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Blood concentration, efficacy, and adverse events of phenobarbital: A prospective study in rural China

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ABSTRACT

Objective: This study evaluated the relationship between blood concentration of phenobarbital (PB) and its efficacy as well as adverse events in people with epilepsy in rural China.
Methods: People with epilepsy being treated with PB monotherapy were recruited and followed up for averagely 2.5 years. Data of clinical characteristics were collected using a standardized questionnaire by face-to-face interviews both at baseline and follow-up. Plasma concentration of PB was detected by the high-performance liquid chromatography.
Results: Data on treatment response and PB blood concentration was obtained from 225 subjects. Among them, 119 (52.9%) were recognized as effective cases and 106 (47.1%) as ineffective cases. In the effective group, the blood concentration of 95% subjects ranged from 1.22 μg/ml to 41.36 μg/ml with a median at 13.18 μg/ml (IQR = 8.32–20.19 μg/ml). The PB concentration of 95% of the subjects in the ineffective group ranged from 2.73 μg/ml to 70.16 μg/ml with a median at 19.80 μg/ml (IQR = 11.30–30.40 μg/ml), which was significantly higher than that of the effective group ($p < 0.001$). Multivariate logistic regression analysis showed that PB concentration ≥26.38 μg/ml was related to a 4.5-fold (95% confidence interval [CI], 1.85–11.08) higher risk of inefficacy. A receiver operation characteristic curve was performed to determine the cutoff value of concentration for PB efficacy at 19.02 μg/ml.
Significance: Blood concentration may be an important indicator for clinical decision making when PB monotherapy cannot achieve a good efficacy and more attention should be paid on it in clinical practice especially in resource-poor settings.

1. Introduction

Epilepsy, with approximately 50 million people affected worldwide, is one of the most common serious neurological disorders, with no age, racial, social class, national, or geographic boundaries [1]. With the correct diagnosis and treatment, many people with epilepsy will have a significant reduction in seizure frequency or be seizure-free [2]. Up to 80% of people with epilepsy live in low- and middle-income countries, and 60–90% of them receives no treatment or is inadequately treated because of deficiencies in healthcare resources and delivery, and social stigma [3].

In 1997, the World Health Organization (WHO), in cooperation with the International League Against Epilepsy, launched the Global Campaign Against Epilepsy [4]. The project in China included an epidemiological survey, an intervention trial, and an educational program in the target areas [3]. Patients with convulsive seizures were treated with phenobarbital (PB) by primary-care physicians; more than half of the patients became seizure-free by the end of the study, and no patient withdrew because of severe adverse events [5]. Another advantage of PB is its low cost (the annual cost in China is about US$2.5 per patient), which is important in resource-poor countries [6]. It was therefore concluded that the PB treatment protocol is feasible, and PB has good efficacy and tolerability as well as low cost, therefore it can help to reduce the large treatment gap in resource-poor countries [7,8].

Previous researches above only focused on the relationship between the therapeutic dose range and efficacy as well as adverse events of PB. However, the drug concentration, efficacy, and adverse events differ greatly among individuals even treated by the same dosage of PB. Personal variability (idiosyncrasy) in drug metabolism, weight, and body surface area all can impact drug concentration and subsequent efficacy and adverse events. Additionally, the data of PB dosage come from the

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self-reported questionnaire that could lead to recall bias and could also be influenced by patient compliance.

In hospitals with a neurology department, blood concentration of antiepileptic drugs (AEDs) monitoring is a routine procedure on treatment and adverse events evaluation to people with epilepsy. From 2005 in China, with the expanded project of the Global Campaign Against Epilepsy, free PB was provided to approximately 100,000 people with epilepsy in rural areas; however, PB concentration monitoring was not included in the project. We conducted a follow-up assessment of the people with epilepsy who were certified on regular treatment of PB monotherapy in order to evaluate the relationship between PB blood concentration and its efficacy as well as adverse events in people with epilepsy in rural China.

2. Methods

2.1. Study subjects

People with epilepsy aged ≥ 14 years and permanently resident in rural Shanxi and Ningxia provinces were eligible and were recruited between May 2010 and June 2011. Trained local primary care physicians made the initial diagnosis using a specially designed questionnaire to screen possible cases of convulsive epilepsy. A supervising neurologist then assessed screen-positive individuals to confirm the diagnosis. In the current study, we included study subjects who have been treated with PB monotherapy for at least two weeks. People who met the following criteria were excluded from the study: provoked seizures only (e.g., seizures induced by drugs, or alcohol, or insomnia, or febrile seizures, or pregnancy); age under 14 years at the time of the study; presence of a progressive neurological condition; presence of cardiac, hepatic, or renal disorders, current adequate medical treatment; or severe hypertension; status epilepticus alone; treated with other AEDs or polytherapy.

The study was approved by the Medical Ethics Committee of Huashan Hospital Fudan University, Shanghai, China. All participants and/or their legally acceptable guardians provided informed consent.

2.2. Assessment of clinical characteristics at baseline and follow-up

At baseline, local physicians conducted a face-to-face interview to collect information using a standardized questionnaire including demographics, disease duration, seizure frequency (the average number of seizures per year), seizure type (partial seizures and generalized seizures), and PB dosage. A follow-up assessment of the study subjects was conducted between June and December 2013. Seizure-free cases were defined as the patients who became seizure-free during the last 6 months. Effective cases were defined as those with >50% reduction in the seizure frequency compared to that of the baseline [9]. The effective group included seizure-free cases and effective cases, and the remaining was defined as the ineffective group. The efficacy of PB treatment was determined in terms of the percentage of seizure-free and effective cases at the 2.5-year follow-up.

2.3. Plasma concentration of PB

The PB blood level was measured at baseline. Blood was obtained by venipuncture from study subjects with fasted abdomen in the morning. After centrifugation, plasma was collected for PB concentration measurement. The plasma samples were first stored at −80 °C and then transported by cold chain to center lab at Huashan hospital.

A simple reversed-phase high-performance liquid chromatography (HPLC) method had been developed for the simultaneous determination of PB and several antiepileptic drugs in human plasma. Plasma (100 μl) was pretreated by deproteinization with 300-μl methanol containing 20-μg/ml propranolol hydrochloride as internal standard. The HPLC was performed on a C8 column (4.6 mm × 250 mm; particle size 5 μm) with methanol–acetonitrile −0.1% trifluoroacetic acid, 235:120:645 (v/v), as mobile phase at a flow rate of 1.5 ml/min. Phenobarbital was monitored by ultraviolet (UV) detection at 215 nm. Relationships between response and concentration were linear over the concentration ranges 5–100 μg/ml. The method was proved to be accurate, reproducible, convenient, and suitable for therapeutic monitoring of the PB [10,11].

2.4. Statistical analysis

Analysis dataset was defined as completed data of clinical outcome assessment and PB concentration at the follow-up. Patients whose PB concentration was zero were excluded from the dataset.

Data are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) if the variable was not normally distributed; categorical variables are given as frequencies (%). Continuous data were compared by Student's *t*-test or Mann–Whitney *U* test, as appropriate, and categorical data by chi-square test. Logistic regression analysis was performed to analyze the relation between PB efficacy or adverse events and PB concentration, by adjusting confounders such as gender, age, duration, and seizure frequency. To determine the cutoff points of plasma concentration for PB efficacy and adverse events assessment, receiver operating characteristic (ROC) curve analysis was performed. The ROC curve of PB plasma concentration was constructed by plotting sensitivity against 1-specificity at a range of thresholds. Area under the curve (AUC) was used as the measure of overall diagnostic accuracy. The optimal cutoff points were determined using Youden's index.

All of the p-values and 95% confidence intervals (CIs) were estimated in a two-tailed manner. Differences were considered to be statistically significant at $p < 0.05$. Data were analyzed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Data of treatment response and PB blood concentration was obtained in 225 people with epilepsy who were on PB monotherapy. Among them, 119 (52.9%) were recognized as effective cases and 75 (33.3%) became seizure-free for at least 6 months. The descriptive statistics for the demographic, clinical characteristics, and treatment variables of the subjects were summarized in Table 1. Among 225 subjects, 52.9% was determined as the effective group and the remaining 47.1% was in the ineffective group. No significant difference was found between the two groups on gender composition, age, disease duration, seizure frequency, seizure type, and occurrence of adverse events.

The distribution of PB blood concentration was significantly different between the two groups (Table 1; Fig. 1A). The PB blood concentration in the effective group ranged from 0.21 μg/ml to 66.14 μg/ml and 95% distributed in 1.22–41.36 μg/ml. In the ineffective group, PB blood concentration ranged from 0.76 μg/ml to 76.87 μg/ml and 95% distributed in 2.73–70.16 μg/ml. Moreover, the median of PB concentration of the ineffective group (19.80 μg/ml, IQR = 11.30–30.40 μg/ml) was significantly higher than that of the effective group (13.18 μg/ml, IQR = 8.32–20.19 μg/ml, $p < 0.001$). In line with blood concentration, distribution of self-reported PB dose in the two groups was significantly different ($p = 0.039$). The median of the PB dosage of the ineffective group was 120 mg/day, which was significantly higher than that of the effective group (90 mg/day, $p = 0.005$).

Multivariate logistic regression analysis was performed to analyze the relation between PB efficacy and concentration by adjusting confounders such as gender, age, duration, and seizure frequency (Table 2). The PB concentration ≥ 25.86 μg/ml was related to 4.5-fold (95% CI, 1.846-11.076; $p = 0.001$) higher risks of inefficacy compared with the reference concentration category. To find out the cutoff value of PB concentration to efficacy, an ROC curve of PB blood concentration was performed with an AUC of 0.644 (95% CI, 0.571–0.716) (Fig. 2A).

Table 1
Comparisons of variable between the effective group and the ineffective group.

	Total	Effective	Ineffective	p-Value
Number of patients (%)	225 (100)	119 (52.9)	106 (47.1)	
Variable				
Gender				0.663[a]
Male (n, %)	135 (60)	73 (61.3)	62 (58.5)	
Female (n, %)	90 (40)	46 (38.7)	44 (41.5)	
Age (year), mean (SD)	39 (14)	41 (13)	38 (14)	0.084[b]
Disease Duration (year), median (IQR)	20.0 (12.0, 27.0)	20 (11.0, 28.0)	20 (12.5, 26.0)	0.978[c]
Seizure Frequency (/year), median (IQR)	5.5 (1, 24)	4 (0, 24)	6 (1, 18)	0.549[c]
Type				0.189[a]
Partial (n, %)	100 (44.4)	48 (40.3)	52 (49.1)	
General (n, %)	125 (55.6)	71 (59.7)	54 (50.9)	
Concentration (μg/ml)				**0.001**[a*]
[0.21, 8.98] (n, %)	56 (24.9)	33 (27.7)	23 (21.7)	
[8.98, 15.20] (n, %)	57 (25.3)	38 (31.9)	19 (17.9)	
[15.20, 25.86] (n, %)	57 (25.3)	31 (26.1)	26 (24.5)	
[25.86, 76.87] (n, %)	55 (24.4)	17 (14.3)	38 (35.8)	
Concentration (μg/ml)				**0.000**[c*]
Min, Max	0.21, 76.87	0.21, 66.14	0.76, 76.87	
Median (IQR)	15.20 (8.98, 25.86)	13.18 (8.32, 20.19)	19.80 (11.30, 30.40)	
Self-reported PB Dose (mg/day)				**0.039**[a*]
≤60 (n, %)	70 (31.1)	45 (37.8)	25 (23.6)	
>60 and ≤180 (n, %)	138 (61.3)	68 (57.1)	70 (66.0)	
>180 (n, %)	17 (7.6)	6 (5.0)	11 (10.4)	
Self-reported PB Dose (mg/day), median (IQR)	90 (60, 150)	90 (60, 120)	120 (90, 150)	**0.005**[c*]
Adverse Effect				0.114[a]
Yes	57 (25.3)	25 (21.0)	32 (30.2)	
No	168 (74.7)	94 (79.0)	74 (69.8)	

IQR: interquartile range.
[a] Pearson's chi-square test.
[b] Student's *t*-test.
[c] Nonparametric Mann–Whitney test.
[*] $p < 0.05$.

The diagnostic specificity for PB inefficacy increased, and the sensitivity decreased with increasing PB concentration. Youden's index identified the optimal cutoff point as 19.02 μg/ml. At this threshold, the sensitivity was 53% and the specificity was 74%.

Adverse effects reported by at least 1% of study subjects were shown in Table 3. The most reported adverse effect was drowsiness (14.4%). The PB concentrations of 95% of the subjects without adverse events were distributed in the range of 1.55–52.79 μg/ml, and that of 95% of the subjects with adverse events 1.97–65.72 μg/ml (Fig. 1B). Although no significant difference was found by the multivariate logistic regression analysis, odd ratio (OR) increased as PB concentration augment suggesting that the risk of adverse events elevated while PB blood concentration augment (Table 2). The ROC curve of PB concentration for adverse events revealed an AUC of 0.56 (95% CI, 0.472–0.649) indicating a poor overall diagnostic accuracy of the test, which might result from the small sample size of adverse events (Fig. 2B).

Table 2
Multivariate logistic regression analysis of variables associated with inefficacy and adverse effect.

	Ineffective		Adverse effect	
Covariate	OR (CI)	p-Value[a]	OR (CI)	p-Value[a]
Concentration (μg/ml)		**0.001**[*]		0.406
[0.21, 8.98]	Ref.		Ref.	
[8.98, 15.20]	0.732 (0.324, 1.612)	0.428	0.805 (0.320, 2.022)	0.644
[15.20, 25.86]	1.463 (0.652, 3.284)	0.365	0.960 (0.389, 2.366)	0.929
[25.86, 76.87]	4.522 (1.846, 11.076)	**0.001**[*]	1.654 (0.679, 4.030)	0.268

OR: odd ratio; CI: confidence interval; Ref: reference category for the odds ratio.
[a] p-Value was calculated using multivariate regression analysis.
[*] $p < 0.05$.

4. Discussion

In this study, we carried out a follow-up assessment of people with epilepsy who were certified on regular treatment of PB monotherapy by drug concentration. We found that the PB blood concentration level of the ineffective group was higher than that of the effective group. Blood concentration of 95% of the subjects in the effective group ranged from 1.22–41.36 μg/ml. High blood concentration was related to an elevated risk of inefficacy with a cutoff value for inefficacy at 19.02 μg/ml.

Phenobarbital, a broad-spectrum drug in WHO's List of Essential Drugs, had been demonstrated as an efficacious drug for both partial and generalized tonic–clonic seizures [12]. Previous studies had confirmed that PB was the most cost-effective pharmacologic treatment for epilepsy, and it had played and would still play an important role in closing the treatment gap in low- and middle-income countries [7,13–15]. The community-based intervention trial in rural China that enrolled 2455 patients showed that, in 68% of patients who completed 12 months' treatment, seizure frequency was decreased by at least 50%, and a third of the patients were seizure-free [7]. Seventy-two percent of the patients who completed 24 months of treatment had reduction of seizure frequency of at least 50% and a quarter of the

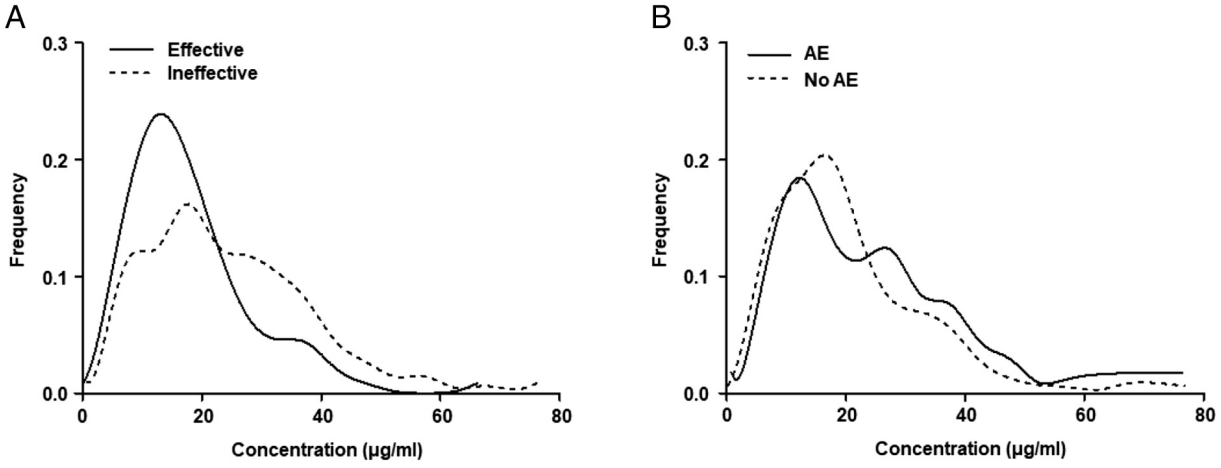

Fig. 1. Distribution of PB concentration. (A) Distribution of PB concentration in the effective group and the ineffective group. (B) Distribution of PB concentration in subjects with and without adverse events (AE).

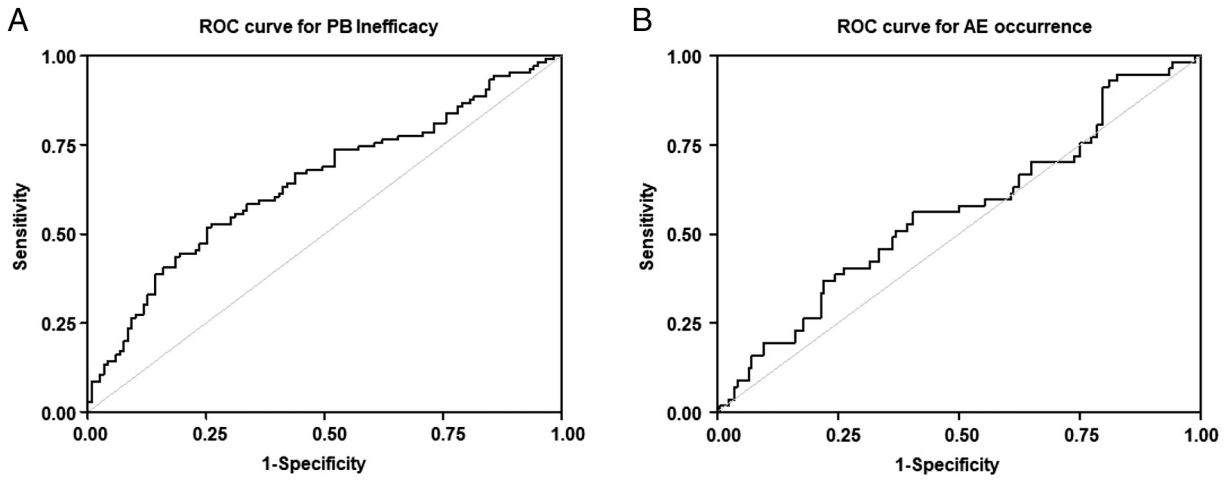

Fig. 2. Receiver operating characteristics curves of concentration for PB inefficacy and AE occurrence.

patients remained seizure-free. Besides, PB had been demonstrated to maintain its benefits in the long-term, with an estimated probability of 0.76 and 0.53 for people remaining on treatment at 2 and 6 years, respectively [8]. A recent study in rural area of Jilin province in China, in which 1379 patients with convulsive epilepsy received standard PB therapy, reported that the seizure frequency decreased by more than 75% in 71.3% of 349 patients who were followed up for 12 months from the beginning of the PB treatment. The average dosage of PB in these patients was 94.31 ± 45 mg/day, which was similar to our result in the effective group [16]. In the current study, patients whose seizure frequency decreased by at least 50% with PB monotherapy consisted of 52.9%, which was a little lower than efficacy rates reported in previous studies [7,8,16]. It may be resulted that patients with poorly controlled seizures might be more active to participate in this program for more contact with doctors and better control over their seizures.

In consistency with previous study, about 25.3% (57 in 225) reported adverse events, and drowsiness was the most reported in this study [8]. Much attention had been given to it, but the evidence on the propensity of PB to cause neurobehavioral effects was still conflicting. In a double blind, counterbalanced, crossover study, children performed significantly less well on neuropsychological tests, and had worse behavior while receiving PB than when receiving valproic acid both for 6 months [17]. A multicenter, case–control, parallel, follow-up design study in rural China found that cognitive test score and mood ratings in 136 people with epilepsy receiving PB for a year were similar to those in 137 age-, sex-, and education-matched controls in a number of Chinese villages [18]. Memory decline and mental slowing were the main manifestation in our study.

The PB blood concentration had been adopted in clinical practice by the early 1960s. A range of 10–30 μg/ml was postulated in adults as the therapeutic range and a lower limit of 15 μg/ml suggested for children with febrile seizures [15]. In this study, we found that the blood concentration level of subjects in the ineffective group was much higher than that of the effective group ($p = 0.001$), and PB blood concentration ≥ 25.86 μg/ml was related to 4.5-fold (95% CI, 1.846–11.076; $p = 0.001$) higher risks of inefficacy. It was indicated that the efficacy rate of PB was not always increased with blood concentration. The cutoff value of concentration for efficacy assessment in this study was 19.02 μg/ml. Furthermore, the strength of the association between PB concentration and adverse events increased as the augment of blood concentration. These results revealed that if PB blood concentration was close to or higher than the upper limit of therapeutic range, better efficacy could not be acquired and the risk of adverse events would increase. If PB monotherapy could not achieve a satisfied seizure control, blood concentration should be determined rather than blindly increase the PB dosage. It was better to add or change to another drug if the threshold of concentration is reached. Currently in resource-poor areas, PB blood concentration measurement might not yet be available and popularized in primary care level in consideration of the cost and technical requirement. Despite this, it was still necessary to monitor PB blood concentration especially in rural areas.

The relationship between PB blood concentration and the occurrence of adverse events was confusing. Some of adverse events were dose-related, such as drowsiness and neurologic toxicity characterized by dysarthria, ataxia, incoordination, and nystagmus [19]. As the blood concentration augment, PB can cause a concentration-dependent reduction of Ca^{+}-dependent action potentials in presynaptic membrane, which may lead to drowsiness [20]. Mechanisms underlying other adverse events were still unknown. Further study with a large sample size is needed to figure out the relationship between PB blood concentration and the occurrence of adverse events as well as the cutoff value of the ROC curve. Then blood concentration could be used as a routine method and an objective indicator to adverse events monitoring and prevention. We can try to avoid adverse events by following the principle of dosage titration, enhancing prevention awareness, detecting blood biochemical indexes regularly, and monitoring blood concentration.

Our study has several limitations. First, clinical outcomes were assessed at a single follow-up visit, thus it was not possible to accurately ascertain their various temporal patterns in this study. Second, PB blood concentration was the measurement of one test at baseline. One spot measurement might not represent well the trend of changes in PB blood concentration during the follow-up period. Third, the sample size was relatively small. Thus, it was hard to determine the concentration threshold for adverse events occurrence and the relationship between PB blood concentration and each subtype of adverse events. Besides, we had included patients with a >50% seizure reduction in the effective group with those that were seizure-free for at least 6 months, and it would be a better way of illustrating these data by

Table 3
Adverse event experienced over follow-up periods.

	Number of patients (%)
Drowsiness	33 (14.4)
Dizziness	5 (2.2)
Fatigue	17 (7.4)
Cognitive impairment	13 (5.7)
Headache	4 (1.7)
Mental symptoms	6 (2.6)
Gastrointestinal complaints	4 (1.7)
others	7 (3.1)

analyzing them separately. However, we did not find a significant result because of the small sample size in each group. Further study with large sample size was needed to overcome these limitations.

5. Conclusions

Phenobarbital had been demonstrated as the most cost-effective AED and was important to close the treatment gap in resource-poor settings. Our study suggested that high PB blood concentration was related to elevated risk of poor seizure control. When PB monotherapy cannot achieve a good efficacy, blood concentration could be a practical indicator for clinical decision making. Phenobarbital concentration monitoring should apply as a routine procedure in the campaign against epilepsy in resource-poor settings.

Author disclosures

All the authors have no disclosures to report.

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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