

Original article

Monitoring adherence to beclomethasone in asthmatic children and adolescents through four different methods

Background: Suboptimal adherence to inhaled steroids is a known problem in children and adolescents, even when medications are administered under parental supervision. This study aimed to verify the adherence rate to beclomethasone dipropionate (BDP) by four currently available methods.

Methods: In this concurrent cohort study, 102 randomly selected asthmatic children and adolescents aged 3–14 years were followed for 12 months. Adherence rate was assessed every 2 months by self and/or parent report, pharmacy dispensing data, electronic device (Doser[®]; Meditrack Products, Hudson, MA, USA) monitor, and canister weight.

Results: Mean adherence rates to BDP by self and/or parent report, pharmacy records, Doser, and canister weight were 97.9% (95% CI 88.0–98.6), 70.0% (95% CI 67.6–72.4), 51.5% (95% CI 48.3–54.6), and 46.3% (95% CI 44.1–48.4), respectively. Agreement analysis between (Doser) and canister weight revealed a weighted kappa equal to 0.76 (95% CI 0.65–0.87).

Conclusions: Adherence was a dynamic event and rates decreased progressively for all methods over the 12-month follow-up. Canister weight and electronic monitoring measures were more accurate than self/parent reports and pharmacy records. Rates obtained by these two methods were very close and statistical analysis also showed a substantial agreement between them. As measurements by canister weight are less costly compared with currently available electronic devices, it should be considered as an alternative method to assess adherence in both clinical research and practice.

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Inhaled corticosteroids (ICS) are the mainstay of asthma treatment and their correct and regular use results in decreased hospitalizations and emergency department visits, and better quality of life (1). However, regular use of ICS is difficult because of the treatment's long duration, route of administration, number of puffs per day, and the occasional use of more than one inhaled drug or inhalers (2). Consequently, suboptimal adherence is common and is associated to increased morbidity, mortality, poor clinical outcome, and increased use of healthcare services (3).

There is no gold standard for quantifying adherence to ICS. Conventionally, it can be verified by self or parent reports, pharmacy records, canister weight, and electronic measurements (4, 5), the latter being the most accurate. Adherence rates in children and adolescents usually range from 30% to 90%, depending on the assessment method (6, 7).

Patient and parent reports, especially when dealing with children, can be carried out through diaries, interviews, or questionnaires. Several studies have documented its limited validity, ascribed to exaggerated

self-report adherence, when compared with other methods. In two studies, adherence was self-reported as 90% and 95.4%, whereas it was electronically measured at 34.0% and 13.7% (8, 9).

Pharmacy dispensing data is a practical and low-cost method that records the difference between number of medication doses prescribed to patients and what was actually consumed when patients later return canisters. These data can be used to calculate the average dose per day, and as more pharmacy data are made available online, this strategy can be used widely and inexpensively. With this method, adherence rates were of 41–61%, also in pediatric populations (10–14).

Canister weight quantifies the weight variation from the beginning of treatment, subsequent clinical visits, up to the point when the canister is empty. It is a relatively simple and objective method. Bender et al. (15), in a study with 27 children and adolescents, found self-reported adherence over 80%, 69% by canister weight, and 50% by electronic device.

Differently from the above mentioned methods, electronic devices record and store date and time of medica-

tion use for weeks or months (16). Because of their high cost, however, they are not widely available, which restricts their application mainly to clinical research. In three studies assessing adherence in children and adolescents, the rates measured electronically ranged from 13.7% to 55.0% (17–19).

The present study was carried out to assess the adherence rate to beclomethasone dipropionate (BDP) by the four currently available and above-mentioned methods. Our literature review did not produce any study in a pediatric population simultaneously assessing adherence rate by these four methods in a randomly assigned sample of pediatric subjects followed for 12 months.

Materials and methods

Patients, study period, and design

The study was carried out between January 2002 and December 2006, and recruited 102 randomly selected asthmatic patients who attended a referral Pediatric Pulmonology Outpatient Clinic linked to the Municipal Public Health System that assists only patients from low-income families. It was a prospective cohort study in which after admission, adherence assessments were performed in six occasions, i.e. every 2 months during 1-year follow-up.

Beclomethasone dipropionate canisters containing 200 puffs (Clenil®; Chiesi, São Paulo, Brazil, 250 mcg per puff), the ICS standardized in the asthma program managed by the Belo Horizonte Municipal Health Authority (BHMHA), along with pear-shaped plastic valved spacers (Flumax®; Flumax Medical Equipments, Belo Horizonte, Brazil) were dispensed free of cost, as in all other outpatient clinics and respective pharmacies belonging to the BHMHA. Because of limited financial resources in our setting, no add-on therapies were provided to participants of the current study.

Inclusion and exclusion criteria

Steroid-naïve children and adolescents, aged 3–14 years with mild, moderate, or severe persistent asthma, classified according to GINA criteria were admitted (3). We excluded children with other concurrent diseases.

Adherence assessment

All subjects attended the outpatient clinic every 2 months for clinical and adherence assessment and were given BDP prescription at this time. Adherence data were obtained simultaneously for each patient, by self/parent report, pharmacy records, canister weight, and electronic device.

Self/parent reporting was performed by filling out a diary, in which parents or patients wrote the date and time of medication use. The diary was completed every day and collected every 2 months during the scheduled follow-up visits. Pharmacy dispensing records were filled out by the pharmacist of the same outpatient clinic. Adherence rate was obtained according to a standardized protocol (number of doses dispensed/number of doses that should have been used between the date medication was provided and the date of return, multiplied by 100). As each canister of BDP contained 200 puffs, and the highest prescribed dose was two puffs per day, pharmacy records were verified in average every 100 days, and

therefore it was not possible to obtain data from the second month. On the 60th day, assuming an adherence of 100%, the consumption should have been of 120 puffs. Canister weight loss (in milligrams) was measured on a calibrated digital scale (Marte AS1000; Marte Scales and Precision Equipments, São Paulo, Brazil). It was assessed as described elsewhere. For electronic monitoring, BDP-pMDI canisters were inserted into Doser® (Meditrack Products, Hudson, MA, USA), a device that records the date and time of each inhaler actuation.

Statistical aspects

Because a previous study (14) carried out in the same clinic indicated that adherence rates by pharmacy records were similar to those obtained in studies in the developed world, we arbitrarily adopted an intermediate adherence rate by electronic devices obtained in studies conducted in those countries in order to calculate sample size (19, 20). Considering that there were 303 eligible patients and assuming an adherence rate of 45% with electronic device, alpha error of 5%, margin of error of $\pm 7\%$, the required sample size should be of 119 patients.

Descriptive statistics were calculated to characterize the studied population. Adherence mean between the four different methods were compared by Wilcoxon signed rank test; 95% confidence intervals for means were also calculated. Agreement between measurements obtained by canister weight and Doser was analyzed by weighted kappa. Significance level was $P < 0.05$. All analyses were performed through SPSS version 12.0.

Ethical aspects

The study protocol and the informed consent form were approved by the Committee of Ethics in Research of the Federal University of Minas Gerais. Patients and their parents/legal guardians were aware of all the methods used for measuring adherence.

Results

Out of the 119 previously selected patients, 102 children and adolescents (85.7%) attended all follow-up visits and concluded the study. Descriptive characteristics of these patients are shown in Table 1.

Most were males (58.8%) and suffering from mild or moderate persistent asthma (91.2%). Mean age at admission was 6.2 (± 3.1) years. Being steroid-naïve, the majority had already been hospitalized before study enrollment (86.3%) and had required unscheduled emergency department visits (58.8%). At admission, BDP dose was 500 $\mu\text{g/day}$ (two puffs per day) for 97 (95.1%) of the 102 subjects.

Table 2 shows mean adherence rates, collected every 2 months, for each of the four methods used in the study.

Adherence rate decreased progressively and consistently during the follow-up period with all four methods. All participants filled in their diaries and self/parent reports reached 100% (95% CI 97.4–98.4%) in the second month and stayed high until the 12th month, dropping to 96.4% (mean rate 97.9% for the whole study

Table 1. Baseline characteristics of the 102 studied subjects

	<i>n</i>	%
Gender		
Male	60	58.8
Female	42	41.2
Age group (years)		
Up to 4	48	47.0
5–9	34	33.3
More than 9	20	19.7
Asthma severity		
Mild persistent	43	42.2
Moderate persistent	50	49.0
Severe persistent	9	8.8
Previous hospitalization because of acute asthma		
Yes	88	86.3
No	14	13.7
Previous emergency department visits because of acute asthma		
Yes	60	58.8
No	42	41.2
Becomethasone dipropionate dosage at admission (mcg/day)		
500	97	96.1
750	5	4.9

period, 95% CI 88.0–98.6%). With pharmacy records adherence rates ranged from 77.7% to 65.7% (mean rate 70.0%, 95% CI 67.6–72.4). As for the adherence verified by Doser, the variation was of 58.3–34.9%, a mean of 51.5% (95% CI 48.3–54.6%). Adherence rate for canister weight ranged from 52% to 42.8% (mean rate 46.3%, 95% CI 44.1–48.4). It is important to note that the upper limit of the 95% CI is similar to the lower limit of the 95% CI estimated for Doser.

A boxplot comparing adherence mean obtained for all four methods is shown in Fig. 1.

All differences between means were statistically significant, including the relatively small one verified by Doser and canister weight (51.1% *vs* 46.3%, respectively; $P = 0.003$).

Table 3 displays the agreement analysis between canister weight and Doser. Among the participants whose adherence measured by canister weight was lower than 40%, 70.3% also had adherence by Doser lower than 40%; by canister weight between 40% and 50%, 52.2% also had the same rates for Doser; and finally, among those with adherence by canister weight above 50%, the vast majority (90.5%) also presented Doser above 50%. Thus, agreement between the two methods was substan-

Table 2. Adherence rate (%) by four methods throughout the 12-month period

Method	Second month	Fourth month	Sixth month	Eighth month	Tenth month	Twelfth month
Self/parent report	100.0	99.4	98.4	97.5	96.1	96.4
Pharmacy records	–	77.7	73.1	69.4	69.2	65.7
Canister weight	52.0	46.7	45.1	46.8	44.7	42.8
Doser	58.3	48.5	43.9	34.9	36.4	34.9

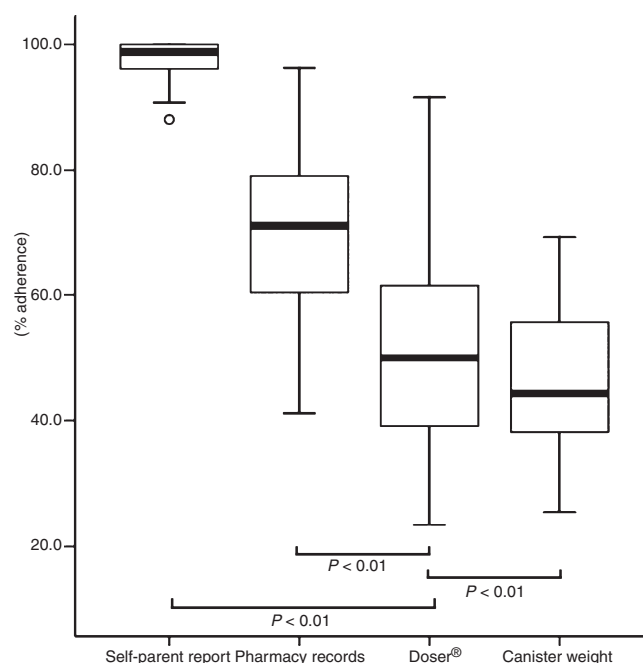


Figure 1. Adherence rate for each of the four different methods.

tial (kappa = 0.76) and significant, as the confidence interval does not include 0.

Discussion

Although a high adherence rate to asthma medications is necessary, achieving optimal adherence can be difficult given the peculiarities of inhalation therapy. Partial adherence is a known problem in children and adolescents, even when medications are administered under parental supervision.

The present study showed a high discrepancy between self/parent reporting and the other three methods, which may be ascribed to recall bias and/or the parent's wish to please the doctor or not openly recognizing their omission in administering medication (20). Overall, the high

Table 3. Agreement between canister weight and Doser according to three categories of adherence rate

	Doser		
	<40%	40–50%	>50%
Canister weight			
<40%	26 70.3%	8 21.6%	3 8.1%
40–50%	4 17.4%	12 52.2%	7 30.4%
>50%	1 2.4%	3 7.1%	38 90.5%

Weighted kappa = 0.76.
95% CI 0.65–0.87.
 $P < 0.01$.

reported adherence obtained with our subjects is in accordance with the literature (18, 19). We also demonstrated that adherence was a dynamic event and rates decreased progressively throughout the 12 months of follow-up, as verified by others (14, 19). This suggests that the longer the treatment, the more rigorous the clinician should be in verifying adherence.

Although in a lesser degree than self/parent reports, adherence by pharmacy records was also overestimated and could be explained by conscious discharging, and/or failure in medication intake, among other reasons. Previous works that used this method found a range from 57.2% to 61% (10, 13, 14), lower than the rates verified by us.

Our results suggest that canister weight and Doser measurements are the most reliable methods. However, in the literature, there were discrepancies in adherence rates obtained with both methods. Measurements by canister weight have ranged from 44% to 72% (21, 22); electronic devices have ranged more widely, from 13.7% to 68% (17–19, 22). Such discrepancies among the studies and our present study are probably related to methodological aspects, mainly sample size, duration of follow-up, adherence assessments strategies, and the subjects and/or parents' awareness of the ways in which adherence was measured.

The difference of 5.2% between the mean rates verified by canister weight and Doser in the current study was relatively low. The substantial (weighted kappa = 0.76)

and statistically significant ($P < 0.01$) agreement suggests that canister weight could be an alternative to the expensive electronic monitoring in both clinical practice and research. Digital scales have multiple uses in health facilities and could be used for verifying adherence, especially for patients with partial control or problematic control of asthma, to confirm or rule out poor adherence.

The results of the present study have other implications for clinical practice. As adherence rates tend to decrease over time, in addition to verifying it systematically, the clinician must, in each appointment, be attentive to the degree of clinical and functional asthma control. It is well known that adherence can be increased with educational strategies, and if patients believe that the treatment is efficacious and safe. Communication between patient and physician and healthcare team must also be improved for that goal (23).

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