

Effects of Theophylline on Immune System

Ali A. AL-Janabi*

*University of Karbala, College of Pharmacy

Summary

Theophylline is one of xanthine compounds. It is mainly used in the treatment of asthma and other types of allergy in the pulmonary system. The main action of theophylline in the immune system is a depressing effect and this is one of its characters which are used in the treatment of asthma and COPD. Different kinds of defense processes in the body that are related to immune system are affected by theophylline or its derivative. These processes include cellular immunity, phagocytosis, release of substances from immune cells and complements, all are discussed in this review.

Key words: Theophylline, immune system, release substances, pulmonary system, sthma.

Effect of theophylline on immune system

Theophylline, 1, 3-dimethylxanthine, occurs naturally in the leaves of tea plant. It is commonly used in the treatment of asthma and chronic obstructive pulmonary disease (COPD) [1]. One of the most important characters of theophylline is related to its activities on the immune system which is mainly participated in its treatment ability. Depressing the immune system is the suggested function of theophylline as mode of action [2], but some studies refluxed this function to be activation of immune cells against foreign bodies' e.g. Macrophage cells were activated by aminophylline (theophylline derivative) to destroy *Toxoplasma gonidii* [3]. Activation of immune cells could have more harmful effects than useful ones e.g. therapeutic concentration of aminophylline given to individual with asthma will stimulate neutrophil cells to release H₂O₂ and radical toxic oxygen (O⁻²) as defense substances, but these substances will cause obstruction in blood vessels and tissue damage [4]. The activity of theophylline is variable between *in vitro* and *in vivo* where it is very clear in situation of inhibiting natural killer (NK) cells in human [5] and suppression of PMN (polymorphonuclear neutrophilic leukocyte) and T-lymphocyte aggregation after *in*

vitro test [6], whereas these inhibited activities occur *in vivo*. The general characters of theophylline in the immune system could be summarized as follow:

1-Effect on the cellular immunity

Most activities of immune cells are inhibited by theophylline as noted with 6 % reduction of cytotoxic T-lymphocyte activity after 24 hours of treatment with theophylline in tissue culture and the percentage of inhibition increases after 48 hours [7]. Theophylline has shown its action on the immune cells through moderate elevation of CAMP concentration in these cells, in to PGD₂ (prostaglandin D₂) and which stimulates the production of high concentration of intracellular [8]. The activity of theophylline is also studied against generation of lymphatic cells in tissue culture and it was found to have inhibitory effects, especially at the. Beginning of treatment with decreased of inhibition to become significant after 20 hours, mainly in the third (M3) and fourth (M4) generation of lymphocyte life cycle [9]. Analysis of sputum for cells is recorded to be useful indicator for anti-inflammatory effect of theophylline [10].

The total count of inflammatory cells, especially Neutrophil, is declined approximately 21% after treatment with 9-11 mg/L of theophylline with decreased chemotaxation ability of these cells [11, 12]. DTH (delayed T-cell hypersensitivity), which is mediated by immune cells, is also inhibited by theophylline [13].

2- Phagocytosis

Phagocytosis, non specific immunity, is the first line of body defense. PMN and macrophages play an important role in this type of immunity. Different concentrations of aminophylline, including 25 mg/Kg, 50 mg/Kg and 100 mg/Kg inhibit phagocytosis process in the body of the mouse when they are tested *in vivo* [13]. Phagocytosis against yeast or bacteria was also inhibited by theophylline. The function of PMN and macrophage as phagocytic cells in alveoli were declined against *Proteus mirabilis* and *aureus* when

80 mg/kg of aminophylline was injected intravenously [14].

The mode of inhibitory action of theophylline is related to the inhibition of PDE (Phosphodiesterase enzyme) which increased cAMP concentration [15]. This mechanism will be reached to 196% in the PMN [16] without any effect on the migration and aggregation of macrophage cell [9].

3- Release of substances from immune cells

Other activities of theophylline are its effect on the release and function of immunity mediator substances. Generation of Isoproterenol and PMN leukotriene B₄ by Eosinophil cells are inhibited by 50 % after treatment with 9 µ/ml of theophylline [16], whereas Bibi found that theophylline had no effect on those types of mediators at concentration 10-20 µ/ml when it had been given to children (12 years) for 8 months [17].

High concentration of theophylline (10^{-3} M) inhibited the release of toxic oxygen ions ($O_2^{\cdot -}$) from Neutrophil in human and Guinea pigs and this effect decreased at $10^{-5} - 10^{-6}$ M [18]. Eosinophil activating factor (EAF) was also prevented to release from monocyte at 0.1 mg/ml of theophylline, while the killing activity of monocyte was not affected by this concentration [19]. Yao et al observed that IL-13, a central mediator of airway inflammation, produced by macrophage was dramatically suppressed by theophylline [2]. Phytohemagglutinin (PHA) generation (T-cell activator) was also affected by theophylline where its activity was inhibited [20].

The release of histamine from basophile and mast cells was blocked after contacting with theophylline and that is what reduces the sensitivity of nose toward pollen grains [8]. This activity of theophylline is performed via blocking of positions in the Eosinophil cells which release MBP protein that is responsible for catalysis of histamine release [21].

4- Other functions of theophylline in the immune system include, inhibition of complement proteins e.g. 10-1000 µM of theophylline prevents the work of C5a to degranulated of Neutrophil [22].

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