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Incidence of hypokalemia after nebulization with salbutamol & levosalbutamol in children

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Abstract
Levosalbutamol offers health care provider and patients a safe, well tolerated and efficacious bronchodilator. Levosalbutamol appears to be more efficacious than RAC in terms of PEFR, SPO2 and asthma score while deleterious effects of tachycardia and fall in Serum K+ levels were seen with RAC and the total cost of therapy remained comparable. Hence Levosalbutamol should be considered as first line therapy in situations in which a short acting beta agonist is warranted.
Nebulized salbutamol (2.5 mg) diluted in 2.5 ml NS was administered 3 times during the 1st in Group A and Levosalbutamol (6.3 mg) diluted in 2.5 ml NS to Group B. The total drug volume was 2.5 ml in nebulizing chamber & nebulized over a period of 8-10 minutes and patient was instructed to inhale from his mouth.
A significant hypokalaemia occurred but extra caution needs to be taken when subjecting patients with gastroenteritis, on oral steroids, diuretics, underlying renal or hepatic disease, cardiac cases etc. who are more prone for to develop the electrolyte imbalances to nebulized salbutamol.

Keywords: nebulization, levosalbutamol, salbutamol, asthma etc.

Introduction
Salbutamol is a medication that opens up the medium and large airways in the lungs. It is used to treat asthma including asthma attacks, exercise-induced bronchoconstriction, and chronic obstructive pulmonary disease (COPD). It may also be used to treat high blood potassium levels. Salbutamol is usually used with an inhaler or nebulizer but is also available as a pill and intravenous solution. Onset of action of the inhaled version is typically within 15 minutes and lasts for two to six hours. Common side effects include shakiness, headache, fast heart rate, dizziness, and feeling anxious. Serious side effects may include worsening bronchospasm, irregular heartbeat, and low blood potassium levels. It can be used during pregnancy and breastfeeding, but safety is not entirely clear. It is a short-acting β2 adrenergic receptor agonist which works by causing airway smooth muscles to relax [1].
Salbutamol was first made in 1967 in Britain and became commercially available in the UK in 1969. It was approved for medical use in the United States in 1982. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. Salbutamol is available as a generic medication. Salbutamol is typically used to treat bronchospasm (due to any cause – allergic asthma or exercise-induced), as well as chronic obstructive pulmonary disease. It is also one of the most common medicines used in rescue inhalers (short-term bronchodilators to alleviate asthma attacks) [2].
As a β2 agonist, salbutamol also has use in obstetrics. Intravenous salbutamol can be used as a tocolytic to relax the uterine smooth muscle to delay premature labor. While preferred over agents such as atosiban and ritodrine, its role has largely been replaced by the calcium channel blocker nifedipine, which is more effective, better tolerated, and administered orally. Salbutamol has been used to treat acute hyperkalemia, as it stimulates potassium flow into cells, thus lowering the potassium in the blood [3].
Levosalbutamol is a short-acting β2 adrenergic receptor agonist used in the treatment of asthma and chronic obstructive pulmonary disease (COPD). Evidence does not show that levosalbutamol works better than salbutamol, thus there may not be sufficient justification for prescribing it. The drug is the (R)-(−)-enantiomer of its prototype drug salbutamol. It is available in some countries in generic formulations from pharmaceutical companies including Cipla, Teva, and Dey, among others.
Hypokalemia, also spelled hypokalaemia, is a low level of potassium (K+) in the blood serum. Normal potassium levels are between 3.5 and 5.0 mmol/L (3.5 and 5.0 mEq/L) with levels below 3.5 mmol/L defined as hypokalemia. Mildly low levels do not typically cause symptoms. Symptoms may include feeling tired, leg cramps, weakness, and constipation. It increases the risk of an abnormal heart rhythm, which is often too slow, and can cause cardiac arrest [4].
Causes of hypokalemia include vomiting, diarrhea, medications like furosemide and steroids, dialysis, diabetes insipidus, hyperaldosteronism, hypomagnesemia, and not enough intake in the diet. It is classified as severe when levels are less than 2.5 mmol/L. Low levels can also be detected on an electrocardiogram (ECG). Hyperkalemia refers to a high level of potassium in the blood serum.
Although levosalbutamol [(R)-salbutamol] has been introduced in the management of asthma and COPD since 1999, it is available only in a liquid formulation to be

Administered by a nebulizer. The pressurized metered dose (pMDI) inhaler is the most widely used device for drug delivery in patients with asthma. It is convenient, cheap, easy to use and effective. Salbutamol administered via pMDI is widely used in the management of symptomatic relief of acute asthma, and when administered via a spacer, is as effective as that administered via a nebulizer in patients with acute severe exacerbations [4].

Though salbutamol is an effective treatment of acute exacerbations but its use is associated with undesirable side effects like tachycardia and hypokalemia. Hunt for a more effective drug with less side effect is still on. Hence based on above literature survey this study has been planned to know the Incidence of hypokalemia after nebulisation with levosalbutamol in children.

Methodology

The study was planned in Dr. R. M. L. &PGIMER, new Delhi in Department of Paediatrics in 50 patients. The aim of the study is to compare the efficacy and tolerability of levosalbutamol and racemic salbutamol to know the Incidence of hypokalemia after nebulisation. The approval of Intuitional Ethical Committee was taken prior to conduct of this study. All the patients enrolled into the study were informed consents.

Inclusion Criteria: Patient aged between 5 and 15 years presenting with acute exacerbation of asthma.

Exclusion Criteria: Age >15 and <5 years, severe asthma, children already on preventive therapy (inhaled steroids or long-acting bronchodilator), patients on treatment diuretics, aminoglycosides, bicarbonates, acute gastroenteritis, the presence of baseline hypokalemia, congenital heart diseases and patients with hepatic, pre-existing renal disease.

Nebulized salbutamol (2.5 mg) diluted in 2.5 ml NS was administered 3 times during the 1st in Group A and Levosalbutamol (6.3 mg) diluted in 2.5 ml NS to Group B. The total drug volume was 2.5 ml in nebulizing chamber & nebulized over a period of 8-10 minutes and patient was instructed to inhale from his mouth.

The following baseline clinical characteristics were recorded initially and after giving 3 nebulisations at 20 min. intervals in the 1st hour of ED presentation viz. respiratory rate (RR), Heart rate (HR) oxygen saturation in room air (SPO2), PEFR (peak expiratory flow rate) & Serum K+ level.

Results & Discussion

The 50 patients were divided in two study groups as 25 patients in group A and 25 patients in group B. Nebulized salbutamol (2.5 mg) diluted in 2.5 ml NS was administered 3 times during the 1st in Group A and Levosalbutamol (6.3 mg) diluted in 2.5 ml NS to Group B.

Table 1: Age distribution

Age in years	Group A Levosalbutamol	Group B Salbutamol
5-8	4	5
9-11	12	10
12-15	9	10
Total	25	25

Table 2: Pre-treatment observations

Parameters	Pre-treatment Levosalbutamol	Pre-treatment salbutamol
RR	28.69±0.7	27.35±0.5
HR	99.5±7	102±6
SPO2	92.5±0.5	93.1±0.6
FEV1	53.2±0.4	55.9±0.5
Serum potassium level mEq/L	4.55±0.6	4.15±0.3
Asthma score	6.5±0.3	6.6±0.4

Table 3: Post-treatment observations

Parameters	Post-treatment Levosalbutamol	Post-treatment salbutamol
RR	21.6±1.1	22.3±1.2
HR	103.5±9	122.5±6
SpO2	99.2±3	97.3±1.5
FEV1	68.2±1	66.3±1.7
Serum potassium level MEq/L	4.4±0.5	3.6±0.3
Asthma score	4.9±1.2	5.2±0.8

Salbutamol is the most commonly used β2 agonist for the treatment of asthma. Synthetic β2 agonist bronchodilators including salbutamol are developed, based on the structure of the epinephrine and thus are supposed to mimic their bronchodilating action. However, endogenous epinephrine produced in human body is a pure single isomer R-epinephrine whereas most of the β2 agonist drugs including salbutamol are racemic drugs containing mixture of 50%-50% of 'R' (Levo) and 'S' (Dextro) optical isomers (also known as enantiomers). Only R-isomer fits into three-dimensional conformation of β2 adrenoceptor proteins.

S-salbutamol causes bronchial hyperresponsivenes by a cholinergic dependent β2 adrenergic independent mechanism. [5] It has been observed that when S salbutamol or LEV is exposed to isolated human bronchus, S-salbutamol enhances and LEV inhibits the contractile response to histamine and leukotriene C4 [6]. These pharmacologic actions, if translated clinically, suggest that in the absence of LEV induced smooth muscle relaxation, S-salbutamol has the potential to induce bronchoconstriction in asthmatic patients [7]. S-salbutamol may promote airway obstruction by increasing mucus secretion by airway epithelial cells and interfering with mucociliary clearance [8]. Airway mucus plugging and increased number of neutrophils and cytotoxic T cells in the lung have been associated with fatal exacerbation in asthma patients [9].

Results of this double blind randomized trial suggest that administration of levosalbutamol by nebulizer in children between the ages of 5 to 15 yr presenting with acute exacerbation of asthma causes statistically significant greater improvement in terms of PEFR, SPO2, RR, and asthma score, as compared to salbutamol inhalation. There was no increase in heart rate or fall in K+ levels with levosalbutamol.

Another study has compared LEV with a combination of salbutamol and ipratropium bromide (IB) in children between 6-18 yr presenting with acute asthma and reported that LEV was associated with less tachycardia but had shown no other advantage over RAC with IB.5 In the present study also tachycardia was less. Hypokalemia was also significantly less with LEV in the present study, this issue has not been

addressed in any of the previous studies.

Conclusion

Levosalbutamol offers health care provider and patients a safe, well tolerated and efficacious bronchodilator. Levosalbutamol appears to be more efficacious than RAC in terms of PEFR, SPO2 and asthma score while deleterious effects of tachycardia and fall in Serum K+ levels were seen with RAC and the total cost of therapy remained comparable. Hence Levosalbutamol should be considered as first line therapy in situations in which a short acting beta agonist is warranted.

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