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SHORT COMMUNICATION

Inhaled Corticosteroids and the Occurrence of Oral Candidiasis: A Prescription Sequence Symmetry Analysis

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Abstract
Objectives The primary aim of the study was to gain insight into the relative risk of clinically relevant oral candidiasis following inhaled corticosteroid (ICS) initiation over time. A secondary aim was to analyse the influence of patient characteristics and co-medication on the occurrence of this adverse effect.
Methods Drug prescription data from 1994 to 2011 were retrieved from the IADB.nl database. To study the influence of ICS use on occurrence of oral candidiasis, a prescription symmetry analysis was used, including patients using medication for oral candidiasis up to 1 year before or after ICS initiation. The relative risk was calculated by dividing the number of patients receiving medication for oral candidiasis after ICS initiation by the number of patients receiving the same medication before ICS initiation. Sub-analyses were conducted to compare the relative risks at several time points after ICS initiation and to account for therapy persistence by only including chronic users of ICS. A multivariate logistic regression model was used to identify predictive factors.
Results A total of 52,279 incident users of ICS therapy were identified, of which 1,081 received medication for oral candidiasis up to 1 year before or after ICS initiation. A total of 701 patients received medication for oral candidiasis after ICS initiation, while 361 received these medications in the reversed sequence, resulting in a sequence ratio (SR) of 1.94 (95 % CI 1.71–2.21). In the first 3 months after ICS initiation, the SR was 2.72 (95 % CI 2.19–3.38) and then decreased to 1.47 (95 % CI 1.11–1.95) 9–12 months after ICS initiation. Predictive factors were higher daily dose of ICS and concomitant use of oral corticosteroids.
Conclusions This study found a significant and clinically relevant increased number of patients receiving medication for oral candidiasis in the first year after therapy initiation with ICS. Relative risk is highest in the first 3 months, but remains increased up to at least 1 year after ICS initiation. This study stresses the need for patient education and inhalation instruction.

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1 Introduction

Inhaled corticosteroids (ICS) are widely prescribed as maintenance therapy for respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). ICS suppress inflammation in the lower airway tract, thereby reducing inflammation-driven airflow obstructions and improving disease outcomes. ICS cause fewer adverse effects than systemic-acting corticosteroids due to the local mode of action. Nonetheless, adverse effects still occur, mostly on a local level. The most common local adverse effects of ICS are oral candidiasis, dysphonia, pharyngitis and cough [1–3]. These adverse effects may decrease therapy adherence and quality of life [2, 4].

Oral candidiasis is thought to be a consequence of local immunosuppression at the oral mucosal surface by deposition of ICS particles in the higher respiratory airways [1, 4]. Importantly, the therapeutic efficacy of ICS is localized in the lower respiratory airways [5].

In healthy patients, oral candidiasis primarily leads to local discomfort such as altered taste sensation, but in immuno-compromised patients, the local infection may enter the bloodstream and develop into a potentially systemic life-threatening infection [6]. The main treatments for oral candidiasis are nystatin mouthwashes or miconazole oral gels [7]. Local administration of methylrosaniline and amphotericin B may be prescribed in patients showing insufficient response to nystatin and miconazole [8].

Various studies have been conducted assessing the association between ICS and the occurrence of oral candidiasis [9–12]. One review reported incidence rates between 0 and 70 %, based on four studies performed between 1974 and 1990 using different diagnostic criteria [2]. A recent meta-analysis reported an odds ratio of 3.6 for oral candidiasis in ICS users compared with placebo, regardless of dose or device [13]. This meta-analysis included 23 randomised controlled trials (RCTs) performed between 1994 and 2003, with an average follow-up of 12 weeks.

Although incidence and risk factors are well known, the relative risk during long-term ICS use has not previously been studied. Furthermore, data from actual clinical practice as opposed to clinical trials are scarce.

The primary aim of the present study was to gain insight into the relative risk of clinically relevant oral candidiasis following ICS initiation over time. The secondary aim was to analyse the influence of predictive factors such as patient characteristics and co-medication on the occurrence of this adverse effect. Results of this study will assist healthcare professionals in developing and providing tailored patient interventions and education.

2 Methods

2.1 Data Source

Drug dispensing data from Dutch community pharmacies were obtained from the IADB.nl database, which holds prescription records of over 500,000 individuals in The Netherlands. The IADB.nl prescription database has been validated for drug-utilization studies [14, 15] and has previously been used for such studies [16]. Dutch patients usually register at a single community pharmacy and therefore prescription records can provide an almost complete listing of the subjects' prescribed drugs [17]. Data in the database contain information on drug name, anatomical therapeutic chemical (ATC) classification, dispensing date, dosage and defined daily dose (DDD) as provided by the World Health Organization (WHO). Data between January 1994 and December 2011 were used for analyses.

2.2 Analysis and Outcomes

To study the influence of ICS use on occurrence of oral candidiasis, a prescription symmetry analysis was used. This method determines whether medication for oral candidiasis is prescribed more frequently following ICS initiation than the other way around. A recurrent problem of other types of analyses, such as case-control or cohort designs, is the inherent tendency of drugs to accumulate in certain patients, such as elderly or otherwise frail individuals. The prescription symmetry analysis corrects for these confounding factors, as long as they remain constant over time. The advantages and limitations of the method are discussed in more detail by Hallas [18]. The method has been used to study the occurrence of side effects for different drug classes [18–20]. The outcome of the prescription symmetry analysis is the sequence ratio (SR), calculated as the number of patients starting ICS first and medication for oral candidiasis second, divided by the number of individuals starting these medications in the reverse sequence. The SR was adjusted for incidence trends of the drugs, to account for potential increasing or decreasing prescription incidence over time [18].

The SR is an estimate of the relative risk of oral candidiasis in patients receiving ICS compared with patients not receiving ICS [18, 21]. By including only cases in which medication was prescribed, the study focused on clinically relevant oral candidiasis. The 95 % confidence interval was calculated as $e^{\ln(SR)\pm 1.96\times SE}$, in which SR is the sequence ratio and SE the standard error, estimated as $\sqrt{}$ ((1/patients starting ICS first) + (1/patients starting ICS second)).

2.3 Population

All incident users of both ICS and medication for oral candidiasis within a year timespan of each other were selected for analysis. Incidence was defined as a period of 2 years without use of the study drugs, while being present in the database. ICS included were beclomethasone, budesonide, fluticasone, ciclesonide and ICS combination inhalers with long-acting beta agonists. Medication for oral candidiasis were local oral formulations of nystatin, miconazole, methylrosaniline and amphotericin B.

2.4 Sub-Analyses

Sub-analyses were conducted to compare the relative risks at several time points after ICS initiation and to account for therapy persistence by only including chronic users of ICS. Chronic use was defined as having at least four follow-up prescriptions in the year after initial prescription. Furthermore, a sensitivity analysis was performed in which we

changed the period of no use ('wash-out') from 2 to 3 years.

2.5 Potential Effect Modifiers

A multivariate logistic regression model was used to identify predictive factors of the 'ICS followed by oral candidiasis' order compared with the reverse order, including low (≤10 years) or high (≥60 years) age, sex, year of ICS therapy initiation (per year), total daily dose of ICS (beclomethasone equivalent), type of inhaler (pressurized metered dose inhaler [pMDI], dry powder inhaler [DPI] or nebulizer) and co-medication with antibacterials and oral systemic corticosteroids 1 month prior to oral candidiasis. The influence of co-morbidities known to be associated with increased frequency of oral candidiasis, namely diabetes mellitus and HIV [22, 23], was also determined.

Note that the odds ratios (OR) calculated in the multivariate model are not risk factors for oral candidiasis but rather effect modifiers of the prescription order 'ICS followed by medication for oral candidiasis'.

Statistical analyses were performed using SPSS 18.0.3 (SPSS Inc. Chicago, IL, USA) and Microsoft® Excel 2010.

3 Results

A total of 52,279 incident users of ICS therapy were identified; 1,081 of these were incident users of medication for oral candidiasis within 1 year before or after ICS initiation. A total of 19 (1.8 %) patients started both therapies on the same day and were excluded from further analyses. In the remaining 1,062 patients, mean age at ICS initiation was 54.2 ± 20.7 years and 62.6 % were female. A total of 80 (7.5 %) were diabetes patients and none received HIV medication.

A total of 701 patients received medication for oral candidiasis after ICS initiation, while 361 received these medications in the reversed sequence, resulting in an SR of 701/361 = 1.94 (95 % CI 1.71–2.21). The results were not influenced by time trends in prescribing (correction factor = 0.999).

3.1 Sub-Analyses

The sub-analysis showed the number of prescriptions for oral candidiasis medication were highest in the first 3 months after ICS initiation, resulting in an SR of 2.72 (95 % CI 2.19–3.38). This decreased to 1.47 (95 % CI 1.11–1.95) in the 9–12 months after ICS initiation (Fig. 1).

A total of 387 patients were included when using the criterion for chronic exposure. Of these, 277 patients started ICS first and 107 started oral candidiasis medication first, resulting in an SR of 277/107 = 2.59 (95 % CI 2.07–3.24).

When the wash-out period was changed to 3 years, 954 patients were included and this yielded an SR of 629/309 = 2.04 (95 % CI 1.78–2.33).

3.2 Effect Modifiers

The results of the multivariate logistic regression analysis are shown in Table 1. There was a significantly increased OR for receiving oral candidiasis medication after ICS initiation when using a medium daily ICS dose or with concomitant use of oral corticosteroids. Using a high dose also increased the OR, although not significantly. Concomitant use of antibacterials or use of a pMDI significantly decreased the OR. Age, sex or year of ICS initiation and selected co-morbidities were not significant predictors.

4 Discussion

This study found a significant and clinically relevant increased number of patients receiving medication for oral candidiasis in the first year after therapy initiation with ICS. The relative risk was highest in the first 3 months of ICS use but remains increased up to at least 1 year after ICS initiation. In addition, higher dose of ICS and concomitant use of oral systemic corticosteroids were predictive factors that strengthen this relationship.

Use of pMDI or concomitant use of antibacterials were identified as negative predictive factors.

4.1 Comparison with Other Studies

The predictive factors for oral candidiasis medication following ICS initiation identified in our study were high ICS dose and use of oral systemic corticosteroids. These factors were also reported in previous studies [1, 2, 4, 11–13].

A meta-analysis of Rachelefsky et al. [13] reported a 3.6-fold greater risk for oral candidiasis following the first 12 weeks after ICS initiation, while we found an approximately twofold greater risk. This difference may be explained by the duration of follow-up in studies included in the meta-analysis, which was approximately 12 weeks, whereas our study covers a period of 12 months. Indeed, we noted an increased effect in the first 3 months after ICS initiation.

Notably, our study reported a decreased risk for oral candidiasis when using pMDI, while Rachelefsky et al. reported an increased risk. This may be explained by use of different ICS drugs, such as high prescription rates for fluticasone and low rates for mometasone.

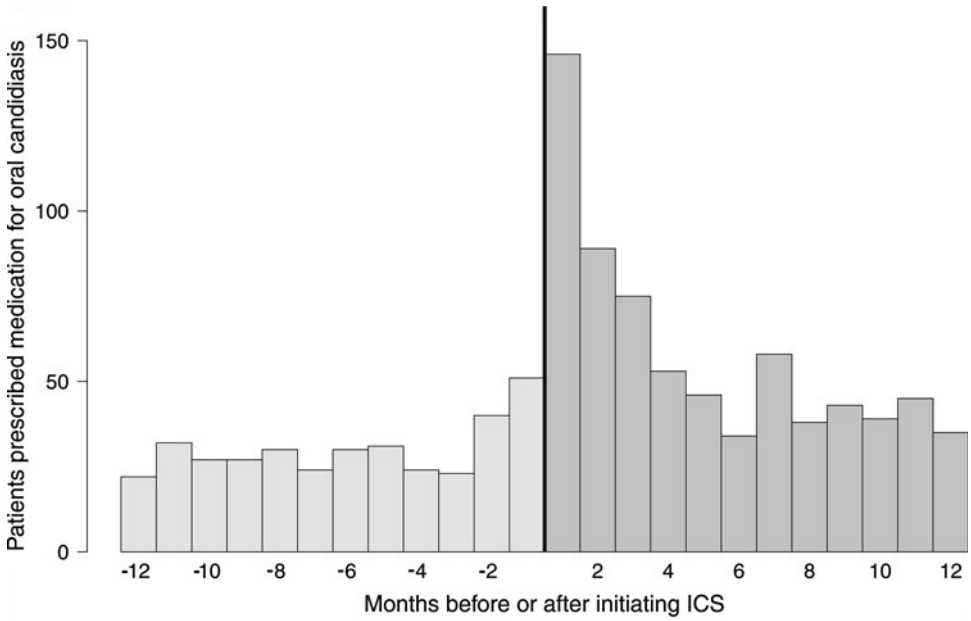

Fig. 1 Medication for oral candidiasis is prescribed more often following ($n = 701$) than before ($n = 361$) inhaled corticosteroid (ICS) initiation

Table 1 Variables predicting the prescription order 'inhaled corticosteroids followed by medication for oral candidiasis' compared with 'medication for oral candidiasis followed by inhaled corticosteroids' ($n = 1{,}062$)

Variable	Patients with variable [n (%)]	OR	95 % CI
Age			
Young age (≤10 years)	50 (4.7)	1.143	0.585–2.231
High age (≥60 years)	468 (44.1)	0.944	0.712–1.252
Age 11–59 years	544 (51.2)	Reference	
Female sex	665 (62.6)	0.892	0.678–1.176
Daily dose of ICS			
Low dose (≤400 μg)	286 (26.9)	Reference	
Medium dose (401–800 μg)	527 (49.6)	1.402*	1.012–1.942
High dose (>800 μg)	249 (23.4)	1.356	0.928–1.982
Type of inhaler			
pMDI	305 (28.7)	0.710*	0.522–0.964
DPI	747 (70.3)	Reference	
Nebulizer	10 (0.9)	0.497	0.135–1.832
Year of ICS initiation (per year)	–	0.974	0.941–1.008
Co-medication			
Antibacterials	386 (36.3)	0.579*	0.436–0.770
Oral corticosteroids	221 (20.8)	2.239*	1.552–3.229
HIV	0 (0)	NA	NA
Diabetes mellitus	80 (7.5)	0.897	0.546–1.474

CI confidence interval, *DPI* dry powder inhaler, *ICS* inhaled corticosteroid, *NA* not applicable, *OR* odds ratio, *pMDI* pressurized metered dose inhaler

* $p < 0.05$

4.2 Strengths and Limitations

By including patients with prescriptions for oral candidiasis medication, only clinically relevant oral candidiasis was included. We included only first time users of both ICS and medication for oral candidiasis, but we have to consider that the outcome of our study may be a contraindication for exposure to ICS. There may be a risk that a physician is less willing to prescribe ICS to a patient who is already suffering from oral candidiasis and consequently these patients will selectively be excluded from the proportion that is prescribed ICS after oral candidiasis. A limitation of the prescription database used in our study is that no indications are recorded. Thus, antifungal drugs may have been prescribed for other indications, such as intestinal candidiasis. On the other hand, clinically relevant oral candidiasis may have remained untreated or treated with other medications in some patients. However, these limitations are not expected to have an impact on the reported SR.

Incident ICS use was defined as having not been prescribed the drug for at least 2 years. It is possible that patients redeemed their ICS prescription before this period, thereby being incorrectly defined as incident users in our analysis. A sensitivity analysis was therefore performed in which the required period of non-use was 3 years; however, this did not influence the results.

The risk for oral candidiasis is highest in the first month after ICS initiation and decreases thereafter (Fig. 1). This may be due to the fact that patient inhalation technique improves. However, we cannot rule out the fact that patients discontinue their ICS after first prescription and are consequently no longer at risk. For some patients, continuous use of ICS may not be mandatory, but for some patients, especially those with asthma, ICS are essential therapy for disease control.

A separate analysis was therefore performed for patients with chronic ICS exposure. This analysis yielded slightly higher risk estimates. The interpretation of this result should take into account the lower patient number available for analysis because a large number of patients were excluded. If a patient initiates ICS and a violent oral candidiasis occurs shortly after, he or she might not redeem a second prescription and this might consequently bias the results.

Furthermore, it is recommended that further study on this topic should include the use of spacers as a variable in the regression analysis, because spacers have been shown to lower oropharyngeal deposition and this may reduce the occurrence of oral candidiasis [4]. Unfortunately, the use of spacers was not recorded in the prescription database used in these analyses.

4.3 Clinical Implications

Although oral candidiasis is a common adverse event of ICS, the occurrence in the general population over time has not been studied before. This information may assist healthcare professionals in developing tailored interventions to prevent oral candidiasis.

Oral candidiasis from ICS use is believed to be mainly caused by ICS deposition in the higher airways [1]. Proper inhalation techniques and use of spacer devices, as well as rinsing the mouth after ICS inhalation, are effective [24–26] in lowering oropharyngeal ICS deposition, and thereby may reduce the occurrence of oral candidiasis [4]. Unfortunately, patient education about inhaler devices and inhalation techniques is not always given and when given, instruction is often rushed, of poor quality or not reinforced [27, 28]. This is further complicated by suggestions that knowledge of correct inhalation techniques decreases quickly after use in clinical practice [29]. In children, between 30 % (using one inhaler) and 54 % (using multiple inhalers) of patients do not use their inhalation medication well enough to gain optimal benefit and minimize the chance of adverse effects [30].

Although the risk for oral candidiasis was highest in the first 3 months following ICS initiation, an increased number of patients are prescribed oral candidiasis medication after this period. The follow-up time of this study was limited to only 1 year after ICS initiation, but if the present trends are continued in longer follow-up periods, the number of patients receiving oral candidiasis medication will stay increased.

These results demonstrate not only the need for inhalation technique education at first prescription but also the need for long-term follow-up instructions or periodical inhalation checks, as suggested in earlier studies [31, 32].

Healthcare professionals in primary care, pharmacists and general practitioners, can improve patients' inhalation technique by providing proper inhalation instructions. Patient education in this respect may lead not only to clinical improvements but also to cost reductions [33].

5 Conclusions

This study found a significant and clinically relevant increased number of patients receiving medication for oral candidiasis in the first year after therapy initiation with ICS. Relative risk is highest in the first 3 months, but remains increased up to at least 1 year after ICS initiation. Mainly, this study stresses the need for patient education and inhalation instruction, especially in the first 3 months of ICS initiation but also in the long term. Pharmacists and general practitioners can improve patient care by providing these instructions in order to avoid this local adverse effect, thereby increasing therapy effectiveness and patients' quality of life and reducing waste of healthcare resources.

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