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A preliminary observation of the adverse effects of phenobarbital among patients with convulsive epilepsy in rural West China

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ABSTRACT

Background: This study explored the adverse effect (AE) profile of phenobarbital (PB) among patients with active convulsive epilepsy (ACE) from resource-poor areas.
Methods: Patients with ACE were enrolled into an epilepsy management project in rural West China. Information was obtained from monthly follow-up questionnaires. The demographic and clinical features of the patients with AE were firstly described. After that, the occurrence rate was estimated for each subtype of AE at three different severity levels (mild, moderate, and serious). Survival analysis was used to determine the potential risk factors of AEs.
Results: A total of 7231 patients (3780 men) were included in the present cohort. During the follow-up time period (average 33.4 months), the most common AEs were drowsiness (moderate: 4.4%, serious: 0.68%), dizziness (moderate: 3.7%, serious: 0.5%), and headache (moderate: 2.9%, serious: 0.41%). In the confirmed AE groups (moderate and serious severity levels), the symptoms tended to be transient, with durations of less than 3 months. Polytherapy was an independent risk factor for AEs and had an increasing risk when the severity of the AE increased (Hazard Ratio 1.12, 1.55, and 2.52 for mild AE, moderate AE, and serious AE, respectively). Receiving a high dosage of PB (>180 mg/day) indicated a slightly elevated risk (Hazard Ratio 1.22 and 1.27 for mild AE and moderate AE, respectively).
Conclusion: Phenobarbital demonstrates overall tolerability, and serious AEs were not common. Patients receiving a high dose of PB or polytherapy are at increased risk of developing AEs.

1. Introduction

Phenobarbital (PB) has been used for more than 100 years and is one of a few old antiepileptic drugs (AEDs) that is recommended by the WHO as a first option therapy for convulsive epilepsy in adults and children [1]. In light of its proven efficacy and low cost, PB has remained on the essential AEDs list of the WHO [2] and is strongly recommended as a first-line therapy in resource-poor countries. A better understanding of the adverse effects (AEs) of PB is essential for improving guidance on its usage and avoiding unexpected severe consequences, particularly in less developed areas where medical resources are scarce. Adverse effects of PB are widely reported; however, they seem to be less commonly reported from resource-poor countries [1]. Currently, PB is not prescribed as often in Western practice, perhaps because of a lack of marketing support and new AED options. Furthermore, the perception of PB as a highly neurotoxic compound may have hampered recent investigations [3], making studies on the AEs of PB in resource-poor areas particularly significant.

Large randomized controlled trials involving PB in the developed world have been reported mostly in the last century [4,5]. In these studies, PB was found to be more likely to be discontinued than other old AEDs (e.g., phenytoin, carbamazepine, and valproate).

In 1997 and 2000, a series of epilepsy management projects was initiated in China [6–8]. In 2006, one study from the northern and eastern rural areas of China covered by the epilepsy management program evaluated the occurrence of PB's AEs across different time periods, but more emphasis was placed on its treatment efficacy [7]. In 2005, a project with the same protocol and a PB intervention program were extended to the rural areas of West China [9,10]. In contrast to the previous study in China [7], the current study in West China used the same PB intervention protocol, but was dedicated to investigating detailed aspects of PB use. The results of the present study are from this prospective observational cohort receiving PB intervention and aimed at providing robust evidence of clinical PB utilization in resource-poor settings.

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2. Methods

2.1. Subject recruitment and study sites

This study was approved by the Sichuan University Ethical Standards Committee on Human Experimentation. All participants or their guardians provided written informed consent.

The study cohort consisted of individuals with active convulsive epilepsy (ACE) (>2 seizures in the recent 12 months before recruitment) that was managed via an epilepsy management program at the primary health-care level in 16 counties of Sichuan Province, West China (Fig. 1), which covered 10.5 million people, from May 2005 to December 2013. Local primary care physicians screened the patients by using a specially designed questionnaire [7]. Supervising neurologists then assessed those potential candidates to confirm the diagnosis. Exclusion criteria as previously reported [7] included: 1. provoked seizures only; 2. age under two years at the time of the recruitment; 3. the presence of a learning disability or behavioral disorder; 4. the presence of a progressive neurological condition; 5. the presence of cardiac, hepatic, or renal disorders, or severe hypertension; 6. status epilepticus alone; 7. current adequate medical treatment; and 8. an active psychiatric condition.

2.2. Management procedures

The epilepsy management program and management procedures have been well described in previous reports [7,8,11,12] and were based on an efficient network of care management in West China [9,10]. The epilepsy management program was implemented in target counties in a successive fashion, and participants from each county were followed from the time of PB intervention to the end point (death, withdrawal, or December 31, 2013, when data were reviewed). A pragmatic PB intervention as the first option (monotherapy or first adjunctive drug) was given to those with ACE who were enrolled in the management program. Because each participant was required to pick up a one-month supply of PB in designated clinics, monthly follow-up was carried out to monitor the treatment efficacy and AEs. A follow-up questionnaire was given at each clinic visit by primary health-care physicians. Numbers of seizures and AEs experienced by the patient in the previous month were recorded. That information was used to make dose adjustments, assessment of AEs and adherence, and consideration of further supplies of medication.

2.2.1. PB treatment protocol

According to the protocol, in general, PB was initiated at 60 mg per day (administered before bedtime) for adults (age ≥ 15 years old or weight ≥ 30 kg) and was increased by 30 mg per day to reach the maintenance dose if seizures were not controlled after one month of observation. The maximum dosage for adults was 240 mg per day, and adverse effects were intensively monitored when a high dosage was taken. For children (age < 15 years old or weight < 30 kg), treatment started at a low weight-related dose of 30 to 60 mg per day (calculated by 2 mg/day/kg) and increased by 1 mg/day/kg if seizures were not well controlled after the one-month observation. The maximum dose was up to 5 mg/day/kg, and adverse effects were intensively monitored when a high dosage was taken. Neurologists were responsible for the supervision of the local primary care physicians and to assist them in making therapeutic decisions for patients with uncontrolled seizures or

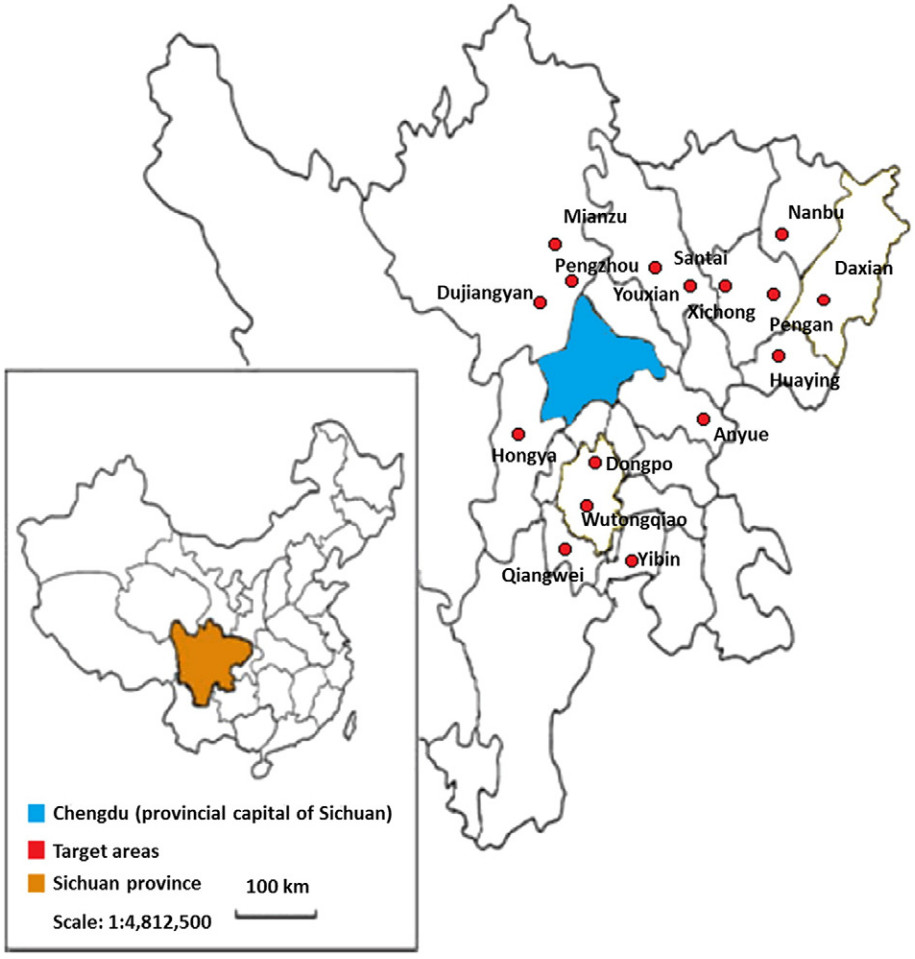

Fig. 1. Location of the target areas.