

Validation of the Doser, a new device for monitoring metered-dose inhaler use

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Background: Electronic monitoring of medication use has proved valuable in both clinical and research settings. The Doser, a new and inexpensive commercially available device for monitoring metered-dose inhaler (MDI) use, displays 3 measures of daily use of an attached MDI: (1) the daily total of actuations, (2) the number of doses remaining in the MDI, and (3) the number of actuations on each of the preceding 30 days for later recall.

Objective: We sought to validate the accuracy of the Doser with several commonly prescribed MDIs.

Methods: In the laboratory, clinic personnel actuated an MDI with an attached Doser several times in succession on 3 consecutive days and recorded each of the 3 measures of MDI use (study 1). In study 2 clinic personnel carried an MDI and attached Doser with them for 4 weeks, actuating the MDI according to a prescribed protocol each morning and evening and again recording each of the 3 measures of daily use. In addition, during 2 weeks of study 2, a thermistor-based Nebulizer Chronolog was attached to the MDI to electronically record the date and time of each actuation. In study 3 clinic patients had both a Doser and Nebulizer Chronolog attached to their routinely used inhalers for 2 weeks and a Doser alone during a separate 2-week period.

Results: In study 1 agreement was 99% to 100% among the 3 Doser measures, and each measure agreed with actual use by self-report 97% of the time. In study 2 agreement among the 3 Doser measures of use ranged from 98% to 99%. Agreement between each of the 3 Doser measures and the Nebulizer Chronolog ranged from 90% to 93%. Agreement between each of the 3 Doser measures and actual use ranged from 96% to 97%, and the Nebulizer Chronolog agreed with actual use 93% of the time. In study 3 Doser and Nebulizer Chronolog agreement with patient self-report were 85% and 80%, respectively. Agreement between the Doser and Nebulizer Chronolog was 76%. Several failures of the thermistor-based Nebulizer Chronolog occurred, and occasional mechanical problems occurred with the Doser, primarily on particular types of MDI canisters.

Conclusion: The Doser provides an accurate measure of MDI use with most commonly prescribed medications and may be useful for monitoring MDI use by investigators, clinicians, and patients. (*J Allergy Clin Immunol* 1998;102:409-13.)

Key words: Electronic medication monitoring, metered-dose inhaler, adherence, patient compliance

Failure to adhere to physician-prescribed medication protocols is a well-documented problem in both clinical and research settings.¹⁻⁷ Disease exacerbations, severe side effects, and even death have been caused by the failure of patients to adhere appropriately to the medication regimen prescribed by their physicians.^{4,8-11} In clinical trials erroneous conclusions may be reached because of deviations from the prescribed drug protocol.¹²⁻¹⁴ The advent of microelectronic medication monitoring has revealed that patient self-reports, whether by diary or later recall, frequently fail to document doses missed or taken at inappropriate intervals.^{15,16} Data recorded by microelectronic monitors have been used to improve inhaler adherence through subsequent feedback of the downloaded data to patients,¹⁷ although the retrospective nature of the feedback capability of these monitors and their considerable cost limits their usefulness in clinical practice.

The Doser (NewMed Corporation, Billerica, Mass) is a new, inexpensive, microelectronic medication monitor of metered-dose inhaler (MDI) use that is currently approved by the Food and Drug Administration as a device for direct sale to patients, physicians, and pharmacies (Fig 1). The Doser attaches to most commercially available MDIs by means of a soft plastic sleeve that fits over the top of the MDI canister. The MDI is then actuated by pressing on the Doser, which automatically records the actuation and confirms the recording with an audible beep. The Doser provides the patient with a liquid crystal display showing the number of MDI actuations on the current day. Hypothetically, this direct daily visual feedback of actual inhaler use has the potential to improve adherence to prescribed MDI use by providing patients with an accurate measure of doses taken or missed on each day. After entering the number of puffs available in the attached MDI, the Doser also displays the number of doses remaining in the MDI and beeps when only 20 doses are left, thus serving as a reminder to refill prescriptions. In addition, the device stores 30 or 45 days

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FIG 1. Doser attached to top of MDI (*left*). Display shows daily total and doses remaining in MDI inhaler canister. Face of Doser showing recent history of use of attached MDI (*right*).

Abbreviation used

MDI: Metered-dose inhaler

of daily MDI actuation totals in electronic memory for later retrieval by physicians, clinical trials staff, or patients, thereby permitting objective determination of actual recent MDI use.

We report the results of a 5-center study to determine the accuracy and reliability of the Doser and to compare the validity of the Doser with that of the Nebulizer Chronolog, an established microelectronic monitoring device that has been used for over a decade as a research tool in studies of MDI adherence.^{1,2}

METHODS

Three separate validation studies were carried out with the Doser under both controlled laboratory and real-life conditions at 5 sites in the United States and Canada. The model tested was the first version of the Doser, which stores 30 days of MDI use. We did not test the Doser-CT, which provides a 45-day history of MDI use and allows the visual display to be blanked out.

In study 1, two members of the clinic staff at each of the 5 sites attached separate Dosers to each of several different MDI medications. Each staff member actuated a Doser-attached MDI a set number of times in succession on 3 consecutive days according to a predetermined protocol for each type of medication such that the total number of actuations on each of the 3 days was equivalent to approximately one third of the contents of the canister. The number

of actuations and the doses remaining in the canister, as displayed by the Doser, were recorded on a diary card several times during each study day. The daily totals were recalled from the Doser memory 4 and 8 days after the completion of the study.

The medications studied included full-size canisters of albuterol (Proventil and Ventolin), ipratropium bromide (Atrovent), salmeterol xinafoate (Serevent), beclomethasone dipropionate (Vanceril, Beclovent, and Becloforte), triamcinolone acetonide (Azmecort), flunisolide (Aerobid), fluticasone propionate (FloVent), cromolyn sodium (Intal), and nedocromil sodium (Tilade). For ipratropium, cromolyn, and nedocromil inhalers, the clearance between the sleeve of the Doser and the inner surface of the vertical portion of the mouthpiece was too small to permit unimpeded actuation of the MDI; consequently, these particular MDIs were not studied further.

In study 2, 5 clinic personnel at each site kept 1 of the following MDIs with attached Dosers for 4 weeks: albuterol, salmeterol, beclomethasone, triamcinolone, flunisolide, and fluticasone. During the day, the MDI was carried on the person of the clinic personnel (coat or trousers pocket) or in a purse or handbag. The MDIs were actuated according to a randomized predetermined protocol each morning and evening, and the daily dose count and doses remaining in the canister were recorded each time. In addition, in random order during 2 weeks of study 2, a thermistor-based Nebulizer Chronolog (model MC-311; Medtrac Technologies, Inc, Lakewood, Colo) was connected to each MDI with its attached Doser to electronically record the date and time of each actuation.

In study 3, 5 clinic patients at each site had a Doser attached to their routinely used inhalers for approximately 4 weeks while using their MDIs according to their physicians' usual instructions. Patients were selected to provide a broad representation of the different types of commercially available MDIs, with the exception of ipratropium, cromolyn, and nedocromil. A diary of actual MDI use was kept, but no record of the daily use from the Doser display was made. A Chronolog was also attached to each patient's MDI for either the first or last 2 weeks of the study, with the order being determined randomly.

For all 3 protocols, the MDI canisters were weighed before and after each study period to provide estimates of actuations based on changes in canister weight for comparison with the other measures. The protocol was approved by the institutional review board at each of the participating institutions.

Data analysis

Absolute differences between canister weights and other measures were used, giving equal weight to positive and negative deviations. Rates of agreement (the percent of data recordings on which 2 measures agreed) were calculated for each pair of 4 daily electronically derived measures: (1) the daily actuation total (studies 1 and 2); (2) the doses remaining in the MDI transcribed each day from the Doser's display to the subject diary (studies 1 and 2); (3) the daily total as retrieved from the 30-day memory (all 3 studies); and (4) the total number of actuations recorded on each day by the Chronolog (studies 2 and 3). The chi-square test was used to compare the percent of agreement of the Doser and Chronolog measures with actual use. Kruskal-Wallis rank-sum analysis of variance was used to compare the percent of agreement of Doser and Chronolog measures with actual use across centers and types of MDIs.¹⁸

RESULTS

Results for all studies are summarized in Tables I and II. In study 1, which was carried out in the laboratory, internal agreement between the 2 Doser displays (the daily actuation counter and the doses remaining in the MDI) was very high (99.8%; $n = 1125$ data pairs).

TABLE I. Percent perfect agreement between measures

Study*	Doser daily counter† vs actual use	Chronolog history vs actual use	Doser daily counter vs Doser history
1	96.7	—	100
2	95.8	92.5	97.7
3	84.5	77.4	—

*Study 1: Three days of bench testing by technicians in lab; study 2: used by technicians outside of lab for 4 weeks (2 weeks with Chronolog); study 3: used by patients with regular medications for 4 weeks (2 weeks with Chronolog).

†Doser daily counter in studies 1 and 2 and Doser history in study 3.

TABLE II. Percent agreement between measures (discrepancies of 2 puffs per day or less)

Study*	Doser daily counter† vs actual use	Chronolog vs actual use	Doser daily counter vs Doser history
1	99.6	—	100
2	99.8	99.0	99.8
3	97.4	97.2	—

*Study 1: Single day of bench testing by technicians in lab; study 2: used by technicians outside of lab for 4 weeks (2 weeks with Chronolog); study 3: used by patients with regular medications for 4 weeks (2 weeks with Chronolog).

†Doser daily counter in studies 1 and 2 and Doser history in study 3.

The Doser measures agreed with the actual number of actuations discharged by the technicians 96.7% of the time, with 89% of all deviations from perfect agreement representing underreporting by the Doser. When disagreement was redefined as a deviation of the Doser by no more than 2 actuations from actual use, agreement with actual use was 99.6%. There was 100% agreement between the daily totals read from the Doser history (stored in its memory) after each study and the Doser display as recorded each day in the diary during the study. The Doser history agreed with actual use on 87.8% of all study days ($n = 156$), with 84% of the discrepancies again representing underreporting by the Doser. There were no statistically significant differences in agreement between Doser daily counts or history and actual use across centers or types of MDIs tested. The Doser display of doses remaining in the canister paralleled the daily counter display; the change in doses remaining was equal to the daily counter 99.8% of the time. The canister weight differences deviated from the expected value on the basis of the actual number of actuations by an average of 2.4%. The mean difference between the Doser histories and the canister weights was 3.1%.

In study 2, in which clinic personnel kept an MDI with an attached Doser for 4 weeks and actuated the MDI a predetermined number of times twice daily, a total of 460 data points were collected. Agreement between the Doser daily counter and actual MDI use, as recorded on the daily diary, was 95.8%. Considering discrepancies of 2 actuations or less as acceptable, Doser agreement with the daily diaries was 99.8%. Internal agreement was 97.6% between the Doser daily counter and the number of doses remaining, and it was 97.7% between the daily counter and the Doser history retrieved after the study. The change in the Doser display of doses remaining in the canister on each day exactly reflected the daily

counter reading on 97.6% of all readings. Agreement between the Chronolog and actual use was lower than the agreement between the Doser history and actual use (92.5% and 97.2%, respectively). There were no statistically significant differences in agreement of the Doser or Chronolog with actual use across centers or types of MDIs tested ($P = .25$ to $.90$ as determined by the Kruskal-Wallis test). The canister weight differences deviated from the expected value on the basis of the actual number of actuations by an average of 3.0%. The mean difference between the Doser histories and the canister weights was 3.4%.

Study 3 was similar to study 2, except that clinic patients had Dosers attached to their routinely used MDIs and used them according to their physicians' instructions. A total of 607 days of data were recorded. Agreement between Dosers and the patient daily diaries was obtained on 84.5% of all patient days, or 97.4% when allowing deviations of up to 2 actuations per day. Chronolog agreement with the diaries was 77.4% and 97.2%, respectively. When only the days on which both electronic monitoring devices were used together are included, percent agreement of the Doser and the Chronolog with the diaries (with no deviations) was 87.3% and 77.4%, respectively, a statistically significant difference ($P < .001$ as determined by chi-square test; $n = 323$). There were no statistically significant differences in agreement between either the Doser or the Chronolog and actual use across centers ($P = .93$ and $.55$ as determined by the Kruskal-Wallis test, respectively). The canister weight differences deviated from the expected value on the basis of the actual number of actuations by an average of 8.9%. The mean difference between the Doser histories and the canister weights was 9.3%, whereas the Chronologs averaged a 9.4% difference from canister weights.

Both the Doser and Chronolog occasionally malfunctioned, resulting in loss of data. In study 1, in which only the Doser was used, 1 Doser of 53 tested failed to provide a history because of a dead battery. In studies 2 and 3, in which Chronologs were attached to the MDIs during half of the study, 1 of 48 Dosers and 9 of 48 Chronologs failed; some studies were repeated to collect complete data.

DISCUSSION

The Doser is a new device designed to assist patients in adhering to prescribed MDI use by displaying in real time the number of doses used during each 24-hour period and reminding patients when their inhaler is nearly empty. This device also provides dosing history information to medical personnel to allow objective monitoring of adherence. We conducted a multiphase study to validate the accuracy of the Doser under controlled laboratory conditions and in actual use by research personnel and patients. The results of this study demonstrate that the Doser was an accurate indicator of daily medication use (as well as the doses remaining in the canister) and compared favorably with the more cumbersome and expensive Nebulizer Chronolog. Although the Chronolog can provide more precise information than the Doser by recording not only the date but also the time of MDI actuations, the Chronolog had a greater number of errors and was more likely to fail completely and provide no data, a finding which is consistent with several other studies on the reliability of a recent version of the Chronolog (model MC-311).¹⁹⁻²²

Self-reported MDI use was the standard against which the Doser and Chronolog were compared. In the laboratory, where technicians followed a prescribed pattern of MDI use over a relatively short time period (study 1), agreement between the Doser and self-report was highest. Lower rates of agreement were observed when study personnel were assigned Dosers with or without Chronologs to use each morning and evening in irregular, predetermined patterns. Unintended deviations from the prescribed use that the clinic personnel noted, such as missed doses, were taken into account in the analysis, but additional, unacknowledged human errors of omission or commission may have occurred. In addition, during the *real-world* phases of the study (studies 2 and 3), an MDI could have been accidentally actuated while being carried and thus not noted in the daily diary, or the Doser's display could have been incorrectly transcribed onto the diary card. Internal consistency between the 3 Doser measures was generally very high, although the Doser could fail to record an actuation or make a spurious recording of an actuation that did not occur (*misregistration*) and still be *internally* consistent. During further examination of the Doser, we have found that misregistration can occur when the Doser is depressed on the side instead of firmly in the center of its top; this can result in an MDI actuation without a corresponding record made by the Doser. Also, the Doser records only 1 actuation when pressed twice in very rapid succession (<1 second apart). This time delay is intentional, designed to avoid

spurious recordings because of an unsteady hand when only 1 actuation of the MDI occurs. A further complication that is common to most electronic monitors occurs when puffs are taken after midnight but before the patient retires for the night; these doses will be recorded as having been taken on the following calendar day.

The lowest agreement rates occurred when the Doser and Chronolog were used by clinic patients according to their own schedules. The rate of agreement between the Doser history and the patient diary of daily actuations, although lower than that obtained with clinic staff in study 2 (97.2%), was still relatively high (84.5%) and slightly higher than the agreement between the Nebulizer Chronolog and patient diary (77.4%). Although canister weights showed closer agreement with the daily diaries (91.1%) than did the Doser or the Nebulizer Chronolog, canister weights have the disadvantage that they provide no information on daily patterns of use. Moreover, in clinical trials canister weights are unable to detect intentional canister *dumping*.¹⁵

The Doser has several advantages as a microelectronic monitor of MDI use. It provides daily patient feedback of actual inhaler use, it tracks the medication that is left in the canister, it is small and compact, it is adaptable to most (but not all) MDIs, it is compatible with spacers and holding chambers, and it does not interfere with drug delivery. It is reusable until its battery fails (approximately 1 year), and during that time it can be applied to several different MDI canisters. Its disadvantages include the fact that the data are not downloadable in the current version of the device, it has a relatively short memory (30 days), it does not track actual clock time, and it does not work well with certain MDIs, including ipratropium, cromolyn, and nedocromil.

It is important to note that this study was of short duration and was conducted under conditions that did not always simulate actual clinical use. Furthermore, changes in manufacturing processes or quality control can affect the reliability of any device. All monitoring devices should be tested by the user before being accepted as reliable.

We conclude that the Doser is a valid and reliable microelectronic tool for the following intended uses with MDIs: (1) to remind patients of the number of inhalations taken each day; (2) to warn of the near-empty status of MDI canisters; and (3) to provide physicians and allied health professionals with an acceptably accurate historical record of daily MDI use within the past 30 days. Further studies are warranted to evaluate the effectiveness of the device's daily visual feedback of actual inhaler use in enhancing adherence to prescribed MDI use.

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Correction

The following correction applies to the practice parameter by Nicklas et al entitled "The Diagnosis and Management of Anaphylaxis," which appeared in volume 101, number 6, part 2, pp S465-S528, 1998, of The Journal.

The contribution of Dr Gillian Shepherd to the Parameter on the Diagnosis and Management of Anaphylaxis was inadvertently omitted from the acknowledgments for that parameter. Dr Shepherd contributed significantly to the section on β -lactam antibiotics.