Improving care in paediatric asthma
Vries, Tjalling Wytse de
Chapter 2: Prevalences of eczema, allergic rhinitis and asthma in children in the years 1997-2006, a pharmacoepidemiologic study.

Tjalling W. de Vries, Paul B. van den Berg, Eric N. van Roon, Eric J. Duverman, Lolkje T.W. de Jong-van den Berg.

Submitted
Abstract

Introduction
Allergic diseases like eczema, allergic rhinitis, and asthma are ubiquitous and several epidemiological studies reveal high prevalences. We studied the prevalences based on pharmacy-dispensing drug data in a paediatric population, and looked at disease specific and concomitant prevalences.

Methods
We studied the prescription rates of medications used for eczema, allergic rhinitis, and asthma individually and concomitant over a 10-years period in a large population in the Netherlands. Children who had at least two prescriptions for an ointment containing steroids were considered to have eczema, those who had received at least two prescriptions for a nasal corticosteroid were considered as having allergic rhinitis. A child was considered to be asthmatic when it had received more than one prescription for an inhaled corticosteroid.

Results
Although 20% of all children received one prescription for a medication used for any allergic disease in 2006, only 2.3% was found to have eczema according to the cited criteria, 0.9% had allergic rhinitis and the prevalence of asthma was 2.5%. There were no significant differences with these prevalences in the 10 years before. Five percent of all children had more than one prescription for any steroid, and 0.5% used a combination of steroid formulations.

Conclusions
One in five children receives at least one prescription for any anti allergic medication, and one in ten receives more than one prescription. The prevalences of eczema, allergic rhinitis, and asthma in this pharmacoepidemiologic study are lower compared to questionnaire based studies. Only a relatively small proportion of children with ICS received a prescription for a nasal steroid. The combination of having asthma and allergic rhinitis is lower than expected. About 0.5% of the children uses different applications of topical steroids and is therefore at potentially greater risk of adverse effects due to steroids.
Introduction

Asthma and other allergic diseases are ubiquitous. Several epidemiological studies have demonstrated the presence of these diseases in western and in non-western countries. The work of the International Study of Asthma and Allergies in Children (ISAAC) showed that the incidence of asthma varies from 2% in Indonesia to 32% in the United Kingdom.1 There has been a rise in the incidence of asthma in western countries, but recently it has been shown that this rise has come to an end.2,3,4 Most studies report the prevalence of asthma and other allergic diseases separately. Allergic diseases, however, often go together, partially as a result of common pathogenesis. Therefore, not only insight in the prevalence of the individual allergic diseases is necessary but also in the prevalence of concomitant diseases.

Prescription rates for medications, used for asthma and other allergic diseases, may give information on individual prevalences, but also on the prevalences of concomitant diseases. This is also of interest because the use of different corticosteroid applications by the same individual carries a potentially greater risk of side effects due to cumulative use.

We studied the prevalences of prescription rates for medications used in the treatment of eczema, allergic rhinitis, and asthma over a 10-years-period. The primary aim was to relate medication prescription rates to the outcomes of questionnaire based studies. The secondary aim was to study the prevalence of combinations of anti-allergic therapies.

Methods

This study was performed with data from the InterAction database (IADB.nl), a prescription database containing pharmacy-dispensing data from 55 pharmacies in the Northern and Eastern part of the Netherlands.5 The IADB.nl includes all prescriptions, regardless of prescribing physician, insurance or reimbursement status, apart from over-the-counter (OTC) drugs and drugs dispensed during hospitalization. In the Netherlands, people commonly register with only one pharmacy and obtain all their medication from that pharmacy. Therefore a complete medication history of an individual is available in the pharmacy dispensing records.

The medications we looked for are summarized in table 1 and include systemic drugs used for allergy, and for asthma, allergic rhinitis, and eczema apart. Individuals aged 0 to 19 years who received between 1997 and 2006 at least one prescription for one of these medications were studied. The total population, covered by the pharmacies, was estimated on the national registry (Central Bureau of Statistics). The number of children who had any prescription of a drug of interest was counted and
the prevalences in each year were computed. We considered a child as having eczema when it had at least two prescriptions of an ointment containing steroids per year. Because some pharmacies make the ointments themselves, we also included steroids when given as base material as ‘ointment containing steroids’. A child having at least two prescriptions of nasal steroids was considered as having allergic rhinitis, and when a child had had two or more prescriptions for an inhaled corticosteroid (ICS), it was considered as having asthma. We use the word eczema as recommended by the World Allergy Organisation,6 hay fever is considered as a synonym for allergic rhinitis.

Statistical methods.

This is an observational study. Outcomes are reported as mean and standard deviations or percentages. Student t-test is used for intergroup comparison of percentages, and p-value < 0.05 is considered statistically significant.

### Results

During the study period, the database covered a population of approximately 500,000 people, 120,000 of them in the age of 0 – 19 years. The size of this population increased during the study period but there were no changes in age and gender distribution (table 2). In 1997 20,216 of 95,158 children aged 0 – 19 (21.2%) received at least one prescription for any medication for an allergic disease, summed up in table 1; this prevalence decreased to 18.6% in 2006 (22,987 out of 123,453 individuals); this decrease is statistically significant.

In the youngest age group (0 – 4 yrs of age) more boys than girls received a prescription for one of these medications, at the age of 10 – 14 years the number of prescriptions in boys and girls were equal, and in the older group girls had more prescriptions. The ratio boys-girls declined from 1.24 for in the youngest age group to 0.72 in the oldest group. The prevalence of children who had at least two prescriptions for any drug for an allergic disease was 10.3% in 1997; and 9.2% in 2006.
Eczema

In 2006, 2.3% of all children had had more than one prescription for an ointment containing steroids (table 3). Although about 10.8% of the children from 0 – 4 years of age received one prescription for a dermatological ointment containing steroids in both 1997 and 2006, and 3.7% of the children had at least two prescriptions in 1997 and 3.2% in 2006 (figure 1). This pattern is seen in all age groups. In 1997, the rate of children who had at least two prescriptions declined from 3.7% in the youngest age group to 1.7 at the age of 10 – 14 yrs and increased again to 2.7% in the older age group. This pattern is also seen in 2006. There were no differences in prevalence over time. In the youngest group boys had more eczema, in the older group girls had more. Only a few group of children received a prescription for a calcineurin inhibitor. (data not shown).

Table 2 Baseline demographic data of the children included in 1997 and 2006.

<table>
<thead>
<tr>
<th></th>
<th>1997</th>
<th>2006</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number (0 – 19 yrs)</td>
<td>95,158 (100)</td>
<td>123,453 (100)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48,168 (50.6)</td>
<td>61,719 (50.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Distribution in age groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4 yrs</td>
<td>22,694 (24)</td>
<td>30,608 (25)</td>
<td>n.s.</td>
</tr>
<tr>
<td>5-9 yrs</td>
<td>23,441 (25)</td>
<td>29,275 (24)</td>
<td></td>
</tr>
<tr>
<td>10-14 yrs</td>
<td>23,633 (25)</td>
<td>29,227 (24)</td>
<td></td>
</tr>
<tr>
<td>15-19 yrs</td>
<td>25,390 (26)</td>
<td>34,343 (27)</td>
<td></td>
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Figure 1: Prevalence of children (0 – 4 yrs of age) who had at least one prescription and at least two prescriptions for an ointment containing steroids during the study period.
**Allergic rhinitis**

Intranasal steroids were prescribed for 0.8% of the children in 1997 and for 0.9% of the children in 2006. The prescription rate increased with age, from 0.1% in the youngest age group to 1.4 in the oldest children. The prescription rate did not change in the study period (table 3). Girls had more often at least two prescriptions for nasal steroids, the ratio boys-girls was 0.88 (data not shown).

| Table 3 Comparison between 1997 and 2006 for the numbers and proportions of children in 4 age groups with asthma, allergic rhinitis, and eczema. A child was defined as having asthma when having received at least two prescriptions for inhaled corticosteroids. When a child received at least two prescriptions for a nasal steroid, it was presumed to have allergic rhinitis. A child, who had at least two prescriptions for an ointment containing steroids, was presumed to have eczema. |
|---|---|---|
| | 1997 | 2006 |
| | n (%) | n (%) | p-value |
| all children | 95,158 | 123,453 | |
| **Eczema** | | | |
| 0-4 yrs | 838 (3.7) | 1,004 (3.3) | 0.01 |
| 5-9 yrs | 432 (1.8) | 585 (2.0) | n.s. |
| 10-14 yrs | 412 (1.7) | 467 (1.6) | n.s. |
| 15-19 yrs | 678 (2.7) | 796 (2.3) | 0.01 |
| All age groups | 2,360 (2.5) | 2,852 (2.3) | 0.01 |
| **Allergic rhinitis** | | | |
| 0-4 yrs | 19 (0.1) | 27 (0.1) | n.s. |
| 5-9 yrs | 160 (0.7) | 250 (0.9) | 0.03 |
| 10-14 yrs | 261 (1.1) | 349 (1.2) | n.s. |
| 15-19 yrs | 318 (1.3) | 498 (1.5) | 0.04 |
| All age groups | 758 (0.8) | 1,124 (0.9) | 0.04 |
| **Asthma** | | | |
| 0-4 yrs | 596 (2.6) | 751 (2.5) | n.s. |
| 5-9 yrs | 830 (3.5) | 930 (3.2) | 0.02 |
| 10-14 yrs | 492 (2.1) | 786 (2.7) | <0.01 |
| 15-19 yrs | 293 (1.2) | 572 (1.7) | <0.01 |
| All age groups | 2,211 (2.3) | 3,039 (2.5) | 0.04 |

**Asthma**

At least two prescriptions for ICS were prescribed for 2.5% of the children (0-19) in 2006; which is not significantly more than in 1997. In 1997 4.7% of the children in the age of 0 to 4 years of age received at least one prescription for an ICS, this prevalence rose to 6.7% in 2001 and then declined to 4.7% in 2006. However, the percentage of children (0-4) who received more than two prescriptions for an ICS was 2.6% in 1997 and 2.5% in 2006; this difference is not statistically significant (figure 2). The same
pattern is seen in other age groups. Overall, boys received more ICS prescriptions than girls, the ratio boys-girls was 1.4. The group of 5-9 year old children had the highest prescription rate (3.4%), the lowest rate was found in the oldest group (15-19) (1.4%). In all age groups, the mean usage prevalence of long acting betamimetics was 0.3%, and increased from 0.2% to 0.9% in 2006 (data not shown).

Concomitant diseases

Of all children studied, 0.1% received a combination of at least two prescriptions for both allergic rhinitis medications and ICS. In the children aged 5 – 9 and 10 – 14 the percentage was the highest (0.3%), and in the youngest children the percentage was zero. There was no significant time trend. The highest prescription rate for the combination was found in boys in the age group of 10 – 14 yrs (0.5%). In the children with asthma, the percentage of those with at least two prescriptions for intranasal steroids rose from 0% in the youngest age group to 14% in the oldest group. This means that in 14% of the oldest children with asthma, also medications for allergic rhinitis are prescribed.

When looking at the group of children with at least two prescriptions for an intranasal steroid, none of the children in the youngest group received a prescription for ICS, but the number rose to 38% in children of 5-9 yrs, than decreased again to 27% in the 10 – 14 year olds, and declined further to 14% in the individuals older than 15 yrs.

Figure 3 shows the prevalences of children who received at least two prescriptions for ICS, nasal steroids, and steroid ointments alone and in combination in 2006. Taken together, 6379 children (5.2%) received two prescriptions for at least two steroid medications and 636 children (0.5%) received any combination of at least two steroid-containing medications in 2006 (figure 3).
About 20% of the children had received at least one prescription for a medication for any allergic disease per year; 10% had had at least two prescriptions. The prevalence of eczema was 2.3%, of hay fever 0.9% and of asthma 2.5% in 2006; although the differences are statistically significant, in practice they are unchanged. A combination of at least two steroid containing medications was given to 0.5% of the children; half of these were ICS and nasal steroids.

**Eczema**

The prevalence of eczema, defined in this study as having at least two prescriptions for an ointment containing steroids, was only 2.3% (C.I. 2.2 – 2.4%). This figure is much lower than in other studies. In an Italian study the prevalence of doctor-diagnosed eczema was 5.8% (C.I. 4.5 – 7.1%) in 9 year old children. The prevalence in 7-year-old children was 15.5% (C.I. 14.2-17%), based on questionnaires in a Scandinavian study. In a Dutch survey of 2003, in which eczema was defined as an itchy rash, the prevalence in 12 – 14 year olds was 13.5%. The prevalence of eczema in phase III of the ISAAC in the Western Countries ranged from 5.9 to 16% in 7 and 8 year old children. ISAAC showed an increase of 0.05 to 0.6% per year.

In the present study, the prevalence of eczema was 2.3% and did not increase over time. This figure is lower than in several other reports. Partially, this could be due to our definition. Topical steroids, however, are presented as the treatment of choice. The number of prescriptions for calcineurin inhibitors was almost zero; so there is no reason to expect that these replaced steroids. Although it may
be possible that parents do not use topical steroids despite doctor’s advice and despite the severity of the eczema, which lowers the numbers we have found, we think that the prevalence we found reflects more accurately the number of children with more serious eczema.

**Allergic rhinitis**

According to the ISAAC study the prevalence of allergic rhinitis varies from 5.8% to 10.1% in 6 and 7 year old children and from 9.7 – 20.2% in 13 and 14 year old children. In some countries the yearly prevalence increased, in other countries a decrease was found. In the Dutch questionnaire-based study in adolescents, a prevalence of allergic rhinitis of 28.3% was found. The prevalence in Danish adolescents was 15.7%.

Nasal steroids are recommended as treatment in severe intermittent and in mild and severe persistent allergic rhinitis; they are effective, are relatively easy to use, and have mild side effects. In this study, the mean prevalence of children who had two or more prescriptions for a nasal steroid was 0.9% (C.I. 0.7 – 1.1%) with no increase during the ten year period we studied. In the 6 and 7 year old children the prevalence was 0.8% and in the group with 13 and 14 year old children the prevalence was 1.1%.

This number is far lower than in the ISAAC and other studies. Moreover, there were no significant changes over the years. The differences between the prevalences, reported in the literature and our results could be explained in several ways. First allergic rhinitis is difficult to diagnose and to differentiate it from a common cold is even more difficult for patients. In children under the age of 6 years, the nasal application of steroids is problematic; it could be that in these age groups systemic anti-allergic medication is prescribed. However, in the older age groups, the difference between the prevalences of ISAAC and ours is large. It could be that hay fever is not recognized properly by patients or doctors, and is therefore not treated sufficiently or by OTC medication. On the other hand, allergic rhinitis could be overreported in questionnaires.

**Asthma**

The ISAAC studied the prevalence of asthma using questionnaires. In the 6 and 7 years old children, the asthma prevalence varied from 7.4 to 20.9%. For children of 13 or 14 years old, the lowest prevalence in phase three was 8.3%, the highest was 31.2%. In Danish adolescents a prevalence of allergic asthma of 6.9% was reported, and the Dutch questionnaire study revealed a prevalence of 12.3% in 12 to 14 year old children.
In this study the prevalence of asthma was 2.5% (C.I. 2.4 – 2.6%), and no differences over time were found. This is different from other epidemiological studies in which higher prevalences are described. An Australian study found a prevalence of asthma in children aged 5 year of 11 to 15%, of whom 35% used ICS (3.9 – 5.3% of all children). This figure is comparable with ours. The difference between the prevalences found by questionnaires and those, found in this study, can be that we looked only at the more serious symptoms. Although from an epidemiological point of view it is interesting to know how many children are symptomatic, from a clinical point of view it is also necessary to know for which proportion of children the burden of disease is serious enough to take medication chronically. These children are at risk for more perturbation of their daily life by symptoms of their disease. Therefore, it would be interesting to compare the ISAAC data with prescription data in the same region. However, there is no Dutch branch of the ISAAC study.

Concomitant diseases

Hay fever and asthma often go together, and the combination has led to the concept of the ‘united airways’. Epidemiological studies reveal a prevalence of allergic rhinitis of 70% in asthmatics. In this study, the number of children with the asthma-hay fever-combination is much lower. Although it can be explained because the combination of both diseases occurs after years, it could also be that one of the diagnoses is missed.

Topical steroids are the mainstay of treatment in asthma, allergic rhinitis, and eczema. The safety of these treatments individually has been studied intensively and in normal use the risk for side effects is considered low. However, exposure to high doses of ICS carries increased potential risks for side effects such as influence of growth and subclinical adrenal insufficiency. Children who use combinations of steroids are at greater risk. As far as we know, systematic studies to the adverse effect of combinations of steroid therapy are lacking. In this study, 0.5% of the children use these combinations. In this study we looked for children receiving more than one prescription as a result of an allergic disease including asthma. The prevalence of children is lower than expected from earlier epidemiological studies. One explanation may be that the threshold for obtaining a prescription is relatively higher than that for giving an answer on a questionnaire. This was also seen in the Australian study of children at school-entry in which the prevalence numbers of ICS are comparable with ours.
Limitations:
As in every study using prescription data, no diagnoses are included. However, the medications used
for allergic diseases are highly specific, and by using the prescription of at least two medications,
the children who had only one prescription, prescribed to evaluate if it would help, are excluded. Of
course it may be possible that data are missing because of insufficient input. However, the co-operating
pharmacists are very motivated and there is a regular quality control by the database manager.
Another possible confounder is the use of OTC medication. However, for the more severe forms of the
diseases studied, steroids are necessary and these are only available with a doctors' prescription in the
Netherlands.

Strong points.
This is a population based study and therefore gives more insight than hospital or primary care setting
study. Advantages of the use of questionnaires are that a large number of individuals can be
included and that standardized questions make comparison possible. Disadvantages of questionnaires
are recall bias, especially when time frames such as ‘the last 12 months’ are included, misinterpre-
tation of the questions, and incomplete response. A population and prescription based study gives insight into a large group of patients in whom the disease had lead to a doctor’s visit and a prescription.

Conclusion
One in five children receives at least one prescription for any anti allergic medication, and one in ten
receives more than one prescription. Although the prevalence of allergic diseases has been reported
to be high, this study indicates that the prevalences of chronic and therefore more debilitating forms
of allergic diseases as eczema, allergic rhinitis and asthma are lower.
Only a relatively small proportion of children with ICS received a prescription for a nasal steroid. The
combination of asthma and allergic rhinitis is lower than expected, suggesting that parents and
physicians do not easily recognize the combination. About 0.5% of the children uses different applica-
tions of topical steroids and are therefore at potentially greater risk of adverse effects of steroids.

We thank dr. J. Collins for reviewing the English and K. Koster for the art work.
References

Mark

Mark is 10 years of age and had been diagnosed with asthma at the age of 2 years. Since two years he has been treated with budesonide, 200 microgram twice daily in a Turbuhaler®. Because of increasing frequency of periods with shortness of breath, salmeterol with the help of a Diskus® was added twice daily. Salbutamol in a Diskus® could be used as rescue medication, since the age of 8, in the preceding years he used a pressurised metered dose inhaler.

In recent months he experienced more periods of breathlessness, despite increasing use of medication. His complaints increased when exposed to house dust, cigarette smoke, and on exercise. He had no pets, in his house no-one smoked. There were no symptoms of hay fever.

Inhalation of salbutamol did not relieve his complaints.

Spirometry showed bronchusobstruction and a skin prick test revealed allergy for house dust mite. He was asked to demonstrate his inhalation manoeuvres for both apparatuses. He did not exhale before inhalations and turned the knob of the Turbuhaler only after being asked to do so. Then he inhaled shallowly and too fast.

We advised him to choose one inhaler and the asthma nurse gave instruction on the correct inhalation technique. After a couple of weeks he had only minor complaints and remained so, after prescribing budesonide 200 mcg in combination with formoterol 6 mcg via the Turbuhaler® twice daily and when needed.