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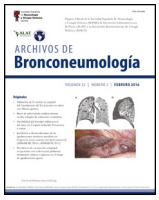

Original Article

Chronic Use of Theophylline and Mortality in Chronic Obstructive Pulmonary Disease: A Meta-analysis☆

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ABSTRACT

Background: Theophylline has been shown to improve respiratory function and oxygenation in patients with chronic obstruction pulmonary disease (COPD). However, the impact of theophylline on mortality in COPD patients has not been not sufficiently evaluated.
Method: Two investigators independently searched for eligible articles in 4 databases. The eligibility criterion for this meta-analysis was an original research article that provided a hazard ratio for theophylline for all-cause mortality of COPD patients. Both randomized controlled trials and observational studies were accepted. After we confirmed no substantial heterogeneity (I^2<50%), the fixed-model method with generic inverse variance was used for meta-analysis to estimate the pooled hazard ratio.
Results: We screened 364 potentially eligible articles. Of the 364 articles, 259 were excluded on the basis of title and abstract, and 99 were excluded after examination of the full text. Our final analysis included 6 observational studies and no randomized controlled trials. One study reported 2 cohorts. The number of patients in each cohort ranged from 47 to 46 403. Heterogeneity (I^2=42%, P=.11) and publication bias (Begg's test r=0.21, P=.662) were not substantial. Fixed-model meta-analysis yielded a pooled hazard ratio for theophylline for all-cause death of 1.07 (95% confidence interval: 1.02–1.13, P=.003).
Conclusion: This meta-analysis of 7 observational cohorts suggests that theophylline slightly increases all-cause death in COPD patients.

Uso crónico de teofilina y mortalidad en la enfermedad pulmonar obstructiva crónica: un metaanálisis

Palabras clave:
Enfisema
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RESUMEN

Antecedentes: Se ha demostrado que la teofilina mejora la función respiratoria y la oxigenación en pacientes con enfermedad pulmonar obstructiva crónica (EPOC). Sin embargo, no está suficientemente evaluado el impacto de la teofilina sobre la mortalidad de los pacientes con EPOC.
Método: Dos investigadores buscaron de forma independiente artículos elegibles en 4 bases de datos. Los artículos seleccionados para el presente metaanálisis debían ser artículos de investigación originales que proporcionaran el cociente de riesgos instantáneos (HR) de la mortalidad por cualquier causa en pacientes con EPOC tratados con teofilina. Se permitió incluir tanto ensayos controlados aleatorizados como estudios observacionales. Después de confirmar que la heterogeneidad no era significativa (I^2 < 50%), para estimar el cociente de riesgos instantáneos del metaanálisis se empleó un modelo fijo con un método de varianza inversa genérica.

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Resultados: Se seleccionaron 364 artículos potencialmente elegibles. De los 364 artículos, 259 fueron excluidos basándose en el título y el resumen, y 99 fueron excluidos después de considerar sus textos completos. Finalmente, nuestro análisis incluyó 6 estudios observacionales y ningún ensayo controlado aleatorizado. Un estudio estaba realizado con 2 cohortes. El número de pacientes en cada cohorte varió de 47 a 46.403. La heterogeneidad (I^2 = 42%, p = 0,11) y el sesgo de publicación (r = 0,21, p = 0,662 en la prueba de Begg) no fueron significativos. El metaanálisis del modelo fijo arrojó un cociente de riesgos instantáneos combinado de mortalidad por cualquier causa con teofilina de 1,07 (intervalo de confianza del 95%: 1,2-1,13, p = 0,003).

Conclusión: El presente metaanálisis de 7 cohortes observacionales sugiere que la teofilina aumenta ligeramente la mortalidad por cualquier causa de los pacientes con EPOC.

Introduction

Chronic obstructive pulmonary disease (COPD), now the fourth leading cause of death worldwide, is a systemic disease characterized by chronic airflow limitation.[1] As such, bronchodilator medications, namely theophylline, long-acting muscarinic antagonists (LAMA), and long-acting beta-agonists (LABA), are understandably used as key medications for treating stable COPD patients.[1] Among these 3 subclasses of bronchodilators, LAMAs and LABAs have repeatedly been reported as safe and effective in randomized controlled trials (RCT) and large observational studies.[1–7] LAMAs and LABAs are, therefore, now regarded as first-line medications for stable COPD.[1] The efficacy of theophylline, meanwhile, has been shown in many observational studies and relatively small RCTs.[8–18] These studies generally indicated that theophylline improves values in respiratory function tests and arterial blood gas analyses, but that it may negatively affect the risk of exacerbation and side effects.[8–18] Even though clinicians are usually interested in patient survival, death was not used as the main outcome. Other surrogate outcomes such as oxygenation or respiratory function were used instead, because an insufficient number of deaths was observed during the follow-up period. However, these surrogate markers do not always reflect the mortality of respiratory disease with airflow obstruction. For example, short-acting beta-agonists improve airflow obstruction, dyspnea, and quality of life in bronchial asthma patients, but regular use of these agents increases the number of deaths from bronchial asthma.[19,20] Accordingly, the impact of theophylline on mortality in COPD patients is still an important research question.

Some observational studies have investigated the impact of theophylline treatment on mortality in COPD patients.[21–26] However, the results of these studies varies widely. The association between theophylline and mortality risk is still an important matter for all clinicians, as theophylline is a common bronchodilator that has been used for decades.[1,27] The aim of this systematic review and meta-analysis, then, was to evaluate the impact of theophylline on all-cause death in COPD patients.

Methods

Study Search Criteria

Requirements for institutional review board approval and informed consent were waived for this study because of the anonymous nature of the data and the fact that it was a review study.

The eligibility criterion for the meta-analysis was an original research article that provided a hazard ratio (HR) for theophylline for all-cause death in COPD patients. Both RCTs and observational studies were accepted. For observational studies, adjusted HR was preferred to non-adjusted HR. Follow-up duration had to be >6 months. Duplicate use of the same data was excluded.

Two investigators independently searched for eligible articles using the MEDLINE, Web of Science, EMBASE, and Cochrane Databases as of January 2014. The search formula for MEDLINE was ((“COPD”[title] OR “chronic obstructive pulmonary disease”[title] OR “chronic obstructive airway disease”[title] OR “emphysema”[title] OR “chronic bronchitis”[title] OR “chronic airflow obstruction”[title]) OR ((“COPD” OR “chronic obstructive pulmonary disease” OR “chronic obstructive airway disease” OR “emphysema” OR “chronic bronchitis” OR “chronic airflow obstruction”) and (“theophylline” OR “xanthine” OR “theophyllines” OR “xanthines” OR “aminophylline” OR “diprophylline” OR “proxyphylline” OR “diprophylline”))) and (“mortality” OR “prognosis” OR “death” OR “mortalities” OR “prognoses” OR “deaths”) and (“hazard ratio” OR “HR” OR “hazard ratios”).

The quality of eligible studies was evaluated using a scale comprising 4 subscales with a maximum of 2 points for each subscale.[28] The subscales were cohort entry, exposure definition, outcome, and cofounding assessment. The scores ranged from 0 to 8, where a higher score signified better quality[28]

Statistics

We extracted HR for all-cause mortality in each study. HR and its 95% confidence interval [95% confidence interval (CI)] had to be clearly demonstrated in a text, a table, or a figure in each original study. Additionally, data for number of patients, concomitant administration of beta-stimulants and anti-cholinergic agents, and covariables adjusted for the Cox model were extracted.

The fixed-model method with generic inverse variance was used for meta-analysis to estimate pooled value, after no significant heterogeneity was confirmed (I^2<50%).[29–31] Heterogeneity among the original studies was evaluated with (i) the Chi-square distribution test with a rejection region of P=.1, and (ii) the I^2 statistics test whereby I^2=0% indicates no heterogeneity, I^2=25% indicates mild heterogeneity, I^2=50% indicates moderate heterogeneity, I^2=75% indicates strong heterogeneity.[30,31] Publication bias was evaluated with a funnel plot, and with Begg’s test using the Spearman’s rank correlation test with a rejection region of P=.1.[32] All analyses were performed using Excel Toukei 2012 (SSRI, Tokyo. Japan), and Review Manager version 5.3 (Cochrane Collaboration, Oxford, UK).

Results

Study Search Results

We screened 364 potentially eligible articles. Of the 364 articles, 259 were excluded on the basis of title and abstract, 99 were excluded after the full text was examined. Lee reported 4 articles analyzing overlapping data reporting risk of death by treatment regimen using HR,[25,33–35] of which we included 1 article that focused on impact of theophylline on death[25] and excluded the others[33–35] due to duplicate use of the same data. Six studies were