

**LACK OF CORRELATION BETWEEN ADHERENCE MEASUREMENT METHODS IN NEW-ONSET EPILEPSY**Widyati*¹, Soediatmoko², Dian Maria³, Zullies Ikawati⁴, Lukman Hakim⁴¹Clinical Pharmacist, Dr. Ramelan Navy Hospital, Indonesia²Lecturer at Pharmacy, Faculty of University of Surabaya, Indonesia³Neurologist, Dr. Ramelan Navy Hospital, Indonesia⁴Senior Lecturer at Pharmacy, Faculty of University of Gajah Mada, Indonesia***Corresponding author e-mail:** widyatiw@yahoo.com**ABSTRACT**

Study aims were (1) to document adherence measurement using 3 different methods. (2) to determine the relationship between each methods. The study was conducted using cross sectional design. Patients were followed-up for 6 months and adherences were measured after 1 and 6 months therapy. The methods used to measure the adherences were 1) Patient/parent-self reported (MMAS-8 questionnaires); 2) Drug level assay and 3) seizure frequency observation. Participants enrolled were 50 patients with new-onset general epilepsy ($M_{age} = 7.2 \pm 2.0$; 54 % male; 46% female Indonesian). Patient/parent-self reported methods resulted mean overall adherence scores across patients during this 6-months period was 4.07 ± 1.15 (81.4%). Meanwhile phenytoin assay indicated only 18% patients reached therapeutics concentration. Seizure frequency observation revealed 81% improvement in seizure frequency ($t = 7.63$, $P = 0.000$) after 6 months therapy. Negative correlations were found between Parents/patients-self reporting with drug levels ($\rho = -0.082$, $P = 0.59$); Parents/patients-self reporting with seizure frequency ($\rho = -0.17$, $P = 0.24$). Correlation between seizure frequency with phenytoin level was also proved by Spearman test as no significant ($\rho = 0.12$, $P = 0.42$). 7 patients (14%) remain had seizure after 6 months but only 2 patients were having miss dose. There were lack of correlation between the various methods of adherence measurement but it does not necessarily reflect a minimum in adherence.

Key words: Adherence measurement, Parents/patients-self report, epilepsy**INTRODUCTION**

Patient adherence to Antiepileptic Drug (AED) continues to be a cause of concern within epileptic patients. For individuals with epilepsy, adherence to medication is crucial in preventing or minimizing seizures and their cumulative impact on everyday life. Non-adherence to antiepileptic drugs can result in breakthrough seizures many months or years after a previous episode and can have serious repercussions on an individual's perceived quality of life¹. Stanaway et al² found that 31% of seizures were precipitated by nonadherence to medication. And, as with other chronic medical conditions, estimates

suggest that between 30% and 60% of patients with epilepsy are not adhere with their drug regimens.^{3,4,5}

In assessing the effectiveness of prescribed medication there is a strong emphasis on the ability of the patient to adhere to the regime recommended by the clinician^{6,7}. Various tools have been developed to measure adherence but have limitations. Most research has concentrated on quantifying levels of compliance/adherence without first defining what is meant by both terms⁸. In a review of adherence studies, Vermeire et al⁹ report that adherence has largely been measured using process-orientated definitions involving number of doses missed or taken incorrectly rather than looking at the end result to health. As Farmer¹⁰ in his review of adherence

measures states, the cut-off point determining whether someone is classed as adherent or not has an important role in assessing drug effectiveness for clinical practice and clinical trials. However, if the importance of adherence is to ensure the best outcome for the patient it may be more beneficial to measure it in terms of the level required for a desirable end result for the individual⁸. The best indicator of adherence is believed to be serum drug levels. However it is difficult to translate into measures serum levels of adherence were worth when the dose or different medication. Furthermore, low serum levels may be caused not only by non-adherence but the need for higher doses, patients with impaired absorption or rapid metabolism^{10,11}. Measuring adherence can be divided into direct (blood levels, observation of drug taking) and indirect methods (patient reporting through questionnaires and diaries, pill counts, electronic monitoring), and all have varying advantages over each other¹².

Purposes: (1) To document adherence as measured by Parent/Patient-self report, phenytoin assay, and seizure frequency observation methods. (2) To examine relationship between parent/patient-self report and serum drug level with seizure frequency.

METHOD

This study was an observational study with cross sectional design that looked at various methods used in measuring adherence at 1 and 6 months. Patients were followed-up for 6 months. During followed-up patients were monitored closely by phone monitoring every month, home visit once in 6 months to assure the adherence

Participants: The present study recruited general epilepsy patients treated with phenytoin who came to Navy Hospital in Surabaya-Indonesia. Exclusion criteria applied were (1) Chronic Liver Disease (CLD), Diabetes Mellitus, Gastritis. (2) Consuming alcohol was either acute or chronic (3) Patients treated with drugs that interact with phenytoin significantly which will result in lower or raise the drug level (4) The patient has hypertension, new and old myocardial infarctions (5) Patient did not come to see the doctor and researcher for minimally 2 consecutive months. An informed consent was signed by each participant and they were personally interviewed for information on drug effects, and adherence. Ethical approval for the studies was granted by the research ethics committees of Navy Hospital in Surabaya.

Parents of children who had a new diagnosis of epilepsy and met inclusion criteria were approached by study personnel during their scheduled clinic visit. After consent was obtained, parents completed a demographics questionnaire. As a part of routine clinical care, patients returned to clinic ~1 month later for a follow-up appointment. Patients included in this study were followed-up for 6 months. Various efforts were undertaken to ensure good adherence among patients that were counseling, telephone monitoring, home visits, meeting with researchers during their clinic visits. Patients were interviewed and counseled on drug matters every visit the Neurology Clinic. Each patient had home visited and phone monitoring by researcher at least 1 time during study period.

Drug Level Assay: Blood sampling were drawn at 1 and 6 months after therapy, then separated using centrifuge into serum. Serum concentration of phenytoin was determined by HPLC. The calibration range was 0.15-50 $\mu\text{g mL}^{-1}$, and within and between day coefficient of variation (CVs) did not exceed 9%. The analytical procedure was started by addition of 50 μL Internal Standard solution (Tadalafil 100 $\mu\text{g/mL}$) into 400 μL defrosted serum along with 50 μL phenytoin 100 $\mu\text{g/mL}$. The solution was then extracted using a vortex mixer. The organic extracts were separated, evaporated to dryness, reconstituted with 150 μL methanol 40%, and transferred to HPLC auto sampling vial. An aliquot of 50 μL was injected onto the HPLC. The instrumentation (Waters Associates, Milford, MA) consisted of a solvent delivery system (flow rate: 0.3 mL min^{-1}), auto sampler, and ultraviolet detector operated at 230 nm. The mobile phase was methanol 40% within 0.5% H_3PO_4 pH 3.0. The column was Symmetry Waters C-18 (7.5cm in length, 3.5 μm in internal diameter). Calibration curves were linear ($r^2 > 0.99$) for both caffeine and phenytoin and intercepts did not differ significantly from zero.

Adherence Measures: Adherence was measured using two indirect methods that were Patient/Parent self-report and seizure frequency observation and one direct method that was drug level assay. Patient/Parent self-report method was conducted using empirically validated questionnaire generated by Donald E Morisky i.e. Morisky Medication Adherence Scale (MMAS-8)¹³. The questionnaire comprised of 8 questions which had total score of 5 for 100% adherence. Therapeutic range concentration of phenytoin in the serum/plasma was 10-20 $\mu\text{g/mL}$ ¹⁴.

Adherence was defined as 80% rate of total pills taken, medication possession ratio, and days covered by prescriptions filled¹⁵.

Statistical Analysis: Descriptive analyses, including means and SDs, were calculated for AED adherence after the first month and 6 months of therapy for children with new-onset epilepsy. Wilcoxon-Sign tests were conducted to examine differences in adherence on the basis parent/patients-self report, drug level. Spearman correlations were used to determine the relation between parent/patients-self report and phenytoin level, seizure frequency at the first clinic visit, and 6 months of therapy. Paired *t* tests and correlations were calculated between seizure frequency for the 1, and 6 months to determine differences in levels. Significance was identified as $P < .05$.

RESULTS

Characteristics of Subjects Research: A total of 50 patients with general epilepsy completed this study which comprise 27 male and 23 female, age at onset of epilepsy were infant to adult (0.6 years to 65 years). Idiopathic epilepsy was found in almost 95% of cases as shown in table 1.

Parent/Patients-self report: MMAS-8 scores at 1 month of therapy showed a wide variation from 0.5 (indicating a very low adherence) to 5.0 (indicating 100% adherence). MMAS-8 lowest score at 6 months was increasing to 1.25 which indicated an increase in adherence as shown in table 2. Mean overall adherence scores across patients during this 6-months period was 4.07 ± 1.15 (81.4%). It increased from 3.95 ± 1.06 (79%) at first month, but not significant according to Wilcoxon-Sign test result ($Z = -0.922$, $P = 0.356$). Patients were 100% adhere to their medications in 31.2% patients at first month then increased to 33.3 % at 6 months therapy, 80-100% adherence in 77% of patients, and 0% adherence in 4.2% at 6 months. Therefore, it can be concluded that overall adherence of patients within 6 months of therapy maintained in good condition.

Phenytoin Level: There were 2 patients at first month and 1 patient at 6 months had level above therapeutic concentration caused by taking too many phenytoin capsules (phenytoin was dispensed in different capsule colors). There were 6 patients (12 %) at 1 month and 9 patients (18%) at 6 months who had level at therapeutics concentration range. Mean overall phenytoin level were $6.77 \pm 6.77 \mu\text{g/mL}$ at 1 month and $6.07 \pm 5.51 \mu\text{g/mL}$. Wilcoxon-Sign indicated no significant differences in those

means ($Z = -0.89$, $P = 0.37$). Meanwhile Spearman correlation revealed no significant association between MMAS-8 with phenytoin level both at 1 ($\rho = -0.051$, $P = 0.73$) and 6 months ($\rho = -0.082$, $P = 0.59$).

Seizure Frequency: A total of 38 patients (76 %) were had 1 seizure when join the study. This number was reduced to 4 patients (8%) after 6 months therapy. Mean of seizure frequency was reduced from 1.21 to 0.23 at 6 months therapy which was significant ($t = 7.63$, $P = 0.000$) according to paired *t*-test. There were 7 patients (14%) who remain seizure after 6 months of treatment but only 2 patients were having miss dose, while 5 patients still adhere to therapy. Another interesting result was 3 patients who had stopped taking phenytoin a few days until a month but had no seizures. Association of MMAS-8 with seizure frequency was proved by Spearman test which result no significant in correlation ($\rho = -0.17$, $P = 0.24$). Correlation between seizure frequency with phenytoin level was also proved by Spearman test as no significant ($\rho = 0.12$, $P = 0.42$).

DISCUSSION

This study was the first study to document 3 different methods used simultaneously and compared in measuring adherence to AED therapy in new diagnosis of general epilepsy. The level of nonadherence, ~20%, MMAS-8 scores above indicates varies adherence level of patients in this study both at 1 and 6 months therapy. This result might be caused by wide range of age of the participants enrolled in this study. According to John E. Zeber¹⁶ older patients were poorly adherent, with rates ranging from 42% to 63% across AEDs. Moreover, adherence for the first month of treatment in children with new-onset epilepsy was 79.4%¹⁷. The score of adherence was slightly increase at 6 months therapy which means adherence was improve and yet maintained around 70%-80%. This number reflecting good adherence compare to what reported by Joane¹⁸ that mean adherence rates ranged from 51%–80% depending on drug regime and how adherence was measured. However, compared to other methods such as electronically monitored, Parent/Patient- reporting methods revealed higher score and have to be adjusted by correction factor 0.83¹⁹. The association between MMAS-8 score and drug level was low and tend to be negative correlation. This might be caused by overestimated adherence resulted by Parents/patients-reporting methods and/or interpatient variability in pharmacokinetics of phenytoin. As mention earlier MMAS-8 was a tool of patient reporting methods

which relies on the patients accurately recalling when doses were missed and/or if they were taken outside the recommended interval. *Errors can occur with this method because the patient did not answer objectively.* Overestimated patient's adherence can occur because of idealism thoughts that are not in accordance with action⁵. Besides, the desire to be judged good by the researcher adds a chance for error with this method. Meanwhile drug levels shows recent doses taken prior to attending the clinic, but a patient may have been omitting many doses previously without this being apparent¹⁸.

Good adherence as shown with MMAS-8 score also accompanied by good seizure control with almost 1.0 (81% seizure reduction) reduce in mean seizure frequency. However, once again there was negative correlation but not significant between MMAS-8 score and seizure frequency. This was similar to Jones et al⁶ who reported that in their group of patients with epilepsy, a negative correlation could be detected between seizure frequency and adherence. Gopinath et al²⁰ also found this in their study of 200 patients with epilepsy.

Quantifying adherence based on phenytoin level was difficult, because interpatient variability and less accuracy in monotherapy²¹. Only 9 patients (18%) whose level categorized as therapeutic level. In addition, mean phenytoin level both at 1 and 6 months were under therapeutic range (10-15 µg/ml). Other reason was that patient might need higher dose. Meanwhile, in seizure frequency there was 81% seizure reduction. However, the association between drug level and seizure frequency was in negative correlation. This might occurred because the measurement is only performed once at a time and the levels did not represent the average level. As mentioned previously, blood level monitoring only shows recent doses taken prior to drug sampling. Drug level assay can be useful in clinical situations that require a rapid onset of effect or for patients who manifest a higher or lower effect than expected. Patient report regarding dosage regimen and missing doses may not appropriately reflect actual adherence. Other explanation from above finding was phenytoin known to have a large variation in pharmacokinetics between individual. Several factors determine the wide variability in serum levels such as age, consumed food and drug interactions⁶. Graves et al²² reported that phenytoin levels different from the baseline value of about 5 µg / ml in patients who adherent. Interpatient variations on phenytoin levels could be as high as 30%²⁰. Although the effective measurement of serum phenytoin levels to assess the intake of the drug in patients with low adherence, but

some researchers do not consider it as a fairly accurate method for optimizing therapy, especially in patients with newly diagnosed epilepsy or get monoterapi²³.

While non-adherence may cause a seizure to occur there are many individuals who do not adhere to medication and do not experience seizures and vice versa. Patients may not perceive non-adherence as the main attributing factor in seizures occurring. When patients were asked if anything increased the likelihood of a seizure 41% mentioned stress/emotion, 19% fatigue, and only 13% stated medication missed. A study by Collin et al²⁴ found that nonadherence accounted for only 29% of the seizure control²². This is understandable because many factors that can lead to seizures and non-adherence was just one of them. Lack of correlation between the various methods of adherence measurement does not necessarily reflect a minimum in adherence. This is possible because of the difficulty of measuring adherence of epileptic patients, especially the lack of a standard measurement method. In addition to the limited research measuring adherence to anti-epileptic drugs to be the reason that reinforces the difficulty of measuring adherence. Achievement of outcomes in the form of decreased seizure frequency is a measure of the effectiveness of therapy²⁴. As Choo et al.²⁵ highlight, the method of measuring adherence is dependent on how the variations in adherence can affect health outcomes. Further recognition and support should be given to patients who have poor seizure control since they are more likely to be more anxious and have unhelpful illness and treatment beliefs⁵.

CONCLUSION

Adherence measurement results using the method of Parents/Patients-self report showed good adherence (70-80%) for 6 months of therapy. While the result of phenytoin assay method showed 18% under therapeutics concentration and seizure frequency observation resulted 81% seizure reduction. Negative correlations were found between Parents/patients-self reporting with drug levels; Parents/patients-self reporting with seizure frequency, however it was not significant. The association between drugs level with seizure frequency was not significant.

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Table 1 Basic characteristics of the study subjects.

Characteristics	Value	Standard Deviation
Gender		
Male	27	
Female	23	
Age	0.6-65 year	1.5
Weight	32.2 kg	1.73
Epilepsy		
Idiopathic	47	
Post-Stroke	3	

Table 2. Result of adherence measurement

Parameter	Range	Mean	Std Deviation
MMAS-8	0.5-5.0	3.95	1.06
At 1 month			
MMAS-8	1.25-5.0	4.07	1.15
At 6 months			
Phenytoin level	0.19-34.75 ug/mL	6.77 ug/mL	6.77
At 0 month			
Phenytoin level	0.05-23.51 ug/mL	6.07 ug/mL	5.51
At 6 months			
Seizure frequency	0-2 times/month	1.21	0.74
At 1 month			
Seizure frequency	0-3 times/month	0.23	0.63
At 6 month			

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