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RESEARCH ARTICLE

Drug Interaction of Aminophylline and Salbutamol Induced extreme Tachycardia in Chronic Obstructive Pulmonary Diseases - A Case Report

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ABSTRACT:
Aminophylline and salbutamol is a more often used drugs as bronchodilators in COPD and asthma worldwide, because it is inexpensive and widely available. Aminophylline **(1, 3-dimethyl-7H-purine-2, 6-dione; ethane-1, 2-diamine)** causes bronchodilatation, cardiac stimulation and vasodilatation by increasing cyclic adenosine monophosphate (cAMP) via the inhibition of phosphodiesterase (PDE). Salbutamol **(4-[2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl) phenol)** causes broncho-dilatation through beta-2 receptor stimulation thereby increasing cyclic adenosine monophosphate (cAMP) formation in bronchial muscle cell. Apart from bronchodilation activity salbutamol also produce vasodilatation, uterine relaxation and lesser cardiac stimulation. Patients receiving salbutamol and aminophylline should be monitored periodically for potential drug interactions, adverse effects, toxicity and other drug related problems. Symptoms of potential interaction between salbutamol and aminophylline is difficult to identify and may becomes increased risk for stroke, sudden cardiac arrest and death. Such potential drug interaction can be identified and minimized by performing therapeutic drug monitoring. We report a case of interaction of salbutamol and aminophylline induced extreme tachycardia in a 45 year old female patient of chronic obstructive pulmonary diseases (COPD) with acute exacerbations. Patient's ECG interpretation was abnormal with elevated vital signs (i.e. Heart rate). Both the sympathomimetic and the methylxanthine compounds frequently used in the management of COPD have been identified as being potentially arrhythmogenic. Although there is good evidence that medications from these two groups have additive bronchodilator effects, few studies have looked at a possible arrhythmogenic interaction between them in COPD. Hence closely monitoring the drug therapy prevent such type of potential interactions.

KEYWORDS: Salbutamol, Aminophylline, Drug interactions, Tachycardia, Chronic obstructive Pulmonary diseases.

INTRODUCTION:
Salbutamol (Selective beta-2 agonists) and aminophylline (methylxanthine derivative) are in wide spread use for patients with asthma and chronic obstructive pulmonary disease (COPD). In addition to their bronchodilating effect, both are capable of producing unfavourable effects on cardiovascular system. A number of previous reports have described a relationship between oral or inhaled beta 2-agonist use and increased cardiovascular morbidity and mortality[1-9].

A number of factors may contribute to the increased cardiovascular risk associated with inhaled beta2-agonists: (i) an increase in heart rate due to systemic absorption of the drug, which may result in a shortening of the diastole, thereby increasing myocardial oxygen consumption and reducing the time for coronary artery perfusion, (ii) a decrease in potassium concentrations, which may exert pro-arrythmogenic effects[10], and (iii) direct effects of salbutamol on beta -adrenoceptors of the heart, resulting in increased sympathetic outflow[11]. A recent report by Kallergis and coworkers[12] has furthermore demonstrated that nebulized salbutamol leads to significant electrophysiological effects, such as increased atrioventricular nodal conduction and decreased atrial and ventricular refractoriness. Salbutamol stimulates both β-1 and β-2 receptors in the heart and can reduce afterload through vasodilation and

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a drop in vascular resistance. These effects can cause significant tachycardia, postural hypotension and myocardial ischaemia. Aminophylline is a combination of theophylline (the active component) and ethylenediamine. Aminophylline has a narrow therapeutic range (10-20mcg/ml), and the associations between elevated levels and unwanted effects are important to consider. The bronchodilator effects of theophylline are proportional to the log of its concentration-in other words, increasing theophylline plasma concentration causes a less than proportional increase in bronchodilation, such that levels higher than 20 mg/L are unlikely to offer additional therapeutic benefit but will increase the risk of toxicity. Furthermore, the clearance rates are affected by factors including age and the use of cytochrome P450 inducers and inhibitors. Thus careful dosing and regular assessments of serum theophylline levels should be maintained**.** Tachycardia is a common dose-dependent side effect of aminophylline and has been implicated in the development of serious atrial tachyarrhythmias in adults[12].Both the sympathomimetic and the methylxanthine compounds frequently used in the management of COPD have been identified as being potentially arrhythmogenic. Although there is good evidence that medications from these two groups have additive bronchodilator effects, few studies have looked at a possible arrhythmogenic interaction between them in COPD. A significant increase in heart rate and supraventricular extrasystoles was associated with the addition of theophylline to salbutamol[13]. Hence closely monitoring the drug therapy prevent such type of potential interactions.

CASE REPORT:

A 45 year old female patient was admitted to general medicine department with difficulty in breathing (class II-dyspnoea) for past 1week. She was also suffering from cough and cold. After admission on 5th day she developed increased wheeze, increased acute exacerbation and persistent cough. Her past medical history includes chronic obstructive pulmonary diseases since 10 years. Past medication history includes Tablet salbutamol-4mg bd and seroflo inhaler-2 puff tds. Her personal history includes dust allergy. System examination of respiratory system revealed wheeze (++). On examination of vital signs pulse rate was found to be 198 beats per minutes, respiratory rate was 26 breathes per minutes and blood pressure was found to be normal. ECG revealed extreme tachycardia on the day of admission after treatment. Other investigations such as sputum AFB is done which was proved to be Non-reactive. Pulse oximetry shows SpO2 (peripheral oxygen saturation)–98% without O2 and heart rate reveals 197 beats per minutes on the day of admission after treatment. Complete blood count, blood sugar, renal profile and urine analysis are investigated which was found to be normal. Injection dexamethasone was started an initial at the time of admission for COPD. On the same day after several hours injection efcortin, injection aminophylline, nebuliser salbutamol, seroflo inhaler was given for COPD. Tablet montelukast-LC was indicated for cold and cough. Nasal O2 is indicated for hypoxemia. The patient was prescribed Tablet carvedilol and Tablet Isosorbidedinitrate(ISDN) for extreme tachycardia and as a prophylactic in order to prevent risk of cardiovascular events such as ischaemic heart disease[14]. Injection efcortin and injection aminophylline is stopped and rest of the drugs are continued for upcoming days. On the 2nd day of carvedilol and ISDN therapy extreme tachycardia, pulse rate was observed to be normal. On the 3rd day the patient was sent to cardiology department for the opinion where ECHO is taken which was revealed as stable cardiac status. On 5th day Prospan cough syrup is added due to persistent cough and stopped the Carvedilol and ISDN therapy.

DISCUSSION:

Drug interaction between Aminophylline and salbutamol have been reported to induce extreme tachycardia by pharmacodynamic level in the form of additive. Both the sympathomimetic and the methylxanthine compounds frequently used in the management of COPD have been identified as being potentially arrhythmogenic. In this case report potential synergism interaction is reduced by stopping the aminophylline infusion. The interaction can be avoided by changing the period of administration and selecting the appropriate alternatives. In this case to treat extreme tachycardia and to prevent the risk of cardiovascular events the patient was given with ISDN and carvedilol. Carvedilol is a contra-indicated in COPD and other bronchospastic conditions[15]. This drug therapy problem can be resolved by prescribing antiarrhythmic drugs.

CONCLUSION:

Patients receiving salbutamol and aminophylline should be monitored periodically for potential drug interactions, adverse effects, toxicity and other drug related problems. symptoms of potential interaction between salbutamol and aminophylline is difficult to identify and may becomes increased risk for stroke, sudden cardiac arrest and death. Effective and safe combination therapy can be achieved by increasing the awareness of potential changes in efficacy and toxicity, rationally selecting alternatives, tailoring drug therapy based on genotype, checking the appropriateness of physician orders, and performing therapeutic and monitoring.

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