



XANTHINES: THE SIDE DOOR BRONCHODILATORS

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In the last several articles we have discussed adrenergic bronchodilators or what I like to term “front door bronchodilators” and anticholinergic bronchodilators, which I term “backdoor bronchodilators” due to how they work on the sympathetic and parasympathetic nervous systems. Xanthines are “side door bronchodilators” because we do not know how they actually work. This article will review xanthine agents available and their indication for use. I will also discuss the proposed theories of how xanthines work.

Xanthine Agents

Theophylline is related chemically to the natural metabolite xanthine. Other xanthenes are caffeine and theobromine. Because of their methyl attachments, these agents are often referred to as methylxanthines. All three agents are found as alkaloids in plant species. Caffeine is found in coffee beans and kola nuts. Caffeine and theophylline are contained in tea leaves, and caffeine and theobromine are in cocoa seeds or beans. Historically, these natural plant substances have all been used as brews for their stimulant effect.

There are several synthetic modifications to the naturally occurring methylxanthines. Theophylline is available in a variety of formulations, including sustained-release oral forms, as aminophylline for oral or intravenous administration, and in rectal suppository forms. Aminophylline has been tried unsuccessfully by aerosol with asthmatic subjects. The aerosol is irritating to the pharynx, has a bitter taste, and can cause coughing and wheezing.

The xanthine group has a number of general physiological effects in humans, including central nervous system stimulation, Cardiac muscle stimulation, diuresis, bronchial, uterine, and vascular smooth muscle relaxation, peripheral and coronary vasodilation, and cerebral vasoconstriction. Some of the effects seen with xanthines are well known to those who drink caffeinated beverages (e.g., coffee, colas, and tea). Coffee in particular can be used for the central nervous system stimulatory effect to remain awake. The diuretic effect after drinking coffee or cola is also well known. Caffeine or theophylline can also cause tachycardia, and the cerebral vasoconstricting effect has been used to treat migraine headaches. Caffeine and theophylline differ in the inten-

sity of the effects. Caffeine has more central nervous system-stimulating effect than theophylline, and this includes ventilatory stimulation. In clinical use, theophylline is generally classified as a bronchodilator, because of the relaxing effect on bronchial smooth muscle.

Use in Asthma

Sustained-release theophylline is indicated as an alternative for maintenance in steps 2-4 in patients older than 5 years of age. Sustained-release theophylline is considered a less preferred alternative to low-dose inhaled corticosteroids. Theophylline is not generally recommended for acute exacerbations. Many clinicians believe that the cromolyn-like agents and antileukotrienes are preferable to theophylline in terms of side effects and therapeutic margin.

Use in Chronic Obstructive Pulmonary Disease

Current guidelines for the treatment of stable COPD state that bronchodilators are central to symptom management. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) states that inhaled bronchodilators are preferred when available. Theophylline is considered effective in COPD but, because of potential toxicity, is recommended as an alternative to the inhaled bronchodilators such as β_2 agonists or anticholinergic agents.

Use in Apnea of Prematurity

If pharmacological therapy is needed to stimulate breathing in apnea of prematurity (AOP), methylxanthines are considered the first-line agents of choice. Theophylline has been most extensively used, but it has been suggested that caffeine citrate may be the agent of choice. Caffeine citrate better penetrates the cerebrospinal fluid and has a higher therapeutic index with fewer side effects compared with theophylline. Caffeine citrate (Cafcit) has been approved for administration either intravenously or orally.

Nonbronchodilating Effects of Theophylline

Although theophylline is classified as a bronchodilator, it actually has a relatively weak bronchodilating action. The efficacy of theophylline in obstructive lung disease may be due to its nonbronchodilating effects on ventilation. Theophylline can increase the force of respiratory muscle contractility, and this

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effect is thought to inhibit or even reverse muscle fatigue and subsequent ventilatory failure. Theophylline can have the same effect on skeletal limb muscle. Methylxanthines also show evidence of increasing respiratory muscle endurance, as well as strength. This can prevent fatigue of the respiratory muscles, especially with increased resistance.

Methylxanthines have also been shown to increase ventilatory drive at the level of the central nervous system. In particular, theophylline can increase phrenic nerve activity for a given level of chemical stimulus. This effect on ventilatory drive seems to occur at the level of the midbrain and may involve the neurotransmitter dopamine. Theophylline use may have nonbronchodilating advantages in subjects with COPD who also have cardiac disease or cor pulmonale. Theophylline has shown an increase in cardiac output, a decrease in pulmonary vascular resistance, and an improvement in myocardial muscle perfusion in ischemic regions.

Theophylline also has some antiinflammatory effects, which may also explain its efficacy despite the fact that the drug is a relatively weak bronchodilator. Evidence indicates that theophylline can produce some degree of immunomodulation, and an antiinflammatory and bronchoprotective effect through inhibition of cAMP-specific phosphodiesterase enzymes, particularly PDE3 and PDE4, in proinflammatory cells and tissues which is discussed below.

Proposed Theories of Activity

The exact mechanism of action of xanthines, and theophylline in particular, is not known. It was originally thought that xanthines caused smooth muscle relaxation by inhibition of phosphodiesterase, leading to an increase in intracellular cyclic adenosine 3',5'-monophosphate (cyclic AMP, or cAMP). An increase in cAMP causes relaxation of bronchial smooth muscle. However, this explanation to account for therapeutic xanthine actions has been questioned. Several alternative theories concerning the action of xanthines have been proposed in addition to phosphodiesterase inhibition.

Inhibition of Phosphodiesterase

Theophylline is a weak and nonselective inhibitor of cAMP-specific phosphodiesterase (PDE). The inhibition can lead to an increase in intracellular cAMP, with consequent bronchial relaxation or antiinflammatory effects. However, at the dosage levels used clinically in humans, theophylline is a poor inhibitor of the enzyme. As a result, this may not be the best theory on how xanthines exert a therapeutic effect. PDE is a generic term referring to at least 11 distinct families that have been identified as hydrolyzing cAMP or cyclic guanosine 3',5'-monophosphate (cyclic GMP, or cGMP) and that have unique tissue and subcellular distributions. The various PDE families differ in substrate specificity, inhibitor sensitivity, and cofactor requirements. There are two cAMP-hydrolyzing PDEs, referred to as PDE3 and PDE4, that may play a role in asthma. PDE4 is expressed in airway smooth muscle, pulmonary nerves, and many proinflammatory and immune cells. PDE4 inhibitors suppress processes thought to contribute to asthma inflammation by blocking the degradation of cAMP in target cells and tissue.

Antagonism of Adenosine

An alternative explanation of bronchodilation is that theophylline acts by blocking the action of adenosine. Adenosine is a purine nucleoside that can stimulate A1 and A2 receptors. A1-



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Receptor stimulation inhibits cAMP, whereas A2-receptor stimulation increases cAMP. Inhaled adenosine has produced bronchoconstriction in asthmatic patients. Theophylline is a potent inhibitor of both A1 and A2 receptors and could block smooth muscle contraction mediated by A1 receptors.

This explanation is contradicted by the action of enprofylline, which is about five times more potent than theophylline for relaxing smooth muscle, yet lacks a sufficient attachment at the nitrogen-1 position to provide adenosine antagonism. This can be seen by comparing the structures of theophylline and enprofylline. In addition, A1 receptors are sparse in smooth muscle, and isolated animal tissue preparations have actually shown smooth muscle relaxation through adenosine stimulation of the A2 receptors.

Catecholamine Release

A third explanation of xanthine action is that these agents cause the production and release of endogenous catecholamines, which in turn could cause muscle tremor, tachycardia, and bronchial relaxation. Studies on plasma levels of catecholamines such as epinephrine have reported conflicting results, with both an increase and no change reported.

Xanthines are another solution in the fight to relieve pulmonary airflow disorders. However, these agents have a narrow therapeutic effect. Although xanthines are considered a bronchodilator you may want to lock the "side door."

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