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THEOPHYLLINE-INDUCED CARDIOVASCULAR EFFECTS: A REVIEW OF TACHYARRYTHMIAS AND HYPOTENSION.

Peddapally Bhargavi*

Department of Pharmacy, RBVRR Women's College of Pharmacy *Corresponding Author

ABSTRACT Theophylline is a 1,3 dimethylxanthine commonly known as Methylxanthine, the mechanism of theophylline involves inhibition of phosphodiesterase that relaxes the airway muscles, and adenosine receptor antagonism, it blocks adenosine which slow down the heart rate. Theophylline has long-term effects on the cardiovascular system due to its narrow therapeutic index category, regular interval monitoring is required to prevent toxicity, approximately 30% of patients experience adverse effects. The traces of theophylline will be present in the blood for long period in most of the patients. It is a pregnancy category c drug which excretes in milk, it should be used with caution only if benefit overweigh risk. It is available in tablet, capsule, elixir, intravenous solution formulation. It is commonly used as a bronchodilator for management of asthma, COPD. Serum concentration < 20mcg/ml causes CNS excitement, tachycardia, flutter, hypercalcemia, exfoliative dermatitis, serum concentration > 30mcg/ml causes myocardial infarction, convulsions. The daily dose of theophylline should not exceed > 25mg/ml IV. The ideal dose of theophylline should calculate using body weight of an individual. Over the past decade the usage of theophylline was limited because of its poisonous effects caused in children and adults but widely used because of low cost and bioavailability.

KEYWORDS : Methylxanthine, Arrhythmia, Tachyarrhythmias, Hypotension, Cardiovascular Effects.

INTRODUCTION

The Cardiovascular effects refer to impact of drugs on heart and vascular system, they are chest pain, Arrhythmia, breathlessness, swelling, fatigue, palpitations, dizziness, heart attacks, heart failures

An Arrhythmia – Irregular heartbeat, based on the speed and origin: they are two types

(A) Bradycardia,
(B) Tachycardia. These are further sub-divided into:
1. Atrial Fibrillation
2. Atrial Flutter
3. Supraventricular Tachycardia
4. Ventricular Tachycardia

(C) Premature beats
1. Premature Atrial Contractions
2. Premature Ventricular Contractions

The causes of Arrhythmias are idiopathic, but it also depends on the life-style habits of the person as well as the condition of the heart, the common causes of the arrhythmia are:

a. Underlying conditions such as- Coronary Heart Disease, Heart failure, Cardiomyopathy.
b. Diabetes Mellitus
c. High blood pressure
d. Social habits – Alcohol, Smoking
e. Psychological factors- Stress, Anxiety
f. Hormonal Imbalances
g. Abnormal electrolyte levels
h. Misuse of medications, for example: NSAIDS.

Based on the severity the symptoms vary from person to person: Lightheadedness, Palpitations, Shortness of breath, Chest pain, Anxiety, Fatigue.

The Arrhythmias are identified by following diagnostic tests, there are: Electrocardiogram, Echocardiogram, Stress test, Electrophysiology Study, Blood tests

Management of the Arrhythmias Involves:

a) Anti-Arrhythmic Agents (Beta- blockers, Calcium channel blockers, Anti-coagulants)
b) Catheter Ablation
c) Pacemaker
d) Implantable Cardioverter Defibrillator
e) Surgery
f) Life-style modifications (Nutrition, Exercise, Rehabilitation, Management of psychological stress, compliance)

Blood pressure is forces present inside the arteries; it is categorized into:

1. Hypertension (Hypertensive emergency and life- threatening)
2. Hypotension (limit blood flow to organs, Shock, life-threatening)
3. Orthostatic hypotension (dizziness, Faint)

The normal blood pressure is 120/80mmhg, it can be measured by systolic (heart contraction) and diastolic (heart relaxation). The blood pressure is influenced by following factors, they are: Age, Stress, Life style modifications, Genetic predisposition, Comorbid conditions such as: underlying kidney and cardiac disease.

Theophylline, a methylxanthine[1], also known as 1,3 dimethylxanthine, it is naturally present in beverages like cocoa bean, tea, and small amount present in kola nuts, guarana. It is initially used as a Diuretic, later introduced in the asthma management. The pharmacological effects are achieved by phosphodiesterase inhibitor[3], adenosine receptor antagonist, Histone deacetylase activator, the pharmaco-dynamic effects are similar to theobromine, used in the management of symptoms and airflow obstruction associated with chronic lung disease: Emphysema, chronic bronchitis, and bronchodilation and anti-inflammation.

Despite of its Narrow margin and adverse effects, but it is widely used to treat conditions within its therapeutic range, slight variation in the serum levels can cause toxicity as well as death of the patient, but it is clinically used in the conditions like Asthma and COPD, Infant apnea, due to less cost and oral availability. The adverse effects of the drug include supraventricular and ventricular tachyarrhythmias, tachycardia, hypotension, lightheadedness, insomnia, seizures, persistent vomiting, chest pain[2]. Close monitoring is essential to avoid toxicity. The factors like age, hepatic and renal impairment, drug interactions, social habits can affect the metabolic action of theophylline. In recent times theophylline is replaced by doxofylline[7].

Pharmacological Profile of Theophylline:

a) CLASS: Methylxanthine derivative
b) MECHANISM OF ACTION: Theophylline blocks PDE3, PDE4 enzymes which is responsible for breakdown of cyclic AMP, this leads to smooth muscle and pulmonary blood vessels relaxation, this mechanism is said to be PDE (phosphodiesterase) inhibition. It is also blocks Adenosine (A1,A2,A3) receptors this mechanism reduces sensitization to allergens and other environmental stimuli, the another mechanism called histone deacetylation in which theophylline activates the histone deacetylase enzyme this action is reliable on inhibition of phosphoinositide 3 kinase delta , this enzyme that naturally reduce activity of histone deacetylase , deacetylation leads to gene suppression, here theophylline helps in managing in overcome the towards reduced levels of histone deacetylase[9].
c) DOSE: it is available in following formulations;

1. Capsules, extended- release (24 hours): 100mg, 200mg, 300mg, 400mg
2. Tablet, extended release (12 hours):100mg, 200mg, 300mg, 450mg.

3. Oral elixir: 80mg/15ml.
4. Intravenous solution: 400mg/250ml, 400mg/500ml, 800mg/500ml.

d) DOSE MODIFICATIONS: the loading should reduce to 0.39 mg/hrs. IV for next 12 hours, 0.08-0.16 mg/kg/hr.

e) INDICATION: It is widely used as bronchodilator in the treatment of Asthma and COPD.

f) PHARMACOKINETICS: It is rapidly absorbed through orally, it follows first order kinetics, it is metabolized by cytochrome CYP450 enzyme CYP1A2, the metabolites are excreted in urine[10].

g) NARROW INDEX OF THEOPHYLLINE: Many cases shown that overdose and under evaluation of serum levels can cause convulsions as well as cardiovascular effects like tachyarrhythmias and hypotension which are rare but clinical importance is required[11].

Theophylline Induced Tachyarrhythmias:

A study conducted on the effects of theophylline using Ambulatory ECG recording where we found sinus tachycardia, supraventricular ectopic beats, ventricular premature beats are common. In the patient with comorbid conditions like COPD – where long term exposure to theophylline develop toxicity, and in the patients with cardiac disease they develop ventricular tachycardia and they are at high risk of having ventricular ectopy. Minor effects theophylline, such as atrial fibrillation multifocal atrial tachycardia, which are found in 1% subjects.

Tachyarrhythmias caused due to abnormal conduction in heart, where the cardiac cells shoot up faster than usual, the triggered activity may be early or delayed after depolarization these is caused due to imbalance of electrolytes, overdose of drugs/ medications, overload of calcium[4,12].

Theophylline Induced Hypotension

The underlying mechanism is theophylline exhibits phosphodiesterase inhibition, adenosine receptor antagonism which causes catecholamine release and excessive vasodilation, severe toxicity leads to tachyarrhythmias, metabolic acidosis, hypovolemia, this combined effect leads to vasopressor resistant hypotension (irreversible hypotension even in the presence of vasopressor)[6].

Diagnosis and Monitoring

The serum levels should be monitored periodically, beyond therapeutic dose leads to severe toxicity, continuous ECG monitoring is essential due to risk of arrhythmias, assessment of vital signs to identify hemodynamic status, neurological evaluation is important to prevent seizures, regular monitoring of electrolyte balance, glucose levels, acid-base levels. Early diagnosis and monitoring are essential to prevent morbidity and mortality toxicity risk of theophylline.

Management of Theophylline Toxicity

The treatment of theophylline toxicity is primarily achieved by supportive therapy such as providing airway, breathing, circulation. To eliminate the drug, among the various decontamination techniques activated charcoal and hemodialysis is widely used, if there are no contraindications. Extracorporeal elimination is essential to reduce morbidity and mortality in theophylline toxicity[5]. Pharmacological treatment involves benzodiazepines are used as a first line agent for seizures which is a major concern in theophylline toxicity, beta blockers are cautiously used in the management of toxicity, management of acid-base balance and control of tachyarrhythmias.

Special Population Considerations

The theophylline should be reduced in special populations due to altered metabolism and clearance of the individuals, here the special populations are neonates (immature liver enzymes), children (faster metabolism), elder (decreased hepatic metabolism and renal clearance), hepatic impairment patient (risk of accumulation), renal impairment patients (accumulation of metabolites), cardiac patients (risk of tachyarrhythmias), pregnancy (placental transfer of drugs).

CONCLUSION

Theophylline is a narrow therapeutic index drug; hence it requires close monitoring of serum levels of drug, slight variation of drugs causes severe toxic effects, irregular monitoring or long-term use of drug can leads to severe and prolonged effects such as tachyarrhythmias, supraventricular ectopic beats, and vasopressor resistance hypotension. Regular monitoring is required to maintain peak plasma concentrations to achieve therapeutic outcome. The pharmacological profile of theophylline states that low doses should be given, >30mcg/ml leads to cardiovascular effects, neurological effects, dermatological side effects. Over the years theophylline usage was limited in countries like united states, Thailand due to studies reported approximately 30% of poison effects caused by theophylline among children and adults. Despite of its severe long-terms effects but still available as an over-the-counter medicine, which is also a factor responsible for increased risk of cardiovascular effects, this is because lack of patient counselling on usage of theophylline administration, and its side effects. Hence it raises the question of patient's education regarding the drug, which is more important to lower the risk of developing cardiovascular effects.

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