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A Clincal Approach to Study the Efficacy of Treprostinil Diethanolamine in Pulmonary Arterial Hypertension Patients

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The hereditary factor may be one of the reasons for this type of hypertension. It affects more men than women. Diet and lifestyle also play a role in pathophysiology. Overweight people often suffer from hypertension. Irregular sleep patterns also lead to hypertension. Hypertension is seen in people with excessive salt intake in their diet[1]. These people are known as "salt sensitive."The aim of the study is to evaluate the efficacy of the treprostinildiethanolamine (IP) compared with placebo in subjects suffering with the pulmonary arterial hypertension (PAH). To evaluate the efficacy and safety in the finished population. To observe and record the response of the IP in the PAH subjects. The 6MWT is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. The strongest indication for the 6MWT is for measuring the re-sponse to medical interventions in patients with moderate to severe heart or lung disease. The 6MWT has also been used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality. Clinical worsening was taken into consideration for the efficacy measurement. Subjects who experienced no clinical is 90 % in both the groups. In test group 15 out of 151 experienced clinical worsening, in the placebo group 8 subjects experienced clinical worsening.9 subjects experienced death in the test drug out of 151,in placebo 6 subjects out of 77 experienced death, the % of death in placebo group is greater than the test group. All parameters like no clinical worsening, clinical worsening, death, hospitalization/ new therapy , 6MWD, transplantation or atrial septostomy were were compared in test and the stardard group. The safety parameter is measured by the adverse reactions reported. Symptoms like headache, nausea, diarrhea, pain in jaw, vomiting, flushing, pain in extremity, abdominal pain, and myalgia were experienced by subjectsshown in the table no 4.the numbers of subjects experienced the adverse reactions.

Key Words: *Hypertenson,* atrial septostomy, treprostinildiethanolamine.

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1. INTRODUCTION

The type of blood pressure where exact cause cannot be pinpointed is known as essential hypertension (primary hypertension). The hereditary factor may be one of the reasons for this type of hypertension[2]. It affects more men than women. Diet and lifestyle also play a role in pathophysiology. Overweight people often suffer from hypertension. Irregular sleep patterns also lead to hypertension. Hypertension is seen in people with excessive salt intake in their diet. These people are known as "salt sensitive." Their bodies exhibit high blood pressure, when the amount of salt in their blood is more than the body requirement. Low potassium and calcium intake,

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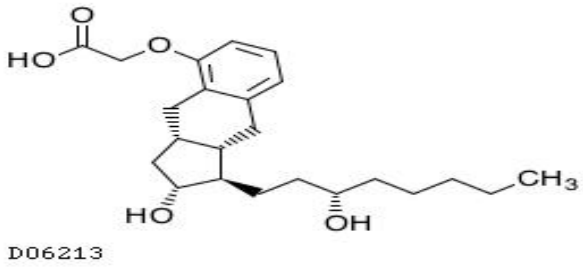
stress are also the causes of high pressure. Secondary hypertension is the condition when one can pinpoint the exact cause of hypertension[3]. Kidney diseases are the most common factor for secondary hypertension. Hypertension can also be caused by tumours of the adrenal glands. These tumours or abnormalities of the adrenal glands cause excessive secretion of hormones that led to hypertension. Oestrogen, the hormone found in birth control pills can also cause the blood pressure to elevate[4]. Pregnancy is another factor that causes hypertension.The development of arteriosclerosis and atherosclerosis are also affected by hypertension. Hypertension reduces the elasticity of arteries causing other secondary conditions which lead to decrease blood flow and ischemic diseases. Hypertension induced arteriosclerosis may lead to atrophy of renal glomeruli and tubules. This causes renal failure and may lead to death. Another serious complication arising due to hypertension is cerebrovascular diseases. Coronary diseases are the most common cause of death for hypertensive patients[5].

The aim and objective of the study is to evaluate the efficacy of the treprostinildiethanolamine (IP) compared with placebo in subjects suffering with the pulmonary arterial hypertension (PAH). To evaluate the efficacy and safety in the finished population.To observe and record the response of the IP in the PAH subjects.

DRUG PROFILE:

Treprostinil

Treprostinil is a synthetic analogue of prostacyclin, used to treat pulmonary hypertension. Treprostinil is marketed as Remodulin, (R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy- 1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl] oxy]acetic acid).This compound belongs to the class of organic compounds known as phenoxyacetic acid derivatives. These are compounds containing an anisole where the methane group is linked to an acetic acid or a derivative. Aromatic homopolycyclic compounds.$C_{23}H_{34}O_5$



INDICATION:

For use as a continuous subcutaneous infusion or intravenous infusion (for those not able to tolerate a subcutaneous infusion) for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise[6].

PHARMACODYNAMICS :

Pulmonary arterial hypertension (PAH) is a disease in which blood pressure is abnormally high in the arteries between the heart and lungs. PAH is characterized by symptoms of shortness of breath during physical exertion. The condition can ultimately lead to heart failure. Treprostinil is a potent oral antiplatelet agent. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

MECHANSIM OF ACTION :

The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In addition to treprostinil's direct vasodilatory effects, it also inhibits inflammatory cytokine. As a synthetic analogue of prostacyclin, it binds to the prostacyclin receptor, which subsequently induces the aforementioned downstream effects[7].

PHARMACOKINETICS :

ABSORPTION :Relatively rapid and complete after subcutaneous infusion, with an absolute

bioavailability approximately 100%. In patients with mild (n=4) or moderate (n=5) hepatic insufficiency and portopulmonary hypertension following a subcutaneous dose of 10 ng per kg of body weight per min for 150 mins the AUC 0-∞ was increased 3-fold and 5-fold respectively.Volume of distribution is 14 L/70 kg.Human plasma protein binding is approximately 91% in in vitro concentrations ranging from 330 to 10,000 µ/L.

METABOLISM :Substantially metabolized by the liver, but the precise enzymes responsible are unknown. Five metabolites have been described (HU1 through HU5) however, the biological activity and metabolic fate of these are unknown. The chemical structure of HU1 is unknown. The metabolite HU5 is the glucuronide conjugate of treprostinil. The other metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Study results of in vitro human hepatic cytochrome P450 demonstrates that treprostinil does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A. Whether treprostinil induces these enzymes has not been studied.

HALF LIFE :Terminal elimination half-life is approximately 2 to 4 hours. Plasma half-life is 34 and 85 minutes for intravenous and subcutaneous infusion of the drug, **respectively.**

TOXICITY : Symptoms of overdose are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of treprostinil.

SIDE EFFECTS MAY INCLUDE:

- a light-headed feeling, like you might pass out;
- easy bruising or bleeding (nosebleeds, bleeding gums), or any bleeding that will not stop;
- unexpected vaginal bleeding;
- coughing up blood or vomit that looks like coffee grounds; or
- blood in your urine or stools, black or tarry stools.
- cough, sore throat;
- pain or irritation in your throat after use;
- dizziness;
- nausea, diarrhea;
- headache; or
- flushing (warmth, redness or tingling).

OVER DOSE :

Signs and symptoms of overdose during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding .In controlled clinical trials, seven patients received some level of overdose and in open-label follow-on treatment seven additional patients received an overdose; these occurrences resulted from accidental bolus administration , errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of produce an event of substantial hemodynamic concern (hypotension, near-syncope).

Pregnancy

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil during organogenesis and late gestational development, at rates as high as 900 ngtreprostinil/kg/min (about 117 times the starting human rate of infusion, on a ng/m2 basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ngtreprostinil/kg/min (about 41 times the starting human rate of infusion, on a ng/m2 basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ngtreprostinil/kg/min, did not affect the growth and development of offspring. Animal reproduction studies are not always predictive of human response[8].

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged ≤16

years to determine whether they respond differently from older patients.

Patients with Hepatic Insufficiency

Clearance is reduced in patients with hepatic insufficiency. In patients with mild or moderate hepatic insufficiency, decrease the initial dose of to 0.625 ng/kg/min ideal body weight, and monitor closely has not been studied in patients with severe hepatic insufficiency.

2. METHODS AND MATERIALS:

The 6MWT is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the dis-tance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and in-tegrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism[9]. It does not provide specific informa-tion on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capac-ity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better reflect the functional exercise level for daily physical activities[10.]

INDICATIONS AND LIMITATIONS :

The strongest indication for the 6MWT is for measuring the re-sponse to medical interventions in patients with moderate to severe heart or lung disease. The 6MWT has also been used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality.

3. RESULTS:

Table 1: Baseline Characteristics

BASELINE CHARE	TEPROSTINIL (n =151)	PLACEBO (n = 77)
AGE	37.8	42.5
FEMALES	108	58
MALES	43	19

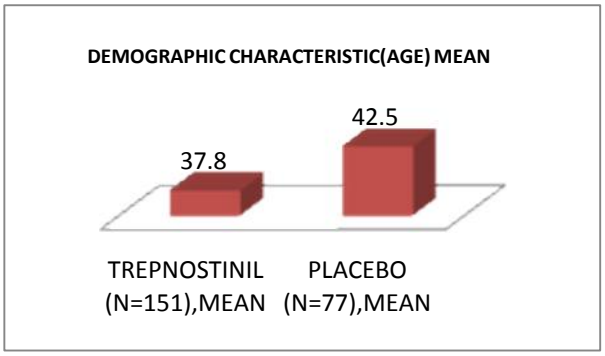


Fig 1: Demographic Characteristic Age

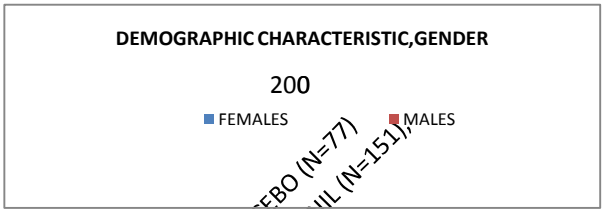


Fig 2 : Demographic Paremeter /Characteristic Gender

Table 2: PahEtiology

PAH ETIOLOGY	TEST (N=151) (%)	PLACEBO(N=77) (%)
IPAH/ HPAH	114 (75)	56(73)
CVD	26(17)	17(22)
REPAIRED CHD	10(7)	3(4)

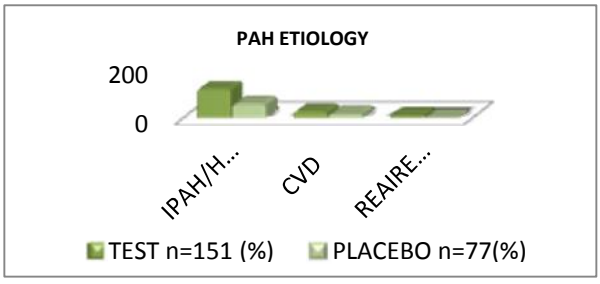


Fig 3: PahEtiology

Table 3: Clinical Worsening

CATEGORY	TEST n=151 (%)	PLACEBO n=77 (%)
NO CLINICAL WORSENING	136 (90)	69 (90)
CLINICAL WORSENING	15 (10)	8 (10)
DEATH	9 (6)	6 (8)
HOSPITALIZATION/NEW THERAPY	6 (4)	1 (1)
6MWD WHO	0 (0)	1 (1)
TRANSPLANTATION OR ATRIAL SEPTOSTOMY	0(0)	0 (0)

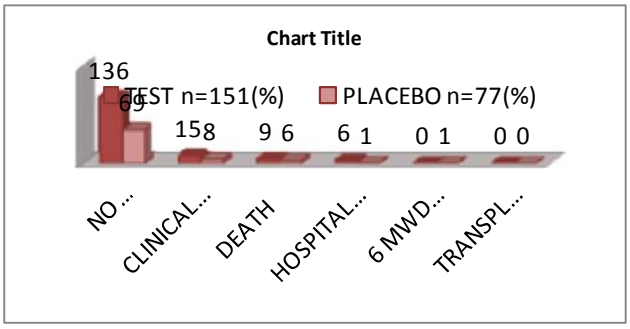


Fig 4: Clinical Worsening

Table 4: Adverse drug reactions

ADVERSE REACTION	TEST GROUP N=151 (%)	PLACEBO N=77 (%)
ANY EVENT	138 (91)	68(88)
HEADACHE	95 (63)	15 (19)
NAUSEA	45 (30)	14 (18)
DIARRHEA	46 (30)	12 (16)
PAIN IN JAW	17 (11)	3 (4)
VOMITING	26 (17)	12 (16)
FLUSHING	23 (15)	5 (6)
PAIN IN EXTREMITY	21 (14)	6 (8)
ABDOMINAL PAIN	13 (9)	4 (5)
MYALGIA	6 (4)	0 (0)

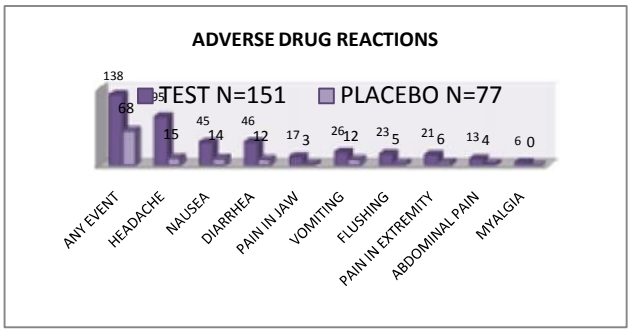


Fig 5: Adverse event reporting

4. DISCUSSION

- Total 300 patients were enrolled ,out of them 72 subjects were dropped out of the study. The subjects were randomized in to two groups, test (ip)151 and the reference (placebo)77.
- Subjects were asked to give consent,the response was taken in the case repot forms prepared according to the protocol.
- Demographic parameters of the enrolled subjects in the study were collected i.e. age and gender which is shown in table 1 and plotted in the graph no 1 and 2. In both the groups females were more in number than males. subjects were in between 12 to 73 years old.
- In table no.3 we can see etiology of PAH in both the groups. In the test group out of 151 subjects 114 subjects were under IPAH/HPAH that is 75% of the subjects and 26 subjects (17%) of subjects were under CVD disorders. In placebo group 17 (22%) subjects were under CVD. The etiology of PAH for both the groups were plotted in the graph no 3.
- Clinical worsening was taken into consideration for the efficacy measurement. Subjects who experienced no clinical worsening in test was 136 out of 151 , in placebo 69 out of 90 experienced no clinical worsening which is 90 % in both the groups.
- In test group 15 out of 151 experienced clinical worsening, in the placebo group 8 subjects experienced clinical worsening.9 subjects experienced death in the test drug out of 151,in placebo 6 subjects out of 77 experienced death, the % of death in placebo group is greater than the test group. All parameters like no clinical worsening, clinical worsening, death, hospitalization/ new therapy, 6MWD, transplantation or atrial septostomy were were compared in test and the stardard group and plotted in the graph no:4.
- The safety parameter is measured by the adverse reactions reported. Symptoms like headache, nausea, diarrhoea, pain in jaw, vomiting, flushing, pain in extremity, abdominal pain, and myalgia

were experienced by subjectsshown in the table no 4.the numbers of subjects experienced the adverse reactions were plotted in graph number 5.

5. CONCLUSION

The evaluation of efficacy and safety of treprostinildiethanolamine 4mg was studied compared with placebo in the finished population. Oral treprostinil is the first oral prostacyclin analogue to meet the primary endpoint in a randomized controlled trial in the PAH patient population. The results of this study support the use of oral treprostinil as initial therapy in PAH patients with class II or III symptoms. Maximal therapeutic benefits would be seen at 1 year treatment. Additional studies are needed to investigate the long-term impact of oral treprostinil therapy on PAH disease progression.

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