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PROF. PETER WOLF (Orcid ID : 0000-0003-2547-976X)

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Single antiepileptic drug levels do not predict adherence and non-adherence

Mariana Lunardi[1,2], Katia Lin[1,2,3], Roger Walz[2,3], Peter Wolf[2,4]*

[1] Neurology Division, Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil

[2] Medical Sciences Post-graduate Program, Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil

[3] Center for Applied Neurosciences (CeNAp), Federal University of Santa Catarina, (UFSC), Florianópolis, SC, Brazil

[4] Danish Epilepsy Centre, Dianalund, Denmark

*Corresponding author:
Peter Wolf
Dag Hammarskjölds Allé 5
DK- 2100 Copenhagen
e-mail: wolfcph@gmail.com
Tel: +45-40106511

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Abstract

Objectives: To investigate the significance of ”subtherapeutic” versus ”therapeutic” antiepileptic drug (AED) plasma levels with respect to treatment adherence.
Material & methods: 170 patients with refractory temporal lobe epilepsy who underwent video-EEG monitoring in view of a surgical indication had their AEDs (carbamazepine, phenobarbital, phenytoin and valproate) rapidly withdrawn following a standardized schedule. Plasma levels were measured at admission, and during the two days of drug withdrawal. Adherence and non-adherence were identified by the development of Plasma levels from day 1 through day 3. Frequencies of an initial level below the reference range in both groups were compared.
Results: Adherence was found in 73.2% of cases, and non-adherence in 26.8%. Low levels were seen equally often (about 1/4 of cases) in adherent and non-adherent cases. The vast majority (73.7%) of low levels had another explanation than non-adherence (e.g. low-dose treatment or enzyme induction). Of 42 non-adherent cases the vast majority of 76.2% had unsuspicious Plasma levels at admission.

Conclusions: "Subtherapeutic" AED Plasma levels only rarely are caused by non-adherence whereas levels in the "therapeutic range" by no means prove that the patient is adherent to treatment. For meaningful interpretation, any level needs to be compared with other levels of the same patient. Our findings strongly emphasize the principle of individualized therapeutic AED monitoring as promoted by the Therapeutic Strategies Commission of the ILAE.

Key words: bioequivalence - enzyme induction – individualized therapeutic level – preparation shifts - rapid metabolization – therapeutic antiepileptic drug monitoring – therapeutic range - therapeutic threshold

Introduction

Therapeutic or reference ranges (RR) of plasma levels (PLs) have been formulated for many antiepileptic drugs (AED) to help with the management of epilepsy. Non-adherence to AED treatment is a frequent problem in epilepsy and has been reported in 26 – 79% of cases[1]. It varies widely, from occasional missed doses to deliberate refusal of pharmacotherapy. Among the clinically most relevant cases are those that affect the prescribed drug's steady state concentration. PL determinations, if applied correctly[2], can help to reveal these. A PL below the general RR will raise a suspicion of non-adherence. However, low AED levels may have many other reasons including low-dose treatment, pharmacokinetic interactions, or absorption issues. Controlled AED withdrawal during presurgical intensive video-EEG monitoring, a well-established clinical procedure[3], provides a unique opportunity, by assessing the evolution of PLs at taper, to identify cases of substantial non-adherence. The aim of our analysis is to provide clinicians with data to better interpret levels in and below the RR with respect to adherence.

Material and methods

We reviewed the records of all consecutive adult patients with pharmacoresistant mesial temporal lobe epilepsy related to hippocampus sclerosis who from November 2008 to July 2013 were admitted for video-EEG monitoring of seizures during presurgical evaluation at the Centro de Epilepsia de Santa Catarina (CEPESC), at Hospital Governador Celso Ramos, Florianópolis, Brazil.

In the 24 months preceding the video-EEG, all patients had received monotherapies with maximal tolerated doses of at least two AEDs during which they had at least one focal unaware seizure per month (median 5, interquartile range 3-8). The treatment at admission, however, was different, often representing a viable compromise between drug load and seizure frequency. In order to provoke seizures, all patients underwent a standardized controlled stepwise AED withdrawal.

Prior to admission to the monitoring unit, all patients gave their consent for investigations on patient's records. All records were reviewed for the purpose of this study which was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 2014) and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. This work was approved by the Ethics Committee for Research in Humans of the UFSC (process 1954, FR 432374).

The AED withdrawal was rapid[4], was accompanied by daily AED serum level monitoring, and was performed as follows: all patients were admitted on Sunday evening (day 0) on which they had taken their usual AED dose at home. On Monday morning (day 1) a trough AED level (PL1) was determined whereafter patients received half their habitual daily dose divided in two equal or quasi-equal (morning and evening) doses, only in the case of phenobarbital in one evening dose, and a trough PL (PL2) was measured again on the next morning (Tuesday = day 2). After blood-sampling patients received their last AED dose equal to Monday morning, and a third sample (PL3) was taken on Wednesday morning (day 3). This stepwise procedure was applied both with monotherapy and AED combinations. As the only exception, phenobarbital in daily doses up to 100 mg was withdrawn immediately. With this procedure, a stepwise fall of the PL (PL1 > 2 > 3) should be observed.

The hospital laboratory measured AED plasma levels by Abbott Laboratories fluorescence polarization immunoassay for carbamazepine (CBZ, RR 4-12 µg/mL), phenytoin (PHT, RR

10-20 µg/mL), valproate (VPA, RR 50-100 µg/mL), and phenobarbital (PB, RR 15-40 µg/ml[2,5] .

All information on doses and PL was prospectively entered in a database that provides the basis of the present evaluation. PL 1 was compared with the reference ranges of the relevant AEDs and rated as “low” when it was below the RR, and as “standard/high” when it was within or above the RR. In AED combinations, each drug was considered separately and in this report constitutes a “case”. Adherence and non-adherence were established according to the PL development from PL1 over PL2 to PL3.

Adherence was assumed when the levels showed the expected stepwise fall of PL1 > PL2 > PL3. Maintenance or increase of PL on day 2 indicates that the nominally reduced dose on day 1 was most probably not below the dose taken at home. Therefore, non-adherence was assumed when the levels did not fall, or even increased, from PL1 to PL2.

Statistical analysis was performed using GNU PSPP4 software package for Mac OSX. Descriptive analysis was made to characterize the sample. Quantitative variables were expressed as mean ± standard deviation (SD), and qualitative variables were expressed as percentage values. Pearson's chi-square test was used. The stepwise fall in plasma levels was evaluated by a one-way repeated measures analysis of variance (ANOVA). A p-value < 0.05 was considered statistically significant.

Results

One hundred and seventy patients were admitted to video-EEG between November 2008 and July 2013. The mean length of the video-EEG monitoring was 4.07±1.80 days (0-10 days). Patients’ demographic and clinical variables are described in Table 1.

< Table 1 approx. here >

102 patients were on monotherapy, 67 on double, and one on triple medication, so there were a total of 239 individual “cases” of drug administration. Of these, 24 were with drugs for which the laboratory did not offer determination (clobazam, lamotrigine, oxcarbazepine). Of the remaining 215 cases, 39 had to be eliminated because of missing

data, and 17 CBZ cases were excluded due to therapeutic deviation from protocol by administration of CBZ rescue medication on day 2 in response to secondarily generalized tonic-clonic seizures. The stepwise fall in plasma levels with taper is shown in supplementary table 2.

The results with respect to adherence are presented in figure 1. Overall, 115 cases (72.3%) presented good adherence whereas 42 (26.4%) showed poor adherence. 2 cases with PB (1.3 %) presented a small decrease from PL1 to PL2 followed by a small increase to PL3 which is difficult to explain. They were rated as “inconclusive”.

< Figure 1 here >

When cases with good and poor adherence were compared with respect to PLs at admission, there was no significant difference. About one quarter of cases in both groups was admitted with low AED plasma levels (figure 2). No zero value was found in any case. Of 38 cases with low levels, the vast majority of 28 (73.7%) proved adherent. Of the 42 cases identified as poorlyadherent, the vast majority of 76.2% were admitted with an inconspicuous PL. We could exclude bias caused by exclusion criteria by assessing the rate of low levels also in those cases with missing data where PL1 was known (6 out of 18).

Intriguingly, low levels were much more frequent with PB, PHT and VPA than with CBZ.

< Figure 2 here >

Discussion

Results: Outside specialized epilepsy centres it is often assumed that “subtherapeutic” AED levels indicate that the patient is not adherent to the prescribed treatment. Our data show that this conclusion is erroneous. Low levels were found with about equal frequency in adherent and non-adherent cases, and ¾ of the cases with low levels proved adherent. Likewise, an AED PL in the general “therapeutic” or “reference” range is by no means proof of adherence. Of the non-adherent patients in our study, the vast majority met at hospital admission with an unsuspicious PL.

There are many possible explanations for a low PL, and the most typical ones follow.

Low PLs often simply reflect low-dose AED treatment chosen because of full treatment effect at low dose or to minimize untoward effects. The first of these two reasons obviously does not apply in our drug-resistant cohort but the second does and may explain the higher rate of low PLs in PB and PHT where there is most concern about side effects. .

Standard doses may produce low PLs in the rare patients who are rapid metabolizers[7]. We had no possibility for pharmacogenetic testing but observed a strongly suggestive case on 1200 mg CBZ with a PL1 of only 3 µg/ml, followed by a perfectly logical stepwise fall over the following days. The level-dose ratio of this case was 0.0025 whereas the normative ratio in adults is about ten times higher (0.02 ± 0.01, SD)[8].The purpose of this investigation is not to elucidate pharmacokinetic mechanisms behind the factual data which we analyze. However, a characteristic cause of low PLs is co-medication with enzyme-inducing drugs[6]. Of the four AED in our study, this applies to VPA whereas the three others are enzyme inducers. Indeed, for 25 combination treatments with VPA even the group average of PL1 was below the RR (44.9 ± 4.8) with 15 cases below 50 µg/ml whereas the PL1 of 8 monotherapies were all but one within the RR, with a group average about double the polytherapies (85.75 ± 8.8). Thus, low VPA PLs were primarily due to enzyme induction. For the three other drugs, PL1 group averages of mono- and polytherapies were essentially the same.

Another possibility, i.e. reduced bioavailability after change of preparation[9,10] is particularly relevant in countries including Brazil where rules for generic substitution result in frequent preparation shifts. This factor we could not assess.

Methods: Any conclusions from AED measurements on adherence presuppose that several PLs of the same patient at the same dose (and ideally with the same preparation) can be compared. An example is the investigation of Carpentier et al[11] who studied 44 patients with refractory focal epilepsies during a 5-day in-hospital observation with controlled intake of AEDs and where drug regimens remained unchanged. PLs were taken on day 1 and 5, and a difference of > 30% was defined as an indication of non-adherence. 18 patients (40.9%) were non-adherent, and overdosing surprisingly was the most common type (two thirds of cases) of nonadherence. This would not have been detected in our study which

can explain the lower rate of nonadherence found in our comparable setting. It should also be noted that our nonadherence rate is per drugs; per patients it would be different.

The procedure we applied cannot identify small deviations from perfect adherence like occasional missed doses, but the detection of non-adherence also is not the purpose of this study. Our findings reveal, however, that even deviations from dose that are substantial enough to affect steady state plasma levels only rarely result in a single PL below reference range.

In the optimal case, a questionable PL can be compared with the patient's already established individual therapeutic level[2,12] or, even better, therapeutic threshold[13] . This approach was taken by Specht et al[14] who were in care of residents of a vocational training centre for young adults with epilepsy where therapeutic AED monitoring is a standard procedure. They determined immediate postictal PLs to clarify unexpected breakthrough seizures in a group of 52 patients. Nonadherence was assumed when the postictal PL was <50% of the mean of 2 previous PLs on the same medication at steady state. It explained seizure recurrence in 44.3% of cases.

Limitations: Our data were generated in a cohort of pharmacoresistant TLE patients prepared to try epilepsy surgery, and do not represent the general epilepsy population. Our operational definition identifies substantial non-adherence that affects steady state plasma levels but no minor deviations from perfect adherence. The identified cases, however, are clinically more relevant.

Conclusions

Our data show that single PL determinations do not predict adherence or non-adherence. A "subtherapeutic" AED plasma level in most cases has other causes like deliberate low-dose treatment, enzyme induction by co-medication, rapid metabolization and others. Likewise, the finding of a PL "in the reference range" does not mean that the patient is fully adherent and no attention needs to be paid with him/her to the matter. For any meaningful interpretation, a given PL needs to be seen in context with comparable measurements in the same patient.

Our findings thus strongly emphasize the principle of individualized therapeutic AED monitoring which was promoted in recent years by the Commission on Therapeutic Strategies of the International League against Epilepsy[2] and in its educational journal[12], and which is central to the correct use of drug monitoring in the treatment of epilepsy.

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Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1. Clinical and sociodemographic characteristics of 170 temporal lobe epilepsy patients submitted to video-EEG.

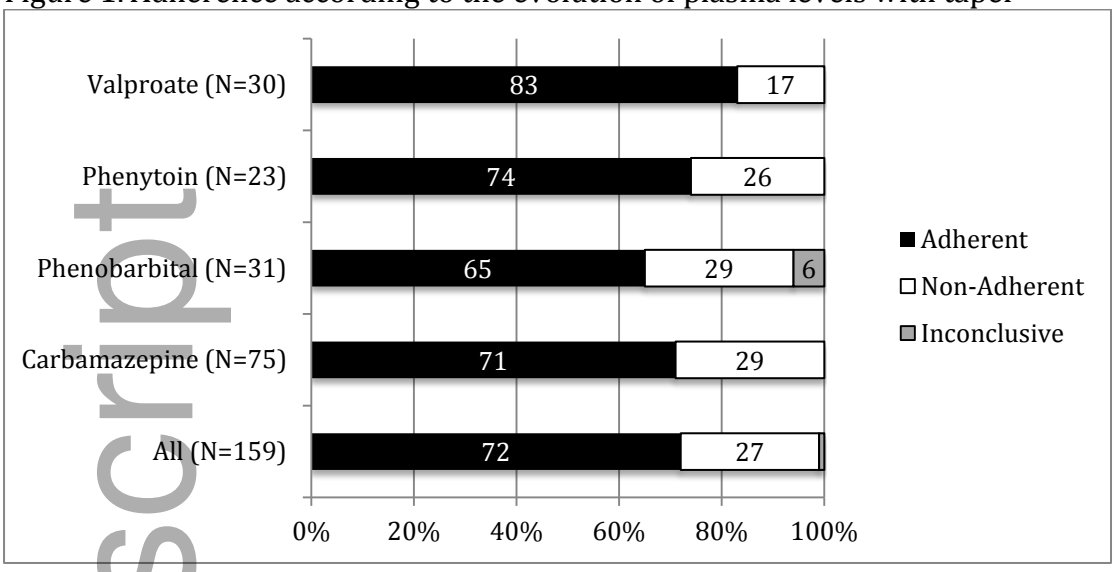
Clinical and sociodemographic characteristic	Frequency or Mean±SD	Range
Sex	91 women	
Age at VEEG (years)	35.52±10.35	12-63
Mean age of onset of epilepsy	11.87±9.57	0-45
Mean duration of epilepsy (years)	23.73±12.25	2-57
Number of CPS/day	0.47±0.81	0-7
Number of GTCS/day	0.02±0.10	0-0.93

Table 2. Plasma levels on first, second and third day of monitoring.

AED	Mean±SD	Range	Reference range	Decrease from PL1 to 3	p^a
Carbamazepine			4-12 µg/ml	27.6%	< 0.001
PL 1	7.08±2.86	1-14			
PL 2	6.11±2.91	1-15			
PL 3	5.13-3.15	0.25-12			
Phenobarbital			15-40 µg/ml	24.0%	< 0.001
PL 1	21.27±10.84	5-49			
PL 2	17.66±8.99	3-40			
PL 3	16.17±7.75	5-30			
Phenytoin			10-20 µg/ml	21.3%	< 0.001
PL 1	11.60±6.78	3-31			
PL 2	11.04±7.96	2-38			
PL 3	9.13±8.64	1-38			
Valproate			50-100 µg/ml	62.0%	< 0.001
PL 1	54.78±29.80	7-108			
PL 2	39.82±29.57	1-112			
PL 3	20.73±27.36	0-89			

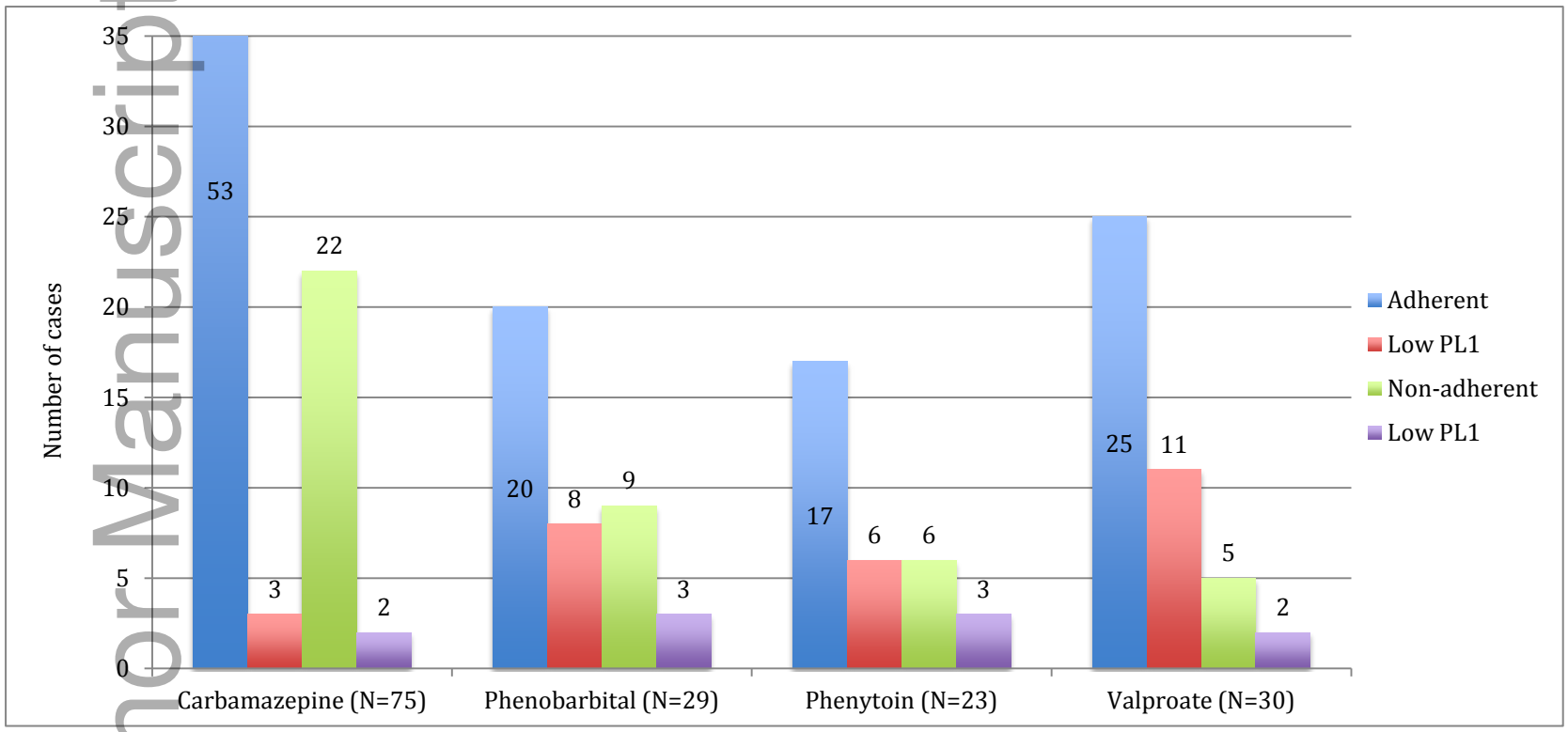
[a] A one-way repeated measures analysis of variance (ANOVA) was conducted to evaluate the null hypothesis that there is no stepwise fall in patients' plasma levels (PL1 > 2 > 3). The results of the ANOVA indicated a significant fall of the plasma levels, for example, for Carbamazepine, Wilks' Lambda = 0.46, $F(2, 53) = 30.29$, $p < 0.001$, $\eta^2 = 0.53$. Follow-up comparisons indicated that each pairwise difference was also significant, $p \leq 0.05$, except for Phenytoin PL1-PL2 only. Therefore, plasma levels significantly decreased over time.

Figure 1. Adherence according to the evolution of plasma levels with taper



The figures in columns represent percentages

Figure 2. Low plasma levels at admission (PL1) associated with adherence vs. non-adherence



The two inconclusive cases were eliminated.
Lower plasma level is less frequent with CBZ than the three other drugs that are about level (Chi^2 test, $p < .0001$)
Lower plasma level is not more frequent with non-adherence (Chi^2 test, n.s.)