Prescribed doses of inhaled steroids in Dutch children: too little or too much, for too short a time

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Aims

To investigate the dosage and duration of inhaled steroids prescribed to children and to compare the prescribed doses with recommended doses for the treatment of asthma in children.

Methods

For 2514 Dutch children aged 0–12 years who had used inhaled steroids in 2002, pharmacy dispensing data were obtained from the InterAction database, type of steroid (beclomethason, budesonide, fluticasone) and type of user (first time or existing) and the average prescribed doses according to age were determined and compared with the doses as recommended in the national Dutch Nederlands Huisartsen Genootschap (NHG) guideline. Furthermore, for all first-time users the duration of therapy with inhaled steroids was determined using a Kaplan–Meier analysis.

Results

The major findings were that: (i) overall 43% of children starting inhaled steroids were prescribed doses that are half the recommended dose or less; (ii) overall 8% of the children starting inhaled steroids were prescribed doses that were twice the recommended dose or more, up to 50% in the 12-year-olds fluticasone group; and (iii) only 8% of the children who started with inhaled steroids used them continuously for a full year.

Conclusions

Doses of inhaled steroids for many children deviate from those recommended, with lower doses more frequently occurring than higher doses. Less than 10% of the children receive prescriptions for a prolonged period of time.

Introduction

Preventive treatment has become the cornerstone of asthma management. Inhaled corticosteroids (ICS) effectively control asthma and minimize pulmonary damage and therefore play a central role in preventive treatment of asthma. Both national and international guidelines recommend treatment with ICS for all children with persistent asthma and ICS are therefore widely used [1–7]. A study in the Netherlands, for

example, showed that, of children using anti-asthmatics, 60% used ICS [8].

ICS are generally regarded as safe in children, although at higher doses systemic adverse events such as growth retardation and adrenal suppression have been reported [9–11]. Since these side-effects have been shown to be dose dependent, it is generally recommended to avoid long-term high doses of ICS (i.e. >500 µg fluticasone or equivalent) if possible [9–11].

However, for effective control of asthma it is important that the daily dose of ICS should be sufficient and that the therapy be prescribed for a sufficiently extended period as the preventive effect of steroids is based on continuous treatment [1–7]. Although adequate control of symptoms may easily be confused with absence of disease, a premature discontinuation may lead to recurrence of symptoms and unnecessary pulmonary damage.

Despite the known importance of an adequate dose and duration of treatment with ICS in children, there is no literature that documents doses and duration in daily practice. This study investigates the dose and duration of ICS prescribed to children and compares the prescribed doses with recommended doses for the treatment of asthma in children.

Methods

Population and setting

This study was performed using pharmacy-dispensing data from the InterAction database, which is part of the collaboration between community pharmacists in the northern part of the Netherlands and the University of Groningen [12]. In the Netherlands people commonly register with one pharmacy and obtain all their medication from that pharmacy, so that a complete medication history is available in the pharmacy dispensing records. Outpatient medication is also supplied by community pharmacies and thus is included in the dispensing data. Drugs used during hospital stay (inpatients) and over-the-counter (OTC) medication are not included. Previous studies have demonstrated that dispensing data from Dutch pharmacies offer an accurate survey of the use of prescription drugs [13, 14]. Registration is irrespective of health insurance (including people who are not insured) and thus is representative for the general population.

Dosing

Detailed dosing information is available for a selected number of pharmacies (depending on their computer system), covering a population of approximately 450 000 patients, including 43 000 children aged 0–12 years (age at date of first prescription in 2002) [15]. From this group, all children who had used at least one inhaled corticosteroid in 2002 were identified ($n = 2644$ children). Children with one or more prescription without quantitative dosing instruction (e.g. ‘according to instructions doctor’) were excluded from further analysis (130 children, 4.9%), resulting in a study group of 2514 children. ICS available in the Netherlands are beclomethasone, budesonide and fluticasone (as a single drug or as part of a drug combination). The identified

children were divided into two subgroups: first-time users were defined as children with a prescription for an inhaled steroid in 2002, but none in 2001; existing users had had one or more prescription in both 2001 and 2002. Per child the first prescription in 2002 was taken from the dataset to investigate the prescribed dose. We used only one prescription per child to avoid problems with dependency in the analyses. The prescribed daily dose was manually determined based on dosing instructions for the patient as recorded in the pharmacy dispensing data. In the case of a variable dosing scheme (e.g. twice per day 1–2 puffs) the average was taken. The average and SD of the prescribed doses were determined by age and type of steroid for first-time and existing users separately. In addition, the percentage of prescriptions with a dose of $\leq 50\%$ and the percentage of prescriptions with a dose of $\geq 200\%$ of the dose recommended according to the national Dutch Netherlands Huisartsen Genootschap (NHG) guideline was determined (Table 1) [1]. This guideline is widely used in the Netherlands and is therefore an appropriate reference; the 50–200% boundaries were chosen arbitrarily. Furthermore, as can be seen in Table 1, the doses recommended in the NHG guideline closely resemble those in various international guidelines.

Duration of use

To investigate the duration of ICS use, a Kaplan–Meier analysis was performed. For all first-time users a follow-up window of 1 year (one full year starting at the date of the first prescription for the child in 2002) was set up. For each prescription the duration of use was calculated, based on the quantity dispensed and the prescribed daily dose. Treatment with ICS was considered to have ceased when a child had not used ICS for at least 60 consecutive days. This maximum allowed gap of 60 days was chosen arbitrarily, but had to be sufficiently long to account for small differences between time of prescription and time of actual use. For example, if new ICS were dispensed while previously dispensed steroids had not yet been completely used up, the patient retained a small stock – this may fill a gap later on. With these parameters, the cumulative proportion of children still using ICS was determined per day. All statistical analyses were performed using SPSS (version 12.0; SPSS Inc., Chicago, IL, USA).

Results

In total, 2514 children aged 0–12 years had used at least one type of ICS (beclomethasone, budesonide or fluticasone) in 2002. Of these children, 1047 were first-time users and 1467 were existing users. Tables 2 and 3 show

Table 1

Daily doses advised in childhood asthma according to several guidelines

Author Ref. Age, years	NHG [1] Becl.	Bud.	Flu.	SKL [2,3] Bud.	Flu.	GINA [4] Bud.	BAG [5,6] Becl.	Flu.	NHLBI [7] Becl.
1	400	400	200	500	250		400	200	
2	400	400	200	500	250		400	200	
3	400	400	200	500	250		400	200	500
4	400	400	200	500	250	400	400	200	500
5	400	400	250	500	250	400	400	200	500
6	400	400	250	500	250	400	800	200	500
7	400	400	250	500	250	400	800	200	500
8	400	400	200*	500	250	400	800	200	500
9	400	400	200	500	250	400	800	200	500
10	400	400	200	500	250	400	800	200	500
11	400	400	200	500	250	400	800	200	500
12	400	400	200	500	250	400	800	200	500

Becl., Beclomethasone; Bud., budesonide; Flu., fluticasone; NHG, Dutch College of General Practitioners; SKL, Dutch Paediatric Respiratory Society; GINA, Global Initiative for Asthma; BAG, British Asthma Group; NHLBI, National Heart, Lung, and Blood Institute.*Change in preference from aerosol inhaler + spacer to powder inhaler results in a lower dose.

the average dose and SD as related to age and type of ICS, dosage being based on the first prescription in 2002, for first-time and existing users separately. Unlike the recommended initial doses as shown in Table 1 (same dose for all ages), the average daily prescribed daily dose gradually increased with age for first-time users.

As can be seen by the SD, variability in the prescribed daily doses is wide for all three types of ICS. Of all first prescriptions, 43% had a prescribed dose of at most 50% of the recommended initial dose of the Dutch NHG guideline. For prescriptions for existing users this was 35%. Fluticasone and, to a lesser extent, budesonide prescriptions had at least twice the recommended dose in a substantial proportion of the prescriptions. More than one in every three children aged ≥ 10 years treated with fluticasone had received such a high dose.

Figure 1 shows the duration of inhaled steroid use for all first-time users. The proportion of children with extended use of ICS rapidly decreased with time. The estimated median duration of therapy was 78 days (95% confidence interval 63, 93). Of the children who started therapy with ICS in 2002, 8% continuously used them for a full year. A maximum gap of 60 days between two subsequent prescriptions was allowed in these analyses. In cases where a maximum gap of 15, 30, 90 or 180 days was allowed, the estimated median treatment duration was 60, 60, 96 and 100 days, respectively. There was no

Figure 1 Kaplan-Meier curve for first-time users of inhaled steroids ($n = 1047$)

clinically relevant difference between different age groups (median times of 87, 66 and 66 days for the age groups of <4 years, 4–7 years and >7 years, respectively, using a maximum allowed gap of 60 days). In none of the analyses included in this study was there a clinically relevant difference between boys and girls.

Discussion

The major findings of our study are, first, that overall 43% of children starting inhaled steroids were pre-

Table 2Prescribed daily doses of inhaled steroids for first-time users ($n = 1047$ children)

Type of steroid	Age, years	NHG dose, μg	No. of children	Average dose, μg	SD	Percentage of children with daily dose:	
						$\leq 50\%$ of NHG	$\geq 200\%$ of NHG
Beclometasone	0	400	54	169	70	91	0
	1	400	39	182	102	87	0
	2	400	33	179	82	88	0
	3	400	35	194	95	80	0
	4	400	23	167	95	91	0
	5	400	26	223	114	81	0
	6	400	19	258	117	68	0
	7	400	24	279	195	58	4
	8	400	18	414	310	44	17
	9	400	17	271	149	71	0
	10	400	12	292	162	58	0
	11	400	20	305	143	45	0
	12	400	17	394	277	41	12
	All	—	337	—	—	75	2
Budesonide	0	400	43	300	207	51	5
	1	400	15	240	140	60	0
	2	400	14	236	134	64	0
	3	400	15	280	126	47	0
	4	400	11	318	125	36	0
	5	400	7	329	125	29	0
	6	400	9	344	113	22	0
	7	400	10	380	193	20	10
	8	400	8	363	213	38	13
	9	400	11	364	81	18	0
	10	400	9	378	120	22	0
	11	400	6	467	207	17	17
	12	400	10	515	186	0	20
	All	—	168	—	—	39	4
Fluticasone	0	200	123	179	81	39	2
	1	200	83	199	100	36	6
	2	200	42	214	102	33	5
	3	200	51	190	65	27	0
	4	200	35	266	117	11	9
	5	250	45	242	136	16	4
	6	250	25	262	100	8	12
	7	250	28	301	129	4	25
	8	200	22	264	194	18	14
	9	200	22	320	207	9	32
	10	200	35	374	224	6	46
	11	200	14	363	138	0	50
	12	200	17	324	155	12	47
	All	—	542	—	—	24	12
Total	All	—	1047	—	—	43	8

SD, Standard deviation; NHG, Dutch guideline (see Table 1).

Table 3Prescribed daily doses of inhaled steroids for existing users ($n = 1467$ children)

Type of steroid	Age, years	NHG dose, μg	No. of children	Average dose, μg	SD	Percentage of children with daily dose:	
						$\leq 50\%$ of NHG	$\geq 50\%$ of NHG
Beclometasone	0	400	6	233	137	67	0
	1	400	20	200	127	75	0
	2	400	31	181	75	94	0
	3	400	31	215	115	84	0
	4	400	40	203	106	78	0
	5	400	41	194	105	88	0
	6	400	52	228	112	73	0
	7	400	42	250	129	74	2
	8	400	44	256	122	59	0
	9	400	39	268	107	59	0
	10	400	41	349	224	44	7
	11	400	25	296	188	52	4
	12	400	24	363	141	29	4
	All	—	436	—	—	68	1
Budesonide	0	400	5	390	225	40	20
	1	400	16	334	233	56	6
	2	400	23	274	176	52	0
	3	400	23	300	132	39	0
	4	400	29	353	140	24	3
	5	400	21	421	223	24	19
	6	400	18	392	256	33	11
	7	400	19	347	158	32	5
	8	400	23	332	150	30	4
	9	400	18	347	161	28	6
	10	400	27	406	180	22	11
	11	400	20	380	154	25	5
	12	400	19	466	207	16	16
	All	—	261	—	—	31	7
Fluticasone	0	200	18	192	100	39	6
	1	200	60	185	87	40	3
	2	200	63	237	86	13	6
	3	200	65	227	104	22	9
	4	200	78	260	143	18	14
	5	250	71	235	125	28	13
	6	250	82	251	125	17	13
	7	250	67	274	152	16	21
	8	200	65	259	137	17	23
	9	200	65	282	159	11	26
	10	200	52	325	175	6	40
	11	200	43	379	263	5	40
	12	200	41	380	274	2	44
	All	—	770	—	—	18	19
Total	All	—	1467	—	—	35	12

SD, Standard deviation; *NHG*, Dutch guideline (see Table 1).

scribed doses that were, at most, half of the recommended dose. Among beclomethason users <1 year old, this figure was 91%. Second, 8% of the children starting inhaled steroids were prescribed doses that were twice the recommended dose or more, reaching 50% in the 12-year-old fluticasone group. Finally, only one out of 12 children who started with inhaled steroids used them continuously for a full year.

The major strengths of this study are the population-based coverage, the prospective recording of pharmacy dispensing data and the completeness of pharmacy dispensing data in comparison with other sources, such as registration of general practitioners. An important limitation of our study design is that our exposure and dosing information is based solely on the dispensing of the drug from the pharmacy and we have no information about actual drug intake in terms of either duration or dose. In addition, pharmacy dispensing data do not include diagnoses and do not therefore offer reasons for following or deviating from guidelines.

Since the doses recommended by the NHG are initial doses, the best comparison is between NHG doses and doses prescribed to first-time users. An explanation for the large proportion of children receiving low doses may be that fear of systemic effects, such as growth retardation and adrenal suppression, prevents doctors from prescribing higher doses [16].

Several studies have investigated the safety profiles of the different ICS [9–11]. The evidence that fluticasone generates fewer side-effects than other inhaled steroids is not conclusive. Some studies, indeed, have shown that fluticasone has a limited oral absorption and a large hepatic first-pass effect, leading to less systemic availability [17]. However, other studies have shown that fluticasone is more easily absorbed from the lung, leading to more systemic adverse effects [16, 18, 19]. Interestingly, fluticasone is less frequently prescribed in a low dose. For all three inhaled steroids, adverse effects normally do not occur at doses recommended in the guidelines [9–11].

The NHG guideline recommends starting with a moderate dose, trying to lower the dose gradually when asthma has been effectively controlled for at least 3–6 months; if this leads to a deterioration of symptoms then the higher dose is given again [1]. Two alternative methods exist: the step-down approach, and the step-up approach. In the step-down approach a high dose is tapered off: start with a high dose (e.g. fluticasone 1000 µg) to reduce aggressively airway inflammation, gradually reducing the dose to the lowest effective dose (this approach is not included in the NHG guideline) [20, 21]. Consequently, with the step-down approach

higher or lower doses than the fixed recommended initial dose may occur and this may also be an explanation for the considerable variability. Since the step-down approach has no proven benefit over the constant dose approach, but rather the high initial doses frequently result in side-effects, it is not recommended. A step-up approach may also be an explanation for low doses, but this approach is not recommended by any of the guidelines listed in Table 1.

Since this study was undertaken, revised guidelines have been published [22], in which the recommended initial dose for children with asthma is reduced to 200 µg day⁻¹. Even compared with these guidelines, the prescribed doses in this study were still too low.

Although the general picture emerging from Tables 2 and 3 shows that doses were low, a substantial number of children received inhaled steroids with daily doses of at least 200% of the recommended initial dose, especially with fluticasone. Approximately 12% of the fluticasone doses for first-time users were ≥500 µg (200%). As mentioned above, doses of this magnitude may occur as part of a step-down approach, but for existing users they may also be for children with severe persistent asthma, for which doses had to be increased several times before achieving sufficient control of symptoms. Whereas side-effects do not normally occur at the doses recommended in the guideline, side-effects may be expected at doses of this level [10, 16, 19].

We do not know why these high doses were prescribed. Fluticasone is at present available in dry powder inhalers with 100, 250 or 500 µg per dose. This means that, when taken twice daily, increments in doses go from 200, 500 or 1000 µg. The lack of formulations with doses in between could possibly play a role. Lack of awareness of the advice to add long-acting β₂-agonists or leukotriene receptor antagonists could also be a factor. As far as we know, the reasons for prescribing such high doses have never been studied.

Considering that the preventive effect of ICS is based on continuous treatment, the duration of treatment may seem rather short for many children. The proportion of children receiving ICS after 6 and 9 months was approximately 17% and 11%, respectively, and only 8% of children in our study used inhaled steroid throughout the entire year. For all children >3 years old the Dutch NHG guideline advises evaluation of the effects of the ICS every 3 months and, when effective, to try to reduce the dose gradually over a period of 3–6 months [1]. This would mean that for children with newly diagnosed asthma who respond well to therapy with ICS, the minimum period of treatment is 6–9 months. Obviously, for children with persistent asthma longer treatment may be

required. In the framework of the NHG guideline, therapy for less than 6–9 months may therefore occur only in cases where children do not respond to treatment with ICS. This may be the case if steroids are used as a diagnostic instrument. In such cases, children with airway obstruction are prescribed ICS and, if these are effective, diagnosis of asthma is more likely and therapy with ICS may be continued. In view of our findings that many children receive low doses, it is important to note that therapy with ICS may show less effect if the dose is too low. An alternative explanation may be that during an exacerbation a short course of ICS is prescribed. Besides the fact that this is not recommended in the guidelines, this explanation would imply that many children have exacerbations and therefore raises questions about possible undertreatment.

ICS may also be used in the treatment of periodical viral wheeze. There is some evidence that this may be effective [23]. Due to the limited duration of periodical viral wheeze, the use of ICS for this indication may have biased our analysis of the duration of treatment towards a shorter treatment. However, none of the guidelines mentioned in Table 1 recommend the use of ICS for this indication. In addition, initial doses for this periodical viral wheeze should be high and therefore may not be an explanation for the low doses found in our study.

Considering all the data, it appears that the guidelines concerning the prescription of ICS in children, although widely available at that time, were not adhered to. Not following guidelines has been recognized in the treatment of asthma in children. Reported reasons for this include lack of knowledge, fear of side-effects and non-accessibility to guidelines [24].

In conclusion, we have found that doses of ICS for many children starting ICS deviate from those recommended, with lower doses occurring more frequently than higher doses. Few children were treated for a prolonged period of time. Current insights show that recommended doses of ICS are safe in children [9–11]. It would therefore be regrettable if fear of side-effects leads to too conservative prescribing, possibly leading to recurrence of symptoms and unnecessary pulmonary damage.

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