THEOPHYLLINE EFFECTS ON ACUTE CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN EMERGENCY MEDICINE

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Summary:
Recently, Methylxanthines have become third line treatment for patients presenting with acute Chronic Obstructive Pulmonary Disease in Emergency Room settings because of the extreme variability in Theophylline plasma concentration. TPH plasma concentration can be affected by several underlying factors not always apparent to clinicians. TPH toxicity cannot be known without measuring the plasma concentration. For these reasons, the use of TPH is less than ideal in ER settings. It is shown that use of aminophylline has not any advantages comparing with beta agonists, anticholinergics and corticosteroids. In conclusion recommendations are given for treatment of acute exacerbation of chronic obstructive pulmonary disease in ER and statement that aminophylline is not recommended.

Key words: acute exacerbation of chronic obstructive pulmonary disease, theophylline effects, emergency medicine

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INTRODUCTION

Theophylline is a xanthine derivative used to treat asthma in both long-term prophylaxis and acute severe attacks (Hardman & Reynolds, 1992). Recently, Methylxanthines have become third line treatment for patients presenting with acute Chronic Obstructive Pulmonary Disease (COPD) in Emergency Room (ER) settings because of the extreme variability in Theophylline (TPH) plasma concentration (Hardman & Reynolds, 1992; Chung, 1991; Ogilvie, 1978). TPH plasma concentration can be affected by several underlying factors not always apparent to clinicians. For this reason the use of TPH in the ER can be unpredictable in its outcomes. TPH can be highly toxic in specific ranges, and because of its variability, can be damaging for the overall health of the patient. The therapeutic to toxic ratio is comparatively small: only by measuring the plasma TPH concentration can the dosage be measured for individual patients (Hardman & Reynolds, 1992). This variability in individuals is due to the half-life of the substance, which can be from 3-13 hours, depending on several weighing factors that is specific to each patient (Hardman & Reynolds, 1992; Ogilvie, 1978).

Peak concentrations of uncoated TPH occur between 0.5 – 2.0 hrs after administration, and 96 % of the substance is absorbed (Ogilvie, 1978). Intravenous preparation with Aminophylline (a sister of TPH) contains 75-85 % of TPH by weight. Volume distribution in the steady state averages 0.5 l/kg regardless of sex or age, tobacco use, asthma, or acute pulmonary oedema (Ogilvie, 1978). This practice can be detrimental to patients because variability in TPH depends on these factors, especially neonates, adults with acidemia and hepatic cirrhosis or obesity (Ogilvie, 1978). These patients tend to have larger volumes of distribution for TPH.

Toxicity and adverse effects

The therapeutic range of TPH is in the general concentration of 55 - 110 μmol/l. Within these parameters, patients may experience gastrointestinal symptoms, insomnia, nervousness and headache (Hardman & Reynolds, 1992). These symptoms do not always precede more serious ones. TPH symptoms can also mirror those of an acute attack of asthma, thus making it difficult to differentiate between the two problems. Severe adverse effects of TPH occur at levels greater than 110 μmol/l. Specifically, at approximately 190 μmol/l, patients experience tachycardia, arrhythmias, cardio-respiratory arrest, and seizure (Hardman & Reynolds, 1992; Stoller, 2014). TPH toxicity cannot be known without measuring the plasma concentration (Stoller, 2014). For these reasons, the use of TPH be less than ideal in ER settings. TPH requires consistent evaluation by staff and physicians in order to avoid toxic levels, as well as the consideration of many other factors that affect plasma concentration (Stoller, 2014).

<table>
<thead>
<tr>
<th>Factors that Increase Plasma TPH Concentration</th>
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<tbody>
<tr>
<td>Formulation</td>
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<tr>
<td>Elixirs v modified release formulations</td>
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<tr>
<td>Age</td>
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<tr>
<td>Premature babies, neonates and elderly</td>
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<td>Weight</td>
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<td>Obesity</td>
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<tr>
<td>Diet</td>
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<tr>
<td>High carbohydrate, low protein, dietary Methylxanthines</td>
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<tr>
<td>Diseases</td>
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<td>Chronic obstructive airways disease, pneumonia, hepatic cirrhosis, heart failure</td>
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Table 1. Information extracted from the journal “ABC of Monitoring Drug Therapy”, Theophylline, authored by Hardman & Reynolds, 1992.
Several factors indicated in Table 1 fall outside the scope of the healthcare practitioner's agency, but remain extremely important factors when considering the prescribed TPH dose. In order for toxic levels to be avoided, clinicians must take a thorough account of these factors to decrease toxicity probability. Toxic levels of TPH can be easily reached without thorough examination of the patient at consistent time intervals. The half-life of TPH can range from 4 hours in healthy adult smokers to 25 hours in patients with hepatic cirrhosis (Hardman & Reynolds, 1992). TPH levels can be detected rapidly by immunoassay, which is not widely used because of its high cost and 30 minute result waiting time. With these factors in mind, TPH becomes higher cost than benefit in ER settings because of its ability to cause ambiguous side effects that are not always signs of emergency to physicians in the ER. Additionally, administering Methylxanthines, such as Aminophylline, when the monitoring of TPH levels is not possible presents an even greater threat to the wellbeing of patients.

**Evidence of Treatment**

Methylxanthines do not appear to meaningfully affect respiratory mechanics in patients with mild to moderate exacerbations of COPD (Stoller, 2014). In the largest randomized trial that examined this issue, 80 non-acidotic (pH >7.32) patients with an acute COPD exacerbation received nebulized bronchodilators and oral glucocorticoids, and were randomly assigned to receive intravenous Aminophylline (0.5 mg/kg/hour) or placebo (Stoller, 2014). No evidence was found for any clinically important additional effect of routine Aminophylline treatment when used with high dose nebulized bronchodilators and oral glucocorticoids (Stoller, 2014). Patients were assessed on differences in spirometry, symptom scores, and length of stay (Stoller, 2014). Although the administration of extended release tablets of TPH can be beneficial, it is imperative that any such therapies follow closely the parameters outlined in Table 1.

**Recommended Hospital Management of COPD**

Similar to at-home management, the major components of in-hospital management of exacerbations of COPD include reversing airflow limitation with inhaled short-acting bronchodilators and systemic glucocorticoids, treating infection, ensuring adequate oxygenation, and averting intubation and mechanical ventilation (Stoller, 2002). In-hospital monitoring typically includes frequent assessment of respiratory status (eg, respiratory rate and effort, wheezing, pulse oxygen saturation), heart rate and rhythm, and also fluid status. Arterial blood gas measurement is performed to look for respiratory acidosis (eg, if the patient's respiratory status is deteriorating), confirm the accuracy of pulse oxygen saturation, and to monitor known hypercapnia.

**Oxygen therapy**

The primary goal in the treatment of COPD is to avoid or mitigate life threatening hypoxemia (Tintinalli et al., 6th edition). As such, supplemental oxygen is an essential component of acute therapy. In order to avoid a worsening of hypercapnia, the administration of supplemental oxygen should aim for a pulse oxygen saturation (SpO₂) of 88 to 92 percent or an arterial oxygen tension of (paO₂) of approximately 60 to 70 mmHg (Stoller, 2014).

**Beta adrenergic agonists**

Inhaled short-acting Beta adrenergic agonists (eg, albuterol, levalbuterol) are the first line of therapy for an exacerbation of COPD because of their rapid onset of action and efficacy in producing bronchodilation (Snow, Lascher, Mottur-Pilson, 2001). Further, inhaled short-acting Beta adrenergic agonists minimize systemic toxicity (Tintinalli et al. 6th edition). Medications administered via a nebulizer or a metered dose inhaler (MDI) with a spacer device may be combined with a short acting muscarinic agent (eg, Ipratropium) (Stoller, 2014). At present, there is limited data regarding the specific dosage of Beta adrenergic agonists, however, some general guidelines are available. Typical doses of albuterol for this indication are 2.5 mg (diluted to a total of 3 mL) by nebulizer every one to four hours, as needed, or four to eight puffs (90 mcg per puff) by MDI with a spacer every one to four hours, as needed. Increasing the dose of nebulized albuterol to 5 mg does not have a significant impact on spirometry or clinical outcomes (Ram, Wedzicha, Wright, Greenstone, 2004).
medical practice in Canadian Emergency Rooms suggests that in moderate and severe cases of COPD exacerbations the continuous administration of Beta adrenergic agonists via nebulizer is preferred. This therapy may be administered until the patient indicates improvement, severe side effects appear or, until there is a need for bi-pap, or intubation becomes inevitable.

Anticholinergic Agents

The efficacy of Anticholinergic Agents has not been thoroughly studied, and cannot, thus, be considered a first line therapy, however, there is evidence that combined Beta adrenergic agonists and Anticholinergic Agent therapy may be more effective than Beta adrenergic agonist therapy (Cydulka RK, Emmerman CL, 1995). The standard dose of Ipratropium for an acute exacerbation of COPD is two inhalations by metered dose inhaler (MDI) every four to six hours (Stoller, 2014). The standard doses of combined albuterol and Ipratropium are two inhalations by MDI every four to six hours; or, one inhalation by soft mist inhaler (SMI, Respimat) every six hours (Stoller, 2014). In addition, current medical practice in Canadian Emergency Rooms suggests the combined Ipratropium and Beta adrenergic agonist therapy be administered in three individual doses.

Corticosteroids

At present, there is no definite consensus on the use of systemic steroids in the treatment of exacerbations of COPD. In severe exacerbations of COPD and occurrences of respiratory failure, a short, 7-14 day, course of systemic steroid therapy may be effective; its efficacy remains unclear, however, in mild and moderate exacerbations (Tintinalli et al., 6th edition). In the event that there is an asthmatic component to the exacerbations, this line of therapy may be effective. Recommended dosing ranges between one and three times the maximal physiologic adrenal secretion rate (Tintinalli et al., 6th edition). It is important to note that current views hold that steroid responsiveness occurs on a continuum and, as such, a poor bronchodilator response does not preclude a good response to steroid therapy (Tintinalli et al., 6th edition). In addition, depending on the type of steroid, it may take anywhere between 4-8 hours to achieve relief; however, the tremendous anti-inflammatory effects of the treatment render it a significant factor contributing to the stabilization of the patient.

Antibiotics

The need for antibiotic treatment should be assessed early on in the course of the exacerbation. There are a plethora of resources addressing this topic.

Home Management of COPD Exacerbations

Home management of COPD exacerbations includes intensification of bronchodilator therapy, and Ipratropium, as well as, the initiation of a course of oral glucocorticoids. Oral antibiotics are added based on individual characteristics.

CONCLUSIONS AND RECOMMENDATIONS

COPD exacerbations in ER settings require close monitoring and prompt treatment. Oxygen therapy may be administered in order to ensure that oxygen saturation remains between 88 and 92%. Beta adrenergic agonists may be aggressively administered on the basis of a dosing continuum via a nebulizer. Ipratropium can be initially administered at 2.5 mg in a combine Beta adrenergic agonist therapy three times; all other administration of this therapy should be given at p.r.n. Corticosteroids may be given early in the course of the disease. The role of Methylxanthines, TPH and Aminophylline is unwarranted in acute exacerbations of COPD. TPH is generally considered the third line of treatment after inhaled Beta-2 agonists, anticholinergics and corticosteroids. Due to the narrow therapeutic range, severity of side effects and the difficulty in monitoring, this line of therapy is not recommended.

REFERENCES


