Int J Pharm Bio Sci 2012 Oct; 3(4): (P) 211 - 217

Research Article **Pharmacology**

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

COMPARATIVE STUDY OF RACEMIC SALBUTAMOL AND LEVOSALBUTAMOL IN PATIENTS WITH BRONCHIAL ASTHMA

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ABSTRACT

To compare the efficacy and tolerability of oral racemic salbutamol and levosalbutamol in patients with mild bronchial asthma. a single blind trial was designed to find out the usefulness of the tablet racemic salbutamol (2mg) and levosalbutamol (1mg) given independently to 25 matched mild bronchial asthma cases who satisfied a rigid inclusion and exclusion criteria at three times daily dosage over a period of 15 days. They were assessed objectively before and after by peak flow meter and serum potassium; and subjectively by palpitation, cough, breathlessness, and wheeze. Data were analysed statistically. The mean peak expiratory flow rate before and after therapy in racemic salbutamol group was 227.50 and 248ml respectively and in levosalbutamol group 231 and 282.5ml respectively with significant improvement in both but more in latter. No significant difference in serum potassium level either in intra or in inter group was noticed. Tachycardia, tremor, and muscular cramps were significantly low in levosalbutamol group. Levosalbutamol was found to be superior to salbutamol in terms of efficacy and tolerability in patients with mild bronchial asthma as evidenced by subjective and objective means.

KEY WORDS: Bronchial asthma, Forced expiratory volume (FEV), Peak expiratory flow meter (PEFM), Racemic salbutamol, Levosalbutamol.

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INTRODUCTION

Asthma is a serious global health problem which affects people of all ages, in all parts of the world. Prevalence, hospitalization and fatal asthma have increased considerably in United States over the past 20 years. Hospitalization for asthma is consistently higher among the blacks between the age 15 & 24.[1] Asthma is defined by American thoracic society as a chronic inflammatory disorder of the airways which causes an increased responsiveness of trachea and bronchi to various stimuli manifested by a wide spread narrowing of airways[2]. Contraction of smooth muscle is easily reversed by agents that relax airway smooth muscle of which β_2 receptor stimulants are most effective and most widely used[3]. Salbutamol the short acting, selective β_2 adrenoreceptor agonist is one of the most commonly used broncho dilators in the treatment of reversible airway obstruction[4]. Salbutamol has been marketed as racemic mixture although β2 agonist activity resides almost exclusively in the R- enantiomer[5] known as levosalbutamol. Published report states that levosalbutamol a molecule approved in 2004 for regular use has better effect than racemic form. However, not much studies have been done on the usefulness of levosalbutamol from south India. Hence the present study is undertaken to assess the efficacy of levosalbutamol compared to racemic salbutamol in patients with bronchial asthma.

MATERIALS AND METHODS

The study was a open label, single centre randomized comparative trial conducted in the department of Thoracic medicine, Government Rajaji Hospital, Madurai between August 2004 and March 2006 following the approval from the institutional ethical committee. Informed consent was obtained from all the patients. Patients of either sex suffering from mild asthma as per GINA(Global Initiative for Asthma)in the age group of 25-40 were selected. Only those patients who showed an improvement of 15% after inhalational bronchodilator therapy were included for the study.

Patients with severe asthma, endocrine disorder, diabetes, hypothyroidism, Chronic Renal Failure, neuropsychiatric illness, cardiac disease, Hypertension, pulmonary hypertension, thoracic abnormalities were excluded. Pregnant and lactating mothers were also not included. Patients > 40 yrs who have associated systemic illness were also excluded from the study. Thus 50 patients were selected over a period of 6 months and randomly divided into two groups, each group consisting of 25 patients. After general physical examination, baseline blood investigations were performed. Patients in group I received racemic salbutamol in the dose of 4mg/tds and group II received tablet levosalbutamol in the dose 2mg/bd daily for 15 days. Patients were advised not to take any other medicine without consulting the investigator. Patients were given a card in their vernacular language with a list of the adverse effects in detail so as to enable them to mark the expected side effects in day to day therapy.

Patients were assessed objectively before and after by Peak Flow Meter and serum potassium and subjectively by palpitation, cough, breathlessness and wheeze. Data were analysed statistically using Students T test.

RESULTS

Fifty patients were included in the study. Group I received racemic salbutamol and Group II received levosalbutamol . All of them completed the study.

TABLE 1
CHARACTERISTICS OF STUDY POPULATION

Basic Characteristics	Racemic Salbutamol	Levosalbutamol
Gender		
Male	11	10
Female	14	15
BMI	19-23	19-23
Economic status (Range in Rupees)	600 – 900	600 – 900
Clinical data ECG	Nil contributory	Nil contributory
X – ray chest	Nil contributory	Nil contributory
Hematology	Nil contributory	Nil contributory

Table 1 depicts demographic data of the patients. In the racemic salbutamol group, 11 were males and 14 were females with their mean age being 31±47 years. Among the patients who received levosalbutamol 10 were males and 15 were females with the mean age of 30±43 years. The mean BMI of both groups was 21. The clinical data, ECG and X ray chest were nil contributory. Past history of allergic disorders were noticed in 3 among 25 in Group I and 5 among 25 in Group II Patients . Family history of allergic illness was found in 2 and 1 among racemic salbutamol and levosalbutamol respectively. Renal function and liver function tests do not reveal any abnormalities.

TABLE 2
PEAK EXPIRATORY FLOW RATE COMPARISON AMONG MOLECULES OF SALBUTAMOL

	Racemic Salbutamol			Levo Salbutamol		
PEFR	Mean ± SD	Median	Mode	Mean ± SD	Median	Mode
Before	249.6 / 66.36	220.0	220.0	254.8 / 50.59	175.29	230
After	265.2 / 64.10*	250.0	250.0	309.6 / 55.94**	202.94	250

***Significant P = 0.0047** ***p = 0.0000175**

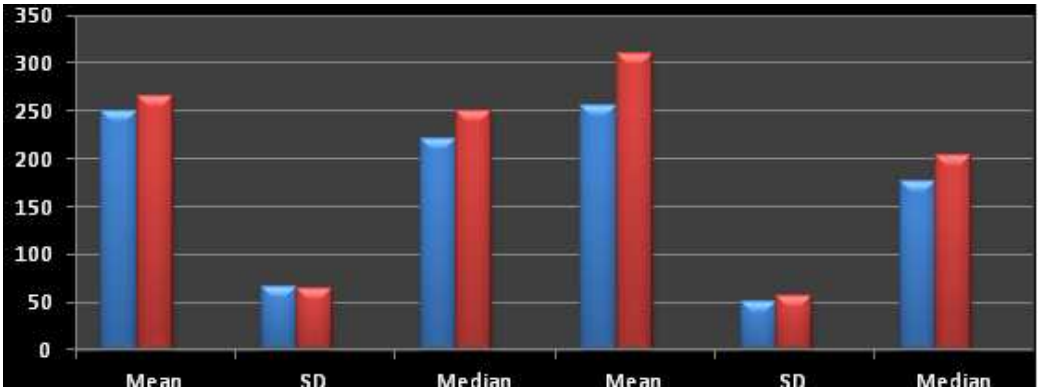

FIGURE I
Peak Expiratory Flow Rate Comparison

The patients were followed up for 15 days and at the end of the study they were assessed for clinical improvement using PEFM. The mean PEFR before and after therapy in group I was 249.6 and 265.2 respectively and in group II, it was 254.8 and 309.6.

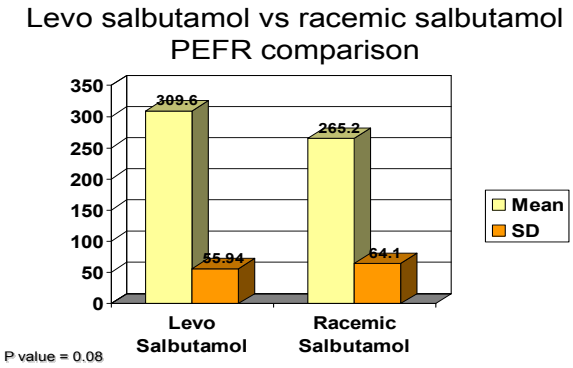

FIGURE II

The pulmonary function improved slightly (Table 2 & Figure II) after oral treatment with salbutamol irrespective of the type. However the improvement was very high in the levosalbutamol group (P<0.00001), which indicates levosalbutamol to be a better and effective bronchodilator.

Table 3
NATURE OF SIDE EFFECTS

Sl.No	Side Effects	Racemic Salbutamol (n=25)	%	Levo Salbutamol (n=25)	%	Significance
1	Palpitation	10	40	2	8	0.0063
2	Muscle Cramps	10	40	3	12	0.0213
3	Tremor	17	68	3	12	0.00001
4	GERD	3	12	0	0	-
5	Polyurea	2	8	0	0	-

The relative side effects observed in both the groups (table 3) were tachycardia, tremor and muscle cramps. They were significantly low in levosalbutamol group. GERD was noticed in 3 patients and polyuria was noticed in a few patients with racemic salbutamol but not in levosalbutamol treated group. Side effects were significantly less with levosalbutamol. In both the groups serum potassium level at the end of 2 weeks was slightly elevated but not statistically significant(table 4).

TABLE 4
SERUM POTASSIUM LEVEL BETWEEN THE STUDY GROUPS

Potassium level	Racemic Salbutamol	LevoSalbutamol
Before: Mean ±SD	4.1 0.4397	4.208 0.4349
After: Mean ±SD	4.204 0.6024	4.28 0.5156

P > 0.01 Not significant.

DISCUSSION

Bronchial Asthma is a disease known for centuries and descriptions made in different systems of medicine. Despite enormous advancement in the management of asthma still we do not have any definitive drugs. However salbutamol is one of the commonly used bronchodilators in day to day practice. In India salbutamol is marketed either in single molecule or in combination with various drugs like corticosteroids in various drug formulations.This widespread, regular use of $beta_2$ agonist, particularly in the absence of inhaled corticosteroids, could potentially lead to worsening asthma control. This may be due to rebound airway hyperresponsiveness. As a result the patient might require higher doses, resulting in incidence of beta-mediated side-effects like tachycardia, tremors, hypokalaemia etc.,[7]. All this has led to relook at the available $beta_2$ -agonists to develop more safer and therapeutically active agents.Salbutamol is a racemic compound composed of a 50 : 50 mixture of 2 non superimposable mirror image isoforms. Although salbutamol was first synthesized in 1969, there is still much research into better, quicker and efficient synthesis of R-Salbutamol.

In the present study, Group II patients, who received oral levosalbutamol for 15 days showed clinical improvement in the form of improved PEFR ($P<0.00001$) in contrast to group I who received racemic salbutamol. Side effects like palpitation, tremors and muscle cramps were also significantly less with levosalbutamol. Since inhaled form of levosalbutamol was used in many studies in different countries, oral form was taken into

consideration for comparative analysis in the present study. Serum potassium level showed slight variations after administration of drug in the present study. This could be due to dietary variation, renal clearance of potassium and pharmacokinetics of levosalbutamol as well as genetic contribution for potassium level in the body. In addition initial serum potassium level also might have contributed. Moreover, the serum potassium level was carried out at two different occasions and this might also have contributed.[8,9].Several studies have suggested an association between Beta agonist use and increased risk of death from asthma. Proposed mechanisms include increased bronchial hyper responsiveness, drug tolerance (or) underlying increased severity of disease. This apparent controversy may be due to the two different isomers having opposite effects. R-salbutamol causes smooth muscle to relax whereas S-Salbutamol causes smooth muscle to contract.[6,7]

S- Salbutamol acts on muscarinic receptors which are G-linked proteins. α – subunit of G-Protein is identical to β_2 receptor. But α–subunit activates phospholipase C , that catalyses the phosphorylation of Phosphotidyl inositol 4,5 – Biphosphate to IP_3 which in turn release ca^{2+} by binding with IP_3 gated Ca^{2+} channels in Endoplasmic Reticulum of muscle cell. This S-salbutamol releases sudden increase in ca^{2+} leads to smooth muscle contraction contributing to more adverse effects.[10] R-Salbutamol being an analog of human (R)-epinehrine is a more natural substrate for the sulfotransferase enzymes and therefore is more rapidly sulphated and eliminated than (S)-Salbutamol. Accordingly markedly elevated plasma levels of (S)-Salbutamol are seen after dosing with racemic salbutamol.This is a major concern when repeated dose of racemic salbutamol are administered, which might lead to accumulation of (S)-Salbutamol which might be responsible for the worsening of the disease, considering the detrimental effects that have been reported with (S)-Salbutamol. Levosalbutamol appears to be stereochemically stable in vivo and does not appear to interconvert metabolically to (S)-Salbutamol.[11,12]

CONCLUSION

The following conclusions were arrived:

A. The efficacy and tolerability of levosalbutamol was better than Racemic salbutamol
B. Side effects were less in the levosalbutamol group
C. Highly significant improvement in PEFR was noticed in those who used levosalbutamol
D. In view of the clinical and therapeutic advantages observed among the patients with mild bronchial asthma, oral form of levosalbutamol is recommended for such cases.

ACKNOWLEDGEMENT

The authors gratefully acknowledge Dr. N.Meenakshiammal, Former Director and Head of the Institute of pharmacology, Dr. P.Thirumalai Kolundu Subramaniam, Head of the Department of Medicine, Dr.C.. Chandrasekar, Head of the Department of Thoracic Medecine, Government Rajaji hospital, Madurai, for their support and guidance for the successful completion of this study.

REFERENCES

1. Mark S.Chesnut,Alex H.Gifford,Thomas J.Prendergast, Pulmonary disorders In:Stephen J.Mcpher,Maxine A.Papadakis CMDT 2010 216-217
2. The Revised British Guidelines on Asthma Management.Thorax 1997;52(suppl 1)
3. Sweetman Sc, Bronchodilators and Antiasthma drugs. In martindale. The complete drug reference PhP Pharmaceutical Press, London, 2002 757-759
4. Boultopn Dwetal, The Pharmacokinetics of Levosalbutamol : What are the clinical implications ? Clin Pharmacokinet, 2001, 40(i) 23-40
5. Ormord D ,Spencer C M.Levosalbutamol In :Biodrugs jun 1999:11:431-438.
6. Boulton D W,Fawcett J P.Enantioselective dispotition of albuterol in humans. In:Clin. Rev.AllergyImmunol. 1996.Spring:14(1):115-38.
7. Milgrom H, Skoner D P,Bensch G, Kim K T, Claus R, Low-dose Levalbuterol in children with asthma: Safety and efficacy in comparison with racemic albuterol, In: J.Allergy Clin.Immunol. 2001.Dec;108(6):938-45.
8. Handley D A, Tinkelman D, Noonan M. Dose-response evaluation of Levalbuterol versus Racemic albuterol in patients with asthma. In: J.Asthma .2000,Jun;37(4):319:27
9. Pancu D, LaFlamme M, Evans E, Reed J (eds).Levalbuterol is as effective as racemic albuterol in Lowering serum potassium In: J.Emerg.Med.2003.Jul;25(1):13-6.
10. Metabolism of Salbut.Sjosward,Kerstin Naidu,Josefsson et al.In:Pharmacol Toxicol, Met.of.Sal. Volunteers. Blackwell Synergy 1:Vol.92,Issue 1:27-32.
11. Schmeket B,Rydberg I,Norlander B et al.,Steroselective Pharmacokinetics of S-Salbutamol after administrative of the racemate in healthy Volunteers. Eur.Respir.J. 1999;13:1320-5.
12. Mitra S,Ugur M,Ugur O et al.,(S)-albuterol increases intracellular free calcium by muscarinic receptor activation and a phospholipase C-dependent mechanism in airway smooth muscle. Mol.Pharmacol. 1998;53:347-54.