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Clinical and experimental studies on theophylline toxicity: In search for an antidote

Arunabha Ray
University of Delhi, India

Theophylline (a methylxanthine), a potent bronchodilator, has reemerged as an important adjunct in the treatment of obstructive airway disease, but its narrow therapeutic index remains a persistent problem with the use of this drug. Neurobehavioral and cardiotoxicity are predominant adverse events after clinical use. Initial clinical studies to evaluate adverse drug reaction (ADR) profiles of patients of bronchial asthma and COPD who were prescribed theophylline showed that such therapy was associated ADRs like anxiety, palpitations, dyspepsia, muscle spasm, paresthesia, etc. Preclinical studies were then conducted to assess the mechanisms of theophylline-induced anxiety and tachycardia in experimental animals. Aminophylline dose dependently induced anxiety and tachycardia which were not attenuated by adenosine agonists or phosphodiesterase inhibitors. Interestingly, pretreatments with the antioxidants, ascorbic acid, α-tocopherol (alone or in combination) attenuated both anxiogenesis and tachycardia in separate sets of experiments. Aminophylline induced anxiety and tachycardia were associated with alterations in the biochemical markers of oxidative stress viz. elevations in MDA levels and reductions in GSH activity in blood and brain. Pretreatments with the antioxidants attenuated the methylxanthine induced changes in oxidative stress markers. Further, L-arginine (NO precursor) pretreatment also reversed aminophylline induced (a) anxiety and tachycardia and (b) brain and blood oxidative stress markers. These results indicate that oxidative stress could be involved in methylxanthine induced toxicity and antioxidants could act as possible antidotes in such situations. Such reverse pharmacology approach could also be effectively used to assess toxicodynamics of drugs with safety concerns and help in devising strategies to prevent them.

Biography

Arunabha Ray is MD, PhD from Faculty of Medicine, University of Delhi, with Postdoctoral experience in Canada and the USA. He is Chair, Department of Pharmacology at the Vallabhbhai Patel Chest Institute, University of Delhi. He has more than 35 years teaching and research experience in basic and clinical pharmacology and toxicology and has been the recipient of several awards and honors for research excellence. He has more than 150 research publications, is author of several text and reference book chapters, editor of 04 books in his areas of expertise, and author of a textbook in pharmacology.

arunabha14@yahoo.co.in