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Review Article

Evidence behind use of levosalbutamol over salbutamol to prevent cardiac side effects

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ABSTRACT

Salbutamol and levosalbutamol are the two most frequently used medications for asthma in pediatrics. Levosalbutamol is more expensive than salbutamol and is usually considered safer option for patients with existing cardiac condition and, to reduce tachycardia in otherwise healthy patients. In this article, we reviewed the literature which included randomized controlled trials, retrospective studies and case reports and compared the cardiac side effects of these two medications with primary emphasis on tachycardia.

Keywords: Heart disease, Levosalbutamol, Salbutamol, Tachycardia

INTRODUCTION

About 300 million individuals presently have been diagnosed with asthma and 25000 deaths occur annually in asthma patients worldwide.[1] Salbutamol or racemic salbutamol (RS) has been the mainstay of acute symptomatic treatment of asthma for more than 40 years; however, since levosal butamol (LS) arrived in the early 90s there has been a constant ongoing debate regarding the safety and efficacy of one against the other. Some evidence suggest LS causes less tachycardia than RS which leads to use of LS whenever there is a concern for tachycardia but the cost of LS is more than RS which brings up the important question of the cost-effectiveness of one against the other.[2]

In this brief article, we review the evidence behind the most common cardiac side effect of the beta agonist which is tachycardia caused by LS and RS in children between age group 1-18 years.

We used key terms like salbutamol (albuterol), levosalbutamol (levalbuterol), asthma, children to search for randomized controlled trials in MeSH, Google Scholar, Ovid, Cochrane database and critically analyzed each study. Initially double blinded randomized controlled trials were selected for review irrespective of follow up duration.

Only trials reported in English were taken into consideration. From individual studies age, number of subjects, dose of LS and RS, mean change in heart rate, final heart rate, QTc interval and any cardiac side effects reported were taken into account. Sponsors for the studies were also taken into account. The studies were compared in terms of the above parameters in a descriptive way.

In the literature search we performed, only 12 RCTs were found that looked at the cardiac effects as a secondary outcome. Some of them did not report the specific heart rate changes they noted with treatment. Hence we included retrospective chart reviews in our study to accumulate more data. Studies performed on adults were not included.

We will also discuss about studies which have looked into patient satisfaction with these treatments.

Pharmacokinetic differences between salbutamol and levosalbutamol

Uspal NG in their study of misconceptions regarding LS in the treatment of acute asthma exacerbations in children surveyed 540 physicians to find that 48% of physicians did not have a clear conception of pharmacological difference between the two and believed LS caused less side effects than RS in general.[3] LS is a pure R isomer of salbutamol whereas RS has a 50-50 mix. Studies done in animal models and in vitro have demonstrated that toxicity of salbutamol is most likely due to its S-isomers though toxicity studies in humans have not been done yet. Pharmacokinetics of S and R enantiomers in humans showed delayed clearing of S isomer. However, it is also argued that the side effects of RS in humans are due to R isomer and the S isomer is relatively inert. Therefore, there is lack of firm evidence that S enantiomer causes toxicity in human beings.[4]

STUDIES AND RESULTS

Between 1981-1983, deaths secondary to the introduction of fenoterol, a highly potent beta agonist, have been reported.[5] This was one of the initial events that led to the association of cardiotoxicity to beta agonists. The cause of the deaths was later suggested to be related to disease severity.

Scattered case reports have suggested that salbutamol can cause sinus tachycardia and can induce tachyarrhythmias such as supra-ventricular tachycardia (SVT). However, the SVT was not always reproducible after reintroduction of salbutamol.[6] The mechanism by which salbutamol causes arrhythmias is unclear. Stimulation of heart rate occurs primarily by expression of beta-1 receptors. Tachycardia can also be caused by reflex vasodilation mediated by beta-2 receptors in peripheral blood vessels. In Electrophysiology studies, isoproterenol is routinely used to enhance conduction through accessory pathways to induce SVT. So in higher doses, when the selectivity for beta-2 decreases there may be increase in chances of SVT with selective beta agonist.[7]

Two landmark studies sponsored by Sepracor, manufacturer of LS in USA that needs mentioning are by Nelson et al and Gwachik et al.

First, Nelson et al in a multi-center, randomized, double-blind, placebo-controlled, trial studied 362 patients with chronic stable asthma. The patients were randomized to treatment with either LS 0.63 mg, LS 1.25 mg, RS 1.25 mg, RS 2.5 mg, or placebo via nebulizer three times daily for 28 days. They showed statistically significant improvement of Forced Expiratory Volume at 1 sec (FEV1) with LS. Heart rate change with 0.63 mg LS was shown to be significantly lower than 2.5 mg RS after the first dose and at 4 weeks (P <0.03). However, the heart rate increase in the groups was only +2 and +6 beats respectively, which is not clinically significant.[8]

Table 1: Change in heart rate across different studies.

Principal investigator	Nelson	Gwachik	Wilkinson	Carl	Andrews	Rahman	Momin	Milgrom	Skoner	Ralston
Year of study	1998	1999	2013	2003	2009	2012	2015	2001	2005	2005
No of patients	362	47	99	482	81	30	100	398	408	140
Age (years)	12-21	3-7	6yr-17	1-18	6-18	8-15	5-15	4-14	2-5	6-15
Change in heart rate with levsalbutamol (bpm)	2	0.46	7.56	N/A	N/A	N/A	N/A	4	3.2 (11.8)	N/A
Change in heart rate with salbutamol (bpm)	4	13.2	12.1	N/A	N/A	N/A	N/A	6	4.1 (8.3)	N/A
Mean HR with salbutamol (bpm)	N/A	N/A	N/A	129.7 (25.5)	130	109.52 (18.56)	109.43 (13.25)	N/A	N/A	26 (2.8)
Mean HR levsalbutamol (bpm)	N/A	N/A	N/A	130.1 (23.3)	137	124 (16.02)	112.52 (16.02)	N/A	N/A	10 (3)
Significance	p=0.03	P=<0.00	p>0.05	P=0.94	P>0.05	P<0.05	P<0.05	p>0.05	p>0.05	P<0.001

Second, a double-blinded randomized controlled study sponsored by Sepracor, by Gwachik et al, compared LS to RS. LS showed improved lung function in children with decreased side effects attributable to beta-receptor stimulation. However, LS 0.63 mg resulted in changes in heart rate similar to those seen in RS groups. Changes in corrected QT interval caused by different doses of

levosalbutamol and salbutamol were statistically significant but clinically very small.[9]

RCTs which were not sponsored by manufacturer of LS showed possible less tachycardia with LS. Rahman et al and Momin et al showed significant increase in heart rate with RS but not with LS.[10,11] However, statistics like paired T test or any other tests to compare head-on the change in heart rate was not done. Ralston et al found RS causes significantly increased final heart rate, maximal heart rate and change in heart rate compared to LS though heart rate changes were not compared with placebo.[12] Children in the 6-10 years age group have higher baseline heart rate than those who are more than age 10, which was not taken into account. Milgrom H in one of the most important RCTs showed LS was clinically comparable to 4-8-fold higher doses of RS and demonstrated more favorable safety profile.[13] The study showed LS 0.31mg has change of heart rate similar to placebo. Higher doses of LS and RS have similar effect on HR. Skoner et al found cardiac effects of LS and RS similar to Milgrom et al.[14] The conclusion from these two studies suggest LS at 0.31 mg is safer. However, this holds no significance for older patients who need LS at 1.25 mg.

There have been multiple randomized controlled studies with LS and RS showing no difference in cardiovascular adverse effects between them (Table 1).[15]

A double-blinded randomized controlled trial by Wilkinson et al compared the two medications as continuous nebulization in acute asthma exacerbation.[16] They had 44 patients in RS group and 55 patients in LS group. They found no difference in the increase in heart rate or complications between the groups. In this study, children receiving RS had higher improvement in FEV1. Also, they found lower serum concentration of S-enantiomer in group receiving LS.

Long-term safety study of LS administered via metered dose inhaler in patients with asthma by Hamilos et al showed no statistical significance of beta receptor-mediated side-effects in 764 children who participated in this multi-center parallel group open labelled trial.[17] In contrast to long term effects, high dose continuous nebulized LS for pediatric status asthmaticus RCT by Andrews et al on 81 patients between 6-18 years of age showed similar tachycardia in both LS and RS groups.[18]

482 children between 1-18 years age were given 6 doses of 2.5 mg of RS or 1.25 mg LS randomized; lower rate of hospitalization was seen in LS group but no statistically significant difference in increase in heart rate was found in between the groups.[19] The validity of the former conclusion of decreased hospital rate has been questioned subsequently by other studies.

A retrospective chart review was done for children 1mo to 12 years of age who received nebulized RS or LS for 3 successive doses. There were 25 patients in each group and they received either 2.5 mg of RS or 0.63 mg of LS. The median of the largest percentage of change in HR was 4.1% (interquartile range [IQR], 1.8-8.7) in the levosalbutamol group compared to 5% (IQR, 1.9-7.8) in the racemic salbutamol group ($p = 0.763$). Four patients in the levosalbutamol group experienced an HR increase of more than 10% compared to 5 patients in the racemic salbutamol group ($p = 1.0$).[20]

Kelly et al, did a retrospective chart review of patients with congenital heart disease and arrhythmia comparing the change in heart rate with racemic RS and LS. They analyzed 192 patients of whom 142 received LS, 40 received RS while 10 patients received both. Inclusion criteria were that the patients should have received at least 3 doses of LS and/or RS, age less than 18 years and diagnosis of congenital heart disease (CHD), cardiomyopathy, or supra-ventricular tachycardia. In patients with CHD, the RS group experienced a mean heart rate increase of 6.6 beats/min compared to 6.3 beats/min in the LS group (which was a statistically equivalent increase).[21] This study is important because it suggests that both racemic salbutamol and levosalbutamol increase heart rates but were equivalent not only in general population, also in children with congenital heart disease.

A patient satisfaction survey comparing LS with RS in children with a size of 76 and 66 for the two groups showed more parental satisfaction with LS in terms of symptom relief. The satisfaction may have been biased by the fact that they were prescribed LS by a pediatrician who prefers LS and hence would have already influenced the parents of the population under study.[22]

Another randomized controlled double blinded 3-way cross over trial with only 16 patients showed increased objective measures of hyperactivity and inattentiveness in asthmatic children with RS over LS. These two studies suggest that in general, LS would be preferred by families over RS.[23]

As per the U.S Food and Drug Administration drug safety data 2012, levosalbutamol (Xopenex), like other beta agonists, can produce ECG changes such as flattening of the T-wave, prolongation of the QTc interval and ST segment depression the (clinical significance of which is unknown). Therefore, Xopenex Inhalation Solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. The same warnings apply to salbutamol.[24]

Levosalbutamol and salbutamol have similar interactions with digoxin (increase serum concentrations), MAO inhibitors (cause excessive vasodilation), diuretics (aggravate ECG changes) and beta blockers (nullify each other's actions).

In other words, although both the medications studied showed increased heart rate, the practical significance of this change in terms of patient discomfort, tachycardia induced cardiac dysfunction or tachyarrhythmia has not been demonstrated. Thus, greater use of LS in pediatric settings and counselling parents with potential benefits of LS over RS is not supported by evidence and leads to false sense of safety in both providers and family.[25]

CONCLUSION

In this brief review of randomized controlled trials, retrospective chart reviews and patient surveys focusing on the cardiac side-effects of LS and RS we can come to the following conclusions. Firstly, no clear clinical trial has been conducted to delineate the cardiac side effects of LS and RS and side effect profiling was a secondary outcome. Secondly, none of the studies performed ECG screening or echo screening to determine if patients have baseline tachyarrhythmia which may influence the final heart rates. Third, studies which showed increased heart-rate in children didn't define tachycardia for the specific age group studied. Until we have more solid evidence, RS and LS should be used interchangeably and based on individual preference and affordability with clear message to the patient about the lack of data.

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