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A Comparative, Multicenter, Observational Study of Medication Adherence in Liver Cirrhosis Patients and Dialysis Patients Using Electronic Event Measurement

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Abstract

Introduction: Medication adherence was only studied in a limited number of potential organ recipients. So far medication adherence was not evaluated by utilizing electronic monitoring systems in dialysis and liver cirrhosis patients. The main objective of the present study was to measure the medication adherence of patients suffering from end stage kidney or liver disease by an objectified method.

Methods: Adult liver cirrhosis patients taking propranolol and dialysis patients taking phosphate binders, each medication 3 times daily, were eligible to be enrolled in the study protocol. Medication adherence was measured electronically with MEMS™-containers over a period of 6 months in each patient.

Results: 34 patients suffering from liver cirrhosis and 36 dialysis patients participated in the study and were analysed per protocol. The Dosing Adherence (DA) rate differed significantly ($p<0.023$) between the two patient groups (mean DA rate of liver cirrhosis patients vs. dialysis patients: 61% vs. 43%).

Conclusion: Low medication adherence rates observed in liver cirrhosis patients and dialysis patients ask for better patient education. Pharmaceutical care programs enhancing adherence should be implemented in both patient groups before transplantation and continued after transplantation.

Keywords: Patient compliance; Adherence; Liver cirrhosis; Haemodialysis; Electronic assessment

Introduction

Medication adherence with immunosuppressive drugs plays a major role in the long-term success and outcome of solid organ transplantation. Low medication adherence rates may lead to rejection, graft loss and death [1,2]. According to the literature, non-adherence rates up to 50% are reported [1-5]. To improve medication adherence after transplantation different interventional methods have been implemented in clinical practice [6-9]. Thereby pharmaceutical care programs revealed to be a favourable option in order to improve medication adherence with immunosuppressive drugs [6-9]. Pharmaceutical care involves cooperation with patients and health care providers. It is necessary to cooperate with the individual patient in order to improve medication adherence, the monitoring of the medication intake, and the prevention of adverse events. Pharmaceutical care programs may also involve the family or other health care providers. Electronic devices or training videos were used as tools. Depending on the study design and type of intervention, improved dosing adherence could be achieved [10]. Two studies including liver transplant patients and one study including kidney transplant patients showed that higher adherence rates are obtained when the patients underwent pharmaceutical care [6-8]. In the study of Klein et al. liver transplant patients were educated by a pharmacist 3, 6, 9 and 12 months post transplant. Dosing adherence measured with electronic Medication Event Monitoring Systems (MEMS™) was significantly higher in the intervention group than in the control group (90.2% vs. 80.8%, p=0.015) [6].

Medication adherence can be measured by different methods which are categorized as direct (e.g. drug concentration measurement in blood or urine) or indirect methods (e.g. self-reports, pharmacy refill, pill count or electronic monitoring). Direct methods are more valid, because medication intake is proven, whereas indirect methods only assume the intake. Direct methods are more expensive and demand a higher level of effort [11,12]. Self-reports and pill count may overestimate the medication adherence. Nowadays MEMS™ are regarded as gold standard. MEMS™ are pill containers with a cap containing a microelectronic chip to automatically register the time and date of every opening of the container automatically [6,7].

Medication adherence has only been studied in a limited number of potential organ recipients. However, medication adherence of kidney recipients prior to the transplantation procedure is accepted as a predictive value for the medication adherence with immunosuppressive drugs after transplantation and the outcome of kidney transplantation

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[13]. In the underlying study 61% of patients classified as non-adherent prior to the transplantation, presented with a kidney rejection episode [13]. When medication adherence with phosphate binders was evaluated in dialysis patients by utilizing pill count or self-reports non-adherence rates up to 62% were found [14]. One reason might be the high medication load of dialysis patients due to the severity of the disease. Patients have to take 19 tablets per day on average, half of them being phosphate binders [15]. For liver cirrhosis patients, medication adherence rates are not reported in the literature. Compared to dialysis patients, liver cirrhosis patients take less medication per day. The aim of this study was to evaluate the dosing adherence rates of potential liver and kidney transplant candidates by an objective electronic measurement method.

Methods

Study design

The study was designed as a prospective, non-interventional, multi-centre observational study for patients suffering from liver cirrhosis or end-stage renal failure. The study was approved by the Ethics Committees (Institutional Review Board (IRB) of the Federal State of Rhineland-Palatinate and Hassia). Liver cirrhosis patients (LC) treated in the 1st Department of Internal Medicine, Johannes Gutenberg-University Medical Center of Mainz and patients undergoing dialysis in two dialysis centers (Kuratorium for Dialysis and Kidney transplantation) in Mainz and Wiesbaden (Germany) aged ≥18 years were eligible for the study. Further inclusion criteria comprised intake of propranolol tablets (three times daily in liver cirrhosis patients used for prophylaxis of variceal hemorrhage) and intake of phosphate binders (three times daily in dialysis patients used for prevention of hyperphosphatemia). Any type and dose of phosphate binders per dose interval was acceptable. The study was performed according to The Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients. Liver cirrhosis patients were recruited on occasion of ambulatory visits to the outpatient clinic and dialysis patients were recruited on occasion of dialysis rounds. Enrollment took place between October 2012 and May 2014.

Medication adherence measurement

Medication adherence was measured electronically with MEMS™-containers (Medication Event Monitoring Systems from MWV, Switzerland) over a period of 6 months in each patient. Data were retrieved from the MEMS™ caps by Power View® 3.5.2. Dosing -, taking -, and timing adherence rates as well as drug holidays were calculated and analyzed. The primary outcome parameter was the dosing adherence rate representing the percentage of days with the correct dosing of the medication. Patients were classified as dosing adherent (DA) when the dosing adherence rate was ≥80%. The taking adherence (TA) rate corresponds to the number of doses taken in relation to the prescribed doses. Patients were dichotomized as taking adherent when TA lay in the range of 90-110%. Resulting data were matched with the results of the pharmacy refill on the individual patient basis. Limits set for the timing adherence (TiA) amounted to ± 2 h. Missing of doses over a period longer than 48 h were documented as drug holidays.

Index medication and stability in MEMS™ containers: As the study was designed to compare two patient groups potentially undergoing solid organ transplantation two specific index medications with the same dosing interval had to be identified. Consequently, propranolol and phosphate binders were chosen as index medication for liver cirrhosis patients and dialysis patients, respectively. For all patients enrolled in the study, the medication remained unaltered. All patients got the same size of MEMS™-containers, which were filled by a pharmacist with the corresponding medication.

For liver cirrhosis patients, mostly Dociton® 10 mg or 40 mg (mibe GmbH, Germany) was prescribed. Due to the small size of the propranolol tablets, the total amount of propranolol tablets to be used during the observation period of 6 months was dispensable in one container. But stability data of propranolol tablets in MEMS™ containers were unknown. Therefore, the physico-chemical stability was determined by a HPLC-UV/VIS-method and the disintegration time of the tablets was measured over a period of 6 months.

Phosphate binders contain different types of active substances and are formulated differently. The following phosphate binders were used by the study population during the observation period:

- **Tablet formulation**

  Calcet 950 mg®, TEVA GmBH: Calcium acetate

  OsvaRen®, Fresenius Medical Care: Calcium acetate und magnesium carbonate

  Dreisacarb®, TEVA GmBH: Calcium carbonate

  Renvela 800 mg®, Sanofi-Aventis Deutschland GmbH: Sevelamer carbonate

- **Capsule formulation**

  Phosphonorm®, MEDICE Arzneimittel Pütter GmbH & Co KG: Aluminium hydroxide-complex

- **Chewable tablet**

  Fosrenol 500 mg or 1000 mg®, Shire GmbH: Lanthanum(III) carbonate

Some of the phosphate binders are delivered in multidose plastic containers. After first opening of the containers and transfer to MEMS containers the in use-stability was limited to 3 months according to the labelling of OsvaRen®. Every 3 months, study medication was sent to the patients' home in order to refill the empty MEMS containers by themselves.

Patients were asked to document in pre-printed forms if they took more than one dosage form out the container per opening or when dialysis patients skipped a meal and therefore no intake of phosphate binders was necessary.

Statistical analysis

Statistical analysis was planned in cooperation with the Institute of Medical Biometry, Epidemiology and Informatics (IMBEI), University Medical Center Mainz, Germany. The sample size of 33 patients per group was calculated for a two-sided nonparametric test to detect a difference of 15% in compliance rates between samples with a power of 80% and a significance level of 5%. The standard deviation in compliance rates was assumed to be 20%. Statistical analysis was performed with IBM SPSS v22.0 full version for Windows. It turned out that for both patient groups the dosing adherence rates and for dialysis patients also the taking adherence and timing adherence rates were normally distributed. Mean, standard deviation, 95% confidence interval, minimum and maximum rates were evaluated. For liver cirrhosis patients, the TA and TiA were analyzed as mean, median, 25th-75th percentile and the min and max rates. The t-test was applied

in order to compare the percentage rate of the dosing adherent patients in both groups. Dosing adherence rates were compared by using the Fisher`s exact test.

Due to the non-interventional study design, different types and doses of phosphate binders were used by the dialysis patients. In a subgroup analysis the mean, standard deviation, 95% confidence interval, minimum and maximum dosing adherence rates and univariate ANOVA were calculated. In the descriptive analysis p-values below 5% are considered to indicate distinct differences.

Results

Study population

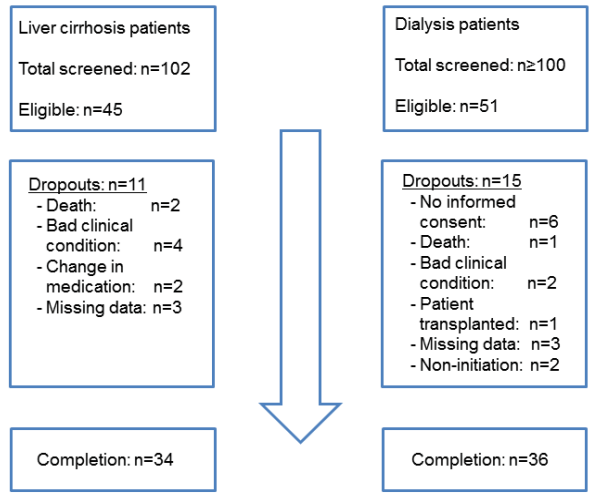
Demographic data of the study population are shown in Table 1.

Less than 50% of the invited liver cirrhosis patients agreed to participate in the study. From the 45 patients enrolled, only 34 patients completed the study (Figure 2). Reasons for decline of enrolment are given in Table 2. During 14 dialysis shifts with 2-10 patients taking phosphate binders, only 51 dialysis patients could be enrolled and only 36 patients completed the study. The reason for dropouts among others were in both groups, death, a bad clinical condition, and loss of MEMS™ caps where the compliance data are stored.

The mean monitoring interval amounted to 182 days (min. 85, max. 260) days for liver cirrhosis patients and 188 days (min. 91, max. 305) for dialysis patients.

Demographic data		Dialysis patients	Liver cirrhosis patients
Number of patients [n]	Enrolled	36	34
	Female	16	11
	Male	20	23
	Waitlisted for Tx	5	10
Age [years]	Mean	59	52
	Min.	25	24
	Max.	87	71

Table 1: Demographic data of patients who completed the study.



n= number of patients

Figure 1: Flow chart of the medication adherence study in liver cirrhosis and dialysis patients.

Medication adherence rates

The DA rate of liver cirrhosis patients (61%) and dialysis patients (43%) differed significantly ($p<0.023$, see Table 3). The average TA rates were higher in both patient groups (LC patients 75%, dialysis patients 71%).

Only 10 LC patients (30%) and 6 dialysis patients (17%) were classified as dosing adherent as shown in Table 4 ($p>0.255$). 12 LC patients and 7 dialysis patients reached TA rates >90% thus being classified as taking adherent. 12 LC (36%) and 14 dialysis patients (39%) missed drug intake longer than 48 h thus taking drug holidays. Only 6 LC patients (22%) and 4 dialysis patients (13%) were classified as adherent according to each of the adherence parameters.

Influence of type and dose of phosphate binders on DA: Patients taking Calcet®, OsvaRen®, Renvela® showed higher DA rates (46%, min. 2%, max. 99%) than patients taking Fosrenol® or Phosphonorm® (24%, min. 5%, max. 88%). Increased numbers of phosphate binder doses to be taken per day correlated with lower DA rates measured by MEMS (Figure 1). For patients taking 1.5 to 3 tablets of a phosphate binder per day, the adherence rates amounted to 55% ± 8%. In patients taking 4-6 tablets per day the adherence rates reached only 37% ±7%. The lowest adherence rates (21% ± 10%, n=5, $p<0.036$) were evaluated for patients with a prescribed dose of more than 7 tablets per day. Nine dialysis patients documented omission of phosphate binder intake, due to skipping of meals or eating less phosphate-rich food.

Pharmacy Refill: When the pharmacy refill rates of propranolol tablets were compared to the measured TA rates in three LC patients a remarkable difference of >40% (TA rates <20% and pharmacy refill rate >60%) was assessed. In total, for six LC patients, differences more than 20% were registered. Exclusion of the data of these six patients resulted in similar TA rates and pharmacy refill rates (median 89% vs. 95%). Contrary to these findings, in dialysis patients, the mean pharmacy refill rate of phosphate binders (70%) was similar to the TA rate (71%).

Discussion and Conclusion

Discussion

The aim of the study was the evaluation and comparison of the DA rates of LC and dialysis patients with an index medication to be taken in the same dosing interval. The index medication chosen for dialysis patients was any type of phosphate binder and propranolol was the medication of choice for liver cirrhosis patients. Both medications are to be taken three times daily by the majority of these patients. Unfortunately, there is no identical medication indicated in both

Reasons for decline to participate	Number of patients [n]	Percentage rate of patients [%]
Preferred a medication dosette	7	12
Switch to Carvedilol	2	4
Bad clinical condition	7	12
Stopped taking propranolol	6	11
Taking propranolol once daily	3	5
Taking propranolol twice daily	4	7
Not aware of taking propranolol	4	7
Not-taking propranolol	8	14
Reason unkown	16	28
Total number of non-participants	57	100

Table 2: Reasons for liver cirrhosis patients not to participate in the study (cursive printed rationales result from deviations between prescription and execution; n=25 out of 57).

Parameter	DA		TA		TiA		DH
	Mean [%]	95%-CI [%]	Mean [%]	25%-75%-Percentile*/95%-CI [%]	Mean [%]	25%-75%-Percentile*/95%-CI [%]	Mean [Number of days]
Liver cirrhosis patients (n=34)	61	49-73	75 (median: 88)	60-96*	64 (median: 75)	49-82*	2
Dialysis patients (n=36)	43	33-53	71	64-78	60	53-68	2

Table 3: Mean adherence rates (DA, TA, TiA) and mean number of drug holidays (DH) in liver cirrhosis and dialysis patients.

Patient groups	Category	DA [n]	TA [n]	TiA [n]	DH [n]
Liver cirrhosis patients	adherent	10	12	7	21
	non-adherent	23	22	20	12
Dialysis patients	adherent	6	7	7	22
	non-adherent	30	29	25	14

Table 4: Number of the liver cirrhosis and dialysis patients dichotomised as adherent or non-adherent according to DA, TA, TiA and DH.

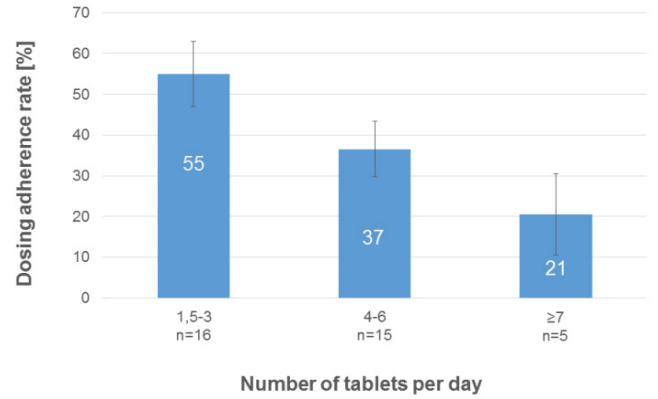


Figure 2: Correlation between dosing adherence rates and the number of tablets of phosphate binders to be taken per day in dialysis patients.

patient groups. Therefore, the comparability of the resulting adherence rates is limited by the indication, side-effects and patients' acceptance of these drugs. Although not assessed in this study, LC patients have to take in general less medication per day than dialysis patients. This fact may also cause a bias between the two groups. In dialysis patients, the size and the number of phosphate binding tablets as well as the overall medication load was suspected to influence the adherence rates.

The study was designed as a prospective, non-interventional, multi-centre study. Patients were informed about the function of the MEMS™ with a potential positive impact on the medication adherence [16]. On the other hand, it is known, that after 4 to 8 weeks, patients fall back into their conventional behaviour pattern [17,18]. As the observation period lasted 185 days on average, confounding effects at the beginning of the observation period should be equalized. Adherence was not promoted by a pharmacist's intervention.

The numerous refills of phosphate binders during the long observation period put a heavy workload on the responsible pharmacist. Patients also had to refill the containers by themselves. OtCM-blister packages with electronic circuit paths for the registration of medication removal, could be a more convenient and reliable tool for electronic event monitoring [19]. The effort to evaluate the adherence data of patients would be much lower and the number of tablets taken per dosing interval can be recorded objectively. Of note, both methods are indirect adherence measurement methods assuming when and how medication is ingested.

The recruitment process may cause a bias for false positive findings. There is a high probability that higher motivated patients are more likely to participate. Only 50% of the dialysis and of the LC patients invited, agreed to participate in the study. Among the participating patients 8 dialysis patients and 13 LC patients were registered on the transplant waiting list. These patients are assumed to be more motivated. In the recruitment phase it became obvious that many LC patients took their medication not as prescribed. This might be due to insufficient information, education and knowledge about the medication.

In both patient groups the measured DA adherence rates were lower than the expected ones (expected 70-80%). Only 10 LC patients (30%) were classified as dosing adherent. In the study of Kaiser et al. in the same hospital, 69% of patients were found to be dosing adherent with their immunosuppressive therapy after liver transplantation [7]. The discrepancy regarding the dosing adherence may be related to the different medication regimens before and after liver transplantation. Moreover, it is well known, that the dosing schedule influences the medication adherence rates and three times daily dosing is unfavourable. In contrast, once daily dosing of tacrolimus came up to a median DA rate of 100% [20-22]. The number of dosage forms to be taken per dosing interval is most probably the reason for the lower DA rate of dialysis patients with phosphate binders (43%) compared to the liver cirrhosis patients with the propranolol therapy (61%). It is well known that once or twice daily dosing correlates with higher adherence rates than three times daily dosing [20-22]. In this study the adherence rate also correlated negatively with the number of dosage forms of phosphate binders to be taken. This was not the case in the previously reported study from Patel et al., that measured adherence rates by self-reports [23].

On the other hand, dialysis patients are educated to adjust their dose of phosphate binders to the phosphate content of the meal. Thereby the calculated dosing adherence rates may be lower than the real ones. Nine dialysis patients documented omission of phosphate binder intake, due to skipping of meals or eating less phosphate containing food. Four patients regularly skipped meals and therefore the DA rates were biased. But dialysis patients should eat regularly due to the protein requirement and phosphate is present in almost every type of food and beverages, even in drinking water. Two other patients omitted the dose of the phosphate binder during the dialysis procedure, although it was not advised by the nephrologist. Taking these deviations into consideration, six additional patients were categorized as dosing adherent.

In this study the percentage rates of patients classified as taking adherent with phosphate binders assessed by MEMS™ (81%) and pharmacy refill (75%) were higher than the rate reported by Chiu et al. (62%) when pill count was used as measurement method [15]. Different results may also derive from different thresholds set. While in this study, a patient was classified as adherent when the adherence rate was >90%, Chiu et al. defined >80% as threshold.

Lower adherence rates were registered when less convenient phosphate binders (Fosrenol®, Phosphonorm®) were prescribed. However, the number of patients in each subgroup was too small to take consequences. Many dialysis patients complained about the large size of the phosphate binder tablets and the acute side effects. Capsules or pellets may represent more advantageous dosage forms. Patients' concern about possible side effects of phosphate binders deriving from absorption of calcium or aluminium can be another explanation for the low adherence rates.

Conclusion

The low medication adherence rates observed in LC and dialysis patients regarding the index medication ask for specific interventions suitable to improve the medication adherence in these patient groups.

Pharmaceutical care programs enhancing adherence should be implemented in both patient groups prior to transplantation and continued after transplantation. As these measures are costly- and time-intensive, non-adherent patients need to be identified and targeted pharmaceutical care programs to be implemented. More studies are needed to evaluate intervention tools and their effectiveness across underlying diseases.

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