Impact of Dosage Frequency on Patient Compliance

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OBJECTIVE — To evaluate the impact of dosage frequency on the compliance of patients who receive their medicines from community pharmacies.

RESEARCH DESIGN AND METHODS — Each month, patients received a supply of their medication in a Medication Event Monitoring Systems container, which registered each opening of the package. At the end of the study, the patients received a short questionnaire. The subjects were 91 diabetic patients using oral antidiabetic agents. Patients taking insulin and those who were unable to collect their medicines from the pharmacy were excluded from the study. Compliance was defined as the percentage of doses taken during the observation period. Another parameter used was compliance with the prescribed regimen, defined as the percentage of days in which the number of tablets were taken as prescribed. As a last parameter, compliance with the prescribed dose intervals was used.

RESULTS — Compliance is influenced by the frequency of doses. The compliance for this group of patients is 74.8%, with an average of 79% in the case of a dose once daily and 38% in the case of a dose three times daily. The predominant type of noncompliance in all groups was dose omissions. However, more than one-third of the patients used more doses than prescribed. Overconsumption is a frequently made mistake by patients on a one-dose daily schedule.

CONCLUSIONS — The reduction of dose frequency may decrease total noncompliance, but at the same time, it increases the risk of overconsumption. Reducing the frequency does not automatically result in a better therapeutic schedule. The choice of once or twice daily should depend on the therapeutic range of the drug.

Noncompliance with medication can be considered one of the most serious problems facing health care (1–7). The effectiveness of treatment of a disease depends mainly on two factors: the efficacy of the treatment prescribed and the rate of compliance of the patient with this treatment (8). In many cases, the desired effect of drugs is not achieved because they are not adequately used (9,10). Problems with medication compliance occur more frequently when patients are older (11,12), receive more medication (13–15), have to take their medicines regularly (16), and over a long period of time (17,18).

Since poor compliance with drugs prescribed is prevalent, uncomplicated measures are needed to improve compliance. From a practical point of view, it can be expected that a simple treatment regimen may improve compliance. Various studies have shown a relationship between the number of doses to be taken and compliance (10,19–30), but others provide no evidence for such a relationship (31–33). The results of these studies are not fully consistent, but they provide in general a view of a higher compliance with once- or twice-daily doses than with three- or once-daily doses (10,25,34–38). The results of some of these studies do not give any evidence of a difference between dosages once or twice daily (10,25,33,39–41); others indicate a clear difference between once and twice daily (28,29,42).

In older studies, compliance is mostly measured by pill counts. This method, however, provides incomplete and unreliable information that leads to doubtful conclusions. Advances in computer technology have made it possible to adapt miniature recording devices to medication dispensers to record drug use. This aid provides a means to obtain details of patients' behavior during the day and over long periods. What is more important, it also provides the possibility to observe partial compliance and the timing intervals between doses. In the past few years, this method has been used frequently to study compliance (10,28,29,34,35,39–50).

In this study, the compliance of a group of NIDDM patients was examined. One of the objectives of the study was to investigate the frequency of noncompliance among patients using drugs chronically and the relationship between dose frequency and compliance.

RESEARCH DESIGN AND METHODS

Population

Patients were recruited from two community pharmacies, based on their chronic use of one of the following antidiabetic agents: acarbose, glibenclamide, glipizide, metformin, or tolbutamide. Patients taking insulin were excluded from the study, as were patients who were unable to come to the pharmacy. The only changes made to the prescribed regimens were initiated by the prescribing physicians for reasons unrelated to this study. Patients using a weekly-dose organizer or another type of special container were also excluded.

As expected, the patients included in the trial (n = 91) were relatively old, and the group included more women (59.6%) than men (40.4%). This is in accordance with Dutch morbidity data (51,52). The mean age of the female patients was 70.1 ± 10.7 years, and the mean age of the male patients was 67.8 ± 11.2 years. The eldest patient was 90 years of age and the youngest was 45 years of age; both were female. The average number of treatment years was 7.1. All but two patients lived independently; one-

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Abbreviations: MEMS, Medication Event Monitoring Systems.

third of them lived alone. Almost one-fifth of the patients (18.5%) had complaints possibly related to complications caused by diabetes. One tablet daily was the most common dosage schedule (44.0%), twice daily was used by 39.6% of the patients, and three times daily was the least common regimen (16.5%).

Table 1—*Compliance and dosage*

Dosage	Compliance (%)	Range (%)	95% CI
Once daily	98.7 ± 18.6	19–123	92.8–104.7
Twice daily	83.1 ± 24.9	9–109	74.7–91.5
Three times daily	65.8 ± 30.1	7–102	49.1–82.5

Data are means ± SD, unless otherwise indicated.

Research design

A total of 91 patients received a 30-day supply of their medication each month in a Medication Event Monitoring Systems container, which was the only modification in their normal drug supply. This was done for 6 months. Patients were asked to keep their medication in this container, not to transfer their medication to another container, and to return it for each refill. At the start of the study, patients were asked to take part in a research project on a new type of container. Two patients refused to enter the study. All enrolled patients agreed with the procedure. At the end of the study, all patients received a questionnaire about their actions in the case of forgetting to take a tablet and about the way they normally prepare and take their medication, what they do if a dose is missed, how long they receive treatment, etc. Also, the working of the containers was explained.

Measurement of compliance

During the study, three different methods were used to measure the patients' compliance:

Electronic monitoring with MEMS. MEMS (AARDEX, Zurich, Switzerland) is a medication bottlecap with a spring-loaded device, which, when opened, triggers a switch connected to a microprocessor that records the date and time of opening. Its electronic memory also stores information about the drug (name and dosage) and the patient (patient number). Sequential openings—oocasions when containers are opened more than once in a brief period—are reported as false ones. Data were collected from the monitors by connection to a microcomputer. MEMS generates an objective simple report of the patient's dosing record continuously since the last dispensation.

Pill count. Each time the patient came back to the pharmacy for his or her prescription refill, the number of pills left in the container was counted by the technician or pharmacist who prepared the refill.

Pharmacy records. Date of refill, dosage, number of tablets, and the theoretical date when next refill would take place were registered at the pharmacy. (In The Netherlands, patients usually go to the same pharmacy for each prescription they get.)

Data from the questionnaires were used to interpret the data from MEMS. The questionnaire contained only a few questions about baseline data, such as the number of years the medicines had been used. It also contained data about the patient's habits in dealing with his or her medicine (e.g., storing in other containers) and to control if they knew their dose schedule. The mean number of days registered per patient was 154.8 ± 54.4.

Compliance

Compliance has been defined as "the extent to which the time history of drug administration corresponds to the prescribed regimen" (53). It includes both dose-taking and dose-timing aspects. In this study, compliance was defined as the number of doses taken (number of container openings) divided by the prescribed number of doses during the observation period multiplied by 100. This parameter includes partial compliance as well as overconsumption.

Another parameter used was the regimen compliance. This was defined as the percentage of days in which the prescribed dose regimen (twice, three times, or once daily) was taken as prescribed.

Deviation from the prescribed dosing intervals was another aspect of compliance. This was defined as the percentage of prescribed doses taken within 25% of the prescribed interval. For example, if the prescribed regimen was twice daily, a time period of 9–15 h between the two doses met this criterion. For once-daily prescriptions, such a time interval was 18–30 h and for three times daily it was 6–10 h.

Refill compliance was calculated with data in the medication history of the patient at the pharmacy. In this study, only too-late refills were recorded. Early refills can have other reasons apart from overconsumption.

Statistical analysis

Analysis of variance (and Tukey's honestly significant difference [HSD] test) and Student's *t* test with Bonferroni multiple comparisons were used for group comparisons. When nonparametric tests were required, the Kruskal-Wallis test was used. A value of <0.05 was considered statistically significant. Effect size statistics were calculated with Cohen's *d*.

RESULTS— The mean percentage of prescribed doses taken was 74.8 ± 26.0%, with a range from 7 to 123%. The mean percentage of days in which the doses were taken as prescribed (regimen compliance) was 67.2 ± 30.0%, with a range from 0 to 97%. These percentages are a little higher than the results obtained by other studies on compliance with chronic drug use (1,7,18,43,54,55), but are lower than those of other studies of compliance and oral antidiabetic agents (56).

In this study, the data showed a clear relationship between compliance and the number of daily doses. This in accordance with other studies (10,19–27,30). The compliance increases with a reduction of the number of doses.

Table 1 lists the compliance percentages as measured with MEMS data with once, twice, or three times daily dosage regimens. Table 2 shows the compliance with the prescribed regimen. In both cases, the differences among the three dosage regimens are significant ($P < 0.05$).

Also, the effect size statistics show a difference between the dosage regimens (Table 3). According to Cohen's interpretation of these descriptions (57), the differences in compliance between once and twice daily and between twice and three times daily can be considered medium and between once and three times daily as large. The compliance with the prescribed regimen also shows a difference: medium between once and twice daily and large between once and three times daily and between twice and three times daily.

The higher compliance with once-daily dosage schedules can be understood from observing the chronology of the different

Table 2—*Compliance with prescribed regimen*

Dosage	Compliance (%)	Range (%)	95% CI
Once daily	79.1 ± 18.8	8–96	73.2–85.0
Twice daily	65.6 ± 29.7	0–96	56.5–74.1
Three times daily	38.1 ± 35.9	1–97	21.2–55.0

Data are means ± SD, unless otherwise indicated.

patients. The first tablet was mostly taken very regularly (probably during breakfast). The taking of the second and especially the third tablets becomes more irregular.

The mean opening times of the container for patients on a twice-daily dosage (if both tablets are used) were 8:24 A.M. (±2.1 h) and 6:24 P.M. (±4.1 h). For patients on a three times daily dosage, the mean times were 7:48 A.M. (±1.3 h), 1:24 P.M. (±1.9 h), and 6:06 P.M. (±3.9 h). Figure 1 shows the most common pattern of taking medicines with a dosage of once, twice, and three times daily. Also, compliance with dose intervals is influenced by the number of doses. The differences between the three regimens are significant ($P < 0.01$) (Table 4).

The very low compliance with the dose interval at a three times daily dosage can probably be explained by the relationship with meals. Patients are advised to take their medicines with food or during meals. Using MEMS, we can observe that for an important number of people, the time of administration is concentrated during a 10- to 11-h period (between 8:00 A.M. and 7:00 P.M.). However, there is a remarkably wide interindividual variation within the once-daily dosage regimen.

If we calculate compliance using the pill-count data, the percentage of compliant patients was 72.5%. The mean number of returned tablets was 5.6 ± 16.5. The compliance of the whole group was 99.85%. There are no significant differences among the three different dosage regimens. The refill compliance (refilling on time) was 63.6%. If we only consider those patients who returned after ≥6 days noncompliant, then the compliance increases to 77.7%. The average number of days' delay was 7.8, with a maximum of 81 days. There are no significant differences in refill compliance among the different dosage regimens. Baseline patient characteristics such as the number of years the medicines were used, age, and sex do not show a correlation with compliance.

Dose omissions were the predominant type of noncompliance in all groups. But over one-third (37.4%) of the patients used more doses than prescribed. The mean number of days patients took more than prescribed was 7.7 ± 8.9 (mean number registered, 154.8 days). The mean number of extra doses used was 11 ± 16.6 (mean number registered, 306.5 doses). Overconsumption increased with a decrease of the number of doses. Almost 40% of the patients with a once-daily dosage regimen were taking more tablets than prescribed. Almost always the extra dose was taken later in the day. With twice or three times daily dosages, the percentage of overconsumption was much lower (11.1 and 13.3%, respectively). When only the number of tablets taken is used as a measure of compliance, it gives a wrong impression of the compliance of these patients because it disregards the influence of overconsumption.

Patients were questioned about their habits when they expect to overeat. Only one patient indicated that he adjusted his medication to his eating behavior. Overconsumption, thus, must be regarded as inadvertent. Over one-third (34.8%) of the noncompliance resulted in a 24-h period without any dose having been taken. This percentage of a 24-h period without therapeutic covering was higher ($P < 0.05$) among patients with a once-daily regimen than with twice ($d = 0.71$) or three times ($d = 1.12$) daily regimens. Between the last two, there is no significant difference in the number of 24-h periods without therapeutic coverage.

Differences in "drug holidays" among the three groups were less pronounced. A drug holiday was defined as ≥3 days without medication. The mean number of drug holidays was 2.53 with a regimen of once daily, 2.03 with a regimen of twice daily, and 0.59 with a regimen of three times daily. The difference between once and twice daily and thrice daily is significant ($P < 0.05$; $d = 1.71$ and $d = 1.18$, respectively).

CONCLUSIONS— Our investigation was a study of compliance with oral antidiabetic agents in three different dosage schedules. Compliance in our group of patients was 74.8%, and compliance with the prescribed dosage regimen was lower at 67.5%.

In general, diabetic patients can be considered relatively well informed about their disease and the need for medication. The compliance in this study was higher than the results from other studies of chronic drug use, but lower than studies of compliance with oral antidiabetic agents. It seems important to mention the dosages in reports about compliance because of the influence of the number of tablets to be taken daily in compliance. There is a significant difference in compliance between different dosage regimens. There is a difference in the number of tablets used and in compliance with the prescribed regimen. The pharmaceutical industry suggests that a once-daily regimen improves patient compliance. Also, some authors recommend that practitioners select medications that permit the lowest daily dose (58). Earlier, Haynes et al. (59) warned against these claims because they were not warranted.

In this study, making use of MEMS, it was possible to observe the number and moments of (possible) intake. Our results show that the compliance, the percentage of tablets used, and the number of days in which the correct number of doses was used increase with the decrease in the number of doses to be taken daily. Based on these results, it may be recommended to prescribe an easy dosage regimen of one tablet daily, and some authors do (58).

Table 3—*Effect size statistics and dose schedule*

Dosage	Compliance	Compliance with prescribed regimen
Once/twice daily	0.73	0.61
Once/three times daily	1.35	1.60
Twice/three times daily	0.61	0.81

Data are Cohen's *d* statistics.

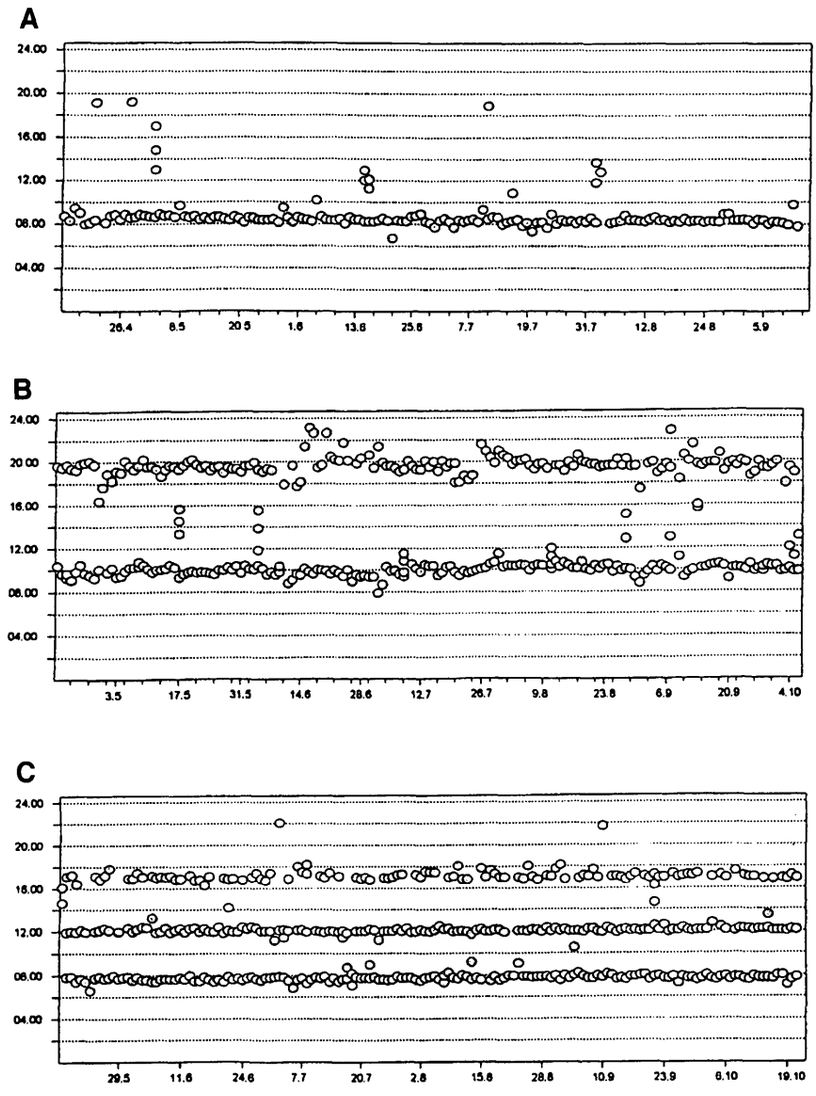

Figure 1—*Examples of once (A), twice (B), and three times (C) daily dosage regimens.*

However, at the same time, our data show that overconsumption is higher with a once-daily regimen than with a twice or three times daily one. Between the last two, there is no significant difference. Some authors recommend a twice-daily dosage as more reliable in case a dose is missed by the patient (60). In support of this practice, the results of our study show a significantly higher number of 24-h periods without therapeutic coverage among patients on a once-daily regimen. On the other hand, there are no differences in the number of drug holidays between once- and twice-daily regimens. As has been pointed out in the past, the reduction of noncompliance obtained by reducing the dosage frequency may be insufficient to overcome the result of missed doses (61).

Our results show that in a group of diabetic patients, overconsumption can also occur. Only manipulating the doses would not always result in a therapeutic optimum. A higher compliance with a once-daily regimen is accompanied by higher overconsumption and more 24-h periods without therapeutic coverage. For the practitioner, this means that he or she has to weigh the risks of partial compliance and overconsumption when choosing a dosage regimen, considering, of course, that underconsumption is more frequent than overconsumption. Also, the risk of days without therapeutic coverage has to be taken into account. The warning of Haynes et al. (59) is still valid: A dosage frequency of once daily is not always the best choice. Generally, studies of patient compliance are focused on partial compliance. The results of this study support the results of a few other studies (33,43,62) that overconsumption also has to be taken into account. Only counting the number of doses consumed overestimates compliance and does not consider the days without therapeutic coverage.

Overconsumption in the group of patients with a once-daily regimen can probably be explained as the result of the insecurity of the patient about his or her own consumption behavior. The additional intakes occur late on the day when the patient probably feels insecure about whether he or she has already taken his or her medicine or not. In the literature, it has been suggested that higher compliance can be reached when aids, such as Doset box, are used (63–66). They give visual clues and show what to discard.

A higher dosage schedule of three times daily is responsible for a higher partial compliance, but this scheme also shows a lower number of drug holidays than the other two dosage schedules. Studies of the administration of eyedrops show a higher compliance with the morning than with the evening dose (67,68). In a study of compliance with anti-epileptics, it was found that the first dose was missed more frequently (69), but in another study, no difference was found between the morning and evening intakes (50).

Table 4—*Compliance with interdose intervals*

Dosage	Compliance (%)	Range (%)	95% CI
Once daily	77.7 ± 21.1	2–98	71.0–84.5
Twice daily	40.7 ± 28.2	0–88	31.1–50.2
Three times daily	5.3 ± 5.3	1–75	2.3–8.2

Data are means ± SD, unless otherwise indicated.

As in other studies (45,49,53), our study found that the morning dose was taken more regularly than the others. A possible explanation for compliance with the first dose may be the fact that these patients are recommended to take their medicines with meals, and, of course, breakfast is the first meal of the day.

In summary, the present study supports the hypothesis that the prescribed dosage frequency influences patient compliance: the lower the dosage frequency, the higher the patient's compliance, but also the higher the overconsumption. Consequently, our results do not suggest that a once-daily regimen is always the first choice. Reducing the frequency of a dosage will not automatically result in a better therapeutic schedule because of the increase in overconsumption with a once-daily regimen and an increase of the number of 24-h periods without medication.

Another aspect is the interval between two doses. Interval compliance is highest among patients on a once-daily regimen and lowest among those on a three times daily regimen. But between once- and twice-daily dosages, there are also significant ($P < 0.05$) differences in compliance with interdose intervals (Table 3). This is the result of the fact that a second dose is taken more irregularly. If interval compliance is important, then it is important to remember that a more complicated dosage schedule may result in a higher noncompliance with interdose intervals.

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