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Pre Clinical Of Drugs For Asthma

[1]Miss. Prerana Ashok Dhore, [2]Mr. Shubham Pradip Chavhan, [3]Miss. Manisha Ramsing Jadhao, [4]Miss. Mukteshwari S. Giri, [5]Dr. Avinash Shesharao Jiddewar.
[1,2,3]Student, [4]Assistant, [5]Priniciple.
[1]Department of pharmacy.
[1]Navsanjeevan Shikshan Mandals College of Pharmacy Darwha, dist. Yavatmal Maharashtra, India.

Abstract: It is well know that Asthma is one of the most common Chronic Inflammatory Disease that Affects 300 million people worldwide of all Ages. Current Therapy of Drug for asthma are highly Effective and have been Improved by Pharmaceutical Developments. Pharmacology has Played critical role in drug development and key in experimental Observations. Pharmacology has taught us in understanding effectiveness of drug therapies & About the underlying mechanisms of Asthma. Pharmacological Therapies includes Bronchodilators Derived From Catecholamines from adrenal medulla & Anti-Inflammatory Agents that Includes Steroids, Leukotriene Antagonists, mast cell Stabilizers, And anti-Immunoglobulin Antibodies are being used currently However despite their efficacy & Safety some limitations do exists. Preclinical studies the critical steps to observe Potency of asthma therapeutic drug or method before translation to clinical trial preclinical studies evaluates the drugs toxicity & Pharmacological outcomes by in-vitro & in vivo laboratory animal testing.

Index Terms **- Asthma, Inflammation, Airway, Hyper-Responsiveness, In-Vivo, In-Vitro, Bronchia, Alveoli**

INTRODUCTION: **:**

It is well Known that Asthma is one the most common chronic inflammatory disease that affects 300 million people worldwide of all ages.[1]
Obstructive disease of lower airway of respiratory tract, with Increasing airway obstruction caused by bronchial spasm & Bronchial Constriction, Inflammation in Bronchioles & thick mucus production.[2]

For this increasingly common disease. We Have now envolved Highly effective drugs for management of asthma that have led to reduction in hospitalization of patients. Most patients with asthma are now able to lead a normal life through the use of medications that are virtually free from side-effects[3]
In pharmacology therapies, Bronchodilators & Anti-inflammatory agents, including steroids, Ieukotriene Antagonists, mast cell stabilizers & the most recent However , Despite their efficacy some limitations exist.[4]

Preclinical Studies is consult with the testing of drug , manner or different clinical treatment In animal before trails can be executed in humans during preclinical drug development, the drugs toxic and pharmacological outcomes needs to be evaluated through in vitro & in vivo Laboratory animal testing[5]
Preclinical Studies are critical steps to observe the potential of a therapeutic drug or method before translation to clinical Trial. Records of Preclinical research are gathered used as evidence & Guide in FDA Programs for the approval of new drugs & Medical method.

Pre-medical study works with main objective to increase adequate facts. Reasonable safety to work with human trails of the drugs.
And with fundamental goal is to assemble the data to submit to the FDA for IND[6]

WHAT IS ASTHMA?

Asthma is a Complex , Persistent , Inflammatory Disease Characterized by airways hyper-responsiveness (AHR) In Association with airway Inflammation.[7]

Asthma is a lung disease in which a person can die during an asthma attack
Asthma is a lifetime disease that doesn`t go away & it can`t be cured but can be managed by monitoring diabetes & High blood pressure.

SYMPTOMS :

Asthma symptoms result from progressing irritation (swelling) that makes your airways routes exceptionally delicate and smaller than normal.
The side effects of asthma are diverse for diverse individuals most individuals who have asthma have one or more of these side effects as follows:

1)Coughing :
Coughing is of two sort either dry hack or damp hacking that brings up bodily fluid. Hack is after more regrettable at night, it can come amid morning or evening or after physical activity.

2)Wheezing :
Wheezing is a whistling sound generation when a individual Breath.

3)Chest tightness :
Chest Tightness is a feeling like something is pressing or silting on your chest.

4)Shortness Of Breath :
Due to Limit airway routes a few individuals can't capture their breath, Or they feel out of breath – like they can`t get sufficient air out of lungs.

5)Feeling Panicked , Fatigue :
Tiredness due to inappropriate air exchange (trade) & Least level of Oxygen in Blood.

6)Grayish or Somewhat blue colouring of Lips
7)Nasal Flaring [8,9,10]

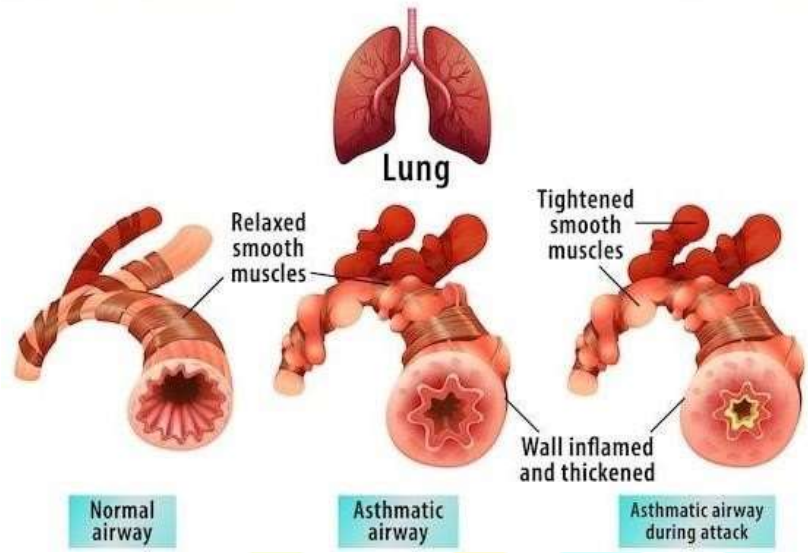

Fig1., Asthmatic lungs and Airways

HOW ASTHMA IS CAUSED ?
Asthma is caused by genetic and environmental Factors that Interact with one another.
These interactions affect how severe asthma is as well as how well it responds to treatment [11,12]

Asthma is a Three Step Problem :
1) Airway Inflammation :
The Airways in out lungs are very sensitive to substances. In normal airways there is enough space for the air exchange. In Asthma, there is inflammation on inner lining of airway and becomes swollen & red.

2) Airways Hyper Responsiveness To Stimuli (Trigger) :
When trigger such as tobacco smoke, dust, chemicals, and pollen or the flu or getting a cold triggering the airways to become more inflamed and hyper- responsive , leaving even less room in the airways for the air to move though.

3) Muscles within Airways Contract :
The Muscles Surrounding The airways to get bigger & Tighten. This squeezes the Airways & makes them smaller (This is Called Bronchospasme). Also Glands In the airways produce lots of thinks mucus which further cause mucus aqumilation & Block the Airways. [8]

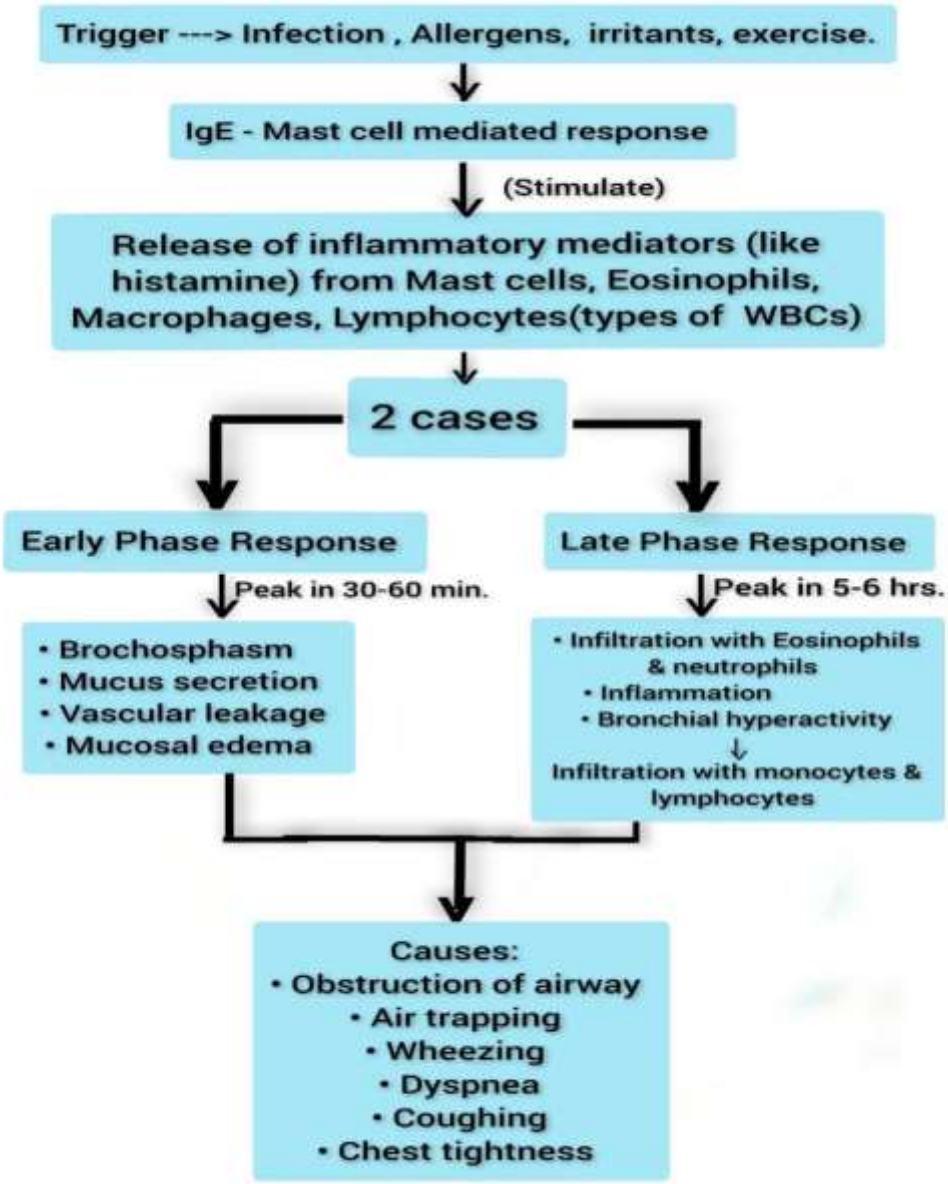

Fig2., Pathophysiology of Asthma

TYPES OF ASTHMA [13]

1) Extrinsic Asthma :

Commonly Known as Atopic Asthma or Allergic Asthma Triggered by a pet Dander , House Dust , Mold (type of Fungal) , Pollen & Food or any other Allergen.

2) Intrinsic Asthma :

Commonly Known as non-atopic asthma or Non-allergic Asthma triggered by weather changes, Respiratory Tract infection(RTI),And emotional Strees & Physical Activity.

3) Mixed Asthma :

Triggered By both Allergens & Non-allergens.

Extrinsic or allergic asthma causes the IgE inflammatory reaction with exposure the IgE antibodies are produced and connected to mast cells in the lungs.

Re-exposure to the antigen causes them to tie to the IgE antibody, discharging histamine and other mast cell item. The discharge of these item causes bronchospasm, mucous layer swelling, and over the top mucous production.

Gas exchange is impaired, causing carbon dioxide to be caught in the alveoli so that oxygen is incapable to enter.

ANTI-ASTHMATIC :
Anti-Asthmatic agents are the drugs that are used in the treatment of asthma by helping to relives symptoms & Improve Breathing.

CLASSIFICATION:

1] Bronchodilators :
(A)Sympathomimetics :Salbutamol , Salmeterol , Ephedrine , Terbutaline

(B)Methylxanthics :Theophylline, Aminophylline , Doxyphylline .

(C)Anticholinergic :Ipratropium Bromide , Tiotropium Bromide.

2] Mast Cell Stabilizer : Ketotifen , Sodium Cromoglycate.

3] Corticosteroids :
(A)Systemic : Hydrocortisones , Betamethasone , Prednisolone.

(B)Inhalational : Beclomethasone Dipropionate , Ciclesonide ,Budesonide.

4] Leukotriene antagonists : Zofirlukast , Montelukast.

5] Anti – IgE Antibody : Omalizumab.

Sympathomimetic:
1) The activation of beta 2 receptors that leads to increased CAMP Formation in Bronchial muscle cells & relaxation , medications of adrenaline promotes Bronchodilation.
2) By elevated CAMP the release of mediates is inhibited in mast cells & other inflammatory cells.
3) Since beta 2 receptors on inflammatory cells shows quick relief , this activity may have minimum or unknown contribution as therapeutic effect of beta 2 against in asthma cases where airway inflammation occurs continuously.

For. Ex : Salbutamol , Salmeterol , Ephedrine , Terbutaline [14]

Methylxanthine:
It has been determined that methylxanthine have three different biological Actions :
1) Ca2+ release form the sarcoplasmic reticulum , particularly in heart & skeletal muscles.
2) Inhibition of the enzyme phosphodiesterase (PDE), which degrades Cyclic Nucleotide Second messengers , may partly explain the action of methylxanthines. These drug inhibits the isoenzymes PDE3 which degrades CAMP & Cyclic guanosine monophosphate (CGMP) & PDE4 which degrades CAMP.
3) Adenosine functions as a local mediator in the CNS, Cardiovascular system & other tissues or organs. It shows gastric secretions, Dilates Cerebral blood vessels, depresses cardiac pacemaker, Contracts smooth Muscles i.e . Bronchial. These effect can be caused by blocking adenosine receptors. The effect of methylxanthines are opposite.

For Ex: Theophylline , Aminophylline & Doxoyphylline

Anticholinergics:
1)Anticholinergic inhibits M3 receptors which mediates cholinergic constriction & promotes bronchodilation by mainly affecting the bigger airways that receive viral innervations.
2)Though they are not virally innervated , some new research show that M3 receptors are present in peripheral bronchiolar muscles as well.

For Ex : Ipratropium Bromide, tiotropium bromide .

Mast Cell Stabilizers:
It is a synthetic chromone subordinate that, in reaction to trigger stimuli, avoids mast cell and other inflammatory cell degranulation. Discharge of asthmatic mediators such as, Limitations apply to histamine, LTs, PAF, interleukins, etc. In spite of the fact that the correct cause of this phenomenon is obscure, it might be related to a delayed Cl^- channel in these cells' layers. Inhibited is the chemotaxis of inflammatory cells. Prolonged treatment decreases the inflammatory reaction inside cells; varying degrees of bronchial Hyperreactivity diminishment occur.

Corticosteroids:
Corticosteroids enter cells and bind to a high partiality cytoplasmic receptor protein → a structural change happens in the steroid receptor complex that permits its movement into the nucleusand binding to glucocorticoid response elements (GRE) on the chromatin → translation of particular m-RNA → control of protein synthesis.

For ex: Hydrocortisone, prednisolone

Leukotriene antagonist:
The advancement of antagonists and synthesis inhibitors for cystenyl leukotrienes (LT-C4/D4) has been sought after since it became clear that these compounds are noteworthy mediators of bronchial asthma. There are two types of cystelucentan antagonists accessible: montelukast and zafirlukast.

For ex: montelukast, zafirlukast

Anti-IgE-antibody:
It is a humanized monoclonal counter acting agent(antibody) against IgE. Administered s.c., it neutralizes free IgE in circulation without enacting mast cells and other inflammatory cells. On antigen challenge, small IgE is accessible bound to the mast cell surface receptors (FcεR1) to trigger mediator discharge and cause bronchoconstriction.

For ex : Omalizumab

IN-VIVO & IN-VITRO SCREENING MODELS OF ASTHMA

IN-VIVO MODELS

There isn't a standardized animal asthma models that takes after asthma in individuals. There isn't a set experimental protocol in place right now. Different laboratories have created their claim model of asthma with major or minor modification. [15]

The following preclinical models utilized for the anti-asthmatic drugs :

1.Histamine and acetylcholine induced bronchoconstriction in guinea pigs
2.Clonidine-induced catalepsy in mice
3.Clonidine-induced pole cell degranulation in rats
4.Milk-induced leucocytosis and eosinophilia in mice
5.Inactive paw anaphylaxis in rats
6.Body plethysmography and respiratory parameters after histamine-induced Bronchoconstriction in anesthetized guinea pigs
7.Impact on broncho alveolar lavage fluid in egg albumin sensitized guinea pigs

1. Histamine and acetylcholine induced bronchoconstriction in guinea pigs:

This is the ordinary immunological model of airways blockage caused by antigens. Asphyctic convulsions and other indications can be brought on by inhaling histamine or other spasmogens. Comparative to guinea pig bronchial asthma. [16] Inhaled histamine and actylcholine induce hypoxia and convulsion in guinea pigs. Strong smooth muscle contraction, extreme hypotension, and cardiovascular system capillary dilatation are all brought on by histamine. Each species has a particular, winning response to histamine, which is the reason for downfall. In this models, the built-in nebulizer of the histamine chamber is to give acetylcholine (10%) and histamine (0.25) as aerosol at a constant pressure of 40 mm/Hg. The guinea pig encounters significant bronchoconstriction due to a articulated impact of histamine and acetylcholine, which result in hypoxia and convulsive dyspnoea. Bronchodilators have the capacity to delay the onset of these symptoms. For each animal, the amount of time required for the histamine and acetylcholine-induced preconvulsive dyspnonea (PCD) to show is noted. This model is usedto evaluate the bronchodilator action of test drug against histamine and acetylcholine initiated bronchoconstriction in guinea pigs. [17]

Procedure :
Expose each creature to histamine (0.25%) or acetylcholine (10% aerosol) ➞ Note pre-convulsive time (PCT) ➞ Evacuate animal from Histamine Chamber (put in fresh air) ➞After 2hr ➞Drug treatment ➞ (After 1 hr) (After 4 hr) (After 24 hr) Repeat procedure 1, 2 and 3. [13]

Evaluation :
Percent of increment of pre-convulsive time is calculated versus control. ED50 values can be found i.e. 50% of increase of preconvulsive time.

2. Clonidine -induced catalepsy in mice :

When an animal suffers from catelepsy, it takes a considerable amount of time for it to return to its normal posture. The additional pyramidal impact of drugs that upgrade or discharge histamine, an inhibitory neurotransmitter, or suppress dopaminergic transmission in the brain can cause catalepsy. A histamine H1 receptor antagonist, but not an H2 receptor antagonist, inhibits the dose-dependent catalepsy caused by the 2-adrenoreceptor agonist clonidine in mice. [18] By lessening the amount of transmitter saves in the nerve terminals, histamine modulates pre- synaptic catecholamine activities in the central nervous system. When histamine is infused intra cerebroventricularly (i.c.v.) into conscious mice, it causes catalepsy, which is restrained by the H1 receptor antagonist chlorcyclizine rather than by metiamide is an agent that block H2 receptors. The brain contains mast cells that are histamine-containing. There is no doubt that brain histamine contributes to the advancement of the extra pyramidal motor symptoms related with catalepsy. Thus, It has been proposed that histamine, which is discharged from brain mast cells in response to clonidine's activation of α2 adrenoreceptors, mediates the cataleptic impact of clonidine in mice through H1 receptor. [19]The most viable method for analyzing a test drug's affect on clonidine-induced catalepsy is the bar test. The mice's forepaws must set on a horizontal bar that is around 1 cm in diameter and 3 cm above the table. Each animal's time required to expel its paws from the bar must be recorded before and one hour after the test medicate is administered. The length of the catalepsy must moreover be measured at intervals of 15, 30, 60, 90, 120, 150, and 180 minutes [20, 21].

Procedure :

Treatment as per group➞ Place forepaws of mice on horizontal bar➞ Measure duration of Catalepsy➞ After 1 hr of treatment➞ Clonidine (1mg/ kg sc) to all groups ➞Measure duration of catalepsy at 15, 30, 60, 90, 120, 150, and 180 min. [20,21]

Evaluation :

Decrease in the duration of catalepsy is calculated versus control. Standard and test group are compared with control group.

3. Clonidine-induced mast cell degranulation in rats:

Rat mast cell granules have been found to contain around 0.3 m of histamine .The Combination of clonidine and Compound 48/80 acts without harming the cell wall by driving the granules to remove powerfully. Comparative to a selective savior like compound 48/80, clonidine too causes the discharge of histamine from mast cells. Sodium cromoglycate, a common mast cell stabilizer, increases cyclic adenosine monophosphate to stop mast cell degranulation. This model is utilized to evaluate a test drug's capacity to stabilise mast cells. [22]

Procedure :

Treatment as per group (for 7 days) ➞ on 7th days, 2 hr after alloted treatment➞ infuse saline solution (10ml) into peritoneal cavity ➞abdomen delicately rub (for 90 sec) ➞ open peritoneal cavity ➞ aspirate fluid containing mast cells➞ collect mast cells in siliconised test tube (7-10 ml RPM-1640 medium pH7.2-7.4) ➞ wash mast cells (centrifugation of 400-500 RPM) ➞ mast cells taken in RPM-1640 medium ➞challenge mast cells suspension (with 0.5µg/ml clonidine)➞stain with 1% toluidine blue ➞observe under high power magnifying lens (45x)➞count 100 cells➞ note intact and degranulated mast cells ➞calculate percent protection by formula. [22] Percent protection against clonidine initiated mast cell degranulation can be calculated by taking after formula.

$$\% \text{ Protection} = \frac{T2-T1}{T2} \times 100.$$

T1 = Control group.
T2 = Test group.

Evaluation :

Percent of diminish in clonidine initiated mast cell degranulation is calculated versus control standard and test group are compared with control gather and control group is compared with % of intact mast cells.

4. Milk-induced leucocytosis and eosinophilia in mice:

Several therapeutic properties have been credited to the plants in the conventional system of medication. The presence of adaptogenic properties in some plant materials is being one of them, as described to be tonics in the Ayurvedic framework of medication. Most vital feature of an adaptogen is that it increases resistance to adverse impact of extensive range of factors of physical, chemical and organic nature which uncovers itself irrespective of the direction of the past pathologic shifts. Ayurveda gives a number of herbs for the treatment of asthma and herbal formulations utilized for the treatment of asthma incorporate some adaptogenic (Nervine support) herbs to enable selection to stress, since excessive stress or nervous debility may disturb the symptoms of asthma. After parenteral administration of milk there is an increment in total leukocyte count (TLC) and this stressful condition can be normalized by administration of an antistress or adaptogenic medicate. Moreover leukocytes enlisted during asthmatic inflammation, discharge the inflammatory mediators like cytokines, histamine, and major basicprotein and advance the progressing inflammation. This model is used to assess the defensive effect of test medicate against milk induced leukocytosis [23].Eosinophilia is an abnormal increment in the peripheral eosinophil count of more

than 4 % of total leukocytes. In the late phase, particularly in the development of allergic asthma, eosinophils play part as an inflammatory cell. Eosinophil secretes mediators such as eosinophil cationic protein (ECP), eosinophil derived neurotoxin (EDNT), granulocytes macrophage colony stimulating factor (GM-CSF), tumor necrosis factor (TNF) and Prostaglandin (PG), which results in epithelial shedding, bronchoconstriction and advancement of inflammation in respiratory tract. Eosinophilia is related with respiratory disorder, frequently allergic in nature together with pulmonary infiltrates that are recognizable on chest films. Parenteral administration of milk produces a marked and significant increase in the leukocytes/eosinophils count after 24 hr. In this model of milk induced eosinophilia in mice, boiled and cooled milk (4 ml/kg, s.c.) is administered and the absolute eosinophil count is recorded before and after administration of milk .

Procedure :
1.Collect blood sample from each animal.
2.Count total leucocytes and eosinophils
3.Treatment as per group (after 1 hr)
4. and cooled milk to test group (after 2 hr)
5.Repeat procedure 1 and 2. [24]

Evaluation :
A blood eosinophilia is trademark of both allergic and non allergic asthma .By noticing the number of leucocytes and eosinophils before and after treatment, the difference is calculated. Standard group is compared with control group and test group is compared with standard group.

5. Passive paw anaphylaxis in rats :
Chronic inflammatory conditions like asthma and allergies are brought on by introduction to allergens, which triggers T-lymphocyte activation. Following discharge of mediators included ininflammation. Immunomodulating drugs help asthma sufferers by preventing the antigen- antibody (AG: AB) reaction, which stops provocative mediators from being discharged. Rats that suffer from detached paw anaphylaxis create antibodies against egg albumin. The animals are made more sensitive by infusing these antibodies. One day following sensitisation, the test medicine is given. Following the administration of a test medicine for an hour, animals are challenged with egg albumin. This model is used to assess the test drug's capacity to avoid allergen-induced passive paw anaphylaxis and, thus, to explore the test drug's impact on the inflammatory reaction mediated by the AG: AB reaction [25]

Procedure :
100 µg egg albumin (on 1st ,3rd and 5th day) ➞blood collection (on 10th day) ➞serum separation(centrifugation at 1500RPM) ➞Sensitization with 0.1 ml of serum (into left hind paw) ➞0.1 ml of saline (into right hind paw) ➞treatment as per group ➞after 1hr➞challenge with 10 µg of egg albumin ➞ measure paw inflammation utilizing plethysmometer calculate difference earlier to and after antigen challenge ➞ calculate percent inhibition of edema. [26]

Evaluation :
Percent of inhibition of paw edema is calculated versus control. Standard and test group are compared with control group.

6. Body plethysmography & respiratory parameters after histamine-induced bronchoconstriction in anesthetized guinea pigs:
A plethysmograph can be used to monitor respiratory parameters in guinea pigs. It is recorded how often and how much the respiratory system breathes. The reduction in respiratory amplitude lessened bronchodilatatory medications reduce the reflectory rise in respiratory frequency following histamine inhalation and the respiratory volume due to bronchoconstriction. By inserting a catheter into the pleural cavity and utilising a Fleisch tube, additional breathing data can be recorded. Animals are subjected to histamine or methacholine aerosol, respectively, in double chamber plethysmographs, or whole body restrained measurement of airway resistance, to observe the airway responsiveness to these often employed mediators. The technique can beapplied to a variety of situations, such as assessing potassium's bronchodilator effects or its antagonistic effects on bradykinin-induced bronchoconstriction. Channel openers or to evaluate how much morphine causes rats to perspire. [27, 16]

Evaluation :
Histamine-induced bronchoconstriction is inhibited at different test chemical dosages, and the corresponding standard is noted. It is possible to compute ED50 values for pulmonary resistance (RL) inhibition. Moreover, it is possible to quantify the histamine antagonistic time course. Compounds can be examined during an intravenous infusion of histamine (intervention) or after an IV injection of histamine (prevention).

7. Impact on broncho alveolar lavage fluid in egg albumin sensitized guinea pigs:
Studying the airway inflammation associated with mild asthma has shown to be facilitated by Broncho alveolar lavage (BAL) [28].
Patients' BAL fluid after asthma attacks is a rich Combination of soluble adhesion molecules, neuropeptides, eicosanoid mediators, and Inflammatory cells and cytokines. An increased concentration of mast cells, lymphocytes, and eosinophils is seen in asthmatic individuals. After being exposed to an allergen, there appears to be a baseline rise in the amount of eosinophils in BAL fluid, although this increase is further pronounced during periods of inflammation. It has also been shown that 19 hours after the allergen was injected endobronchially, the number of lymphocytes and basophils in the BAL fluid increased.

Procedure :

Sensitization (1ml,10 %w/v i.p egg albumin) ➞ test drug to test group (for 15 days) ➞ after 2 hr on 15th day➞ challenge(0.5ml 2% w/v i.v. egg albumin) ➞after 3 hr➞ cannulate trachea and lavage airway with saline at 25°C(two aliquots of 1ml/ 100 g body weight) ➞ collect Broncho alveolar cells (in two successive lavage) ➞ store BALF on ice ➞ count total WBC ➞Count differential WBC (using dilutions of lavage fluid 1 in saline) ➞ Compare the result. [29]

Evaluation :

Total WBC and differential WBC are counted. The result obtained where compare with Controlled with sensitized group and sensitized with treated group.

IN-VITRO MODELS

The use of in vitro models usually provides information in the early stage of preclinical Development regarding probable biological performance of the drug product. It is known that the use of in vitro studies and the experiments done for humans are not easy to integrate.

The following preclinical methods used for anti-asthmatic drug are:

1. Isolated goat tracheal chain preparation
2. Histamine, acetylcholine, serotonin and bradykinin induced contraction in guinea pig Ileum
3. Vascular and airway responses in the isolated lungs
4. Bronchial perfusion of isolated lungs

1. Isolated goat tracheal chain preparation:

This methodology is used to study how antispasmodic medications affect the tracheal Musculature. The approach is predicated on the discovery that the removed goat trachea react to a variety of medications with the well-known activities that these medications are known for, and that the reaction can be monitored and recorded for comparative analysis with the appropriate magnification. While this approach is generally recognized for its use in the investigation of antispasmodic medications, special attention is paid to its application the testing of bronchodilators. The reason for this is the strong anatomical and physiological relationship between the bronchial and tracheal muscles. There is a small population of H2 inhibitory receptors and a majority of H1 excitatory receptors in the isolated goat tracheal preparation. Histamine, acetylcholine, and five on isolated goat trachea, bradykinin and hydroxytryptamine exhibit dose-related contractile responses [30]. Compared to the guinea pig tracheal chain, the concentration required to cause contraction with these agonists is lower in the goat tracheal chain. The screening of spasmogenic activity on respiratory smooth muscle was appropriate for both goat tracheal chain and strip preparation. Goat tracheal chain is more sensitive than guinea- pig tracheal chain and is also easier to handle and prepare .According to reports, the isolated goat trachea contracts in a dose-dependent manner in response to acetylcholine (0.1–12.8 µg), histamine (0.1–102.4 µg), barium chloride (0.1–51.2 µg), and 5-HT within a certain dose range. [31,32] Histamine-induced contractions are inhibited by chlorpheniramine maleate (an H1receptor antagonist), but contractions are intensified by cimetidine (an H2 receptor antagonist). These findings imply that the isolated goat trachea has both H1-excitatory and H2-inhibitory histamine receptors . A dosage response curve study can be used to determine the relative potency of an agonist or medication; a curve that leans more to the left suggests greater potency. Likewise, the slope of the curve represents inaccuracy and precision (reliability) of the bioassay. In the experiment, a steeper slope corresponds to more precision, and vice versa [33]

Evaluation :

Height of the response is measured and dose response graph of acetylcholine and histamine is drawn in the absence and presence of test drug.

2. Histamine, acetylcholine, serotonin and bradykinin induced contraction in guinea pig ileum :

An autocoid with significant physiological impact on the body is histamine. It has a significant role in mediating type I allergies and inflammatory responses that occur instantly. Aside from that It causes a threefold response, and on intestinal smooth muscle, histamine causes a spasmogenic response. It acts on the H1 receptor, which results in the contraction of the intestinal smooth muscle of guinea pigs. Similar to histamine, acetylcholine, serotonin, and bradykinin also produce constriction of the ileum in guinea pigs. Acetylcholine is a cholinergic agonist that acts on muscarinic receptors to produce contraction. This model was used to examine how a test drug affected the contraction of intestinal smooth muscle generated by histamine, acetylcholine, serotonin, and bradykinin. [34]

Evaluation :
Height of the response is measured and dose response graph of acetylcholine and histamine is drawn in the absence and presence of test drug.

3. Vascular and airway responses in the isolated lungs:
It is possible to simultaneously record the pulmonary vascular and airway responses to multiple medications in the isolated perfused rat lung. Airway, pulmonary arterial perfusion pressure and reservoir blood level are electronically averaged, tracked with a polygraph, and continuously monitored. [34]

Evaluation :
Following the injection of test chemicals, changes (increase or decrease) in pulmonary arterial pressure and airway pressure are recorded in millibars (mm Hg) and compared to baseline values.

4. Bronchial Perfusion Of Isolated lungs:
A straightforward technique is bronchial perfusion of the isolated lung. For researching the Bronchiolar muscle's pharmacological responses. The process entails putting fluid down the trachea. Permitting it to exit the alveoli by means of scuffs on the lung's surface via the bronchi. A lower flow rate is the outcome of bronchoconstriction. An increased flow is indicative of bronchodilation. The technique has been used to assess medications that are sympathomimetic. [34]

Evaluation :
Bronchodilating agent activity ratios against the standard can be computed using a 3 + 3 point assay with confidence limits included.

CONCLUSION:

Pharmacology has played an important role in identifying and validating new targets in asthma therapy over the last few years and it will continue to be a vital part of progress in the future. To treat asthma symptoms, a variety of drug classes are used, including 2 agonists, anti-muscarinic, anti-histaminic and anti-inflammatory corticosteroids, allergy medications, etc. Although we haven't studied, new treatments also have a high barrier to overcome in combination therapy is efficacious & it's likely that once-a-day , fast-onset combinations of long- acting beta- agonists & steroids will be available soon.

We have attempted to include the majority of agent types in the screening models for the assessment of anti-asthmatic activity in the current article. This section also covers plausible mechanisms associated with various screening models. A brief attempt has also been made to go over asthma symptoms, causes, and triggers. Students, instructors, researchers, and young scientists working in the subject of respiratory research will find this review article interesting.

A thorough analysis of various antiasthmatic activity screening techniques is necessary to provide valuable insights for future study, ultimately leading to the creation of a novel therapeutic candidate that possesses strong antiasthmatic properties.

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