

Tjalling W. de Vries · Hilde Tobí · Eric Schirm ·
Paul van den Berg · Eric J. Duiverman ·
Lolkje T. W. de Jong-van den Berg

The gap between evidence-based medicine and daily practice in the management of paediatric asthma. A pharmacy-based population study from The Netherlands

Received: 12 October 2005 / Accepted: 9 November 2005 / Published online: 20 December 2005
© Springer-Verlag 2005

Abstract *Objective:* We evaluated the adherence to national guidelines for the treatment of asthma in childhood. *Methods:* Prescriptions for anti-asthma medication for children (0–14 years of age) were retrieved from the InterAction DataBase (IABD) for the year 2002. These were compared with recommendations found in national guidelines. *Results:* Anti-asthma medication was prescribed for 3,612 children (5%) of the paediatric population. Inhaled medication was prescribed for 3,554 (98%) children. In 1,940 of 1,993 (97%) of the children under the age of 6 years pressurised metered dose inhalers (pMDIs) were given. Short-acting β_2 -agonists had not been prescribed in the previous 2-year period in 559 children (15%), 543 children older than 8 years (36%) did not receive a prescription for a dry powder inhalator and 239 children (7%) had more than one type of inhalator. Long-acting β_2 -agonists were prescribed in 396 children, but without concomitant inhaled corticosteroids (ICS) in 35 children (9%). *Conclusions:* Inhalation therapy as the method

of choice in asthma therapy and the use of pMDI in preschool children are widely accepted in the Netherlands. Not all children have been prescribed bronchodilators. Some children have more than one type of inhaler device and others use long-acting β_2 -agonists not in combination with ICS. Although national and international guidelines about the treatment of asthma in children offer evidence-based advice, important principles are not followed. Effective interventions aimed at implementing existing guidelines into daily practice are urgently needed.

Keywords Asthma · Adherence · Pharmacy · Guidelines

Abbreviations IABD: InterAction DataBase · pMDI: Pressurised metered dose inhalator · DPI: Dry powder inhalator · SABA: Short-acting β_2 -agonist · LABA: Long-acting β_2 -agonist · OTC: Over-the-counter · LTRA: Leucotriene receptor antagonist · ATC: Anatomical Therapeutic Chemical classification of drugs

T. W. de Vries (✉)
Department of Paediatrics, Medical Centre Leeuwarden,
P.O. Box 888, 8901 BR Leeuwarden, The Netherlands
e-mail: tjalling.de.vries@znb.nl
Tel.: +31-58-2863385
Fax: +31-58-2863390

H. Tobí · E. Schirm · P. van den Berg ·
L. T. W. de Jong-van den Berg
Department of Social Pharmacy, Pharmacoepidemiology and
Pharmacotherapy, Groningen University Institute for Drug
Exploration (GUIDE),
Ant. Deusinglaan 1,
9713 AV Groningen, The Netherlands

E. J. Duiverman
Paediatric Pulmonology, Beatrix Children Hospital,
University Hospital Groningen,
P.O. Box 30.001, 9700 RB Groningen, The Netherlands

Introduction

In recent years several guidelines concerning the use of drugs in children with asthma or asthma-like symptoms have been published [2, 3, 11, 13]. These guidelines were developed to help the physician to improve the care for children with asthma. Whether physicians used these guidelines ('adherence') has been the subject of several studies. However, these studies concern adherence of paediatricians [7, 12, 22], focus on the use of inhaler devices [8], or study a relatively small number of children [9].

Studies regarding adherence to these recommendations in a general population are lacking. Insight therein is important to identify the most common and serious deviations so that it is possible to develop strategies to improve adherence.

Therefore, we studied the prescription of anti-asthmatic drugs in a Dutch paediatric population and compared this with the recommendations found in the Dutch guidelines.

Table 1 Principles in medical asthma treatment according to the Dutch guidelines

- 1 Every child with asthma should use at least one inhaled medication
- 2 Every child should have been prescribed a short-acting β 2-agonist in the preceding 2 years
- 3 Every child with a long-acting β 2-agonist should have inhaled corticosteroids as well
- 4 Every child should have to use only one type of inhalation device. The only exception to this is when a child uses a pMDI with a short-acting β 2-agonist
- 5 Children <6 years should have a pressurised metered dose inhaler pMDI and spacer^a
- 6 Children >8 years should have a dry powder inhalator (DPI)^a
- 7 Pressurised metered dose inhalers (pMDIs) should always be used in combination with a spacer, or it should be an Autohaler

^aFor the study of the use of inhalation devices, children between the age of 6 and 8 years were excluded because in those ages children change from pMDI with spacer to a dry powder inhalator

Methods

In the Netherlands people commonly register with one pharmacy and obtain all their medication from that pharmacy, so a complete medication history of each patient is available in the pharmacy database. Previous studies have demonstrated that dispensing data from Dutch pharmacies offer an accurate survey of the use of prescription drugs [14, 16, 18]. Outpatient medication is supplied by community pharmacies regardless of prescriber and thus included in the dispensing data, but drugs used during hospital stay (inpatients) and over-the-counter medication (OTC) are not included. This study was performed with pharmacy dispensing data from the InterAction DataBase (IADB). The IADB comprises all prescriptions of approximately 450,000 people since 1997, regardless of insurance of patients or reimbursement status of the drug [26]. Forty-five pharmacies supplied dispensing data and prescriptions of at least 200 physicians are included. It was recently estimated that more than 99% of the entered prescriptions were collected [27]. Population sizes were estimated on the basis of age-specific population statistics (Statistics Netherlands) using a stratified standardisation described elsewhere [21].

Table 1 depicts principles as found in the Dutch guidelines. National as well as international guidelines emphasise the preference for inhaled medications [2, 11]. Every child with asthma should have a short-acting bronchodilator (SABA) for direct relief [11]. Long-acting broncho-

dilators (LABA) should be prescribed only in combination with inhaled corticosteroids (ICS) [11, 30]. For convenience and ease, only one type of inhaler should be prescribed [31]. In children younger than the age of 7 years, pressurised metered dose inhalators (pMDIs) with spacer devices are advised [2, 11, 13]. Different from international guidelines, in the Netherlands prescription of dry powder inhalers (DPI) to children older than the age of 7 years is recommended [13]. Finally, whenever a pMDI is used, even in older children, it should always be used in combination with a spacer device. The only exception to this rule is the Autohaler. In this pMDI the actuation is dependent on inspiratory flow. The guidelines were published in the national medical journal and in the journal of the Dutch College of General Practitioners [10, 13]. After publication numerous seminars and symposia in which the guidelines were explained and discussed were organised.

Medications were defined according to the Anatomical Therapeutic Chemical (ATC) classification [4]. Asthma medication was defined as short- (SABA) and long-acting bronchodilators (LABA), including long-acting bronchodilators combined with inhaled steroids (ATC code R03A), inhaled corticosteroids (R03B), adrenergics for systemic use (R03C), leucotriene receptor antagonists (LTRA) (R03D), and two oral antihistaminics [depropine (R06AX16) and ketotifen (R06AX17)]. Ketotifen and depropine are drugs that were traditionally used in the Netherlands for the treatment of young children with asthmatic symptoms.

Table 2 Asthma medication and inhalation devices, used in the Dutch paediatric population during the study period [4]

Medications	ATC code
Short-acting bronchodilators: salbutamol, terbutaline, fenoterol	R03A
Long-acting bronchodilators: salmeterol, formoterol	R03A
Inhaled steroids: beclomethasone, budesonide, fluticasone	R03B
Other inhaled drugs: ipratropium bromide,	R03B
Cromoglicic acid, nedocromil	R03B
Adrenergics for systemic use: salbutamol, terbutaline	R03C
Leucotriene receptor antagonist: montelukast	R03D
Antihistamines for systemic use: depropine, ketotifen	R06AX16/17
Inhalation devices	
Pressurised metered dose inhaler single: Autohaler	
Pressurised metered dose inhaler in combination with spacers	
Spacer devices: Babyhaler, Volumatic, Nebuhaler, Aerochamber, and Babychamber	
Dry powder inhalers: Diskus, Diskhaler, Turbuhaler, Cyclocaps	

Table 3 Prescription of asthma medication compared with evidence-based principles. *CI* confidence interval

Principle	Children (<i>n</i>)	Nonadherence	
		<i>n</i>	% (CI)
1 Inhaled medication for all	3,612	58	1.6 (1.2–2.1)
2 β 2-agonists for all	3,612	559	15.5 (14.3–16.7)
3 LABA combined with ICS	396	35	8.8 (6.4–12.0)
4 Only one type of inhaler ^a	3,217	239	7.4 (6.6–8.4)
5 pMDI for children <6 years	1,993	53	2.7 (2.0–3.5)
6 DPI for children >8 years	1,525	543	35.6 (33.2–38.0)
7 pMDI prescribed in combination use with a spacer ^b	2,761	978	35.4 (33.7–37.2)

^aExcept for β 2-agonists

^bExcept for Autohaler

Table 2 depicts the asthma medication and inhaler devices available in the Netherlands in 2002. These were available for all patients, regardless of their reimbursement.

For this study, all children aged 0–14 years on 31 December 2001 were identified and selected from the database. For every child included in the study a medication history from 1 January to 31 December 2002 was constructed. We included only children for whom we knew for sure that we had information during the study period. When a child had been prescribed any asthma medication in 2002, the complete history of anti-asthma medications of the previous 2 years prior to the first prescription date in 2002 was retrieved. This was done because all inhaled medication expires 2 years after dispensation. In children younger than the age of 2 years, the medication prescribed since birth was retrieved. For the evaluation of the number of inhalers prescribed we excluded children with a DPI who also had pMDI with a spacer device for inhalation of a reliever, such as salbutamol, because some children prefer the use of these during attacks.

For the study of inhalation devices, children between the age of 6 and 8 years were excluded because in those ages children change from pMDI with spacer to a dry powder inhalator. The 95% confidence intervals were calculated using the Wilson method as recommended elsewhere [1].

Results

In 2002 about 450,000 patients were covered by the database; of these 73,416 were 14 years of age or younger. In this age group 3,612 children (4.9%) had been prescribed anti-asthma medication. These prevalences were compared with data of the national Drug Information Project and no statistically or clinically significant differences were found (data not shown). Table 3 summarises the results of the comparison between actual daily practice and principles in medical asthma treatment.

The vast majority of these children (3,554; 98%) received prescriptions for inhaled medications. In 559 children (15%) no SABA was prescribed during the observation period of 2 years. In 498 of these 559 children (89%) ICS had been prescribed in 2002. In the total group of 3,612 children on asthma medication, 396 (11%) had been prescribed LABA, while 35 (9%) of them had not received a prescription for an

inhaled corticosteroid as well. After exclusion of the children who had been prescribed a pMDI containing SABA, it appeared that 239 of 3,217 children (7%) had been prescribed more than one type of inhalation device.

Of the 1,993 children younger than 6 years 53 (3%) had been prescribed a dry powder inhaler, the youngest child was only 2 years old. Of the 1,525 children older than 8 years 982 (64%) had been prescribed a dry powder inhalator (DPI), the remaining 36% had a pMDI.

Spacers had been provided to 1,783 of the 2,761 children (64.6%) who had been prescribed a pMDI. Thus, the remaining 978 children (35.4%) had a pMDI without a spacer or had a spacer older than 2 years.

Overall, when the recommendations except the prescription of spacer devices are applied, it appeared that of the 3,612 children on asthma medication 2,352 (65.1%) children were prescribed medication according to the recommendations.

Discussion

Although we did not expect a 100% adherence to all guidelines, we found that in one-third of the children who received asthma medication basic recommendations were not followed. It is striking that 4.9% of the children in this population received a prescription for asthma medication and 15% of these children did not receive a prescription for bronchodilators. Nine percent of the children who had been prescribed a LABA did not have any ICS and 7% received prescriptions for more than one type of inhalation device.

This study has some limitations. The diagnosis of asthma was not formally confirmed and therefore it could be that some children received asthma medication for other indications. However, in the Netherlands only doctors prescribe asthma medication. Because we looked at dispensing data, we have no insight into actual use of asthma medication. Finally, as a result of the method, we have no information about the prescribing physician.

The strong points of this study are that it provides detailed information in a relatively large group of patients in a country where general physicians and paediatricians have easy access to specific guidelines. Inevitably, some of the recommendations in the Dutch guidelines differ from those in other countries, e.g. the use of DPI in children

older than the age of 8 years. However, for an evaluation of adherence to guidelines this is not problematic.

Five percent of the children in this total population had received a prescription for asthma medication. This percentage is comparable with results of a German study in which the prevalence of asthma drug usage was 4.8% in 9- to 11-year-old children [6], but is lower than in a recent British survey in which 20% of 9-year-old children used asthma medication [19]. The prevalence of children with anti-asthmatic medication is lower than the reported prevalence of asthma and/or recurrent wheezing in Western countries, which varies between 10 and 20% [17, 25]. The size of the paediatric population was estimated, and although this estimation may be slightly off, it by no means explains the low prevalence we have found. All available asthma medication in the Netherlands was included in this study. Possible explanations for the low figure include underdiagnosis of asthma, undertreatment of diagnosed asthma, and the choice of alternative or non-pharmacological asthma treatments or overestimation of asthma prevalence in epidemiological studies. Alternatively, it could be that the prevalence of asthma is declining, as was suggested recently by Van Schayck [28]. The preferential use of inhaled medication appears to be adopted by Dutch physicians as 98% of the children received inhaled medications. Because children younger than the age of 5 cannot generate sufficient inspiratory flow to achieve optimal deposition while using a DPI [20], it is reassuring that 97% of the children under the age of 6 received prescriptions for a pMDI.

Several deviations from guidelines were found. Fifteen percent of the children had not been prescribed a reliever in the preceding 2 years, whilst in 89% of these children ICS were prescribed. Although it has been suggested to give a course of ICS in periodical viral wheeze in young infants [5], this was not recommended formally in 2002, nor common practice in the Netherlands. Dispensation of drugs by hospital pharmacies is not customary in the Netherlands, due to budgetary reasons, and therefore cannot be an explanation. The fact that 15% of the children do not have a reliever may implicate that in these patients asthma is completely under control with the use of ICS and that relievers are not or rarely needed. Current guidelines advise the tapering of inhaled steroids to the minimum effective dose or even to discontinue them [11]. Apparently, some children continue to use ICS despite minimal disease.

LABA are advised only in combination with ICS because they can mask ongoing symptoms and do not treat the underlying inflammation in asthma [30]. In this study it appeared that despite this, 9% of the children on LABA had no ICS.

The relatively high number of 239 (7%) of children with more than one type of inhaler device is comparable with results of a British study in which 12% of the children used more than one type of inhaler [8]. A proper inhalation technique is essential but difficult to retain. In a recent Dutch study it was found that in 29% of children with a DPI, the technique was insufficient [15]. The use of more than one type of inhaler, and therefore two different

inhalation techniques, is confusing and should therefore be dissuaded [31].

Different from other guidelines, the Dutch guidelines advise DPIs in children older than the age of 7 years, because it is believed that DPIs are more convenient to use and easier to take, e.g. at school and sports [10, 13]. Therefore we included this element in the study. Thirty-six percent of the children older than 8 years did not have a DPI. An explanation could be that some children cannot inhale properly. Another explanation for not using a DPI in this age group is that the use of medication is not checked on a regular basis and therefore the children continue to use pMDIs.

pMDIs should be used with a spacer [2, 3, 11, 13]. It appeared that 65% of the children with a pMDI had received such a spacer device in the preceding 2 years and 35% had not received a spacer device. An explanation could be that the spacers have been in use for a longer period, but it is also possible that some children have no spacer at all.

Possible reasons for not following recommendations are lack of knowledge or non-accessibility to guidelines. In both the national and international literature, guidelines have been published and these publications were readily available to all Dutch physicians, so this cannot be the reason. It has been suggested that sometimes guidelines do not rely on evidence [22]. This cannot explain the non-adherence in this study because the principles studied do rely on evidence. It could be argued that not all guidelines are applicable to all patients. However, the high number of children not treated according to principles makes this unlikely.

Lack of adherence to guidelines is recognised in treatment of asthma in children [7–9, 12, 22], as well as in adults [23, 29]. Several interventions, aimed at the prescribing physicians, such as computer-assisted flow sheets, peer group training, and electronic medical records have been studied. Although every intervention has some beneficial effects, none has proven conclusive [23, 29].

Nonadherence could be explained by the fact that children with asthma are not seen on a regular basis and their medication is not checked properly. In the Netherlands it is customary that patients or their parents send the label of the medication used to the general practitioner, who will provide a repeat prescription without a consultation visit. In this way, patients can receive medications for a long period without being seen by a doctor.

It has been stressed that a health care provider should support patients with asthma to ensure optimal care [11]. A regular check is essential to tailor the treatment to the needs of the patient. Therefore, sending in labels for a repeat prescription of asthma medication should be discouraged. Pharmacists can compare the prescriptions of asthma medication with current recommendations. When a deviation occurs, the pharmacists should inform the prescribing physician. In the treatment of patients with hypertension the involvement of pharmacists improved clinical outcome [24].

In conclusion, although almost all children with asthma medication received a prescription for inhaled medication, not all children have a reliever, and not all children who use a LABA have had a prescription for ICS. Some children have more than one type of inhalator. Apparently, there is still a wide gap between guidelines and daily practice, despite the availability and reliability of guidelines. Probably other methods have to be sought for ensuring asthma treatment according to guidelines. Attention to prescribed medication by pharmacists could be one of these methods.

Acknowledgement We thank Dr. J. Collins for reviewing the English.

References

- Altman DG, Machin D, Bryant TN, Gardner MJ (2000) *Statistics with confidence*. BMJ Books
- Anonymous (1997) Asthma in adults and schoolchildren. The General Practitioner in Asthma Group, the British Association of Accident and Emergency Medicine, The British Paediatric Respiratory Society and the Royal College of Paediatrics and Child Health. *Thorax* 52(suppl 1):s2–s8
- Anonymous (1997) Asthma in children under five years of age. The General Practitioner in Asthma Group, the British Association of Accident and Emergency Medicine, The British Paediatric Respiratory Society and the Royal College of Paediatrics and Child Health. *Thorax* 52(suppl 1):s9–s20
- Anonymous (2004) ATC classification index with DDDs. WHO Collaborating Centre for Drug Statistics Methodology, Oslo, January
- de Baets F, van Daele S, Franckx H, Vinaimont F (1998) Inhaled steroids compared with disodium cromoglycate in preschool children with episodic viral wheeze. *Pediatr Pulmonol* 25:361–366
- Beimfohr C, Maziak, W, Von Mutius E, Hense HW, Leupold W, Hirsch T, Keil U, Weiland SK (2001) The use of anti-asthmatic drugs in children: results of a community-based survey in Germany. *Pharmacoepidemiol Drug Saf* 10:315–321
- Cabana MD, Rand CS, Becher OJ, Rubin HR (2001) Reasons for pediatrician nonadherence to asthma guidelines. *Arch Pediatr Adolesc Med* 155:1057–1062
- Child F, Davies S, Clayton S, Fryer AA, Lenney W (2002) Inhaler devices for asthma: do we follow the guidelines? *Arch Dis Child* 86:176–179
- Dashash NA, Mukhtar SH (2003) Prescribing for asthmatic children in primary care. Are we following guidelines? *Saudi Med J* 24:507–511
- Dirksen WJ, Geijer RMM, de Haan M, Koning G, Flikweert S, Kolnaar BGM (1998) Guidelines for the treatment of asthma by general practitioners. *Huisarts Wet* 41:103–143
- Global Initiative for Asthma (GINA) (2002) *Global strategy for asthma management and prevention*. National Institutes of Health. National Heart, Lung, and Blood Institute. Bethesda, MD
- Haby MM, Powell CV, Oberklaid F, Waters EB, Robert CF (2002) Asthma in children: gaps between current management and best practice. *J Paediatr Child Health* 38:284–289
- Hoekstra MO (1997) Medical treatment of asthma in children; revised guidelines by paediatric pulmonologists. *Ned Tijdschr Geneesk* 141:2223–2228
- de Jong-Van den Berg LTW, Feenstra N, Sorensen HT, Cornel MC (1999) Improvement of drug exposure data in a registration of congenital anomalies. Pilot-study: pharmacist and mother as sources for drug exposure data during pregnancy. EuroMAP Group. European Medicine and Pregnancy Group. *Teratology* 60:33–36
- Kamps AW, van Ewijk B, Roorda RJ, Brand PL (2000) Poor inhalation technique, even after inhalation instructions, in children with asthma. *Pediatr Pulmonol* 29:39–42
- Klungel OH, de Boer A, Paes AHP, Herings RMC, Seidell JC, Bakker A (1999) Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in the Netherlands. *Pharm World Sci* 21:218–220
- Mutius von E (2003) Epidemiology of allergic diseases. In: Leung DYM, Sampson HA, Geha RS, Szefer SJ (eds) *Pediatric allergy, practice and principles*. Mosby, St. Louis, pp 1–9
- Monster TBM, Janssen WMT, de Jong PE, de Jong-van den Berg LTW (2002) *Pharmacoepidemiol Drug Saf* 11:379–384
- Ng Man Kwong G, Proctor A, Billings C, Duggan R, Das C, Whyte MKB, Powell CVE, Primhak R (2001) Increasing prevalence of asthma diagnosis and symptoms in children is confined to mild symptoms. *Thorax* 56:312–314
- Pedersen S (1994) Inspiratory capacity through Turbuhaler in various patient groups. *J Aero Med* 7:S55S–S58S
- Schirm E, Monster TBM, De Vries R, Van den Berg PB, de Jong-van den Berg LTW, Tobi H (2004) How to estimate the population that is covered by community pharmacies? An evaluation of two methods using drug utilisation information. *Pharmacoepidemiol Drug Saf* 13:173–179
- Shiffman, RN, Freudigman A, Brandt CA, Liaw Y, Navedo DD (2000) A guideline implementation system using handheld computers for office management of asthma: effects on adherence and patient outcomes. *Pediatrics* 105:767–773
- Smeele IJM, Grol RPTM, Van Schayck CP, Van den Bosch WJHM, Van den Hoogen HJM, Muris JWM (1999) Can small group education and peer review improve care for patients with asthma/chronic obstructive pulmonary disease? *Qual Health Care* 8:92–98
- Sookaneknu P, Richards RME, Sanguanserm Sri J, Teerasut C (2004) Pharmacist involvement in primary care improves hypertensive patient clinical outcomes. *Ann Pharmacother* 38:2023–2028
- Strachan DP (1995) Epidemiology. In: Silvermann M (ed) *Childhood asthma and other wheezing disorders*. Chapman & Hall, London, pp 7–31
- Tobi H, van den Berg PB, de Jong-van den Berg LTW (2000) The InterAction database: synergy of science and practice in pharmacy. *Lect Notes Comput Sci* 1933:206–211
- Tobi H, van den Heuvel NJN, de Jong-van den Berg LTW (2004) Does uncollected medication reduce the validity of pharmacy dispensing data? *Pharmacoepidemiol Drug Saf* 13:497–500
- Van Schayck CP, Smit HA (2005) The prevalence of asthma in children: a reversing trend. *Eur Resp J* 26:647–650
- Veninga CCM, Lagerlov P, Wahlstroem R, Muskova, Denig P, Berkhof J, Kochen MM, Haaijer-Ruskamp FM (1999) Evaluating an educational intervention to improve the treatment of asthma in four European countries. *Am J Respir Crit Care Med* 160:1254–1262
- Verberne AAPH, Frost C, Roorda RJ, Van der Laag J, Kerrebijn KF, The Dutch Paediatric Asthma Study Group (1997) One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med* 156:688–695
- Warner JO (2003) Guidelines for treatment of asthma. In: Leung DYM, Sampson HA, Geha RS, Szefer SJ (eds) *Pediatric allergy, practice and principles*. Mosby, St. Louis, pp 350–356