

## EDITORIAL

# Possible Harms of Theophylline in Chronic Obstructive Pulmonary Disease

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Editorial to accompany the article: „The Effects of Theophylline on Hospital Admissions and Exacerbations in COPD Patients—Audit Data From the Bavarian Disease Management Program“ by Johannes Fexer, Ewan Donnachie et al. in this issue of *Deutsches Ärzteblatt International*

**D**ata from large studies show that theophylline is still being prescribed for up to 35% of patients with chronic obstructive pulmonary disease (COPD) (1), although the currently valid guidelines define it as a third-line medication. The role of theophylline in the treatment of asthma and COPD has changed drastically in recent decades, primarily due to the introduction of new classes of substances—the long-acting bronchodilators (beta-2 sympathomimetics and anticholinergics) and inhaled steroids—with high efficacy and a more favorable side effect profile.

## New study on the risks of theophylline

In view of the limited indication for theophylline, the study by Fexer, Donnachie and co-authors in this issue of *Deutsches Ärzteblatt International* is highly significant (2). The authors compared two groups of almost 1500 patients: the treatment in one group included theophylline, while in the other group no theophylline was prescribed. All patients were observed for a period of 9 or 10 quarter-years. The authors selected clinically and economically relevant endpoints. It emerged that the risk of suffering an exacerbation (hazard ratio 1.41) or being admitted to hospital (hazard ratio 1.61) during the observation period was significantly higher in the theophylline group.

In common with other database analyses, this study has a number of limitations, as the authors themselves point out. The most important weaknesses are that the data documented by the patients' physicians were used without verification and that no information is available concerning the precise dosage and time of intake. Moreover, a considerable proportion of the patients treated with theophylline may have received the drug as a result of "indication bias"; in other words, the physicians may have considered the patients so ill that they prescribed theophylline in addition to other treatment. Indeed, circa 18% of the theophylline patients were also given systemic steroids and almost 8% received long-term oxygen therapy. On the other hand, however, the fact that approximately the same number of patients in each group were treated with steroids and/or oxygen speaks against a possible influence of disease severity on the decision to prescribe theophylline.

Further limitations are that the patients were not selected in random fashion and there were no strict inclusion and exclusion criteria. However, this also represents a strength of the study, in that randomized controlled trials have high internal validity but only low external validity—in other words, they are an incomplete reflection of reality.

Two particular aspects of the study enhance its validity: First, the patients were participating in a structured disease management program (DMP), so their management is likely to have been optimal. Second, the authors used propensity score matching. This is a statistical technique employed in observation studies to avoid potential bias and render populations comparable at the beginning of the study period. The baseline characteristics of the two groups of patients after matching show that this procedure was successful.

## Beneficial and adverse effects of theophylline

The results reported by Fexer, Donnachie et al. support the published findings of other recent COPD studies in which the beneficial and adverse effects of theophylline were analyzed in the stable phase and during exacerbation:

- In patients in the stable phase of the disease, orally administered theophylline had on one hand a slight bronchodilatory effect and led to amelioration of the symptoms. On the other hand, theophylline proved less effective and was less well tolerated than inhaled long-acting bronchodilators (3, 4).
- In patients being treated with parenteral theophylline for exacerbations of COPD, the beneficial effects were slight and inconsistent, the adverse effects substantial (5, 6).

The broad spectrum of potential adverse effects is linked with the fact that theophylline is a nonspecific phosphodiesterase inhibitor. As a consequence, cardiac arrhythmias (supraventricular and ventricular), seizures, headache, insomnia, nausea, and heartburn may arise. Furthermore, theophylline is metabolized via cytochrome P450, with the possible consequence of significant interactions with a number of other medicinal drugs such as vitamin K antagonists and digitalis preparations (7).

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Owing to this combination of relatively low efficacy and pronounced adverse effects, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) does not recommend the use of theophylline, even when other bronchodilators are unavailable or unaffordable (7).

### History and outlook

Following its discovery in 1888 by the later Nobel laureate Albrecht Kossel (“Über das Theophyllin, einen neuen Bestandteil des Thees”, [On theophylline, a new component of tea] [in 8]), theophylline was used for a number of indications. Initially it was employed as a diuretic and for treatment of angina pectoris, then in 1921 a bronchodilatory effect on isolated bronchial muscle was described. It was not until the 1950s, however, that theophylline was mentioned as a therapeutic agent for asthma in the pharmacological and medical literature (8). In the first recommendations of the German Airways League (*Deutsche Atemwegsliga*), published in 1995, theophylline is recommended for every patient whose symptoms are not adequately ameliorated by administration of beta-2 sympathomimetics and anticholinergics (9).

Is the story of theophylline drawing to an end, after all the findings published in recent years and now the results of the study by Fexer, Donnachie et al.? It's hard to judge. New studies are being planned following the discovery that reduced activity of histone deacetylases in COPD is apparently a major reason for the limited efficacy of corticosteroids in this disease. Low-dose theophylline has been shown to increase the activity of histone deacetylases and improve the anti-inflammatory effects of corticosteroids (10). It remains to be seen whether these effects will be reflected in clinically relevant endpoints.

#### Conflict of interest statement

The author declares that no conflict of interest exists

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