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Perspective

Pharmacological Effects of Theophylline and it's Adverse Effects

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DESCRIPTION

Under a variety of brand names, theophylline, also known as 1,3-dimethylxanthine, is a phosphodiesterase inhibitor used in the treatment of respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD) and asthma. It is a member of the xanthine family and shares structural and pharmacological similarities with theobromine and caffeine. It is abundant in nature and can be found in tea (*Camellia sinensis*) and cocoa (*Theobroma cacao*). One of the byproducts of caffeine metabolic processing in the liver is theophylline. Acebrophylline, an anti-inflammatory and airway mucoregulator, is a combination of ambroxol and theophylline 7 acetic acid.

Pharmacokinetics

Absorption: Bioavailability of theophylline is 100% when administered intravenously.

Distribution: Theophylline is found in extracellular fluid, the placenta, mother's milk, and the central nervous system. The distribution volume is 0.5 L/kg. Protein binding accounts for 40% of the total. The volume of distribution may increase in neonates and those suffering from cirrhosis or malnutrition, while it may decrease in obese people.

Metabolism: Theophylline is extensively metabolised in the liver (up to 70%). It is N-demethylated by cytochrome P450 1A2. It is broken down *via* the parallel first order and Michaelis-Menten pathways. Even within the therapeutic range, metabolism can become saturated (non-linear). Small dose increases may result in disproportionately large serum concentration increases. In the infant population, methylation to caffeine is also important. It is metabolized differently in smokers and people with hepatic impairment. Tetrahydrocannabinol and nicotine have both been shown to accelerate theophylline metabolism.

Excretion: Theophylline (up to 10%) is excreted unchanged in the urine. Children (ages 1 to 12), teenagers (12 to 16), adult smokers, elderly smokers, cystic fibrosis, and hyperthyroidism all have higher drug clearance. The drug's clearance is reduced in the following conditions: the elderly, acute congestive heart failure, cirrhosis, hypothyroidism, and febrile viral illnesses.

The elimination half-life varies: 30 hours for premature neonates, 24 hours for neonates, 3.5 hours for children aged one to nine, 8 hours for nonsmokers, 5 hours for smokers, and 24 hours for those with hepatic impairment. 12 hours for those suffering from congestive heart failure New York Heart Association (NYHA) class I-II, 24 hour for congestive heart failure patients Class III-IV NYHA, 12 hours for the elderly.

Pharmacodynamics

Theophylline, like other methylated xanthine derivatives, is a competitive non-selective phosphodiesterase inhibitor, raising intracellular cAMP, activating PKA, inhibiting TNF-alpha, and leukotriene synthesis, and reducing inflammation and innate immunity and non-selective adenosine receptor antagonist, antagonizing A1, A2, and A3 receptors almost equally, explaining many of its cardiac effects.

Theophylline has been shown to inhibit TGF-beta-mediated conversion of pulmonary fibroblasts into myofibroblasts *via* the cAMP-PKA pathway in COPD and asthma, as well as suppress COL1 mRNA, which codes for the protein collagen.

Theophylline has been shown to reverse clinical observations of steroid insensitivity in patients with COPD and asthmatics who are active smokers (a condition that causes oxidative stress) *via* a distinct mechanism. *In vitro,* theophylline can restore the reduced HDAC (histone deacetylase) activity caused by oxidative stress (in smokers), restoring steroid responsiveness to normal. Furthermore, theophylline has been shown to activate Histone Deacetylase-2 (HDAC2) directly. (Corticosteroids suppress the inflammatory response by inhibiting the expression of inflammatory mediators *via* histone deacetylation, an effect mediated by histone deacetylase-2 (HDAC2). Once deacetylated, DNA is repackaged, making the promoter regions of inflammatory genes inaccessible to transcription factors such as NF-B, which act to activate inflammatory activity. It has recently been demonstrated that the oxidative stress associated with cigarette smoke can inhibit the activity of HDAC2, thereby blocking corticosteroid anti-inflammatory effects.

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Adverse effects of theophylline

Theophylline's use is complicated by its interactions with other drugs as well as its narrow therapeutic window (20 mcg/mL). To avoid toxicity, it must be used in conjunction with direct measurement of serum theophylline levels. It can also cause nausea, diarrhoea, an increase in heart rate, irregular heartbeats, and CNS excitation (headaches, insomnia, irritability, dizziness, and lightheadedness). Seizures, which are considered a neurological emergency, can also occur in severe cases of toxicity. Erythromycin, cimetidine, and fluoroquinolones like ciprofloxacin increase its toxicity. Some lipid-based theophylline formulations can cause toxic theophylline levels when taken with fatty meals, a phenomenon known as dose dumping, but this does not occur with most theophylline formulations. Beta blockers can be used to treat theophylline toxicity. Tachyarrhythmias, in addition to seizures, are a major concern. Theophylline should not be taken with the SSRI fluvoxamine.

Medical uses

Theophylline's main actions are as follows:

- bronchial smooth muscle relaxation
- increasing heart muscle contractility and efficiency (positive inotrope)
- increases blood pressure
- increases renal blood flow
- has anti-inflammatory properties
- Stimulatory effect on the central nervous system, primarily on the medullary respiratory centre.

Theophylline's main therapeutic applications are as follows:

- obstructive pulmonary disease (COPD)
- Asthma and infant apnea
- Adenosine is an inhibitory neurotransmitter that induces sleep, contracts smooth muscles, and relaxes cardiac muscle.
- Post-dural puncture headache treatment

CONCLUSION

Theophylline is a nonselective adenosine receptor antagonist antagonizing A1, A2, and A3 receptors almost equally. It can cause nausea, diarrhoea, an increase in heartbeats, and CNS excitation. Seizures, which are considered a neurological emergency, can also occur in severe cases of toxicity. Theophylline is an inhibitory neurotransmitter that induces sleep, contracts smooth muscles, and relaxes cardiac muscle. It is extensively metabolised in the liver (up to 70%) and is broken down *via* the parallel first order and Michaelis-Menten pathways.