organic phase, causing the creation of a polymer-rich phase known as Coacervates.
The drug particles are disseminated in a polymer solution, and an incompatible polymer is added to the system, causing the first polymer to phase separate and swallow the drug particles.
The addition of a non-solvent causes the polymer to solidify.
This approach used butadiene as an incompatible polymer to create poly lactic acid (PLA) microspheres.
The rate of achieving coacervates impacts the dispersion of the polymer film, particle size, and agglomeration of the produced particles, hence process variables are crucial.
The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment. **[Bansal H, Alagusundaram M]**

6. **Spray drying and spray congealing:**

These techniques rely on the drying of a polymer and drug mist in the air.
Spray drying and spray congealing are two processes that are distinguished by the removal of the solvent or the cooling of the solution.
First, the polymer is dissolved in a suitable volatile organic solvent like dichloromethane or acetone.
Under high-speed homogenization, the drug in solid form is dispersed in the polymer solution.

This dispersion is then atomized using a hot air stream.
The atomization results in the formation of small droplets or fine mists, from which the solvent evaporates instantly, resulting in the formation of microspheres with sizes ranging from 1-100 m.
The cyclone separator separates the micro particles from the hot air, while vacuum drying removes any traces of solvent.
One of the process's main advantages is its ability to operate under aseptic conditions.
Various penicillin's are encapsulated using the spray drying process.
Spray congealing is used to encapsulate thiamine mononitrate and sulpha ethylthiadizole in a mixture of mono- and diglycerides of stearic acid and palmitic acid.
However, extremely rapid solvent evaporation causes the formation of porous micro particles**.**
[Bansal H, Alagusundaram M]

7. **Solvent extraction:**

The solvent evaporation method is used to make micro particles and involves extracting the organic phase from aqueous or non-aqueous solvent.
Isopropanol and other water miscible organic solvents are used in this method.
Water extraction can be used to remove the organic phase.
The microspheres' hardening time is reduced as a result of this process.
Direct incorporation of the drug or protein into a polymer organic solution is one variation of the process.
The rate of solvent removal by extraction depends on water temperature, emulsion volume to water ratio, and polymer solubility profile. **[Patel N. R., Bansal H, Alagusundaram M.]**

8. **Quassi emulsion solvent diffusion:**

In the literature, a novel quasi-emulsion solvent diffusion method for making controlled release microspheres of drugs with acrylic polymers has been described.
An external phase containing distilled water and polyvinyl alcohol can be used to make microsponges using a quasi-emulsion solvent diffusion method.
Drugs, ethanol, and polymer make up the internal phase.
Plasticity is increased by increasing the polymer concentration.
The internal phase is first made at 60 degrees Celsius, then mixed with the external phase at room temperature.
The mixture is constantly stirred for 2 hours after the emulsification process.
The micro sponges can then be separated by filtration of the mixture.
After that, the product is washed and dried for a day in a vacuum oven at 40°C**. [Bansal H, Alagusundaram M.]**

Polymerization techniques:

Polymerization techniques for preparing microspheres are generally classified as follows:

1. Normal polymerization
2. Interfacial polymerization.

Both are done in a liquid state.
Normal polymerization: This is done in a variety of ways, including bulk, suspension, and precipitation, emulsion, and micellar polymerization. To initiate polymerization, a monomer or a combination of monomers, as well as the initiator or catalyst, are usually heated in bulk.
The resulting polymer can be molded into microspheres. During the polymerization process, drug loading may be done. Bead or pearl polymerization is another name for suspension polymerization.
It's done by heating the monomer or monomer composition as droplets dispersion in a continuous aqueous phase. An initiator and other additives may be present in the droplets.
Emulsion polymerization differs from suspension polymerization because an initiator is present in the aqueous phase, which then diffuses to the micelle surface. Bulk polymerization has the advantage of producing pure polymers.
Interfacial polymerization: This is the reaction of various monomers at the interface between two immiscible liquids to form a polymer film that envelops the dispersed phase. **[Patel N. R, Ramteke K.H, Sahil K, Pavan Kumar B]**

MICROSPHERE EVALUATION:

- **Size and shape of the particles**

Traditional light microscopy (LM) and scanning electron microscopy (SEM) are the most common methods for observing micro particles (SEM).

- **Chemical analysis with electron spectroscopy**

Chemical analysis can be used to determine the surface chemistry of the microspheres using electron spectroscopy (ESCA).

- **Calculation of density:**

Using a multi volume pycnometer, the density of the microspheres can be determined.

- **Isoelectric point:**

Micro electrophoresis is used to determine the isoelectric point of microspheres by measuring their electrophoretic mobility.

- **Angle of contact:**

The wetting property of a micro particulate carrier is determined by measuring the angle of contact.

- **Methods used in vitro:**

Release studies for various types of microspheres are carried out using various dissolution media, the most common of which is the rotating paddle apparatus (USP/BP).

The following equation can be used to calculate drug entrapment efficiency:

Percent Entrapment = Actual content/Theoretical content x 100.

- **Swelling index:**

The microsphere's swelling index was calculated using the formula:

Swelling index= (mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres) 100. **[Singh C, Sahil K, Pavan Kumar B, Dhakar R. C, Parmar H]**

HYPERTENSION

WHO has identified hypertension as one of the most significant risk factors for morbidity and mortality worldwide, with approximately nine million people dying each year **[Organisation WH].**

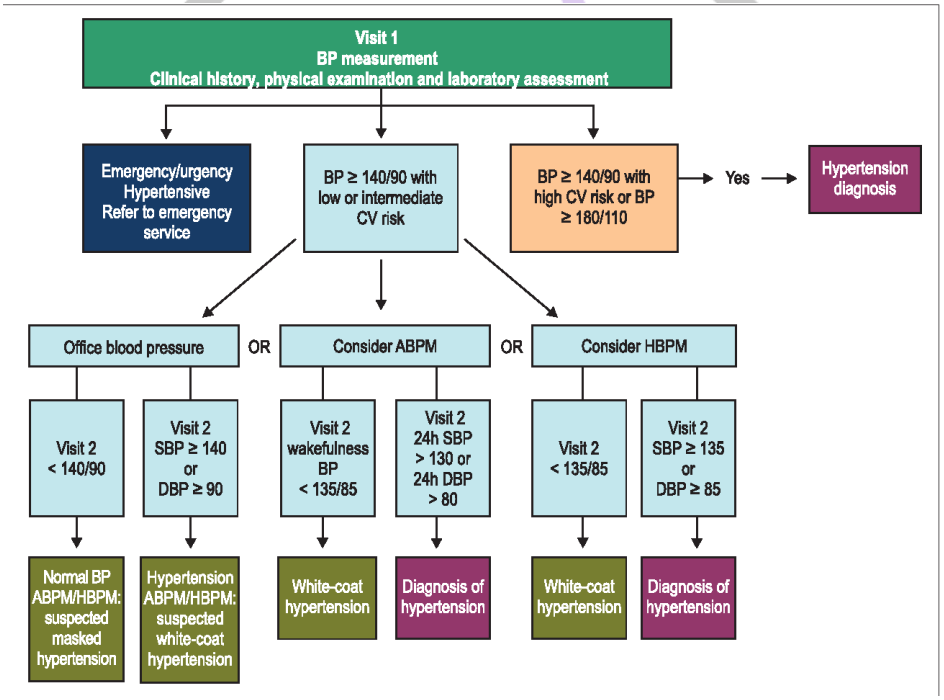
High blood pressure (BP), also known as hypertension, is defined as a clinic blood pressure of 140/90 mmHg or higher confirmed by a subsequent ambulatory blood pressure monitoring daytime average (or home blood pressure monitoring average) of 135/85 mmHg or higher by the National Institute for Health and Care Excellence (NICE) **[Excellence NIFC].**

Hypertension is a "**silent killer**" because it causes no symptoms at first.

The most common type of hypertension, affecting 95 percent of hypertensive patients, is idiopathic (essential) hypertension, which is caused by a combination of genetic and environmental factors.

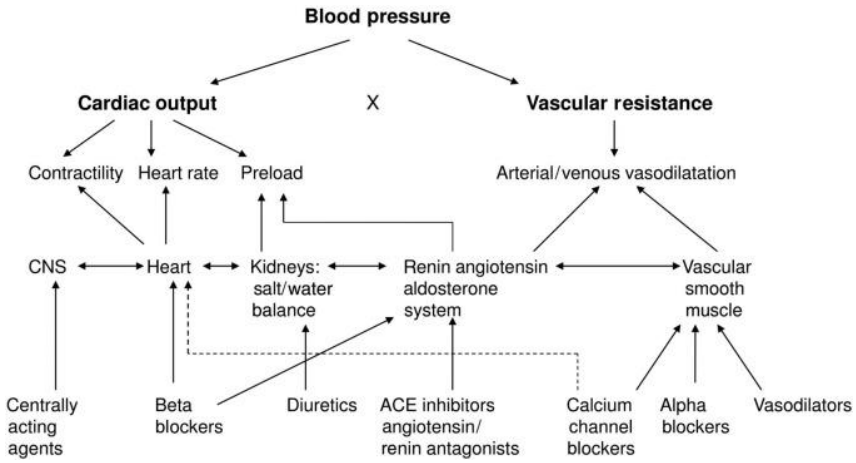
It raises the risk of stroke, heart attack, and kidney failure.

Excess salt, abnormal arteries, increased blood volume, genetic disorders, stressful life, recreational drugs, health conditions, pregnancy, hormone therapy, and other factors all contribute to hypertension.



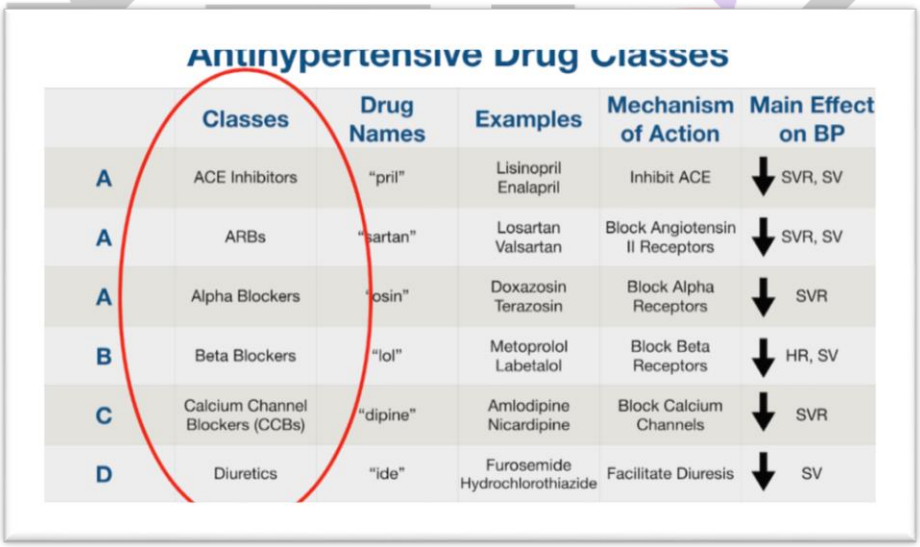
The following are the treatments for hypertension:

Antihypertensive drugs, nonpharmacological hypertension management, weight loss, sodium restriction, alcohol restriction, and physical activity **(Midha Kanav et al.).**



Antihypertensive drug

Antihypertensive are a class of drugs that are used to treat hypertension (high blood pressure)
[Antihypertensive Agents at the US National Library].
Antihypertensive therapy aims to prevent high blood pressure complications like stroke and myocardial infarction.
Evidence suggests that lowering blood pressure by 5 mmHg can reduce the risk of stroke by 34%, ischemic heart disease by 21%, dementia, heart failure, and cardiovascular mortality. **[27.Law M, Wald N]**
Antihypertensive come in a variety of forms that lower blood pressure in different ways.
Thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists (ARBs), and beta blockers are among the most important and widely used medications.
Several large studies and national guidelines have been conducted to determine which type of medication to use first for hypertension.
The primary goal of treatment should be to prevent important hypertension end points like heart attack, stroke, and heart failure.
Patient age, associated clinical conditions, and end-organ damage all influence the dosage and type of medication given. **[Nelson, Mark]**
The fact that multiple factors contribute to hypertension may theoretically favor combination therapy.
It may not be possible to control blood pressure with a single agent acting through a single mechanism **[Y. Lam].**
In the last two decades, controlled drug delivery by encapsulating the drug inside polymeric carriers has made significant progress, as it can improve drug release while reducing side effects.**[Kristmundsdottir T].**



Calcium channel blockers

Calcium channel blockers prevent calcium from entering artery muscle cells.

1. **dihydropyridines:**

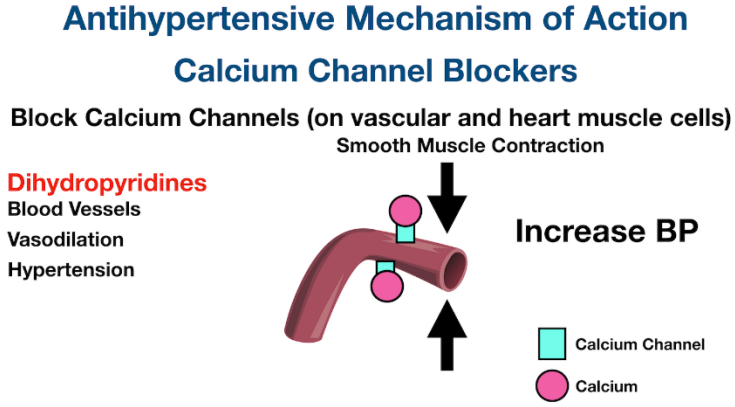
- ✓ amlodipine
- ✓ barnidipine
- ✓ cilnidipine
- ✓ clevidipine
- ✓ felodipine
- ✓ isradipine
- ✓ lercanidipine

- ✓ levamlodipine
- ✓ nicardipine
- ✓ nifedipine
- ✓ nimodipine
- ✓ nisoldipine
- ✓ nitrendipine

2. **non-dihydropyridines:**

- ✓ diltiazem
- ✓ verapamil

For all patients, regardless of age or race, the 8th Joint National Committee (JNC-8) recommends calcium channel blockers as a first-line treatment, either alone or in combination with thiazide-type diuretics, ACE inhibitors, or angiotensin II receptor antagonists. **[James PA, Oparil S]**



Calcium channel blockers (CCBs) were first introduced over 35 years ago for the treatment of coronary heart disease (CHD), but their effectiveness in hypertension was quickly recognized (HTN).
Angina, peripheral vascular disease, and some arrhythmic conditions were among the initial indications, in addition to HTN. **[Tringle DJ]**

Contraindications

While it is generally safe to use in patients with aortic stenosis (narrowing of the aorta where it meets the left ventricle) because it does not inhibit ventricle function, it can still cause collapse in severe stenosis [Grimard, Brian H].
Patients with severe hypotension may experience an increase in their low blood pressure, and patients with heart failure may experience pulmonary edoema.
Amlodipine is unable to be fully metabolized by those with impaired liver function, resulting in a longer half-life than usual [electronic medicines compendium (emc)].

Adverse Effect

Constipation, worsening cardiac output, and bradycardia are all possible side effects of non-dihydropyridines.
Lightheadedness, flushing, headaches, and peripheral edoema are all possible side effects of dihydropyridines.
The redistribution of fluid from the intravascular space to the interstitium is most likely the cause of peripheral edoema.
Gingival hyperplasia has been reported as well. [Hernandorena I, Jurić D]

Overdose

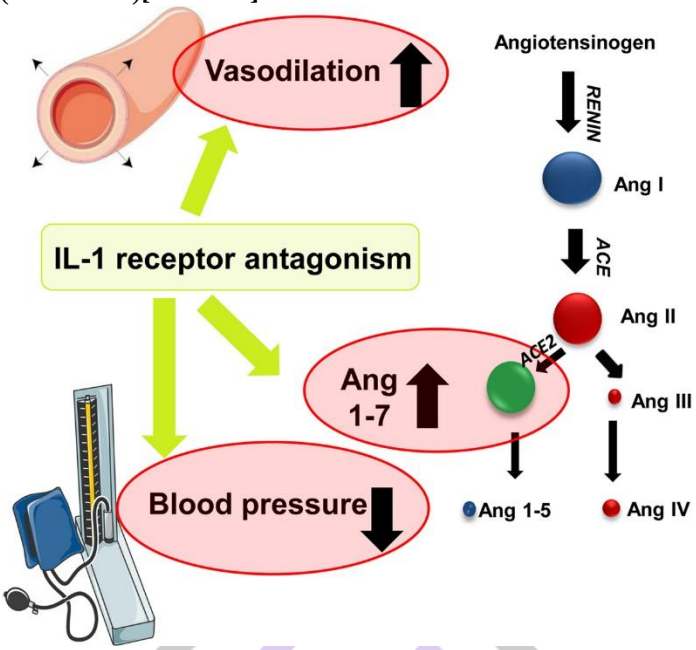
A high mortality rate is associated with severe calcium channel blocker (CCB) overdose.**[Hofer CA]**
CCBs are responsible for more than a third of deaths caused by cardiovascular drug overdose.**[Olson KR]**
Cardiovascular depression is caused by an overdose of CCBs, which is often resistant to standard resuscitation methods.
High doses of catecholamines, glucagon, and measures to prevent further drug ingestion and absorption are used to treat severe intoxication. **[Kenny J, Shepherd G]**

Antagonists of the angiotensin II receptor

Angiotensin II receptor antagonists work by inhibiting angiotensin receptor activation.

- ✓ azilsartan
- ✓ candesartan
- ✓ eprosartan
- ✓ irbesartan
- ✓ losartan
- ✓ olmesartan
- ✓ telmisartan
- ✓ valsartan
- ✓ Fimasartan

The evidence for and against the suggestion that angiotensin receptor blockers may increase the risk of myocardial infarction was examined in a 2004 BMJ article (heart attack)**[Verma S].**



Absorption

The dosage determines absolute bioavailability.

Food reduces bioavailability slightly (a decrease of about 6 percent is seen when the 40-mg dose is administered with food).

Contraindications

Valsartan, irbesartan, and candesartan have all been linked to serious drug interactions.

Because olmesartan is not metabolised by the cytochrome P450 enzyme system, it is less likely to interact with drugs that are.**[US-based Sankyo Pharma Inc]**

Consequences

Tachycardia and bradycardia (fast or slow heartbeat), hypotension (low blood pressure), and edoema are all common side effects of angiotensin II receptor antagonists (swelling of arms, legs, lips, tongue, or throat, the latter leading to breathing problems).

Allergic reactions are possible**[Micardis].**

Pharmacology

Essential hypertension, renovascular hypertension, congestive heart failure, and renal diseases associated with albuminuria are all linked to the renin-angiotensin system, specifically angiotensin II. **[Burnier M, Bumier M, Rodgers JE]**

The use of ACE inhibitors to block the renin-angiotensin system has proven to be effective in treating these conditions; however, some of the side effects of ACE inhibitors appear to be unrelated to angiotensin II blockade.

Other effects of ACE inhibition, such as the degradation of bradykinins and prostaglandins, cause cough and angioedema**. [Burnier M]**

Mechanism of action

The ARBs' mechanism of action, which involves selective inhibition of angiotensin II through competitive antagonism of angiotensin II receptors, has been proposed as a way to reduce side effects and possibly improve clinical efficacy.

ARBs reduce blood pressure by antagonising angiotensin II–induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic response.**[Bumier M]**

Pharmacokinetics

The substance is quickly absorbed from the gut, but to varying degrees.

The average bioavailability is approximately 50% (42–100%).

The kinetics of telmisartan are unaffected by food intake in clinical trials.

Over 99.5 percent of plasma proteins bind to albumin and alpha-1-acid glycoprotein**.[Haberfeld, H, ed. (2015)].**

It has the longest half-life of any ARB for angiotensin II receptors (24 hours**)[Pershadsing, Benson SC]**

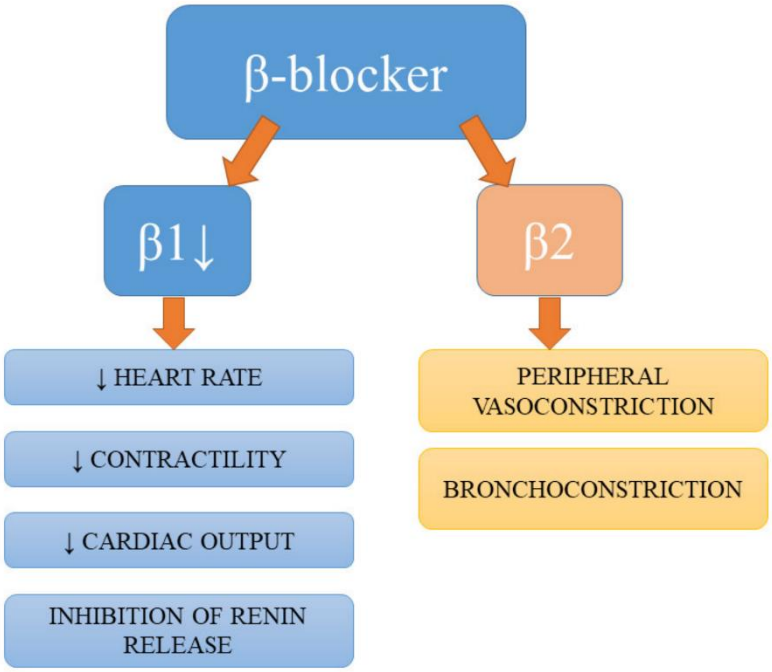
BETA-BLOCKERS

Beta-blockers are a diverse pharmacological class, with pharmacodynamic properties that are determined by cardiac selectivity, partial agonist activity, and associated vasodilating properties.

They all lower blood pressure to the same extent, albeit with varying degrees of cardiac output and vasodilation, depending on their pharmacological properties.

Beta-blockers are a type of medication that is used to treat heart disease and other conditions.

[do Vale GT, Ceron CS]



Beta receptors exist in three distinct forms: beta-1 (B1), beta-2 (B2), and beta-3 (B3). Beta-1 receptors located primarily in the heart mediate cardiac activity. Beta-2 receptors, with their diverse location in many organ systems, control various aspects of metabolic activity and induce smooth muscle relaxation. Beta-3 receptors induce the breakdown of fat cells and are less clinically relevant at present. Blockade of these receptors by beta-blocking medicines is used to treat a broad range of illnesses. **[do Vale GT, Ceron CS]**

Mechanism of Action

Catecholamines, epinephrine, and norepinephrine bind to B1 receptors in the heart, increasing cardiac automaticity and conduction velocity.
Renin is released when B1 receptors are activated, which raises blood pressure.
Binding to B2 receptors, on the other hand, causes smooth muscle relaxation as well as increased metabolic effects such as glycogenolysis.
Beta-blockers have different specificities for different receptors, so the effects produced vary depending on the type of receptor(s) blocked and the organ system involved.
Some beta-blockers bind to alpha receptors to some extent, allowing them to have a different clinical effect in certain situations.
Beta-blockers block these effects by binding to the B1 and B2 receptors.
As a result, the chronotropic and inotropic effects on the heart are inhibited, causing the heart rate to slow.
Beta-blockers lower blood pressure through a variety of mechanisms, including reduced renin and cardiac output.
Angina improves after beta-blocker use because of the negative chronotropic and inotropic effects, which result in a lower oxygen demand.
These drugs also have a potent antiarrhythmic effect and prolong atrial refractory periods.
Beta-blockers classify as either non-selective and beta-1 selective. There are also beta-2 and beta-3 selective drugs; neither has a known clinical purpose to date. Non-selective agents bind to both beta-1 and beta-2 receptors and induce antagonizing effects via both receptors. Examples include propranolol, carvedilol, sotalol, and labetalol. Beta-1 receptor-selective blockers like atenolol, bisoprolol, metoprolol, and esmolol only bind to the beta-1 receptors; therefore, they are cardio-selective. **[Gorre F] [Rehsia NS] [Machackova J]**

Administration

Beta-blockers come in oral, intravenous, and ophthalmic forms, as well as intramuscular injections. Depending on the medication, different dosage ranges are available.

Adverse Effects

Beta receptors are found throughout the body and are responsible for a wide range of physiological effects. Beta-blocker medications that block these receptors can have a variety of side effects. Bradycardia and hypotension are two of the most common side effects. There have also been reports of fatigue, dizziness, nausea, and constipation. Erectile dysfunction and sexual dysfunction have been reported by some patients. Bronchospasm occurs less frequently in beta-blocker patients. Asthmatic patients are more vulnerable. **[Marques de Mello L]**

Contraindications

Beta-blockers have traditionally been avoided by asthmatic patients.

Cardio-selective beta-blockers, also known as beta-1 selective, are now approved for use in asthmatics, but non-selective beta-blockers are not.
Beta-blocker use is generally contraindicated in patients with acute or chronic bradycardia and/or hypotension.
Depending on the patient's medical history, certain beta-blockers are contraindicated.
Sotalol should not be used by patients with long QT syndrome or who have previously experienced torsade's de pointes.
Beta-blockers should be avoided by patients with Raynaud's phenomenon to avoid exacerbation. **[De Vecchis R, Ariano C] [Etchegoyen CV, Keller GA]**

Monitoring

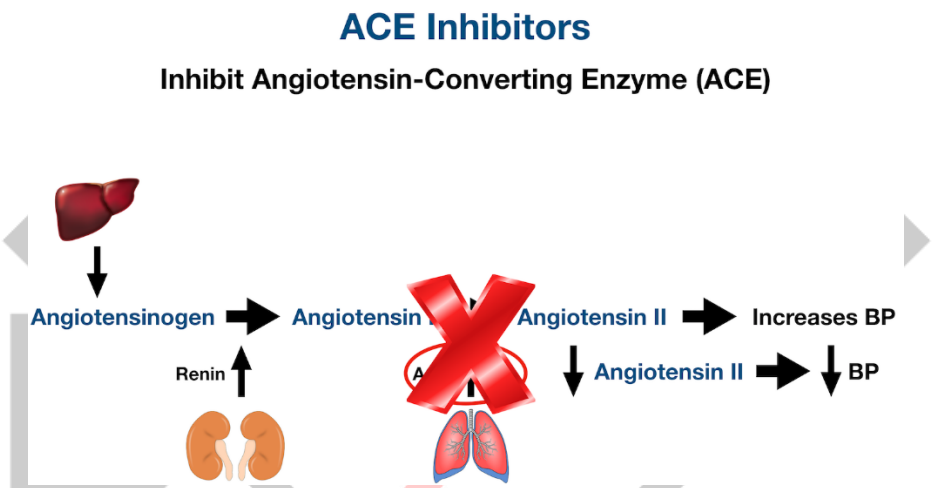
While taking beta-blockers, the patient's heart rate and blood pressure must be monitored.
Because sotalol has QT-prolonging effects, the clinician must keep an eye on the QTc interval when using it. **[Farzam K, Tivakaran VS]**

Toxicity

Glucagon is the antidote for beta-blocker overdose.
It's particularly helpful in the case of beta-blocker-induced cardiotoxicity.
If glucagon fails, cardiac pacing is the next best option.

Angiotensin Converting Enzyme Inhibitors (ACEI)

The most commonly prescribed medications for the treatment of cardiovascular and renal diseases, such as heart failure, acute coronary syndrome, nephrotic syndrome, diabetes, and hypertension, are angiotensin-converting enzyme inhibitors (ACEIs). **[Nasution SA]**
In both hypertensive and normotensive subjects, angiotensin-converting enzyme inhibitors effectively lower mean arterial blood pressure, as well as systolic and diastolic blood pressure. **[Vidt DG, Bravo EL][Todd PA]**



Multiple randomised controlled trials have looked at angiotensin-converting enzyme inhibitors as antihypertensive drugs. **[Messerli FH]**
The Eighth Joint National Commission (JNC8) published evidence-based guidelines for treating high blood pressure in adults in 2014, recommending ACE inhibitors as one of four drug classes for adults with elevated blood pressure as initial therapy**[James PA].**
Calcium channel blockers, thiazide diuretics, and angiotensin receptor blockers are the other three drug classes that are used as initial therapy in the nonblack population.
For the general black population with high blood pressure, only thiazides and calcium channel blockers are recommended as first-line treatments.**[Page MR]**
ACE inhibitors are also recommended as first-line antihypertensive therapy by the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC).
Especially in patients with diabetes mellitus and cardiovascular diseases. **[Whelton PK, Williams B]**

Mechanism of Action

Angiotensin II causes direct vasoconstriction of precapillary arterioles and postcapillary venules, inhibits norepinephrine reuptake, stimulates catecholamine release from the adrenal medulla, reduces sodium and water excretion in the urine, stimulates aldosterone synthesis and release, and stimulates hypertrophy of both vascular smooth muscle cells and cardiac myocytes**. [FOLKOW B, Bell L, Madri JA]**

Adverse Effects

A dry, nonproductive paroxysmal cough affects 1 to 10% of people, and there is no treatment for it. **[Pinargote P, Guillen D][Israili ZH, Hall WD]**
Nonsteroidal anti-inflammatory drugs (NSAIDs) and intermediate-dose aspirin (500 mg) have been shown in studies to help with ACE inhibitor-induced cough. **[Tenenbaum A, Grossman E]**

Cough caused by ACE inhibitors is more common in women than in men. **[Os I, Bratland B]**
The cough is usually dry, and it necessitates stopping the medication.

Contraindications

Patients with a history of angioedema or hypersensitivity to an ACE inhibitor, as well as those with hereditary or idiopathic angioedema, should avoid taking ACE inhibitors. [Brown NJ, Ray WA]
In pregnancy, ACE inhibitors should be avoided.
Under the old FDA system, they were classified as Category D in pregnancy because it has been linked to skull hypoplasia, anuria, hypotension, renal failure, lung hypoplasia, skeletal deformations, oligohydramnios, and death.**[Quan A]**

Monitoring

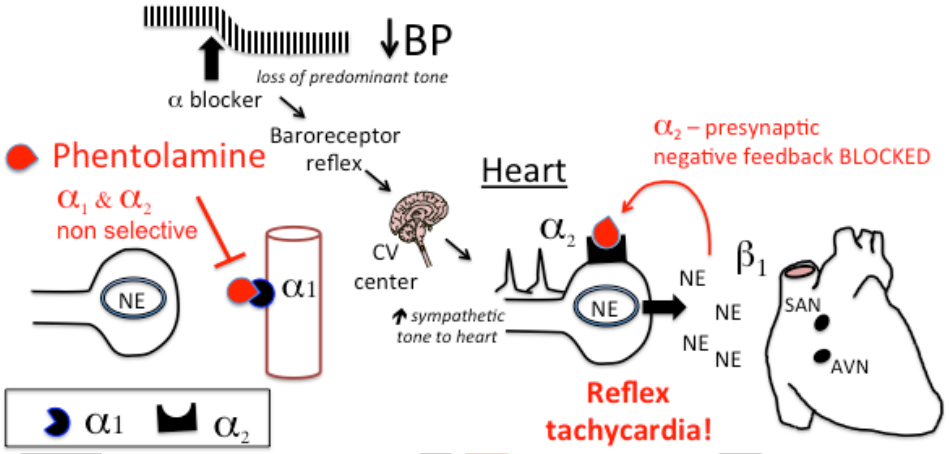
Because of the drug's effects on the renin-angiotensin-aldosterone system, renal function and electrolytes must be monitored on a regular basis.
If a patient's potassium level rises, their GFR drops, or their creatinine rises, the drug must be adjusted or discontinued.**[Christie GA, Lucas C]**

Toxicity

ACE inhibitors in high doses are usually well tolerated, but they can cause hypotension, a drop in GFR, and electrolyte imbalances. ACE inhibitors can also cause hyperkalemia and hyponatremia because they block aldosterone. **[Sorodoc V, Sorodoc L] [Varughese A, Taylor AA]**

Alpha Blockers

Essential hypertension, benign prostatic hyperplasia (BPH), and pheochromocytoma are all treated with alpha-blockers.
This activity examines the indications, contraindications, activity, adverse events, and other key aspects of alpha-blocker therapy in the clinical setting as they relate to the essential points needed by members of an interprofessional team managing the care of patients with the conditions listed above.



1. **Nonselective Alpha-blockers (alpha-1 and alpha-2)**

Phenoxybenzamine and phentolamine are nonselective alpha-blockers.
Both of these medications have been approved by the FDA for use in phochromocytoma patients.
Alpha-blockers phenoxybenzamine and phentolamine are irreversible and reversible, respectively.
During pheochromocytoma removal, both are used intraoperatively to manage hypertensive crisis. [Yu M, Han C][Sambhunath D, Pankaj K]

2. **Selective Alpha-1 Blockers**

The suffix "-osin" denotes a selective alpha-1 blocker.
Alfuzosin, doxazosin, terazosin, tamsulosin, and prazosin are some of these medications.
These drugs have been approved by the FDA to treat benign prostatic hyperplasia (BPH).
These drugs could also be used to treat essential hypertension.
They are, however, rarely used as first-line treatments for hypertension. [PubMed]]

3. **Selective Alpha-2 Blockers**

Yohimbine and idazoxan are examples of selective alpha-2 blockers.
Yohimbine has been used to treat male sexual dysfunction, but its efficacy has yet to be proven, and it is not currently FDA approved for this or any other use.
Idazoxan is being used in clinical trials, but no clinical role has been established. [Cui T, Kovell RC]

Mechanism of Action

The sympathetic nervous system is manipulated by alpha-blockers to produce their pharmacological effects.
Alpha-1 and alpha-2 receptors are the two types of alpha-adrenergic receptors.
The majority of alpha-1 adrenergic receptors are found on vascular smooth muscle (in the skin, gastrointestinal sphincters, kidneys, and brain), and when activated by catecholamines like epinephrine and norepinephrine, they cause vasoconstriction (NE).
Both systemic arterial blood pressure and peripheral resistance rise as a result of vasoconstriction.
Norepinephrine binds to this receptor more strongly than epinephrine.

When activated, alpha-2 adrenergic receptors on peripheral nerve endings inhibit the release of NE, providing a feedback mechanism for NE to inhibit its release.[Nash DT]

Administration

Phenoxybenzamine is an oral medication that should be started 10 to 14 days prior to the Pheochromocytoma being removed.
Phentolamine is a drug that can be given intramuscularly or intravenously to help with the removal of pheochromocytoma. **[Naranjo J, Dodd S]**

Adverse Effects

Hypotension, weakness, tachycardia, and tremulousness are all side effects of nonselective alpha-blockers.
The inhibition of alpha-1 receptors causes vascular smooth muscle relaxation and vasodilation, resulting in hypotension.
When alpha-2 receptors are simultaneously antagonised, the remaining negative effects are due to increased norepinephrine release.
Because of the spillover of norepinephrine, this release stimulates beta receptors, causing tremulousness and tachycardia. [Frishman WH]

Contraindications

Individuals who are hypersensitive to alpha-blockers or any other component of the drug formulation should avoid taking them.
When giving alpha-blockers to elderly patients or those who have had cataract surgery, use caution.
These drugs can make cataract surgery more difficult by causing iris prolapse and pupil constriction during the procedure, a condition known as "intraoperative floppy iris syndrome."
[PubMed]] [Alpha 1 Adrenergic Receptor Antagonists] [Christou CD, Tsinopoulos I]

Monitoring

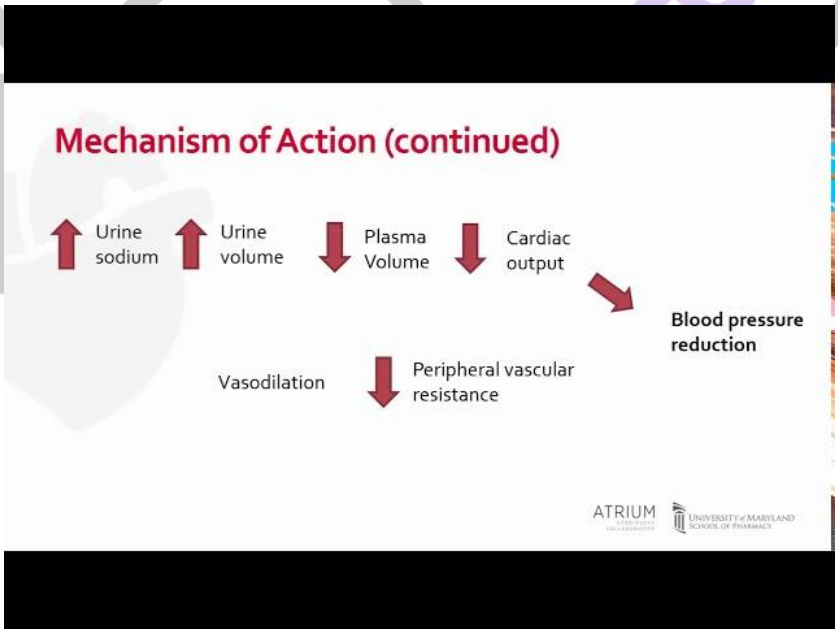
Because of the risk of hypotension and tachycardia when using phentolamine intraoperatively for pheochromocytoma removal, blood pressure and heart rate must be closely monitored**. [McMillian WD]**

Toxicity

The elderly male population is frequently prescribed alpha-blockers, and toxicity is common in these individuals.
Hypotension is the most common side effect.
Ischemic insult to major organs can occur with extremely low blood pressure, which increases the risk of falling.
If toxicity is suspected, general measures to lower blood pressure are required. [J. Ramirez]

Diuretics

Diuretics are a valuable and diverse class of drugs that are commonly used to treat hypertension, heart failure, and electrolyte imbalances.
The basic characteristics of diuretics, such as their mechanism of action, indications, adverse effects, and duration of action, are summarized in this review, which is followed by a review of recent findings from randomized trials.



For the latter, we used PubMed to conduct a systematic review of the last five years.**[Roush, G. C.]**

Mechanisms of Action

Although diuretics are a diverse group of medications, there are a few generalizations that can be made.
All diuretics work by blocking sodium reabsorption in various sites within the renal tubules, with the exception of mannitol and vasopressin receptor antagonists.
Carbonic anhydrase inhibitors, loop diuretics, thiazide diuretics, and thiazide-like diuretics are delivered to their sites of action through the organic acid secretory pathway.
Aldosterone antagonists, on the other hand, enter the bloodstream and act on the principal cells of the cortical collecting duct.**[Roush, G. C.]**

Pharmacodynamics

Diuretics are divided into three categories: thiazide diuretics, loop diuretics, and potassium-sparing diuretics. The use of potassium diuretics in congestive heart failure is discussed here.

In this article, we'll look at Thiazide and Loop diuretics in particular.

The nephron in the kidneys is the primary site of action for diuretics.

The various classes of diuretics are distinguished by their different mechanisms of action and specific target locations within the nephron.

Thiazide diuretics work by preventing sodium reabsorption in the nephron's distal tubule.

More sodium remains within the nephron as a result of this inhibition, creating an osmotic force that allows for water retention in the nephron and ultimately water excretion **[Laurent S].**

Many physicians consider thiazide diuretics to be the drug of choice for long-term hypertension treatment **[Ernst ME].**

Loop diuretics, like thiazide diuretics, work by inhibiting sodium and chloride reabsorption by targeting a sodium potassium chloride cotransporter, but they work in the ascending limb of the Henle loop.

Loop diuretics prevent water reabsorption by targeting these two specific electrolytes.

Increased sodium excretion causes a decrease in plasma volume, which reduces venous return and lowers cardiac output **S [Laurent].**

Pharmacokinetics

Orally absorbed and widely distributed diuretics are found in all classes.

Thiazide diuretics bind to plasma proteins extensively, limiting their filtration and promoting appropriate tissue delivery. However, they undergo extensive hepatic metabolism which plays into the dose and frequency of administration. The half-life of thiazides is approximately 8 to 12 hours allowing for a single daily dosing. **[Ernst ME].**

On the other hand, loop diuretics are known to be less effective than thiazides, and have a short duration of action at approximately 6 hours **[Ernst ME].** Loop diuretics are indicated for patients with coexistent renal or heart failure, in circumstances when thiazide diuretics are rarely effective. **[Shah SU, Anjum S, Littler WA]**

Adverse Effects

Diuretics' side effects are dose-dependent and primarily metabolic in nature.

Electrolyte imbalances, such as hypokalemia or hyponatremia, and excessive fluid depletion are the most common side effects. **[Sarafidis PA, Georgianos PI]**

Hypokalemia is one of the most common side effects of diuretics, and it can cause serious metabolic and cardiac problems.Due to the activation of the baroreceptor reflex, excessive fluid depletion may result in a reflex increase in cardiac output and vascular resistance.This increased demand on the heart can be problematic for patients, particularly those with heart disease. **[Ciccone CD]**

Orthostatic hypotension and hyperlipidemia are two other diuretic side effects. **[Palmar BF].**

Patients who have been diagnosed with gout should avoid diuretics,**[Ernst ME, PharmD, and Moser M, M.D]**

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