

Noncompliance and treatment failure in children with asthma

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Background: Accurate and reliable information about children's use of inhaled medications is needed because of the growing reliance on these drugs in the treatment of asthma and the excessive morbidity and mortality attributable to this disease.

Objective: This study was designed to evaluate the adherence of children with asthma to regimens of inhaled corticosteroids and β -agonists.

Methods: Data collected electronically by metered-dose inhaler monitors were compared with data recorded by patients on traditional diary cards. A volunteer sample of 24 children, between 8 and 12 years old, who had asthma for which they were receiving both inhaled corticosteroids and β -agonists, participated over a 13-week period. Each child was accompanied by a parent to all study visits. The main outcome measures were the use of medication as reported by diary card entries and recorded by electronic monitoring and disease exacerbation, as indicated by requirement for oral corticosteroids.

Results: The median use of inhaled corticosteroids reported by patients on their diaries was 95.4%, whereas the median actual use was 58.4%. More than 90% of patients exaggerated their use of inhaled steroids, and diary entries of even the least compliant subjects reflected a high level of adherence. The children who experienced exacerbation of disease sufficient to require a burst of oral corticosteroids differed markedly from the others in their adherence to prescribed therapy as recorded by the electronic monitors. The median compliance with inhaled corticosteroids was 13.7% for those who experienced exacerbations and 68.2% for those who did not.

Conclusions: Electronic monitoring demonstrated much lower adherence to prescribed therapy than was reported by patients on diary cards. Low rates of compliance with prescribed inhaled corticosteroids were associated with exacerbation of disease. Poor control of asthma should alert the physician to the possibility of noncompliance. (*J Allergy Clin Immunol* 1996; 98:1051-7.)

Key words: Asthma, compliance, children, treatment failure

Asthma managed appropriately rarely leads to hospitalization; yet 43% of its economic impact is related to emergency department use, hospitalization, and death, all resulting from the failure of preventive treatment.^{1,2} Prolonged and consistent antiinflammatory therapy is required, even in the absence of symptoms.^{3,4} Such care leads to better

Abbreviation used

MDI: Metered-dose inhaler

control of disease, averts the trauma associated with its exacerbation, and diminishes the need for aggressive intervention.

The extent to which an individual conforms to a medical regimen is an essential determinant of clinical success.⁵ In patients with asthma, objective measures have documented that only about 50% of inhaled medication is taken as prescribed and that compliance does not improve with rising severity of illness.⁶⁻⁸ Most importantly, patients commonly

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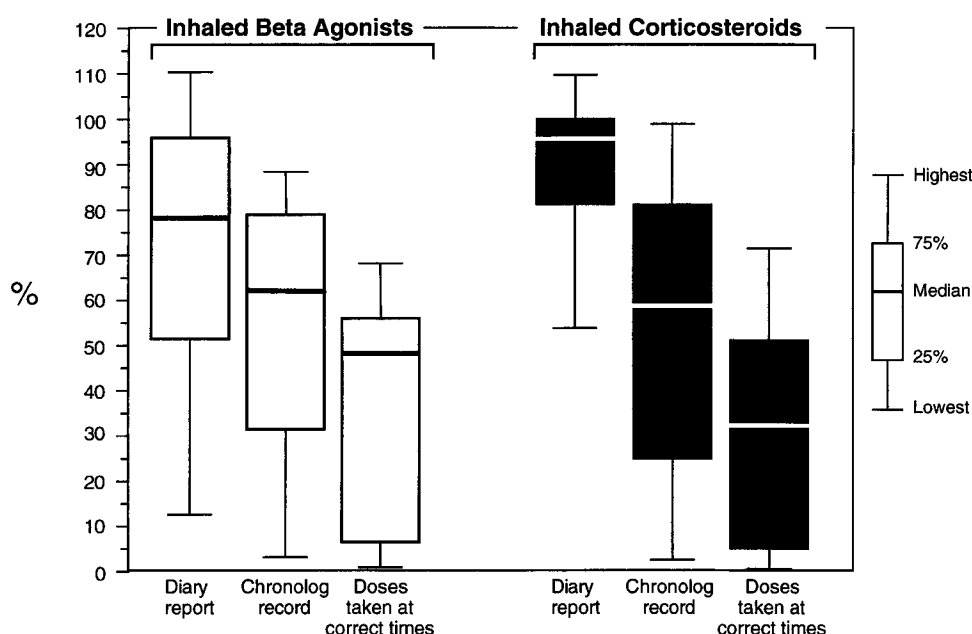


FIG. 1. Summary of compliance data for inhaled medications taken over 13 weeks. Percentages of prescribed doses reported to have been taken in patient diaries are compared with doses actually taken documented by Chronolog record (raw compliance) and with doses taken at correct times (time-corrected compliance).

TABLE I. Summary of study results

Variable	β -Agonist median (IQR) %	n*	Inhaled steroid median (IQR) %	n
Ratio of diary doses to prescribed doses	78.2 (51.7, 95.8)	16	95.4 (81.4, 100.0)	24
Raw compliance	62.1 (31.7, 78.6)	16	58.4 (25.1, 80.6)	24
Time-corrected compliance	47.6 (07.2, 55.6)	16	31.8 (05.1, 51.4)	24
Percent of days without medication	20.4 (12.6, 72.8)*	16	24.4 (02.8, 58.2)	24
Raw compliance for bursted group	62.2 (09.0, 84.6)	6	13.7 (03.3, 45.9)	8
Raw compliance for nonbursted group	60.5 (45.6, 72.6)	10	68.2 (45.3, 93.4)	16

IQR is the interquartile range: the 25th and 75th percentiles. Bursted group is comprised of those children who required oral corticosteroids; nonbursted group is comprised of those children who did not require oral corticosteroids.

*Excludes patients receiving β -agonists on an as-needed basis.

overreport their medication use,⁶ and physicians do not judge patients' compliance accurately.^{9, 10}

Although most recent studies of adherence to treatment in asthma have been carried out in adults, currently available data indicate that the mortality and morbidity rates associated with this disease are increasing most rapidly among younger patients.² Because of the growing reliance on aerosolized medications in the treatment of children with asthma, it is of foremost importance to assure that these agents be used optimally. The MDI Chronolog (Forefront Technologies, Inc. Lakewood, Colo.), an electronic monitoring device, has been used to provide detailed assessment

of compliance in research protocols.^{8, 11-13} Accurate and reliable information about children's use of medication is needed equally in clinical situations.

METHODS

Subjects

The study participants were 24 children (14 boys and 10 girls) with asthma, between 8 and 12 years old. They were recruited from an ambulatory clinic by using a convenience sample of children who required both inhaled corticosteroid and β -agonist therapy and reliably kept their clinic appointments. Children who were known to be noncompliant with therapy were excluded.

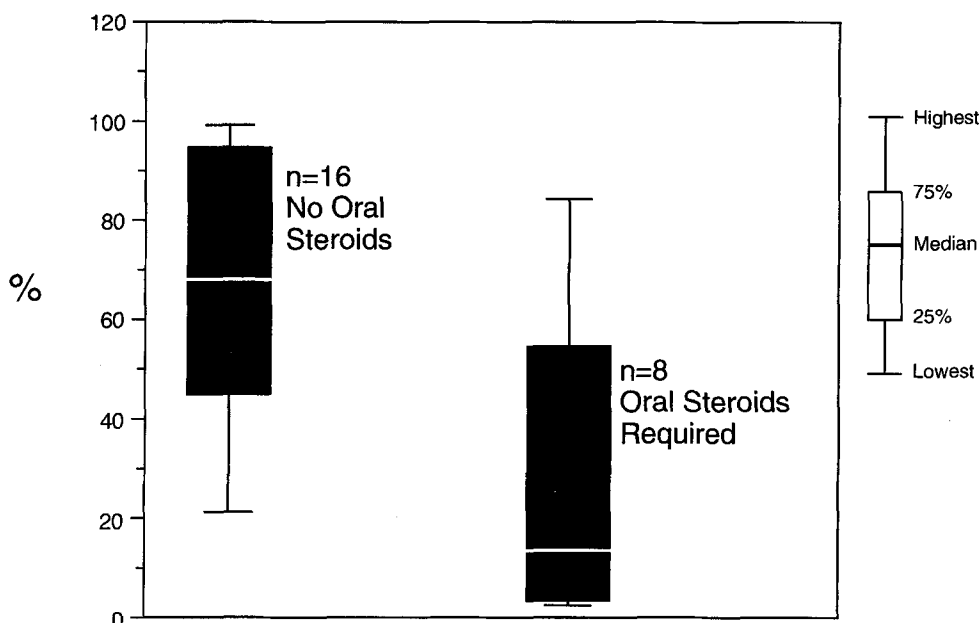


FIG. 2. Compliance with inhaled corticosteroids: comparison of percentages of prescribed doses actually taken, as recorded by Chronolog (raw compliance), by patients whose asthma was stable throughout the study (no oral steroids) with those who required bursts of oral corticosteroids.

Each child was accompanied to every visit by a parent. All subjects had been prescribed inhaled corticosteroids and β -agonists before the study and continued to receive both medications throughout its duration. Patients were not using spacers, and nebulized medications were not prescribed. All patients were instructed to take inhaled corticosteroids according to a fixed regimen. Eight of the 24 patients were taking β -agonists only as needed; the data from these subjects are not included in the analysis. Only the doses of β -agonists taken according to the fixed regimens were included in the analysis. The patients remained under the care of their personal physicians who made all decisions regarding any changes in therapy. Children and their parents participated in an asthma education program and demonstrated their knowledge of the correct use of both medications by passing a multiple choice quiz. Of the 24 children, only nine filled out their own diaries; a parent completed the diaries of 15 children. In all cases the parents assumed the responsibility for supervising their children's recording of information on diary cards.

Equipment

The MDI Chronolog is an electronic device built into the sleeve housing a metered-dose inhaler (MDI) that records the date and time of each actuation. The children were issued two MDI Chronologs and diary cards on which to mark down each time they used their inhalers. They were instructed to use medication exclusively from these devices, except when they were at school.

Design

This study was approved by the Institutional Review Board of the National Jewish Center for Immunology and Respiratory Medicine. All patients and their parents read an informed consent statement. Parents signed the consent form, and the patients signed an assent statement drafted for children. Until the conclusion of the study, neither the children nor their parents were made aware of the MDI Chronologs' ability to record medication use. The study consisted of four visits over 13 weeks. At visit 1, each subject received diary cards and two MDI Chronologs, one for the inhaled steroid and one for the β -agonist. Patients and their parents were instructed in the proper use of the inhalers and diary cards. At visit 2 (week 1) and visit 3 (week 5), the subjects returned to confirm that proper procedures were being followed and to exchange their Chronologs and completed diary cards for new ones. At visit 4 (week 13) diary cards and MDI Chronologs were collected.

All information from the MDI Chronologs was downloaded to an IBM PC computer (IBM Corp., Armonk, N.Y.), and data from the diary cards were entered for analysis.

Data analysis

The diary entries recorded by the patients indicated the number of puffs and the time of administration of doses of both medications. The Chronolog data recorded the exact time of every actuation of an MDI. To compare the two recording methods, a Chronolog

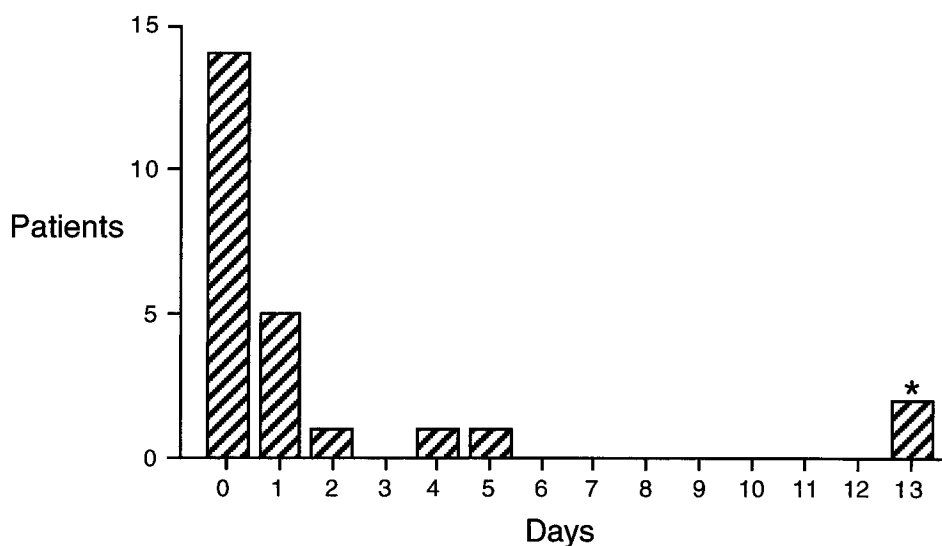


FIG. 3. Days of high use of inhaled β -agonists, as recorded by Chronolog (raw compliance). High use is defined as more than 12 puffs taken in a single day. *Note that the two patients with 13 days of overuse required hospitalization.

dose was defined as the total number of puffs taken within an hour. No Chronolog records of actuations during the school day were available from those patients who kept additional inhalers at school. In such cases all doses taken during the middle of the day (between 10:00 AM and 6:00 PM) were deleted from the analysis, and the subjects' data were analyzed as if the prescription were for administration twice daily.

Information concerning the prescribed number of doses and all changes in regimen was obtained at study visits and confirmed by a review of the medical record. Total prescribed doses were calculated for each subject for the entire study period. Raw compliance was defined as the percentage of prescribed doses taken as measured by the Chronolog. The number of puffs constituting a dose was not considered. To assess adherence to a dosing schedule, time windows were defined for each fixed regimen. The time-corrected compliance was defined as the percentage of prescribed doses consisting of at least the correct number of puffs taken within the correct time window. The windows were defined for administration twice daily (6:00 AM to 10:00 AM, 6:00 PM to 10:00 PM), three times daily (6:00 AM to 10:00 AM, 10:00 AM to 6:00 PM, 6:00 PM to 10:00 PM), and four times daily (6:00 AM to 10:00 AM, 10:00 AM to 2:00 PM, 2:00 PM to 6:00 PM, 6:00 PM to 10:00 PM).

To summarize compliance measures across subjects, medians and interquartile ranges (25th and 75th percentiles) were used because the distributions were often skewed. To compare two groups of subjects, Wilcoxon rank sum tests were used. All analyses were done by using PCSAS version 6.04 (SAS Institute, Cary, N.C.).

RESULTS

Primary results are summarized in the Table I. Diary entries stated that the median use of β -agonists was 78.2% of prescribed dose and that steroid use was a striking 95.4%. The median raw compliance for β -agonist and inhaled steroid doses taken, as recorded by the Chronolog, was 62.1% and 58.4%, respectively. However, the time-corrected compliance comprising only doses taken within the correct window was 48% for β -agonists and 32% for inhaled corticosteroids (Fig. 1). Ninety-two percent of the patients exaggerated the use of corticosteroids and 71% overreported the use of β -agonists in their diaries. Even the least compliant patients recorded a high level of adherence with inhaled steroids on their diary cards. Of the six patients whose raw steroid compliance was less than 25%, three recorded having taken approximately 100% of prescribed doses on their diary cards, and three recorded having taken between 54% and 69%. Median days without medication were 20.4% for β -agonists (8 patients receiving as-needed β -agonists were excluded from the analysis) and 24.4% for inhaled steroids. It is noteworthy that 25% of the patients did not take inhaled corticosteroids on more than 60% of the days.

During their 13-week participation in the study, eight of the 24 patients had exacerbation of disease serious enough to compel their personal physicians to prescribe a course of oral corticosteroids. This

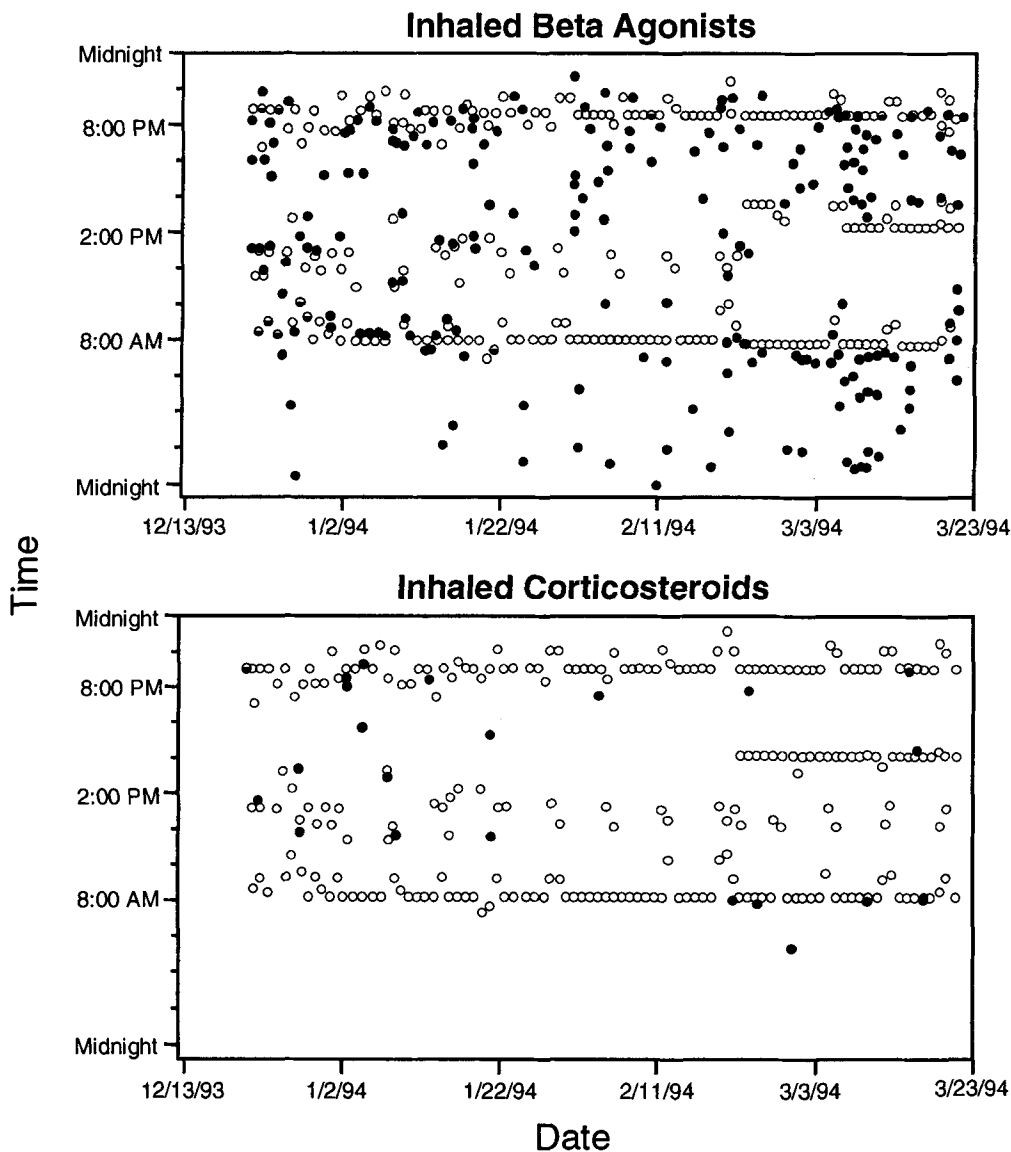


FIG. 4. Comparison of Chronolog (filled circles) and diary (open circles) data of one patient.

group's use of β -agonists was similar to that of patients who did not require such intervention. Median raw compliance values were 62.2% and 60.5%, respectively ($p = 0.79$). However, the children who required a burst of oral corticosteroids differed markedly from the others in their compliance with prescribed inhaled corticosteroid therapy. The median raw compliance values were 13.7% and 68.2%, respectively ($p = 0.008$) (Fig. 2). Two children required hospitalization, one during the study and the other 1 week after its conclusion. These children took only 7.1% and 28.7% of the doses of their inhaled steroids. Although their bronchodilator use over the entire 3-month period

was not excessive, it is noteworthy that the same two patients discharged their β -agonist inhalers more than 12 times on 13 days each (Fig. 3).

Review of data obtained from individual patients showed discrepancies between reported and recorded medication use (Fig. 4). Such information may be valuable in planning clinical interventions and avoiding unnecessary escalation of therapy.

DISCUSSION

This study compared information regarding the use of medication from patient diaries with that recorded by electronic monitoring devices. Chil-

TABLE II. Dosing schedules and compliance

Dosing schedule	β -Agonist median compliance (min/max)	n	Inhaled steroid median compliance (min/max)	n
BID	46.7 (00.6, 64.8)	7	22.2 (00.0, 71.4)	13
TID	53.1 (08.8, 55.5)	3	39.6 (23.3, 59.7)	7
QID	50.0 (30.6, 55.2)	3	05.8	1
QD		0	46.2	1
QD/BID*	04.8	1	03.0	1
BID/TID*		0	52.8	1
TID/BID*	42.6	1		0
QID/BID/TID*	67.5	1		0

BID, twice daily; TID, three times daily; QID, four times daily; QD, once daily.

*The regimens of these patients were altered by their physicians during the course of the study.

dren and their parents were not informed about the recording capability of the Chronologs and did not receive any feedback, nor were data analyzed until the study was completed. It is important to emphasize that this investigation was conducted without disturbing the preexisting doctor-patient relationship. Each patient's care was directed by his or her own physician, whose clinical recommendations were based on the patient's condition and not on any requirements imposed by the study. Thus any failure to comply cannot be attributed to participation in a research protocol.

This study demonstrates a dramatic discrepancy between the diary entries and Chronolog records of children with asthma (Figs. 1 and 4), a disparity that cannot be attributed to inadequate comprehension of the appropriate use of medication by either parent or child. All patients and their parents participated in asthma education classes, and all demonstrated knowledge of the roles of both medications in their therapy. More significantly, the consistency of the diary entries clearly reflected an accurate understanding of the prescribed regimens. Moreover, not a single patient reported in his or her diary the use of less than half of the prescribed corticosteroid doses, whereas 25% of patients recorded less than 50% use of β -agonists. This indicates that the patients understood the need for constancy in prophylactic therapy and the allowance for more flexible dosing of rescue medication.

Good clinical outcomes in the management of asthma require treatment that is consistent, thus eliminating recurrent exacerbations and ensuing escalation of therapy. Such optimal care, however, is difficult to attain when patients do not adequately follow therapeutic recommendations. The rising morbidity and mortality rates associated with

asthma in young persons may be attributed in part to inadequate compliance coupled with patients' inability to accurately assess the severity of their airway obstruction.^{2, 14, 15} Most patients in this study exaggerated their use of inhaled corticosteroids in their diaries, and there was a striking relationship between poor steroid adherence and exacerbation of asthma. Five of the eight children who required courses of oral steroids, including the two who were hospitalized, were among the least compliant.

This study did not use random selection of patients, and there is no assurance that patients did not use medications from other sources that were not monitored. Because of the small sample size, no direct relationship between dosing regimen and compliance was noted (Table II). However, a clear relationship linking compliance and treatment outcome is indicated by the difference in the compliance with inhaled corticosteroids between the group that required oral prednisone and the group that did not.

This study raises issues that should be of concern. The children failed to comply with inhaled corticosteroid therapy, they misrepresented their steroid use, and they did so with the tacit approval of their parents. Failure to comply was linked with exacerbation of disease and the resultant need for administration of systemic steroids and hospitalization. Both the human toll and the financial burden may have been reduced by more conscientious adherence and reliable reporting. Inadequate control of asthma should alert the physician to the possibility of noncompliance, a behavior that is widespread and clearly not limited to those who are poorly informed or overtly uncooperative. A compelling need exists for objective means of assessing adherence because patient reports are

unreliable and physicians do not judge compliance accurately.^{9, 10} As clinicians, we must find ways that will encourage patients to comply with their therapy. It is evident that providing them with accurate information, though necessary, is not sufficient. Our responsibility extends beyond accurate diagnosis and appropriate recommendations. It is essential that we acknowledge and accept the responsibility for patient compliance, a direction more likely to result in better control of asthma than efforts to seek out more aggressive or innovative therapies.

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