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ORIGINAL ARTICLE

Prevalence of prednisolone (non)compliance in adult liver transplant recipients

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Summary

Limited evidence is available concerning (non)compliance with the immunosuppressive regimen in adult liver transplant recipients. In our study we prospectively assessed prednisolone (non)compliance in 108 adult liver transplant recipients using electronic event monitoring (EEM) in an outpatient setting. The EEM is a pill bottle fitted with a cap containing a microelectronic circuit that registers date and time of bottle openings and closings. Median taking compliance was 100% (range 60–105%), median dosing compliance was 99% (range 58–100%); median timing compliance (TIC) was 94% (42–100%). A drug holiday (DH) of ≥48 h was found in 39% of the patients of ≥72 h in 16% of the patients. Using EEM in liver transplant recipients, we found an overall high level of compliance for prednisolone, except that TIC was low in about one third of the patients. Age below 40 years was found a significant risk factor for decreased TIC and for DHs of ≥48 h.

Introduction

Compliance can be defined as 'the extent to which a person's behavior – taking medications, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider' [1]. The effectiveness of any treatment does not only depend on the right choice of therapy, but also on the active co-operation of the patient in the therapeutic regimen [2]. If prescribed drugs are crucial for maintaining vital physiological functions, then the medical and economic consequences of variable compliance can be large [3]. It has been reported that noncompliance with immunosuppressive drugs after kidney or heart transplantation can lead to rejection [4–7], causing graft loss or even death [8]. The presence of noncompliance after heart transplantation has been shown to relate to increased numbers of readmission's and higher total medical costs [9]. Research on compliance with immunosuppressive medication in adult liver transplant recipients is limited. Medication noncompliance as detected by unexplained low levels of cyclosporine has been found in 8–23% of patients [4,7,8,10,11]. Medication noncompliance based on self-report was found to be 3% [11]. One study reported an increase of episodes with late acute rejection in the noncompliant patient group [4].

In studying noncompliance two approaches can be identified [5]. In the first approach, 'clinical' noncompliance is assessed in relation to the occurrence of a clinical event such as a rejection episode, graft loss, or death. For example, in a retrospective review of 375 liver transplant patients (post-transplant status longer than 6 months)

Mor *et al.* [4] showed that noncompliance was a major cause of late acute rejection. A total of 31 episodes in 26 patients were identified: 18 episodes were associated with subtherapeutic cyclosporine blood levels; 7 of these episodes were due to noncompliance. The second approach focuses on subclinical noncompliance, i.e. situations not yet accompanied by, but potentially leading to a clinical event. The first approach includes only the tip of the proverbial iceberg and captures only a small proportion of the actual noncompliers. In contrast, the second focuses on the iceberg as a whole as it enables us to detect all noncompliant patients regardless of their present clinical status [5]. In the present study we are interested in the second approach in order to detect all patients showing medication noncompliance after liver transplantation regardless of their clinical status.

A 'gold standard' for measurement of medication (non)compliance does not exist [12]. The methods for compliance assessment in liver transplantation so far have been: review of patients records [13], questionnaire [11], patient interviews [8], and monitoring blood levels of calcineurin inhibitors [4,7,8,10,13]. These methods have their specific limitations [14–18]. A technologically advanced and more sophisticated method for the measurement of (non)compliance is the use of electronic devices [14,15,19]. Electronic event monitoring (EEM) refers to a pill bottle fitted with a cap containing a microelectronic circuit [14,15]. Date and time of opening of the bottle by removal of the cap is electronically registered. With EEM, frequency of over- or under-dosing, and trends in noncompliance during week or month are registered [14,18]. The data registered also allows detecting patterns of noncompliant behavior [15]. Despite the fact that electronic monitoring does not actually prove ingestion of a pill [20] it has shown to be the most sensitive measure of medication compliance research to date [18,21]. Experience with the use of EEM showed that it is highly improbable that pills are consistently removed from the bottle without being ingested by the patient over a monitoring period of approximately 90 days [21].

The aim of the present study was to assess the prevalence of prednisolone (non)compliance using EEM methodology in adult liver transplant recipients on outpatient setting. In addition, the possible relation between several variables, such as age and complexity of overall medication, was studied in order to find risk factors for noncompliant behavior.

Materials and methods

All adult patients with a follow-up of at least 1 year after liver transplantation were eligible for the present study. The study was approved by the Medical Ethical Committee of the University Hospital of Groningen. Inclusion criteria were the use of 10 mg of prednisolone once daily as part of the immunosuppressive regimen, stable clinical situation in out-of-hospital setting, literacy (Dutch language), and written informed consent. The patients were invited to participate during their protocolled yearly control after liver transplantation and were subsequently enrolled. From the medical records data were collected concerning date of transplantation, gender, age, primary liver disease, complexity of the medication regimen (immunosuppressive and other drugs) in terms of number of pills per 24 h, number of medications and number of administrations, and body mass index (BMI).

The EEM: compliance with prednisolone therapy was assessed using the Medication Event Monitoring System (Aardex® Ltd., Zug, Switzerland). The EEM consists of a pill bottle fitted with a cap containing a microelectronic circuit registering the date and time of bottle opening and closings. Openings of the bottle are recorded as presumptive doses. Stored data are downloaded to a personal computer for further analysis. Data are presented in calendar plots and a chronology. For an example see Fig. 1.

The following compliance definitions with electronic monitoring were used in this study: Taking compliance (TC) describes the percentage of bottle openings compared with the total number of doses (openings) prescribed. For example, overcompliance can be registered in this way. Dosing compliance (DC) describes the percentage of days on which the patient has correctly opened the bottle as prescribed (in our study once daily). A day was defined to begin at 03:00 a.m. local time and ending at the following day at 02:59:59 a.m. Patients who took their 1-day dose after midnight but before 3:00 a.m. were not rated as noncompliant based on this definition of a day. Timing compliance (TIC) describes the percentage of days that opening of the bottle was within 3 h of the subject's chosen time of day to routinely take their prednisolone dose. A drug holiday (DH) was defined as no medication intake (bottle opening) during 48 h or more (DH-48) or during 72 h or more (3 consecutive days) (DH-72).

For the present study the content of the EEM-medication bottle was prepared by the Pharmacy of the University Hospital Groningen and filled with 150 capsules of 10 mg prednisolone per bottle. This amount of capsules was amply sufficient for a measurement period of 4 months.

Study patients received verbal and written information about how to use the EEM-medication bottle and when to return the bottle. They were told that the cap 'registered' the intake of the prednisolone capsule. The patients were instructed to use the EEM-medication bottle for a 4-month period and take one capsule a day. After this

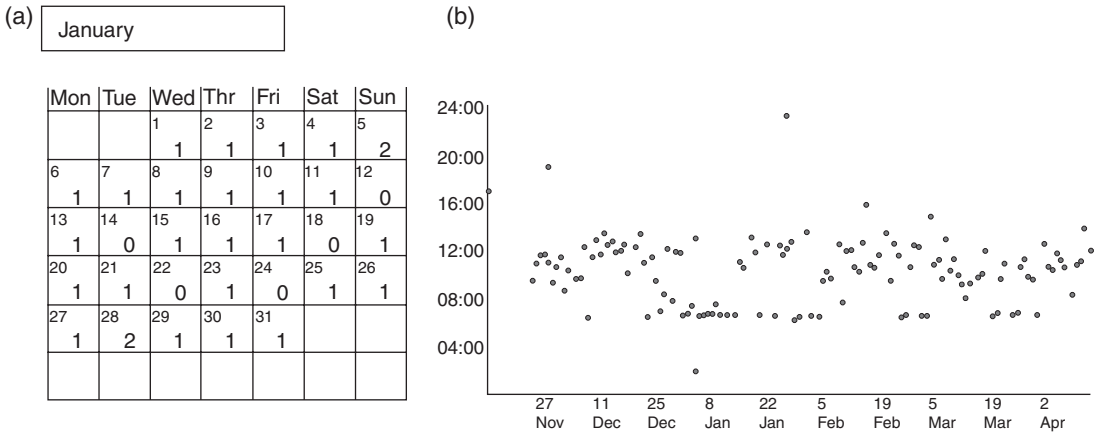

Figure 1 (a) Calender plot and (b) chronology of a study participant with poor compliance. Prescribed regimen is one capsule of 10 mg prednisolone per day at a fixed time.

period the bottle could be returned by mail free of charge.

Compliance with EEM-guidelines was determined at the completion of the study period (once the EEM-medication bottle was returned) by means of an interview by telephone.

Statistical analysis

Data were checked for normality. Descriptive statistics and frequencies were calculated for relevant parameters. Spearman correlation and Mann–Whitney *U* were used where appropriate. A *P*-value below or equal to 0.05 was considered to indicate statistical significance. All data were analyzed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Study group

Initially 123 patients fulfilled the inclusion criteria and started with EEM. However, one patient stopped EEM at the very beginning of the measurement period due to a change of prednisolone dose. The exclusion interview by telephone at the completion of the study revealed that 12 patients had violated the EEM-guidelines. The reasons were as follows. Four patients explained that they were afraid to forget their pills because they were used to a medication box. They returned to their own medication routine. Six patients admitted to take the prednisolone capsule out of the EEM-medication bottle in the evening but swallowed the capsule in the morning. And two patients did not independently manage their medication as they had partners who took completely care of the medication regimen. In addition the data of the EEM-caps of two patients could not be retrieved. Thus, after exclusion of these 15 patients, the study group consisted of 108 patients with a median age of 47 years (range 22–71); 66 were female. Patient characteristics are listed in Table 1.

Table 1. Patient characteristics ($n = 108$).

Gender (male/female) (*n*)	42/66 (39%/61%)
Age (years)	47 (22–71)
Primary liver disease (*n*)	
Primary biliary cirrhosis	20 (19%)
Primary sclerosing cholangitis	24 (22%)
Auto-immune hepatitis	16 (15%)
Cryptogenic liver cirrhosis	12 (11%)
Alcoholic liver cirrhosis	7 (6%)
Other	29 (27%)
Years after transplant	4 (1–18)
Medication complexity	
Number of pills per 24 h	10 (4–24)
Number of medications	6 (1–11)
Number of administrations	3 (1–9)
Immunosuppressive regimen (*n*)	
Pred/aza/cya	61 (56%)
Pred/aza	39 (36%)
Pred/cya	7 (7%)
Pred/tacrolimus	1 (1%)
Body mass Index (BMI)	25 (18–45)
% Overweight†	54%

pred, prednisolone; aza, azathioprine; cya, cyclosporine.
†Overweight: BMI > 25 kg/m^2.

The major etiological causes of primary liver disease were primary biliary cirrhosis (19%) and primary sclerosing cholangitis (22%). The median follow up after liver transplantation was 4 years (range 1–18). The medication regimen consisted of median 10 pills (range 4–24) and median six different drugs (range 1–11) distributed

Table 2. Prevalence of prednisolone noncompliance (%).

Compliance	Lowest	P*10	P25	P50	P75	P90	Highest
Taking compliance	60	94	98	100	100	101	105
Dosing compliance	58	92	97	99	100	100	100
Timing compliance	42	67	87	94	98	100	100

*P, percentile.

over median three medication administrations per 24 h (range 1–9). The maintenance immunosuppressive regimen consisted of prednisolone + azathioprine + cyclosporine in 57% of the patients. Overweight (BMI over 25 kg/m^2) was found in 54% of the liver transplant recipients.

Prevalence of prednisolone (non)compliance

Results are shown in Table 2 and Figs 1–3.

The TC was high with a median of 100% (range 60–105%). Twenty of the 108 patients (19%) took more prednisolone than prescribed which resulted in overcompliance. In four patients (4%) TC was below 90%, the lowest being 60% (see Fig. 2).

Median DC was 99% (range 58–100%). Forty-four patients (41%) never forgot to take one capsule each day (DC 100%). In 7 of the 108 patients (6%) DC was below 90%, the lowest being 58% (see Fig. 2).

The TIC showed large variations as can be seen in Table 2. The median TIC was 94% (range 42–100%). Only 13 of the 108 patients (12%) managed to take the capsule always about the same time of the day (TIC 100%). In 37 patients (34%) TIC was below 90%, and in 15 patients (14%) below 75% (see Fig. 2).

A DH of 48 h or more (DH-48) during the 4 months EEM monitoring was seen in 42 of the 108 patients (39%) with a median of 2 DH-48's (range 1–14) per patient. The median duration was 51 h (range 48–192). A DH of 72 h or more (DH-72) was seen in 17 of the 108 patients (16%). The number of DH-72's was median one per patient (range 1–10). The duration was median 105 h (range 72–192).

Relations between the (non)compliance parameters and patient characteristics

Significant correlations were found between TC, DC, TIC, and DH ($P < 0.01$). On the individual level however a low TIC did sometimes concur with a high TC or DC.

With respect to the parameters listed in Table 1, a significant correlation was found between TIC and age ($P < 0.01$) and between age and DHs of 48 h or more

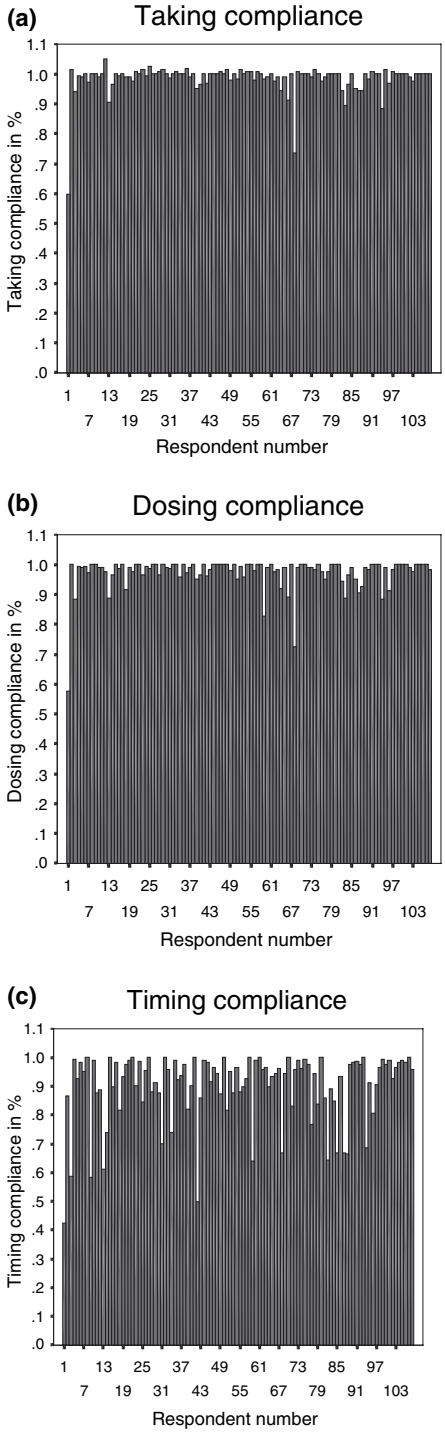

Figure 2 Bar plots of (a) taking compliance, (b) dosing compliance, and (c) timing compliance ($n = 108$ patients).

($P < 0.05$). Patients above 40 years of age showed a significantly ($P < 0.001$) better TIC compared to patients younger than 40 years (Fig. 3). They also had significantly ($P < 0.05$) less DHs of 48 h or more.

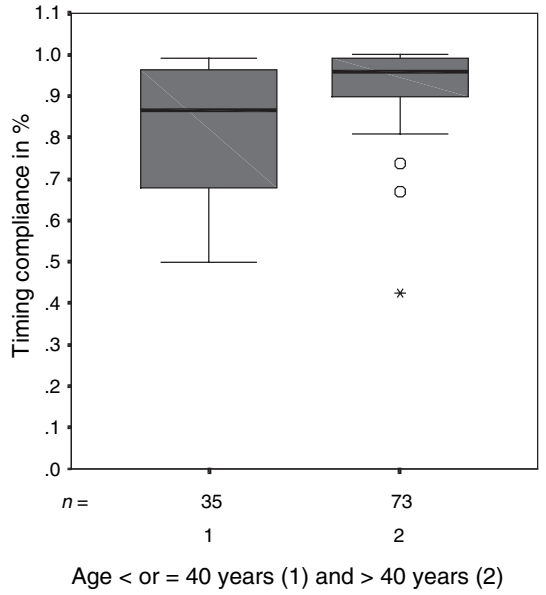

Figure 3 Box plot of relation between timing compliance and age ($n = 108$ patients, $P < 0.001$); *extreme outlier.

Discussion

Using EEM methodology we found an overall high level of compliance for prednisolone, except that TIC was lower in a substantial number of patients, which related to younger age of the patients. Younger age was also related to a higher amount of DHs of 48 h or more. Research on compliance with immunosuppressive medication and causes of noncompliance in adult liver transplant recipients is limited. The majority of studies focusing on compliance issues in liver transplantation studied alcohol recidivism [7,10,11,22,23]. A few studies report on medication compliance, with use of different methods.

Schweizer *et al.* [8] reported the first compliance study among adult liver transplant recipients. It was a prospective study in 13 patients. Patient records were reviewed concerning appointment noncompliance and medication noncompliance. Medication noncompliance was suspected when unexplained decreases in cyclosporine blood levels were observed. Three of 13 (23%) of the liver transplant patients were found to be noncompliant and two of these patients died. Mental disease and alcoholism were identified as determinants of medication and/or appointment noncompliance. Berlakovich *et al.* [10] found that 7.8% of the cyclosporine blood levels of a sample of 44 liver transplant recipients were not within target limits, suggesting subclinical noncompliance with immunosuppressive therapy. In a later retrospective study [7] among 118 patients who had undergone OLT for alcoholic liver cirrhosis drug compliance was one of the subjects investigated. Cyclosporine or tacrolimus blood levels of 19 recipients (16%) were not within the target range. Late acute rejection defined as 'any biopsy-proven acute rejection episode after 3 months following transplantation and requiring rescue therapy,' differed significantly between the compliant (5%) and the noncompliant (21%) group. Osorio *et al.* [11] compared medication noncompliance of 37 patients transplanted for alcoholic liver cirrhosis with a control group of 37 patients transplanted for other reasons using the method of self-report. Noncompliance with medication was found to be 3% in both groups.

In a retrospective review of 375 patients (post-transplant status longer than 6 months) Mor *et al.* [4] showed that noncompliance was a major cause of late acute rejection. A total of 31 episodes in 26 patients were identified: 18 episodes were associated with subtherapeutic cyclosporine blood levels; seven of these episodes were due to noncompliance. Noncompliance with the immunosuppressive regimen was documented by directly confronting the patient or families with the issue of noncompliance.

Our study differs from these studies by the use of EEM methodology which enabled us to study the whole spectrum of compliance in a group of patients not primarily suspected of noncompliance as judged by abnormal liver tests or unexplained low drug levels. The use of cyclosporine or tacrolimus blood levels can be challenged as a reliable measure of noncompliance with immunosuppressive regimen [15,17,18]. Although a drug assay is a direct measure of medication ingestion, results only prove medication intake over the past few days as the half-life of the calcineurin inhibitors prevents extrapolation of results to a longer time interval [15,17,18]. We also did not choose to study a special subgroup of patients like alcoholics. Yet, some comments on our patient group need to be made. First, by choosing 10 mg prednisolone as pill in the EEM-bottle, patients on lower prednisolone dosages, and patients without prednisolone were excluded. As mainly patients transplanted before the 90s, and patients with originally auto-immune diseases use prednisolone as part of their immunosuppressive regimen, our study group counted mainly patients with previous primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis, and lacked patients with viral disease (often former drug addicts) and contained only a small number of patients with alcoholic liver disease (Table 1). Second, by asking for literacy and Dutch language a substantial number of patients from ethnic minorities were excluded. However, although it is our experience that these groups (former alcoholic or drug addicts, patients from an ethnic minority) in general need more attention in order to comply with rules, there are insufficient data that have shown them to be consistently less compliant.

Nevertheless, we should be careful to extrapolate our findings to these groups.

We found high taking and DC in our liver transplant group, median 100% and 99.2%, respectively. These figures are much higher than those reported in several non-transplant patient groups with other drugs, also investigated with use of EEM. For example a TC of 66% is reported for migraine prophylaxis [24], 74% for isosorbid dinitrate [25], 76% for doxycycline [26], 81% in HIV-infected adults [27], 83% for long-term drug treatment in chronic disease [20], 86% for multiple anti-epileptic medications [28]. Interestingly the figures reported in renal and heart transplant recipients are closer to our liver transplant recipients. In 19 adolescent renal transplant recipients, measured for cyclosporine compliance, a TC of 91% (range 64–100%) was reported [29]. In heart transplant recipients [6,16] measured for cyclosporine compliance, TC was 99% (range 84–100%) and DC 99% (range 71–100%). In comparison with the heart transplant recipients the range of compliance was broader in our patients. It might be concluded that in general organ transplant recipients are quite good compliant but best compliant are heart transplant recipients, which seems understandable given the function of the organs.

Most worrisome was the TIC in our patient group. In 34% of patients TIC was below 90%, in 14% below 75%. The heart transplant study mentioned above [6,16] has shown the importance of taking cyclosporine at regular times of the day. It was found that occasionally taking evening doses of cyclosporine after midnight or a median variation of dosing intervals of more than 2 h and 50 min is associated with an increased risk for late acute rejection episodes. In general it is known that recommended intervals of medication intake are set in the interest of maintaining action above some minimum level [19]. When a scheduled dose is delayed it can cause subtherapeutic drug concentrations. On the contrary when a scheduled dose is taken too soon it can cause higher drug concentrations and thereby unwanted side effects.

The consequences of variable TIC with prednisolone remain unclear and need to be further substantiated.

The TIC and DH-48 in our study were found to relate to age, in that younger patients were less compliant and took more DHs. Younger age as a risk factor for non-compliance has also been found in other studies [27,30]. In a study among HIV-infected adults, patients older than 50 years demonstrated significantly better medication adherence than younger patients (88% vs. 78%) [27]. A relation between age and compliance was not present in the study in heart transplant recipients [16], probably because compliance was overall high and because these patients were overall older (median age 56 years) than our liver transplant patients (median 47 years).

If optimal compliance is considered to be at the level of 100%, an important issue is at what level noncompliance becomes clinically relevant. Our feeling is that compliance above 90% is satisfactory, but this can be questioned. Clinically relevant parameters to be investigated prospectively in this respect are related to outcome of the liver, side effects of drugs (overcompliance), costs and number of admissions, etc. Also the importance of TIC versus DC needs further study. Further study is also needed on determinants of noncompliance, besides age, especially psychosocial factors.

The present prospective study of noncompliance is considered a first step in a process to discover pretransplant determinants of noncompliance and subsequently to study the effects of pre and post-transplant interventions (for example specific education for younger patients) on noncompliance and outcome after liver transplantation. The results of the present study already imply that an intervention study will require a much larger number of patients than the present study.

In conclusion, using EEM methodology in liver transplant recipients, we found a seemingly good overall compliance for prednisolone, except that TIC was low in about one third of the patients. Age below 40 years was found a significant risk factor for decreased TIC and for a higher amount of DHs of 48 h or more. Further study is needed to determine the consequences and psychosocial determinants of less than optimal compliance, after which an intervention study can be designed.

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