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Methylxanthine induced cardiotoxicity and its mechanisms: An experimental study

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Original article

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Abstract

Background: Methylxanthines like theophylline are re-emerging as effective adjuncts in the treatment of obstructive airway disease and several newer mechanisms have been proposed. In view of its effectiveness, pharmacoeconomic viability, and easy availability, it could rationalize the drug treatment in bronchial asthma and chronic obstructive pulmonary disorders (COPD) – but its narrow therapeutic index and resultant safety concerns need to be aggressively addressed, particularly in developing countries. Cardiotoxicity and neurotoxicity are amongst the most noted adverse effects associated with its clinical use. The present study evaluated the possible mechanisms involved in aminophylline (water-soluble ethylene diamine salt of theophylline) on potential cardiotoxicity parameters in rats. Methods: Aminophylline was administered in various doses for seven days to rats of either sex weighing 200-250g. The electrocardiogram and blood pressure were recorded on seventh day. After this the blood was withdrawn to estimate various stress and cardiac markers. Results: Aminophylline (50-150 mg/kg for seven days) dose dependently induced tachycardia and elevated mean BP. There were also T-wave inversions and suppressed T-wave areas at higher doses when compared with control group. IBMX (PDE inhibitor) did not influence these parameters per se. Further, pre-treatment with 2-chloroadenosine (adenosine agonist) could not completely attenuate aminophylline effects. The methylxanthine also elevated MDA levels and reduced GSH levels in heart tissue homogenates of aminophylline treated rats. Aminophylline also elevated serum CPK-MBV levels whereas, BNP levels were not much affected. Pre-treatment with the anti-oxidant, alpha-tocopherol (20 and 40 mg/kg) before administration to aminophylline, attenuated the aminophylline induced changes in heart rate, mean BP, and T-wave areas. These cardiac changes after alpha-tocopherol were supported by biochemical findings, wherein antioxidant pre-treatment prevented an increase in MDA and reduced GSH as well as CPK-MB levels. Conclusion: The results indicate the possible involvement of free radicals in theophylline induced cardiotoxicity, and suggest that anti-oxidants could help in reducing the safety concerns associated with this drug.**Key words:** microRNA, heme oxygenase, proximal tubule cells.

Key words: Theophylline, cardiotoxicity, free radicals, antioxidants

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