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Nationwide use of theophylline among adults-A 20-year Danish drug utilisation study

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ABSTRACT

Background: Theophylline, a dimethylxanthine, has been used the last 100 years to treat airway disease. Although it is one of the most widely prescribed medicines to treat asthma and chronic obstructive pulmonary disease (COPD) throughout the years, the utilisation patterns are not well-described.

Methods: Using the Danish Register of Medicinal Products Statistics, we identified adults above 18 years redeeming one or more prescriptions of theophylline between 1997 up to 2017, with a 2-year run-in period from 1995 to 1997. Using descriptive statistics, we reported the development in prevalence, incidence, and a measure of treatment duration (proportion of patients covered).

Results: In total, 55,636 individuals redeemed 1,066,475 prescriptions of theophylline, 30,619 women (55%) and 25,017 men (45%). The prevalence decreased from 401 per 100,000 individuals in 1997 to 26 per 100,000 individuals in 2016. The incidence rate decreased throughout the entire study period (105 per 100,000 person-years in 1997 to 5 per 100,000 person-years in 2016). In total, 52% were still current users three months after theophylline initiation, 33%, 27%, and 23% were current users after 6 months, one year, and two years.

Conclusions: Although newer and more efficient medicines to treat asthma and COPD has been developed, theophylline is still prescribed and used in 2016, but the incidence and prevalence have decreased markedly since 1997.

1. Introduction

Theophylline, a dimethylxanthine, is considered one of the most widely prescribed drugs to treat obstructive pulmonary diseases [1]. The structure is very related to caffeine [2], and theophylline occurs in coffee beans, cocoa beans and tea, although only in trace amounts. Henry Hyde Salter, MD, FRCP, wrote in his report from 1859, that *"One of the commonest and best-reputed remedies of asthma, one that is almost sure to have been tried in any case that may come under our observation, and one that in many cases is more efficacious than any other, is strong coffee*" [3]. As a medical drug, theophylline was initially extracted from tea leaves and synthesised in 1895 as a diuretic [1].

The mechanism of action is not established, but is believed to include phosphodiesterase inhibition, adenosine receptor antagonism, as well as increased interleukin-10 concentrations [1,4]. The drug has two primary pharmacodynamic actions dependent on the plasma concentrations (bronchodilation and antiinflammation). It was initially used as a bronchodilator, but in order to achieve significant bronchodilatation relatively high plasma concentrations are needed (10–20 mg/l) [1,5,6]. Along with introduction of new direct bronchodilators, the drug is now considered inferior for bronchodilation in asthma and COPD treatment due to a weak efficacy combined with common side-effects and risk of toxicity at higher doses [7].

However, in lower concentrations, theophylline is considered to have anti-inflammatory effects, which have been a subject of interest in research the recent years, especially in regards to COPD patients with glucocorticoid resistance [5,8]. Therefore, it is likely that the patient population who receives treatment with theophylline is different now from those who initiated treatment 20 years ago.

Although theophylline has been on the market for almost a century, and significant changes in treatment guidelines of obstructive pulmonary diseases has occurred, very little is known about its utilisation pattern in a population. The few studies available are primarily questionnaire surveys [9,10], or performed on selected patient populations [11,12].

In such, we aimed to describe theophylline use among adults in Denmark since 1997, using drug utilisation statistics developed for individual-level prescription data [13].

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2. Methods

In this nationwide utilisation study, we described the outpatient use of theophylline including assessment of duration during 1 January 1997 to 31 December 2016 among all adult Danish inhabitants.

2.1. Setting

2.1.1. Data sources

Three Danish nationwide registers were used to assess and identify individuals redeeming prescriptions of theophylline: Danish Civil Registration System [14], The Register of Medicinal Products Statistics [15], and The Danish National Patient Register [16]. The Danish National Health Service provides tax-supported health care for the entire Danish population, and due to the unique personal identification number assigned to all Danish citizens it is possible to conduct true population-based register-linkage studies covering the entire population [14].

2.1.2. Study drugs

The DDD for theophylline (ATC R03DA04) is 400 mg, according to the WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD index [17]. The approved therapeutic indication includes asthma bronchiale and other bronchospasms. The marketed formulations are oral sustained release tablets [18].

Each individual was considered as a 'current user' on a given day if they had a recording of a redeemed theophylline prescription with enough doses to cover that day. The duration of each prescription was defined as the number of DDDs dispensed (i.e., assuming a consumption of one DDD per day), while adding 25% to the duration to account for secondary non-compliance or irregular prescription patterns. The addition of 25% to the duration of therapy is based on a definition of 80% compliance, which previously has been used as an arbitrary cut-off [19–21]. We excluded individuals less than 18 years of age and computed a run-in period of two years (1995–1997), in order to decrease the risk of misclassifying new users.

2.2. Analysis

Users were defined as individuals redeeming one or more prescriptions of theophylline in a given year. We calculated the amount of DDD redeemed per individual for each year within the study period.

We calculated the total number of users of theophylline per year and the total annual amount of DDDs filled within the same period, to describe the amount of theophylline used per individual each year.

The number of current users per 1000 in the population, from 1997 up to 2017 was calculated (the point prevalence proportions) using the total population living in Denmark 1 January of each relevant year. The gender and age-specific (1-year intervals) prevalence proportion for 2016 was reported.

We used the 'proportion of patients covered' (PPC) method as an estimation of treatment duration [22]. We followed all users from the date of their first prescription of theophylline. Over time, we estimated the proportion of all individuals still alive after X days, who seemingly still used theophylline at that day (defining current use as in the analysis of point prevalence). Thereby, an individual could be regarded as dropped out of treatment at one point in time and later be re-classified as current user upon filling a new prescription. We divided the analysis into the age groups: 0–18, 19–39, 40–64, and 65–90 + year old. Subgroup analyses included gender, and calendar year of first prescription.

Lastly, we computed Lorenz curves to assess the proportion of theophylline use that was accounted for by percentiles of theophylline users, ranked according to their annual consumption.

Stata Version 14.1 (StataCorp, College Station, TX, USA) was used for all analyses.

2.3. Ethics

The study was approved by the Danish Data Protection Agency. According to Danish law, register-based studies do not require approval from an ethics review board [23].

3. Results

3.1. Demographics

In total, 55,636 individuals redeemed 1,066,475 prescriptions of theophylline. A total of 15,934 (29%) individuals redeemed only one theophylline prescription, 9286 (17%) redeemed 2–4 prescriptions, and 32,304 (58%) redeemed 5 + prescriptions. The median number of DDDs filled per prescription was 75 (Inter Quartile Range [IQR] 63–75).

The median age of individuals initiating theophylline was 69 years (IQR 58–76 years), with a majority of female users (n = 78,760, 55%), who initiated theophylline at a younger age than males (female median age 68 years [IQR 57–76 years], male median age 70 years [IQR 60–77 years], $p < 0.001$). In total, 2.7% (n = 1491) had an asthma-related admission up to a year prior to theophylline initiation, whereas 13.1% (n = 7282) had a COPD-related admission.

3.2. Incident users in 1997–2006 versus 2007–2016

In total, 49.1% the patients who initiated theophylline in 1997–2006 redeemed a prescription of inhaled corticosteroid (ICS), decreasing to 20.3% among new users in 2007–2016. The opposite trend was observed in fixed-dose long acting beta-2-agonists (LABA) in combination with ICS. Among patients who initiated theophylline in 1997–2006 2.0% had redeemed a prescription of long-acting muscarinergic agonists (LAMA) prior to the theophylline initiation, whereas 44% redeemed a prescription of LAMA patients initiating theophylline in 2007–2016. The COPD-related admissions increased from 12.2% among incident users in 1997–2006 to 23.1% among incident users in 2007–2016.

The demographic characteristics of individuals initiating theophylline are presented in Table 1.

3.3. Prevalence, incidence, and amount used

The total amount of DDDs was 10,227,000 in 1997, and 668,000 in 2016. For trends in amounts used, please refer to Fig. 1.

The number of theophylline users in treatment each year decreased during the study period, from 401 per 100,000 individuals in 1997 to 26 per 100,000 individuals in 2016 (Fig. 2). The age-specific point prevalence showed a majority of older users in the four years we have presented (Fig. 3).

The number of incident users decreased from 105 per 100,000 person-years in 1997 to 5 per 100,000 person-years in 2016. A small spike in incidence rates in 2006 is observed. The most pronounced decrease in incidence rates is observed among individuals in the age-group 65 + years (from 377 per 100,000 in 1997 to 13 per 100,000 in 2016) (Fig. 4).

3.4. Duration of usage

Overall, 52% were current users of theophylline three months after initiation, 33%, 27%, and 23% were current users after 6 months, one year, and two years, respectively (Fig. 5). The lowest proportion still treated after two years was among the age-group 18–39 years (7%), whereas 28% of users aged 70–79 years were still treated one year after their first filled prescription.