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SHORT COMMUNICATION

Medication side effects among people with epilepsy taking phenobarbital in Zambia

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Summary Phenobarbital remains one of the most widely used antiepileptic drugs worldwide, yet there are limited data regarding side effects associated with its use in routine clinical care settings in low-income countries. Available data suggests that phenobarbital is as effective as other first-line drugs for treating tonic—clonic seizures, but side effect reports differ widely between high and low-income settings. A better understanding of phenobarbital side effect profile and severity in low-income settings is warranted given its role in efforts to decrease the epilepsy treatment gap. We used the Liverpool adverse events profile (LEAP) to assess side effects in consecutive patients with epilepsy on phenobarbital seeking care in rural Zambia. Data regarding age, gender, medication dose, and medication adherence were also collected. *T*-tests and Spearman's correlation coefficient were used to assess predictors of LEAP score and medication adherence. Thirty-five patients receiving a mean dose of 2.1 mg/kg/day (SD: 2.78 mg/kg/day) of phenobarbital were assessed. All participants reported at least one side effect in the previous four weeks with a median of 6 symptoms (IQR: 4—8) and a mean side effects score of 28/76 (SD: 5.38). Over half reported sleepiness and dizziness. Memory problems and depression were also common (both 46%). Total LAEP score was not associated with age ($p = 0.88$), gender ($p = 0.17$), or phenobarbital dose ($p = 0.13$). Medication adherence was not associated with side effects total score ($p = 0.56$). Rural Zambian adults taking phenobarbital at doses recommended by the World Health Organization report a significant number of side effects. The most common side effects reported were similar to those reported

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in high-income countries. The significant burden of phenobarbital-associated side effects in this African cohort is in contrast to data from non-randomized clinical trials in China that reported phenobarbital to be well-tolerated with few side effects. Additional investigations regarding phenobarbital side effects during routine care in low income settings is warranted.

Introduction

One hundred years after its introduction, phenobarbital continues to be one of the most widely used antiepileptic drugs (AEDs) worldwide. In high-income countries, phenobarbital has been replaced by newer AEDs with fewer reported adverse events (French et al., 2004). Due to its cost, convenient dosing, and broad spectrum of activity, the World Health Organization (WHO) recommends phenobarbital as first-line monotherapy in resource-limited settings (WHO, 2013). The cost advantages of phenobarbital are substantial. In Zambia, where most people live on less than two US dollars (USD) per day, the monthly out-of-pocket cost for phenobarbital in the private sector is about nine USD, half the cost of phenytoin and one third the cost of valproic acid. In the public sector, wholesale costs for adult dosing of phenobarbital are less than a dollar a month (Chomba et al., 2010).

Research from low and high-income settings has shown that phenobarbital is as effective as other first-line AEDs for tonic–clonic seizure control (Tudur et al., 2003). However, meta-analyses suggest that phenobarbital is more likely to be withdrawn due to side effects than carbamazepine, phenytoin, or valproic acid (Tudur et al., 2003; Zhang et al., 2011). People taking phenobarbital in high-income settings experience more frequent/severe side effects than people taking carbamazepine (Baker et al., 1997), phenytoin (Meador et al., 1995), or valproic acid (Baker et al., 1997; Meador et al., 1995) yet, observational studies in low-income settings suggest that phenobarbital is well tolerated (Nimaga et al., 2002; Kwan et al., 2013). As presented in the Supplementary table, randomized trials worldwide have shown mixed results.

Conflicting findings regarding phenobarbital tolerability are largely attributed to heterogeneity between studies (Zhang et al., 2011). Side effect assessment is often a secondary outcome and, as a result, little detail is provided regarding the instruments used. Also overlooked is the potential for disparate presentation of complaints based on culture (Zola, 1966) and acceptance of and minimization of side effects due to limited alternative therapies (Nimaga et al., 2002; Goodacre and Goodacre, 2004). As most AED side effects data in low-income settings are associated with efforts to reduce the epilepsy treatment gap and hence are occurring among patients with limited access to epilepsy treatment, inadvertent overestimation of phenobarbital tolerability may occur (Zhang et al., 2011).

Research in upper-middle and high-income settings suggests that people obtaining AED therapy continue to report AED-related side effects even after seizures are controlled (Carpay et al., 2005). Unfortunately, there are limited data from individuals provided phenobarbital in routine clinical care in low-income settings. We assessed drug side effects experienced by people with epilepsy obtaining phenobarbital during routine clinical care in rural Zambia using a standard instrument. We also examined predictors of phenobarbital-related side effects and medication adherence.

Methods

Consecutive patients presenting to Chikankata Hospital Epilepsy Care Team (ECT) who met the inclusion criteria and consented to participate were interviewed during January 2006. Chikankata Hospital is a mission hospital that provides the only source of health care for a catchment area of approximately 55,000 people in an isolated rural region of Zambian's Southern Province. The ECT consists of a neurologist in residence, on average, six months a year; a clinical officer; a ward auxiliary; and a research assistant/administrator. At the time of survey, phenobarbital was the most widely available AED and was provided at no cost to the patient. Carbamazepine and phenytoin were available as second line treatments at low cost, but both agents were infrequently used due to their limited local supply.

Individuals were eligible for study inclusion if they were at least 18 years old, on a stable dose of an AED for at least two months, and could answer questions in Tonga (the local language) or English. Written, informed consent was obtained from participants in the language of his/her choice. Side effects were ascertained using the Liverpool adverse events profile (LEAP) (Baker et al., 1994). This 19-item instrument queries the severity of common AED side effects during the four weeks prior to interview using Likert-type scales (from 1 to 4) with four representing a symptom that occurs ''often''. A total side effect score is calculated by summing participant responses (range 19–76). The LEAP was translated into Tonga and then back-translated to ensure content validity.

Data was also collected regarding gender, age, and weight. To assess adherence, AED name, dose, number of pills collected, and last pharmacy collection date were abstracted from the patient file. Self-report of last dose taken was obtained. Patients were deemed adherent if they had taken their medication either the day prior to or the day of their appointment and if pharmacy data reflected that they were not overdue on medication collection. This approach has been used to assess adherence in this setting as serum concentrations are not available (Elafros et al., 2013). Previous research suggests that patients are comfortable confiding in the ECT research assistants as they are respected community members but do not hold positions of tribal or local governmental authority (Birbeck et al., 2008).

Summary statistics were performed for all interviewed patients. Two-tailed comparisons were made between total side effects score and gender, age, and phenobarbital dose