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Review on: Experimental Screening Methods for Antihypertensive Agents.

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Abstract: *The main goals of preclinical studies are to determine a starting, safe dose for first-in-human study and assess potential toxicity of the product, which typically include new medical devices, prescription drugs, and diagnostics. Preclinical studies refer to the testing of a drug, procedure or other medical treatment in animals before trials may be carried out in humans. They are done to determine efficacy and safety of the drug. Preclinical studies are performed in vitro, in vivo, ex vivo, and in silico` models to obtain basic information about the safety and biological efficacy of a drug candidate before testing it in a final target population, i.e. humans. In a recent days, hypertension becomes very common disease condition. Sometimes this hypertension gives rise other disease conditions and that might be very serious. Anti hypertensive agents are used, to evaluate the action, adverse effects, efficacy and parameters the experimental screening is done. Different types of in vivo studies are there to check Anti hypertensive agent for eg. to check blood pressure in pithed rats, anti hypertensive vasodilator activity in ganglion blocking, angiotensin supported rats, tail cuff method etc.*

Keywords: Preclinical , anti-hypertensive , in vivo studies

I. INTRODUCTION

Aim and Objectives of Preclinical studies:

The ultimate goals of preclinical studies are to accurately model, in animals, the desired biological effect of a drug in order to predict treatment outcome in patients (efficacy), and to identify and characterize all toxicities associated with a drug in order to predict adverse events in people (safety) for informed.

The goals of antihypertensive drugs, also known as blood pressure medications, are to: Prevent cardiovascular disease, Prevent heart failure, Prevent a heart attack, Prevent kidney failure, and Prevent a stroke.

Antihypertensive drugs work by reducing the severity and likelihood of end-organ damage. The goal is to reduce systolic blood pressure to 110 to 150 mm Hg.

Here are some other things to know about antihypertensive drugs:

There are many classes of antihypertensives, and each lowers blood pressure in a different way.

Antihypertensive treatment usually starts as monotherapy, after lifestyle modification has failed. If an antihypertensive agent isn't effective enough, the dosage may be increased or another drug may be added.

The absolute risk of cardiovascular events is influenced by age, gender, race, and other risk factors. Some studies suggest that antihypertensives may also help with Alzheimer's disease in people with early dementia.

Introduction :

Preclinical Studies

Preclinical studies refer to the system of drug, procedure or other medical treatment in animals before trials may be carried out in humans or laboratory test of new drug or a new invasive medical device on animal subject, conducted to gather evidence justifying a clinical trial.

Why Preclinical Testing:-

1) Whether a drug will move on to studies in humans 2) Designing phase I clinical trials.

Help to identify criteria for evaluating safety in humans.

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Detect overall toxicity
Identify, describe and characterize hazards – reversible or - clinically monitorable.
Establish dose-response estimation of pharmacology and toxic effects
Identify metabolic, kinetic and elimination pathways Assess carcinogenicity, reproductive toxicity and teratogenic potential.
Types of Preclinical testing :-
Short Term Animal Studies (Acute):
Determine pharmacological action and toxicity.
Long Term Animal Studies (Chronic):
Look for potential side effects that may result from long term use such as carcinogenicity.

Species Selection :-
Two species are used to check differences in response.
Rodent – almost always rat, mouse has poorest clinical concordance Non-rodent – dog, non-human primate eg. monkeys, apes.
Preclinical studies to be performed before phase I clinical trials to check :-
1. Pharmacodynamics
Pharmacokinetics
Single dose toxicity in two species
Repeated dose toxicity in two species, minimum 2 weeks.
Local tolerance
Teratogenicity study if fertile women are included in the study.
All genotoxicity studies.
Repeated dose toxicity.
Steps in preclinical trials
Step 1: Get an idea for a drug target.
Drugs target specific points in biochemical pathways. Biochemical pathways are series of chemical reactions occurring within a cell. In each pathway, a principal chemical is modified by chemical reactions. e.g. A B C D E Any step in the pathway, for example from A to B, or B to C, might be a target for the right drug.

Step 2: Develop a bioassay
A Bioassay is a “live” system that can be used to measure drug effect. It may be a culture of cells or organs or a whole animal. For example: Zebra-fish embryos - you can see effect of drugs on bone density, blood vessel growth and manyother systems of the zebra-fish.

Step 3: Screen the drug in bioassay
This is the actual test of the drug on the chosen bioassay. This will determine if the drug is SAFE and if it is EFFECTIVE in the bioassay(BEFORE it is ever tested on humans).

Step 4: Establish effective and toxic doses
Establish what dosage amount of the drug is safe and what dosage amount of the drug is toxic. Most drugs have a toxic level or an amount at which the drug will become harmful instead of helpful.

Step 5: File for approval as IND
Application is made to the Food and Drug Administration (FDA) as an Investigational New Drug (IND)
IND must show how the drug is manufactured.
Appears (colour, solubility, melting point, particle size, moisture content)
Formulated (pills, liquid, etc. inactive ingredients) 5. Will be analyzed for purity, concentration, stability.
6. Will be tested for safety (this will be the basis for allowing first use in human

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What is involved in preclinical studies :-

Wide doses of the drug are tested using in vitro (test tube or cell culture) and in vivo (animal) experiments, and it is also possible to perform in silico profiling using computer models of the drug–target interactions.

II. REVIEW OF LITERATURE

Remington, "The Science &Practice of Pharmacy", 21st edition ,volume 01 ,page no – 965 – 972- This book Gives detail knowledge of Hypertension, there different basic types , introduction of Anti Hypertensive drugs , their Pharmacology, classification etc.

Pharmaceutical Dosage Forms & Drug Delivery systems", 7th edition,by Howard C. Ansel –- This literature helps us in understanding the different process of drug testing and drug formulation. We get knowledge of basic concepts of Preclinical & clinical trials, Also why they are required with their applications.

Harsh Mohan, "Textbook of Pathology", seventh edition, Jaypee Publications, page no - 535- 650 – This Literature gives us briefly review about Pathology, pathophysiology, etiology of Hypertension. Also gives the idea of about the different types of Hypertension and their basic causes and suggests us to work on this causes to get relief from Hypertension.

Essentials of Medical Pharmacology", K.D.Tripathi, 7th edition ,2014 , Jaypee Publications , page no – 558 – 575 -This Literature helps in understanding the basic concept of hypertension & how various endogenous chemicals are involved in maintaining the Normal Blood pressure range. Also this book gives knowledge about the different pharmacology of different Anti Hypertensive drugs classes , their structure and pharmacological actions relationship , interactions with drugs , adverse effects, contradictions etc.

Wilson &Grisevold's , "Textbook of organic Medicinal & Pharmaceutical chemistry", 12th edition, page no - 637- 647 – From this Literature we got the information regarding chemical structures of antihypertensive agents and their relation between the structure and activity.

H. Gerhard Vogel (Ed.), "Drug Discovery and Evaluation Pharmacological Assay", second Edition, A.1.3H- This literature gives brief knowledge of different types of techniques of experimental Screening Anti Hypertensive agents and also from this literature we got knowledge of various techniques by which the hypertension is introduced in the animal model.

Matthew R Alexander, Meena S Madhur _et al_ (2019), "Medscape", "Hypertension",- https://emedicine.medscape.com/article/241381-overview. -This article gives us brief information about pathophysiology of hypertension also gives information about etiology of hypertension. Accessed on 21 june 2021.

Lilach O. Lerman, Theodore W. Kurtz _et al_ (2019), "American Heart Association" , "Animal Models of Hypertension: A Scientific Statement From the American Heart Association",Volume73,Issue6,- https://www.ahajournals.org/doi/10.1161/HYP.0000000000000090 - This article gives us brief information about various animal models of hypertension screening like SHR rat, FSS rat, DSS rat. Accessed on 7 july 2021

Hossein Babaei (2012), "Researchgate", "Antihypertensive Drugs", Edition 1st https://www.researchgate.net/publication/258433869_Antihypertensive_Drugs- This article gives us brief information about New Therapeutics in Hypertension, Potassium-Sparing Diuretics in Hypertension, Hypertension and Renin-Angiotensin System. Accessed on 23 june 2021

Georgios Georginopoulus _et al_ (3 August 2016) , "Frontiers in Pharmacology" , "Hypertension RelatedCardiovascularComplications"- https://www.frontiersin.org/articles/10.3389/fphar.2016.00235/full.

Phases of Drug Development

Investigational new drug (IND)

An Investigational New Drug Application (IND) is a request from a clinical study sponsor to obtain authorization from the FDA to administer an investigational drug or biological product to humans.

Phase I

For studying Safety, During phase I of a clinical trial, investigators spend several months looking at the effects of the medication on about 20 to 80 people.

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Phase II

For studying Safety and efficacy, Phase II of a clinical trial involves several hundred participants who are living with the condition that the new medication is meant to treat. They're usually given the same dose that was found to be safe in the previous phase.

Phase III

For studying Safety and efficacy, in this clinical trial usually involves up to 3,000 participants who have the condition that the new medication is meant to treat. Trials in this phase can last for several year

NDA

The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

Phase IV

Phase IV clinical trials happen after the FDA has approved medication. This phase involves thousands of participants and can last for many years.

Different Animal Models Used In Preclinical Studies :-

THE MOUSE

The mouse is a small mammal that belongs to the order Rodentia. Musmusculus, is the most commonly used for biomedical research.

USES IN RESEARCH

Mice and rats make up approximately 95% of all laboratory animals, with mice the most commonly used animal in biomedical research. Mice are a commonly selected animal model for a variety of reasons, including small size (facilitating housing and maintenance); short reproductive cycle and lifespan; generally mild-tempered and docile.

THE RAT

Rats and humans have a long history of coexistence. The origins of the laboratory rat, also known as the Norway rat, stretch back centuries to the areas of modern day China and Mongolia.

USES IN RESEARCH

Rats possess a number of qualities which make them a highly suitable and much preferred animal model like mice; these traits include relatively small size, known genetic background, short generation time, similarities to human disease conditions. Their tractable nature makes them easier to handle in a laboratory setting than many other rodents. Rats rarely bite their handlers unless extremely stressed or in pain.

THE RABBIT

The ancestral home of the European rabbit (Oryctolaguscuniculus) is the Iberian Peninsula. The earliest archeological evidence of the coexistence of humans and rabbits can be found in excavation sites dated at approximately 120,000 years BCE in Nice, France In antiquity, Romans used rabbits as a food source and are thought to be responsible for their dispersal throughout Europe, although there is no evidence that they attempted to actually domesticate them.

USES IN RESEARCH

European rabbits have been used in research since the middle of the 19th century early work with the species was concentrated on the comparative anatomy of the rabbit with other species, such as the frog, and the unique features of the rabbit's heart and circulatory system. Louis Pasteur used rabbits in a series of experiments that led to the development of the world's first rabies vaccine.

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GUINEA PIGS

Guinea pigs (Cavia Porcellos) are rodents, related to porcupines and chinchillas in the suborder Hystricomorpha. They originate from the mountain and grassland regions along the mid-range of the Andes Mountains in South America They are small, stocky, no burrowing, crepuscular herbivores with short legs and little to no tail, ranging from 700 to 1200 g. females being smaller than males.

HAMSTERS :-

Hamsters are of the Rodentia order, suborder Myomorpha along with the mouse and the rat. There are over 24 species of hamsters described in the literature, with the most common hamster used in research being the Golden or Syrian hamster, Mesocricetusauratus, Originating from the northwest region of Syria, Golden hamsters are thought to be descendants of only three or four littermates collected from Syria in 1930. As their name implies, the typical wild-type coat is reddish gold along their dorsum, with a gray underside. They are granivores and insectivores, weighing 85-150 g.

Introduction to Transgenic Animals :

Transgenesis refers to the phenomenon of introduction of exogenous DNA into the genome to create and maintain a stable heritable character.

The foreign DNA that is introduced is called transgene. And the animal whose genome is altered by adding one or more transgenes is said to be transgenic.

Transgenic Mice:

The first animal used for transgenesis was a mouse. Mouse continues to be an animal of choice for most transgenic experiments.

Being a small animal, it can be easily handled, and mouse is regarded as researcher-friendly by biotechnologists.

General Methods of Preclinical Studies:

In vivo Method	In vitro Method	In Silico Method
• It is techniques which done on whole living organism & also Refers to work that's performed in a whole, living organism.	• It is refers to work, or a process performed or taking place in test tube, culture dish or elsewhere outside a living organism.	• In this, the experiment or research is done with the help of computer modeling or computer simulation.
• The Experiment occurs under natural cellular conditions of living organism.	• The experiment occurs under the artificial conditions provided by the researchers.	• Used to study identification of the drug target molecule by employing bioinformatics tools.
• Generally In vivo are expensive toperform.	• Less expensive	• Technically Simple, by using different software's & modeling.
• Time Consuming.	• Provides Quick Results	• Used in 'Drug Designing'
• But Accuracy is more as compared to In vivo.	• Less precise than In vivo experiments.	• No need of any Expensive Laboratories work & Experiments.
• Widely used for Evaluation of Safety of drugs.	• This are done to estimate therapeutic efficacy of drug on specific cells, tissues .	• Cost is minimum.

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General Introduction to Hypertension:
Normal: systolic lower than 120 mm Hg, diastolic lower than 80 mm Hg
Prehypertension: systolic 120-139 mm Hg, diastolic 80-89 mm Hg
Stage 1: systolic 140-159 mm Hg, diastolic 90-99 mm Hg
Stage 2: systolic 160 mm Hg or greater, diastolic 100 mm Hg or greater

Signs and symptoms of hypertension :-
Hypertension is defined as a systolic blood pressure (SBP) of 140 mm Hg or more, or a diastolic blood pressure (DBP) of 90 mm Hg or more, or taking antihypertensive medication.
Hypertension may be primary, which may develop as a result of environmental or genetic causes, or secondary, which has multiple etiologies, including renal, vascular, and endocrine causes. Primary or essential hypertension accounts for 90-95% of adult cases, and secondary hypertension accounts for 2-10% of cases.
Diagnosis of hypertension:-
The evaluation of hypertension involves accurately measuring the patient's blood pressure, performing a focused medical history and physical examination, and obtaining results of routine laboratory studies. A 12-lead electrocardiogram should also be obtained. These steps can help determine the following

Presence of end-organ disease
Possible causes of hypertension
Cardiovascular risk factors
Baseline values for judging biochemical effects of therapy.

Other studies may be obtained on the basis of clinical findings or in individuals with suspected secondary hypertension and/or evidence of target-organ disease, such as CBC, chest radiograph, uric acid, and urine microalbumin.

Pathogenesis of Essential Hypertension :-
The pathogenesis of essential hypertension is multifactorial and highly complex. The kidney is both the contributing and the target organ of the hypertensive processes, and the disease involves the interaction of multiple organ systems and numerous mechanisms of independent or interdependent pathways.
Factors that play an important role in the pathogenesis of hypertension include genetics, activation of neurohormonal systems such as the sympathetic nervous system and renin- angiotensin- aldosterone system, obesity, and increased dietary salt intake.
Arterial hypertension is the condition of persistent elevation of systemic blood pressure (BP). BP is the product of cardiac output and total peripheral vascular resistance. Multiple factors are involved in short-term and long-term regulation of BP for adequate tissue perfusion; these include the following:
Cardiac output and circulatory blood volume
Vascular caliber, elasticity, and reactivity
Humoral mediators
Neural stimulation

Factors Influencing BP Regulation:-
Regulation of normal blood pressure (BP) is a complex process. Arterial BP is a product of cardiac output and peripheral vascular resistance. Cardiac output is the product of stroke volume and heart rate. The factors affecting cardiac output include sodium intake, renal function, and mineralocorticoids. The inotropic effects occur via extracellular fluid volume augmentation and an increase in heart rate and contractility.
Peripheral vascular resistance is dependent upon the sympathetic nervous system (SNS), humoral factors, and local auto regulation. The vasculature is highly innervated by sympathetic fibers. The SNS produces its effects via the vasoconstrictor alpha effect or the vasodilator beta effect. Along the same line, the renal artery is highly innervated, with the sympathetic activation promoting sodium retention via increased renin secretion.

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The role of renal nerves in BP control and in the pathogenesis of hypertension has been made evident by the effect of renal denervation (RDN) in animal model experiments. The initial two clinical trials of RDN using a percutaneous radiofrequency procedure suggested that the procedure resulted in a reduction of BP in drug-resistant patients. However, the SYMPLICITY HTN-3 trial, which included a sham surgery arm, failed to demonstrate significant reductions in 24-hour ambulatory BP after RDN.

The physiologic mechanisms that account for the heterogeneous decrease in arterial BP following RDN remain unclear and may indicate factors more than simply high renal sympathetic activity. Of all of the variables examined that could influence BP outcomes, the extent of the RDN seems to be of great significance. Respectively, RDN might work if done properly and if used in the appropriate patient population.

Similarly, the role of the arterial baroreflex system in moment-to-moment regulation of BP is well known. Although electrical stimulation of baroreceptors can cause significant reduction in BP in humans with treatment-resistant hypertension, its importance in long-term BP control remains controversial. These studies confirm the role of the SNS as a component in the pathogenesis of hypetension

Auto-regulation of BP :-
Auto regulatory mechanisms maintain the blood flow of most tissues over a wide range of BP according to their specific needs. Auto regulation of BP occurs by way of intravascular volume contraction and expansion regulated by the kidney, as well as via transfer of transcapillaryfluid.

Through the mechanism of pressure natriuresis, salt and water balance is achieved at heightened systemic pressure, as proposed by Guyton et al. Interactions between cardiac output and peripheral vascular resistance are auto regulated to maintain a set BP in an individual. For example, constriction of the arterioles elevates arterial pressure by increasing total peripheral vascular resistance, whereas venular constriction leads to redistribution of the peripheral intravascular volume to the central circulation, thereby increasing preload and cardiac output.

Etiology of Hypertension
Hypertension may be primary, which may develop as a result of environmental or genetic causes, or secondary, which has multiple etiologies, including renal, vascular, and endocrine causes. Primary or essential hypertension accounts for 90-95% of adult cases, and a small percentage of patients (2-10%) have a secondary cause. Hypertensive emergencies are most often precipitated by inadequate medication or poor compliance.
blood pressure (BP), especially in susceptible individuals, mainly by volume expansion.
Nonsteroidal anti-inflammatory drugs (NSAIDs) may also have adverse effects on BP. NSAIDs block both cyclooxygenase-1 (COX-1) and COX-2 enzymes.

Endogenous hormonal causes include the following:
Primary hyperaldosteronism
Cushing syndrome
Pheochromocytoma
Congenital adrenal hyperplasia

Neurogenic causes include the following:
Brain tumor
Autonomic dysfunction
Sleep apnea
Intracranial hypertension
Drugs and toxins that cause hypertension include the following:
Alcohol

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Cocaine
Cyclosporine, Tacrolimus
NSAIDs
Erythropoietin
Adrenergic medications
Decongestants containing ephedrine.
Classification of Antihypertensive Drugs:

Diuretics:-
Thiazides Diuretics : Hydrochlorothiazide, Chlorthalidone, Indapamide High ceiling / Loop Diuretics : Furosemide, Ethacrynic acid, Bumetanide, Torsemide,Indacrinone etc.
K+ Sparing: Spironolactone, Amiloride, Eplerone, Triamterone.

ACE inhibitors:-
Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril, etc.

Angiotensin (AT1 receptor) blockers:-
Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan.

Direct renin inhibitor:- Aliskiren

Calcium channel blockers:-
Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine etc.

B Adrenergic blockers:-
Propranolol, Metoprolol, Atenolol etc.
β+α Adrenergic blockers:- Labetalol, Carvedilol.

α Adrenergic blockers:-
Prazosin, Terazosin, Doxazosin , Phentolamine, Phenoxybenzamine.

Central sympatholytics:- Clonidine, Methyldopa.

Vasodilators
Hydralazine, Minoxidil, Diazoxide -Arteriolar acting & Venous acting- Sodium Nitroprusside
1. DIURETICS :-
Diuretics have been the standard antihypertensive drugs over the past 4 decades, though they do not lower BP in normotensives.
A.High Ceiling Diuretics:-
Furosemide –
Proto type of this class, is a strong diuretic, but the antihypertensive efficacy does not parallel diuretic potency. Furosemide is a weaker antihypertensive than thiazides fall in BP is entirely dependent on reduction in plasma volume and cardiac output.

Mechanism of Action:-
Inhibition of mg2+ Na+/K+/2Cl- Symporter at luminal membrane at ascending limb of loop of henle.
Potent, loop diuretic
Fast acting ,short duration of action
Large losses of fluid approx . 8 litre /day urine output

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chemistry wise it is 5 sulfamoyl -2- Amino – Benzoic acid, less ototoxic.
They are indicated in hypertension only when it is complicated by: (a) Chronic renal failure: thiazides are in effective, both as diuretic and as antihypertensive.(b) Coexisting refractory CHF.

Desirable properties of thiazide diuretics as antihypertensive are:
Once a day dosing and flat dose-response curve permitting simple standardized regimens.
No fluid retention, no tolerance.
Low incidence of postural hypotension and relative freedom from side effects, especially CNS, compared to sympatholytics.
Effective in isolated systolic hypertension(ISH).
Lessened risk of hip fracture in the elderly due to hypocalciuric action of thiazides.
Low cost.

B.Thiazide Diuretics:-
Has wide margin of safety.

Mechanism of action :
Inhibits reabsorption of Na+/K+/cl- symporter at Distalconvoluted tubules (DCT)

Side effects :
Same as that of loop diuretics + Hyperglycaemia.

Contraindication: in diabetes mellitus . And with Cardiac Glycosides.

Uses : First line drug for Hypertension.

C.K+ Spairing Diuretics:-

Mechanism of action :
Act at late distal tubules – inhibit reabsorption of sodium &water,without loss of potassium.

Side effect:
Hyperkalaemia (Spironolactone causes gynaecomastia& impotence)
Uses: spironolactone is DOC for Cirrhotic edema. Hypertension, CHF etc.
2. ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS:-
The ACE inhibitors are one of the first choice drugs in all grades of essential as well as Renovascular hypertension (except those with bilateral renal artery stenosis).Most patients require relatively lower doses (enalapril 2.5–10mg/day or equivalent) which are well tolerated. Used alone they control hypertension in ~50%patients, and addition of a diuretic/β blocker extends efficacy to

Pharmacokinetics:-
About 70% of orally administered captopril is absorbed. Presence of food in stomach reduces its bioavailability. Penetration in brain is poor. It is partly metabolized and partly excreted unchanged in urine. The plasma t½ is ~2 hours, but actions last for 6–12 hours.

Uses:-
Hypertension:
CHF
Myocardial infarction (MI)

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Prophylaxis in high cardiovascular risk subjects
Diabetic nephropathy
Scleroderma crisis

3. ANGIOTENSIN (AT1) RECEPTOR BLOCKERS:-
Over the past 2 decades, several nonpeptide orally active AT1 receptor blockers (ARBs) have been developed as alternatives to ACE inhibitors.
These include losartan, candesartan, valsartan,telmisartan, olmesartan and irbesartan. Selective antagonists of AT2 receptors as well as combined AT1 + AT2 antagonists have also been produced, but are not used clinically.
Adverse effects:-
Angioedema is reported in fewer cases. Headache, dizziness, weakness and upper g.i. side effects are mild and occasional. However, losartan has fetopathic potential like ACE inhibitors not to bead ministered during pregnancy.
Uses of ARBs:-
Hypertension, CHF, Myocardial infarction, Diabetic nephropathy

4. DIRECT RENIN INHIBITORS:
Aliskiren:-
Direct renin inhibitors (DRIs) are the latest class of RAS inhibitory drugs, of which only one member Aliskiren has become available for the treatment of cardiovascular and renal diseases in which ACE inhibitors and ARBs are currently used. Aliskiren is a nonpeptide which binds selectively to the catalytic site of renin and competitively blocks the access of angiotensinogen to this site Ang I is not produced and the chain of RAS is interrupted.
Adverse effects:-
Dyspepsia, Abdominal pain, Loose motions, Headache and Dizziness, Acute hypotension, Hyperkalaemia, Cough, Angioedema and rashes are much less frequent than with ACE inhibitors.
Contra indications –
Aliskiren is contraindicated during pregnancy

5. CALCIUM CHANNEL BLOCKERS:-
Calcium channel blockers (CCBs) are another class of first line antihypertensive drugs. All 3 subgroups of CCBs, viz.
dihydropyridines (DHPs, e.g. amlodipine),
phenylalkylamine (verapamil) and
benzothiazepine (diltiazem) are equally efficacious antihypertensives.
Pharmacological action and adverse effect:-
The common property of all three subclasses of CCBs is to inhibit Ca2+ mediated slow channel component of action potential (AP) in smooth/cardiac muscle cell. The two most important actions of CCBs are:
Smooth muscle (especially vascular) relaxation.
Negative chronotropic, inotropic and dromo-tropic action on heart.

6. ADRENERGIC BLOCKERS:-
They are mild antihypertensives; do not significantly lower BP in normotensives. Used alone they suffice in 30–40% patients—mostly stage I cases. Additional BP lowering may be obtained when combined with other drugs. The hypotensive response to β blockers develops over 1–3 weeks and is then well sustained.

Classification:-
• Nonselective (β1 and β2) :-
Without intrinsic sympathomimetic activity : Propranolol, Sotalol, Timolol.
With intrinsic sympathomimetic activity :
Pindolol
With additional α blocking property : Labetalol, Carvedilol

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• Selective Beta 1 blocker Cardioselective (β1):-
Metoprolol, Atenolol, Acebutolol, Bisoprolol, Esmolol, Betaxolol, Celiprolol, Nebivolol. The pharmacology of propranolol is described as prototype.

Pharmacological action:
1. Cardiovascular system:-
Heart Propranolol decreases heart rate, force of contraction (at relatively higher doses) and cardiac output (c.o.). Cardiac work and oxygen consumption are reduced as the product of heart rate and aortic pressure decreases. Total coronary flow is reduced (blockade of dilator β receptors), but this is largely restricted to the subepicardial region.
At high doses a direct depressant and membrane stabilizing (quinidine like) action is exerted, but this contributes little to the antiarrhythmic effect at usual doses. Propranolol blocks cardiac stimulant action of adrenergic drugs but not that of digoxin, methylxanthines or glucagon.
Blood vessels Propranolol blocks vaso-dilatation and fall in BP evoked by isoprenaline and enhances the rise in BP caused by Adr. There is re-reversal of vasomotor reversal that is seen after a blockade. Propranolol has no direct effect on blood vessels and there is little acute change in BP.

2. Respiratory tract:-
Propranolol increases bronchial resistance by blocking dilator β2 receptors.

3. CNS:-
No overt central effects are produced by propranolol. Propranolol suppresses anxiety in short-term stressful situations, but this is due to peripheral rather than a specific central action.

4. Local anesthetic:-
Propranolol is as potent a local anesthetic as lidocaine, but is not clinically used for this purpose because it causes irritation at the injected site.

5. Metabolic :-
Propranolol blocks adrenergically induced lipolysis and consequent increase in plasma free fatty acid levels. Plasma triglyceride level and LDL/HDL ratio is increased during propranolol therapy.

6. Skeletal muscle:-
It tends to reduce exercise capacity by attenuating β2 mediated increase in blood flow to the exercising muscles, as well as by limiting glycogenolysis and lipolysis which provide fuel to working muscles.

7. Eye Instillation:-
Propranolol and some other β blockers reduces secretion of aqueous humor, i.o.t. is lowered.
Adverse effect and contraindication:-
Propranolol can accentuate myocardial insufficiency and can precipitate CHF/edema by blocking sympathetic support to the heart, especially during cardiovascular stress.
Bradycardia: resting HR may be reduced to 60/min or less.
Propranolol worsens chronic obstructive lung disease,
Propranolol exacerbates variant (vasospastic) angina due to unopposed α mediated coronary constriction.
Carbohydrate tolerance may be impaired in prediabetics.
Plasma lipid profile is altered on long term use: total triglycerides and LDL-cholesterol tend to increase while HDL-cholesterol falls. This may enhance risk of coronary artery disease.
Propranolol is contraindicated in partial and complete heart block: arrest may occur.
Tiredness and reduced exercise capacity

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1. MIXED ACTING ADRENERGIC BLOCKERS

Labetalol –

It is the first adrenergic antagonist capable of blocking both α and β receptors. There are 4 diastereomers of labetalol, each of which has a distinct profile of action on subtypes of α and β receptors.

Uses:-

It is a moderately potent hypotensive and is especially useful in Pheochromocytoma and clonidine withdrawal; can also be used in essential hypertension.Most important side effect is postural hypotension, but this is significant only in some patients. Failure of ejaculation and other side effects of α and β blockers can also occur, but plasma lipid levels are not altered.

2. α ADRENERGIC BLOCKERS :-

Prazosin:-

This prototype selective α1 antagonist dilates both resistance and capacitance vessels; effect on the former predominating.

Adverse effects:-

Prazosin is generally well tolerated at low doses. Apart from postural hypotension related symptoms (particularly in the beginning), other side effects are headache, drowsiness, dry mouth, weakness, palpitation, nasal blockade, blurred vision and rash.

Ejaculation may be impaired in males: especially with higher doses. Fluid retention attending prazosin monotherapy may precipitate CHF.

Uses:-

Prazosin is a moderately potent antihypertensive, but is not used as a first line drug because fluid retention and tolerance gradually develops.

3. CENTRAL SYMPATHOLYTICS :-

Clonidine:-

It is an imidazoline derivative having complex actions. Clonidine is a partial agonist with high affinity and high intrinsic activity at α2 receptors, especially α2A subtype in brainstem. The major haemodynamic effects result from stimulation of α2A receptors present mainly postjunctionally in medulla (vasomotor center). This decreases sympathetic out flow → fall in BP and bradycardia. Enhanced vagal tone contributes to bradycardia. Plasma NA declines.

Side effects:-

Sedation, mental depression, disturbed sleep; dryness of mouth, nose and eyes (secretion is decreased by central action), constipation (ant secretory effect on the intestines). Impotence, salt and water retention, bradycardia.

4. VASODILATORS:-

Hydralazine/Dihydralazine -

Introduced in the 1950s, it is a directly acting arteriolar vasodilator with little action on venous capacitance vessels; reduces t.p.r. and causes greater decrease in diastolic than in systolic BP.

Reflex compensatory mechanisms are evoked which cause tachycardia, increase in c.o. and renin release → increased aldosterone → Na+ and water retention.

Adverse effects:-

Facial flushing, conjunctival injection, throbbing headache, dizziness, palpitation, nasal stuffiness, fluid retention, edema, CHF.

Angina and MI may be precipitated in patients with coronary artery disease.

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Use :-
Hydralazine is now used as a second line alternative only in combination with a diuretic and/or β blocker for patients not achieving target BP with first line drugs. It is one of the preferred antihypertensives during pregnancy, especially preeclampsia, because of decades of safety record. Parenterally, it is occasionally employed in hypertensive emergency.

Experimental Animal Model For Screening of Anti Hypertensive Drugs :-
An ideal animal model of hypertension criteria :
It should be feasible in small animals.
Simple to perform and uniformly reproducible.
Should be able to predict the potential antihypertensive properties of an agent.
Consume minimal quantities of compounds.
It should be comparable to some form of human hypertension.

Animal	Heart Rate	Systolic Blood Pressure	Diastolic blood pressure
Rat	350 to 450 bpm	129	91
Mice	650 to 750 bpm	120	71

Most studies on experimental hypertension were carried out on Dogs. Currently, rat is the preferred animal species. Spontaneous hypertensive rat (SHR), the genetic strain of hypertensive rat, is the animal of choice.
Invivo methods to check the hypertension activity in various animals:-
A) Blood pressure in pithed rats
The pithed rat has been proposed for assessing pressor substances by Shipley and Tilden (1947). The Preparation is frequently used to evaluate drug action.
PROCEDURE:
Male rats weighing 250–350 g are prepared for pithing Under halothane anaesthesia.
The left carotid artery is cannulated for blood pressure monitoring and blood sampling. Furthermore, the trachea and the right jugular vein are cannulated.
The rats are pithed inserting a Steel rod, 2.2 mm in diameter and about 11 cm in Length, through the orbit and foramen magnum down ,the whole length of the spinal canal. Via the tracheotomy tube, the animals are ventilated with a small Animal ventilation pump.
Inspirited air is oxygen-enriched by providing a flow of oxygen across a T-piece Attached to the air intake of the ventilation pump(Harvard Apparatus model 680). The rats are ventilated at a frequency of 60 cycles/min with a tidal volume 2 ml/100 body weight.
Thirty min after pithing, A 0.3 ml blood sample is withdrawn from the carotid Cannula and immediately analyzed for pO2, pCO2, pH, and derived bicarbonate concentration using an automatic blood gas analyzer.
By alterations of the respiratory stroke volume of the pump, the values are adjusted to: pCO2 30–43 mm Hg, pH 7.36–7.50, pO287–105 mm Hg. Continuous registration of blood pressure and cardiac frequency (Hellige He 19 device and Statham P 23Db transducer) is performed via the left carotid artery.
In order to measure α1 and α2 antagonism, first Dose-response curves are registered using doses of 0.1–30 µg/kg i.v. phenylephrine (a selective α1 agonist),And 1–1 000 µg/kg i.v. BHT 920, (a selective α2 agonist). The test drug is administered intravenously and the agonist dose- response curves are repeated again15 min later.

EVALUATION :-
If the curve of blood pressure response to the agonists Is shifted, dose-response curves are plotted on a logarithmic scale and potency ratios are calculated.

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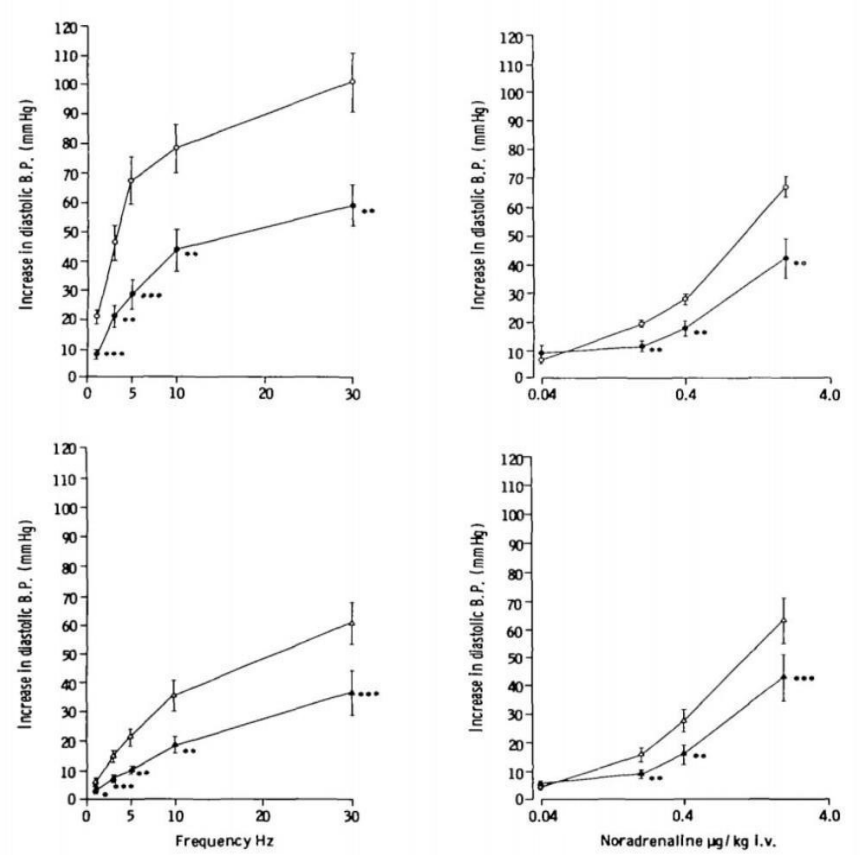

FIGURE 1. *Effect of captopril (1.0 mg/kg intravenously) on vasoconstrictor responses to spinal stimulation and norepinephrine in pithed rats. Upper graphs: SH rats ○ before and ● after captopril (n = 9). Lower graphs: WKY rats △ before and ▲ after captopril (n = 9). ** p < 0.01; *** p < 0.001, significantly different from control value.*

B) Blood pressure in conscious hypertensive Rats (tail cuff method)

Rats with spontaneous or experimentally induced hypertension are widely used for screening of potentially Antihypertensive compounds.

PROCEDURE:

Male spontaneous hypertensive rats (Charles River)Weighing 300–350 g or rats with experimentally induced hypertension are used.

Surgical procedure to induce renal hypertension Male Sprague-Dawley rats weighing 80– 100 g are anesthetized by intraperitoneal injection of 0.8 ml 4%Chloralhydrate solution. Both kidneys are exposed retroperitoneally.

To induce renal hypertension, a silverClip (0.2 mm diameter, 4 mm length) is placed onto both Renal arteries, the kidneys are reposed and the wound Is closed by suture.

Within 5–6 weeks, operated animals attain a renal Hypertension with a systolic blood pressure (BPs) of170–200 mm Hg (mean normal physiological BPs for rats is 100 mm Hg). Only animals with a BPs = 180 mm Hg are used for the tests.

EVALUATION :-

Mean values in systolic blood pressure before and after drug administration and the duration of the effect are determined. Percent decrease in systolic blood pressure under drug treatment is calculated. Statistical significance is assessed by the Student's t-test. Scores for % decrease in systolic blood pressure and For the duration of the effect are allotted.

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C) Direct measurement of blood pressure in Conscious rats with indwellingcatheter :- The method first described by Weeks (1960) allows The direct measurement of arterial pressure in conscious Rats eliminating the influence of anaesthesia on cardio-Vascular regulation.

PROCEDURE :-
Preparation of cannulae :
In order to prepare the cannulae 7 cm and 12 cm long Pieces are cut from PE 10 and PE 20 tubing respectively.
A stylet wire is inserted into the PE 10 tubing And the PE 20 tubing is also slipped over the stylet Wire. The ends of the tubing's are heated in a current of Hot air and fused together.
Ridges are made to anchor The cannula in the animal's tissue. In order to make a Ridge, the stylet wire is left inside the cannula and the Cannula is heated in a fine jet of hot air.
When the Polyethylene at the point of heating becomes soft, the Cannula is pressed slightly and thus a ridge is formed One ridge is formed at the PE 20 tubing, about 0.5 cm
Away from the junction with the PE 10 tubing, and 3 more ridges are formed on the PE 20 tubing at a distance of about 1 cm from each other, first one being Situated about 3 cm away from the free end of the PE 20Tubing.
The stylet wire is then removed from the can-Nula and the PE 10 portion of the cannula near the junction with the PE 20 tubing is wound around a glass Rod with a diameter of 4 mm. Two rounds are made.
Then it is dipped in a boiling water bath for about 5 s. When taken out of the bath, the cannula retains its circles, forming a spring-like structure.

Evaluation:-
Changes of blood pressure are measured for degree and duration. Five rats are used for each dose and compound. The maximal changes of each group are averaged and compared with the standard.

II. CONCLUSION

The information can be collected mainly by 2 sources Primary Sources – Which includes Books, literature, Articles etc And Secondary Sources- Which is mainly Internet survey and review Articles. We collected Information from both the sources. First of all we go through different books and articles thoroughly and gains the information about the general concept of hypertension and preclinical trails. Then We read the book H.Gerhard Vogel briefly and collects the View on different experimentation techniques of hypertension, for eg techniques for introduction of hypertension into normal animal and checking the response by the means of increased blood pressure, after this to check action of anti Hypertensive agents by using various screening methods and Evaluation parameters'. After all of these we go through the different Article, research papers, literature, which helps us to enhanced our point of view towards our project work

REFERENCES

[1]. Remington, "The Science &Practice of Pharmacy", 21st edition ,volume 01 ,page no – 965 – 972.
[2]. "Pharmaceutical Dosage Forms & Drug Delivery systems", 7th edition,by Howard C. Ansel,Page no.326
[3]. "Fundamentals of Pathology", Husain A. Sattar, Medical course & Steps review, 2021 edition, page no – 73 – 85.
[4]. Goodman & Gilman's, "The Pharmacological Basis of Therapeutics" , 13th edition , page no. 507 –527.
[5]. Harsh Mohan, "Textbook of Pathology", seventh edition, Jaypee Publications, page no – 535- 650.
[6]. Wilson &Grisevold's , "Textbook of organic Medicinal & Pharmaceutical chemistry", 12th edition, page no - 637- 647.
[7]. H. Gerhard Vogel (Ed.), "Drug Discovery and Evaluation Pharmacological Assay", second Edition, A.1.3
[8]. "Fundamentals of Pathology", Husain A. Sattar, Medical course & Steps review, 2021 edition, page no – 73 – 85.
[9]. Matthew R Alexander, Meena S Madhur _et al_ (2019), "Medscape", "Hypertension",- https://emedicine.medscape.com/article/241381-overview. Accessed on 21 june 2021

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[10]. Lilach O. Lerman, Theodore W. Kurtz _et al_ (2019), "American Heart Association" , "Animal Models of Hypertension: A Scientific Statement From the American Heart Association",

[11]. Volume 73, Issue 6,- https://www.ahajournals.org/doi/10.1161/HYP. Accessed on 7 july 2021

[12]. Hossein Babaei (2012), "Researchgate", "Antihypertensive Drugs", Edition 1st https://www.researchgate.net/publication/258433869_Antihypertensive_Drugs. Accessed on 23 june 2021

[13]. Georgios Georginopoulus _et al_ (3 August 2016) , "Frontiers in Pharmacology" , "Hypertension Related Cardiovascular Complications"- https://www.frontiersin.org/articles/10.3389/fphar.2016.00235/full. Accessed on 15 june 2021