Use Of 'Low-dose' Theophylline To Reduce Exacerbations Of COPD: A Pragmatic Multicentre Randomised Placebo Controlled Trial.

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In recent years, interest has arisen in the concept of low-dose theophylline in the management of COPD. Laboratory investigations demonstrate that at low plasma concentrations (1-5mg/l) theophylline markedly increases the anti-inflammatory effects of corticosteroids. The Global Initiative for Chronic Obstructive Lung Disease highlights that the clinical relevance of low-dose theophylline is not established, with clinical evidence being limited and contradictory. The theophylline with inhaled corticosteroid (TWICS) study was a multi-centre pragmatic double-blind randomised placebo-controlled trial investigating the effectiveness of adding low-dose theophylline to a drug regimen containing inhaled corticosteroid (ICS) in people with COPD at high risk of exacerbation.

Method: People with COPD (FEV_1/FVC<0.7) on a drug regimen including ICS with a history of ≥2 exacerbations treated with antibiotics and/or oral corticosteroids in the previous year were recruited in 121 UK primary and secondary care sites. Participants were randomised (1:1) to receive low-dose theophylline or placebo for a year. Theophylline dose (200mg once/twice a day) was determined by ideal body weight and smoking status. Primary outcome was the number of participant reported exacerbations in the one year treatment period treated with antibiotics and/or oral corticosteroids. Participants were assessed 6 and 12 months after randomisation. The study was powered to detect a 15% reduction in exacerbations and aimed to recruit 1424 participants.

Results: 1578 people were randomised: 791 theophylline, 787 placebo. There were 11 post-randomisation exclusions, 1567 participants commenced study medication: 788 theophylline, 779 placebo. Participants in the trial arms were well balanced; mean (SD) age 68.4 (8.4) years, 54% were male, 31.7% currently smoked, 80% were using inhaled corticosteroids/long-acting-$beta_2$-agonists/long-acting-muscarinic agents, mean (SD) FEV_1 51.7% (20.0) predicted.

A greater than expected number of participants (26%) ceased study medication, this was balanced between theophylline (n=206) and placebo (n=199) arms and mitigated by over-recruitment (n=154) and high rate of follow up.

Primary outcome data were available for 98% of participants: 772 theophylline, 764 placebo, there were 1489 person years of follow up data. There were 3430 moderate-severe exacerbations: 1727

theophylline, 1703 placebo. The mean (SD) number of exacerbations in participants allocated to theophylline was 2.24 (1.99) and for participants allocated to placebo 2.23 (1.97), adjusted incident rate ratio (95% CI) 0.99 (0.91, 1.08).

Conclusion: For people with COPD at high risk of exacerbation, the addition of low-dose oral theophylline to a drug regimen that includes an inhaled corticosteroid, confers no overall clinical benefit.

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