

Anticholinergic burden and dry mouth among Finnish, community-dwelling older adults

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Abstract

Objective: The aim was to study whether the anticholinergic burden of drugs is related to xerostomia and salivary secretion among community-dwelling elderly people.

Background: Anticholinergic drugs have been shown to be a risk factor for dry mouth, but little is known about the effects of cumulative exposure to anticholinergic drugs measured by anticholinergic burden on salivary secretion or xerostomia.

Methods: The study population consisted of 152 community-dwelling, dentate, non-smoking, older people from the Oral Health GeMS study. The data were collected by interviews and clinical examinations. Anticholinergic burden was determined by using the Anticholinergic Drug Scale (ADS). A Poisson regression model with robust error variance was used to estimate relative risks (RR) with 95% confidence intervals (CI 95%).

Results: Participants with a high anticholinergic burden ($ADS \geq 3$) were more likely to have xerostomia (RR: 3.17; CI: 1.44–6.94), low unstimulated salivary flow (< 0.1 ml/min; RR: 2.31, CI: 1.21–4.41), and low stimulated salivary flow (< 1.0 ml/min; RR: 1.49, CI: 0.79–2.79) compared to reference group (ADS 0). In participants with a moderate anticholinergic burden (ADS 1–2) all the risk estimates for xerostomia, unstimulated and stimulated salivary secretion varied between 0.55–2.85. Additional adjustment for the total number of drugs, anithypertensives, and sedative load caused only slight attenuation of the risk estimates.

Conclusion: A high anticholinergic burden was associated with low unstimulated salivary secretion and xerostomia.

Introduction

Nowadays dry mouth can be seen to consist of two conditions, xerostomia and hyposalivation¹.

Xerostomia is a subjective feeling of dry mouth, whereas hyposalivation is a condition with objectively lowered salivary output in either stimulated or unstimulated salivary secretion. The most important etiological factors for dry mouth among older people are drugs—especially anticholinergic drugs—and polypharmacy^{1,2}.

Anticholinergic drugs include several drugs from different therapeutic categories^{3,4}. Certain drugs, such as atropine or oxybutin, are used specifically because of their anticholinergic properties, while other drugs, such as antidepressants, antipsychotics, and antihistamines, have anticholinergic activities that are not necessarily related to their therapeutic effects. Despite the fact that anticholinergic drugs are associated with serious adverse events, they are commonly used among older people⁵⁻⁷.

Previous studies have shown that drug-induced anticholinergic activity is an additive effect and that there is variability in the anticholinergic potency of drugs^{8,9}. Therefore, several methods have been developed to measure an overall anticholinergic burden caused by drugs used¹⁰. One of these methods is Carnahan's Anticholinergic Drug Scale (ADS)¹¹, which ranks drugs into four categories based on their anticholinergic activity and it takes into account the dose of anticholinergic drugs. An individual's anticholinergic burden is obtained by summing the categorical values of the drugs used. A benefit of using the anticholinergic burden is that it enables the focus to be on the overall anticholinergic effect of all the drugs used instead of just on certain specific drugs with a prominent anticholinergic effect.

It is well known that anticholinergic drugs cause hyposalivation and xerostomia, either by directly affecting muscarinic receptors in the salivary glands or by a secondary effect through the central nervous system^{9,10}. Yet, little is known about the association between anticholinergic burden caused

by all the drugs used and salivary secretion or xerostomia. A study by Kersten et al.¹¹ showed, that among nursing home residents, a high anticholinergic burden ($ADS \geq 6$) was associated with low unstimulated salivary secretion. A high anticholinergic burden measured by another anticholinergic scale, the Anticholinergic Risk Scale, have also been previously reported to be associated with an increased risk of peripheral anticholinergic adverse effects, including xerostomia¹².

Because of the high frequency of anticholinergic drug use among older people and the additive effect of these drugs, it is important to study the effects of overall anticholinergic burden on oral health. The aim of this study was to examine whether anticholinergic burden, measured by the ADS, is related to xerostomia, unstimulated, and stimulated salivary secretion among community-dwelling elderly people.

Material and methods

Our study population is part of a larger Oral Health Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study. The randomly selected participants were 75 year old or older on the first of November in 2003 and lived in the city of Kuopio. The Oral Health GeMS study included 354 people who underwent comprehensive geriatric assessments and oral examinations at the base line of the study. In the present study, the study population was further restricted to community-dwelling, non-smoking, dentate people (at least one clinically visible tooth or dental root), whose salivary secretion was measured, $n = 152$ (109 women and 47 men, mean age 79.4, SD 3.67).

Written informed consent was provided by the participants or their close relatives or caregivers. The study protocol was approved by the ethics committee of Kuopio University Hospital and the University of Kuopio. Further information about the GeMS study can be found from previous studies¹³⁻¹⁵.

A multidisciplinary team (two nurses, two physiotherapists and two physicians) carried out the

comprehensive geriatric assessment, which included interviews and clinical examinations. In situations where the participant could not answer the questions because of his/her cognitive or other impairment, a close relative or a caregiver provided the answers. If the participant was unable to visit the health centre, the interviewer, accompanied by a physician, made a home visit to conduct the interview and clinical examination. The participant's self-reported drug use, both prescription and non-prescription drugs, was verified from prescription forms and drug packages. Additional health data were also taken from the medical records of local municipal health centres, home nursing services, local hospitals, and the Kuopio University Hospital.

Oral examinations of the participants of the Oral Health GeMS study were carried out by two dentists in 2004–2005, an average six months after the comprehensive geriatric assessment. The clinical oral examinations were done in the primary care setting of the Social and Health Centre of Kuopio or in the participant's home. During the examinations a WHO colour-coded periodontal probe, a mouth mirror and a gauze pad were used. The dentists performed the first seven examinations together in order to be calibrated. Since the examination was time-consuming (one hour) and caused strain to the participants, there were no repeated examinations.

Outcome variables

Salivary secretion, both stimulated and unstimulated, and xerostomia were used as outcome variables. All the participants answered questions about xerostomia and provided saliva samples. They were asked to abstain from eating or drinking one hour prior to the saliva collection.

Participants with removable dentures gave an unstimulated saliva sample without the dentures and a stimulated saliva sample with the dentures.

The unstimulated saliva samples were collected using the draining method¹⁶. The participants were instructed to sit straight and bend their head forward. They were asked to swallow to empty their mouth and then to start drooling into a centrifuge tube for 5 minutes. The stimulated saliva samples

were collected after the participants chewed a paraffin capsule for 30 seconds and emptied their mouth of the first saliva. Then the participants were asked to keep chewing the paraffin capsule for 5 minutes and drain the saliva into a centrifuge tube.

The stimulated salivary secretion was classified into two categories: < 1.0 ml/min (low) and ≥ 1.0 ml/min (normal) and the unstimulated salivary secretion also into two categories: < 0.1 ml/min (low) and ≥ 0.1 ml/min (normal). The cut-off values used are based on the literature¹⁷.

Xerostomia was determined with a single-item question ‘How often does your mouth feel dry?’¹⁸. Xerostomia was classified into two categories based on the reported frequency of feeling of dry mouth: never/occasionally vs. often.

Explanatory variable

The anticholinergic burden caused by drugs was measured using Carnahan’s Anticholinergic Drug Scale⁸. The scale has been validated among a group of older long-term care residents and it classifies drugs into four score categories based on their anticholinergic activity, as follows:

- Score category 0 includes drugs with no known anticholinergic activity
- Score category 1 includes drugs with potential anticholinergic activity as evidenced by receptor-binding studies (e.g., furosemide, digoxin or captopril)
- Score category 2 includes drugs that are sometimes noted to have anticholinergic adverse events, usually with excessive doses (e.g., carbamazepine, cyproheptadine or disopyramide)
- Score category 3 includes drugs with marked anticholinergic activity (e.g., amitriptyline, brompheniramine or oxybutynin)

To determine each participant’s final ADS score, dose-adjustments were done for drugs belonging to categories 2 and 3 and then the scores of all the drugs used were summed. This ADS score reflected anticholinergic burden and was classified into three categories: none (ADS 0), moderate (ADS 1–2) and high (ADS ≥ 3).

Other variables

The participant's sedative load was determined using the Sedative Load Model where each drug was placed into one of four categories based on the drug's sedative properties, and each category was assigned a sedative rating^{21,22}.

- Sedative rating 0 was given to drugs with sedation as a potential but rare adverse reaction (e.g., second-generation antihistamines, acetylcholinesterase inhibitors) and to all other drugs with no known sedative properties
- Sedative rating 1 was given to drugs with sedation as a prominent side effect or drugs with a sedating component (e.g., SSRIs, atypical psychotics)
- Sedative rating 2 was given to first-line sedative drugs (e.g., anxiolytics, hypnotics)

To determine the participant's sedative load, all the sedative ratings of the regularly used drugs were summed.

Use of antihypertensive drugs was determined from the drug information and the following drug groups were included: Ca²-channel blockers, angiotensin-converting-enzyme inhibitors, AT₁-receptor antagonists, diuretics, and selective β-blockers. For analyses, the use of antihypertensives was classified into two categories: no *vs.* yes.

Functional capability was determined by using Lawton's Instrumental Activities of Daily Living (IADL) scale¹⁹. The scale is based on a questionnaire with eight fields of daily activities, such as ability to use a telephone or handle medication. The scale scores ranged among the participants from 0 (inability) to 8 (high ability) and they were classified into two categories: 0–6 and 7–8.

A modified version of the Functional Co-morbidity Index (FCI) was used to determine co-morbidities²⁰. The FCI included medical diagnoses of arthritis (rheumatoid arthritis and other connective tissue disorders), osteoporosis, asthma/chronic obstructive pulmonary disease, coronary

artery disease, congestive heart failure, myocardial infarction, Parkinson's disease, stroke, diabetes mellitus, depressive symptoms, visual impairment, hearing impairment, and obesity (body mass index > 30). Each of these diagnoses was given a numeric value of 1 and they were summed together. Diagnoses were determined from the information obtained in the comprehensive geriatric assessment, from medical records or from the Finnish Special Reimbursement Registers maintained by the Social Insurance Institution of Finland.

Statistical methods

In this study, Poisson regression models with robust error variance²³ were used to estimate relative risk (RR) with a 95% confidence interval (CI 95%). All the models were adjusted for age, gender, education, diabetes and rheumatoid disease, and the Functional Comorbidity Index. Three additional sets of models were further adjusted for the total number of drugs, use of antihypertensives, and sedative load. All the statistical analyses were done using SPSS 22.0 software for Windows²⁴.

Results

The socio-demographic and health-related characteristics of the study population are presented in Table 1 and the unadjusted relative risks of the explanatory variables are in Table 2. The adjusted relative risks from the multivariate models are presented in Table 3. In this study population, the ADS scores ranged between 0–9 and about 51 % of the participants ($n = 77$) had no anticholinergic burden (ADS 0), 35 % ($n = 53$) had a moderate anticholinergic burden (ADS 1–2), and 14 % of the participants ($n = 22$) had a high anticholinergic burden (ADS ≥ 3).

The analyses showed that after adjusting for confounding factors (age, gender, education, diabetes, rheumatic diseases and FCI), participants with a high anticholinergic burden (ADS ≥ 3) were more likely to have xerostomia (RR: 3.17; CI: 1.44–6.94) than participants without an anticholinergic burden (ADS 0). While participants with a moderate anticholinergic burden (ADS 1–2) also had a

higher likelihood of xerostomia, the association was not statistically significant (RR: 1.27; CI: 0.57–2.85) compared to participants without an anticholinergic burden. When a continuous ADS was used, the relative risk was 1.20 (CI: 1.06–1.37) (Table 3).

After adjusting for confounding factors, participants with a high anticholinergic burden (≥ 3) had a higher likelihood of low unstimulated salivary flow (< 0.1 ml/min; RR: 2.31, CI: 1.21–4.41) compared to the reference group (ADS 0). The risk estimates for unstimulated salivary flow in the ADS 1–2 group varied between 0.55–2.14. For a continuous ADS the relative risk was 1.22 (CI: 1.10–1.34) (Table 3).

Participants with either a moderate (ADS 1–2) or high anticholinergic burden (ADS ≥ 3) were more likely—although not statistically significantly—to have low stimulated salivary flow (< 1.0 ml/min; RR: 1.19, CI: 0.68–2.11 and RR: 1.49, CI: 0.79–2.79, respectively) compared to participants with an ADS score of 0. When a continuous ADS was used, the relative risk was 1.09 (0.98–1.20) (Table 3).

Additional adjustments for the total number of drugs, antihypertensives, and sedative load were also done for all the outcome variables. These analyses showed only a slight attenuation of the risk estimates for the ADS (Table 3, Models 2-4).

Discussion

The results of the present study showed that a high anticholinergic burden was associated especially with low unstimulated salivary secretion and xerostomia and to a lesser extent with stimulated salivary secretion. These results are in line with earlier studies which have shown associations between anticholinergic burden^{11,12} or the use of multiple anticholinergic drugs^{28,29} and hyposalivation or xerostomia. The novelty of the present study is that the focus was on the association between the anticholinergic burden and dry mouth, measured with both hyposalivation and xerostomia.

In this study population, both stimulated and unstimulated salivary secretions were measured and symptoms of xerostomia were asked during the interview. All three of these were used as outcome variables, which can be considered the most comprehensive method for assessing dry mouth¹. This approach to defining dry mouth differs from most of the earlier studies, as only the study by Dessoutter et al.²⁸ included both unstimulated salivary secretion and questions about xerostomia as outcome variables. Other studies used either unstimulated salivary secretion, measured by a swab method¹¹, or xerostomia^{12,28,29} as an outcome variable. Furthermore, studies by Kersten et al.¹¹ and Rudolph et al.¹² had the main focus on the general anticholinergic adverse effects rather than on the dry mouth itself and they used **the dry mouth** just as a variable among the others to depict **the** peripheral adverse effects of anticholinergic drugs.

In the present study, the Anticholinergic Drug Scale (ADS) was used to measure anticholinergic burden, while earlier studies have used different methods to describe anticholinergic burden or the anticholinergic potential of the drugs used. Kersten et al.¹¹ used the same measurement (ADS) as in this study, while Rudolph et al.¹² used a different ranked list, the Anticholinergic Risk Scale (ARS), to measure anticholinergic burden. In studies by Günes et al.²⁹ and Dessoutter et al.²⁸, only the presence or intake of anticholinergic drugs was determined from the information in a pharmaceutical database or literature, such as Martindale or Theriaque. These studies did not **take into account the total** anticholinergic burden or variance in the anticholinergic potency of drugs^{28,29}.

The abovementioned differences in research methods between the studies make direct comparison of the present findings with earlier results challenging. On the other hand, the earlier results lend support to the conception that anticholinergic drugs cause dry mouth, related to either hyposalivation or xerostomia. The findings of the present study can be seen to further support this conception by showing that the high overall anticholinergic burden was associated with unstimulated salivary secretion and xerostomia.

When studying the effects of drugs on dry mouth, one must take polypharmacy into account.

Previous studies have shown that simultaneous use of multiple drugs, regardless of class or type, can have an additive effect to cause dry mouth, especially xerostomia³¹⁻³⁴. In contrast, our previous study from the same GeMS population³⁴ showed that the number of drugs by itself is not an essential risk factor for hyposalivation, but the effects of the drugs are carried out by drugs with sedative properties. The present study also lends support to the assumption that the total number of drugs itself might not be a major risk factor for hyposalivation or xerostomia.

The analyses (Table 3, Model 2 & 3) showed that the total number of drugs had the weakest association with all the outcome variables, the risk estimates varying between 0.86–1.10, whereas sedative drugs were most strongly associated with stimulated salivary secretion, with the risk estimate for $SL \geq 3$ being 1.57 (0.89–2.75). On the other hand, the anticholinergic drugs had the strongest association with unstimulated salivary secretion and xerostomia. These findings are in line with our previous study, which showed similar results regarding the effects of drugs with sedative properties and the total number of drugs³⁴. Because the adjustments for total number of drugs, antihypertensives, or sedative drugs caused only a slight attenuation of the relative risks, the effect of anticholinergic burden seems to appear to be independent of abovementioned factors.

Measurement of dry mouth

One of the strengths of the study was that both objective measure of salivary secretion and subjective measure of xerostomia were used as outcome variables. This approach is considered the most precise method of describing the dry mouth¹. There are many studies which have studied an association between drugs and xerostomia, but at the same time, there is lack of studies which have focused also on the association between drugs and salivary secretion¹².

Measurement of anticholinergic burden

The Anticholinergic Drug Scale (ADS) was used as a measure of anticholinergic burden and this enabled us to take into account the additive effect and variation in the anticholinergic potency. It adjusts the burden with the dosage of drugs and it has been proven to be a valid measure of anticholinergic burden among the older population, in both institutional⁸ and community settings³⁵. The ADS includes 117 drugs with known anticholinergic activity⁸, whereas the other scales and metrics (e.g., the Anticholinergic Risk Scale or the Anticholinergic Cognitive Burden Scale) include fewer drugs^{12,36}. Furthermore, the ADS covers 88 percent of the regularly used drugs in the study population¹⁶. Even though there is no standardized measurement of anticholinergic burden and discrepancies exist between the rating scales, the ADS has been proven to predict clinical outcomes with similar exactness as the other scales³⁷.

There was on average a six-month time interval between the collection of drug information and clinical oral examinations and this should be taken in to account when interpreting the results. Yet, it is not unreasonable to assume that the time interval had only a minor influence on the results because of its short duration and because medication for chronic diseases is relatively permanent³⁷. Another limitation related to drugs is the xerostomic effects, **un**related to anticholinergicity. The differentiating the main pathways of the xerostomic effect is difficult because the innervations of salivary glands are complex and it is not clearly known how concomitant use of multiple drugs effects on salivary glands at a receptor-level¹. On the other hand, it is known that the most common way drugs cause dry mouth is by their anticholinergic effect and many commonly used drugs have anticholinergic effect⁴, meaning that xerostomic effects, not related to anticholinergicity, have only a minor influence on the results. This notion is further supported by the fact that additional adjustments for the total number of drugs, antihypertensives or drugs with sedative properties did not influence on the results significantly.

Control of confounding

Potential confounding factors such as age, gender, education, diabetes and rheumatoid diseases (the two most common diseases in the study population known to be associated with hyposalivation or xerostomia), and FCI were controlled for in the analyses. Also xerostomic effects of other drugs were controlled for by making models where the total number of drugs, antihypertensives, and drugs with sedative properties were used as covariates. Despite the effort to control for confounding factors, the possibility of residual confounding factors cannot be totally excluded. For example, anxiety³⁹ and stress⁴⁰ have been shown to be associated with hyposalivation or xerostomia, but due to a lack of appropriate data, it was not possible to take these factors into account. Other factors associated with hyposalivation or xerostomia, such as depression, Parkinson's disease, HIV, Hepatitis C or radiotherapy of the head and neck region, were rare in these data.

Lastly, the original GeMS study was designed in such a way that the study population was homogeneous by ethnic background and place of residence. To increase the validity of this study, smokers and institutionalized participants were excluded. On the other hand, these exclusions decreased the size of the study population, which can be seen as a limitation.

Practical implications

In the older population, it is advisable to avoid prescribing excessively anticholinergic drugs because of the increased risk of severe adverse effects on both general health and oral health.

Patients with anticholinergic drugs should be offered guidance and information about proper oral hygiene and treatment of dry mouth; they should receive prophylaxis measures against oral diseases such as dental caries and oral candidosis; and they should have regular recalls for dental examinations.

Conclusion

A high anticholinergic burden was associated with low unstimulated salivary secretion and xerostomia.

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