Availability and Costs of Antiepileptic Drugs and Quality of Phenobarbital in Vientiane Municipality, Lao PDR

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Abstract
Purpose: In developing countries, availability and quality of drugs are critical factors for effective management and control of epilepsy. This study investigated the availability and costs of antiepileptic drugs (AEDs), and the quality of phenobarbital in Vientiane Municipality, Lao PDR. Methods: In March 2004, we enrolled all pharmacies (categories I and II) of four central districts of Vientiane eligible to sell AEDs. Two hundred and eight pharmacies of category III (75.1\% of all registered pharmacies) were excluded as the sale of AEDs was not authorized. All pharmacists were interviewed with a standard questionnaire. Whenever phenobarbital was available, a sample was purchased and assayed by liquid chromatography. Phenobarbital was defined as being of correct quality if the active substance average content corresponded to \pm 15\% of the indicated amount. Results: 66 pharmacies were enrolled (13 and 45 of categories I and II, respectively, and 8 hospital pharmacies). Six generics of AEDs were found (phenobarbital, phenytoin, valproic acid, clonazepam, carbamazepine, diazepam) and all pharmacies sold at least 1 AED. The 2 most widely available drugs were diazepam (5 mg) and phenobarbital (100 mg), present in 87.9 and 53.0\% of the pharmacies, respectively. All 34 phenobarbital samples examined showed a correct concentration of the active compound. However, the concentration of phenobarbital 100 mg tablets produced in Lao PDR (mean concentration 94.7 mg) was significantly lower (p = 0.005) than the imported equivalent (mean concentration 99.7 mg). The direct drug costs of a yearly treatment with phenobarbital were estimated to be at least 25.2 USD. Conclusions: A variety of AEDs are present. Their availability, particularly of phenobarbital, is restricted to higher-category pharmacies and within those it is rather limited. To meet the costs of AEDs in this setting is a major challenge for people with epilepsy. However, the quality of the available phenobarbital was rather satisfactory.
Introduction

Epilepsy is a public health problem, particularly in tropical developing countries because of its high frequency, acuteness, and its sociological, psychosocial [1, 2], and financial consequences. In Southeast Asia, between 7.2 and 14.0/1,000 people suffer from active epilepsy. In Lao PDR, little information is available on epilepsy [3]. A prevalence of 7.7/1,000 people with epilepsy (PWE) was determined in a recent study in a rural district of central Lao PDR [4]. Although parasitic infections are frequent in the country, they seem to play a minor role in its etiology [5]. Fatal outcomes of epilepsy have been observed [6]. However, only 1 of the 33 PWE was under treatment, indicating that awareness of and/or access to treatment may be low.

The availability and the accessibility of AEDs are essential for the management of this disorder. However, in the developing world, the majority of PWE do not receive treatment [1, 7].

The WHO recommends phenobarbital as a first-line drug in developing countries. It can be produced cheaply and has a broad spectrum of activity for various types of epilepsy, except absences [8]. It may aggravate myoclonic seizures [9, 10]. The accessibility of the treatment depends on the availability, the costs and the quality of the drug.

The WHO defines inferior-quality medicine as products whose composition and ingredients do not meet specifications, and which are consequently ineffective and often dangerous for patients [11]. The Food and Drug Administration estimates that this problem affects 10% of the world markets today [11]. This is particularly problematic in Southeast Asian countries in general [12], and in Lao PDR in particular. A survey performed in 1997 and 1999, in central Lao PDR, revealed 46 and 22% of such substandard drugs [13], respectively.

Recent studies on the quality of AEDs also brought to light insufficient quality in African settings [14]. The amount of confidence patients have in their medication is one of the factors influencing its regular intake [15]; therefore, if confronted with ineffective medication of poor quality, confidence in the treatment may be lost.

The current study investigated the availability and costs of AEDs and the quality of phenobarbital in Vientiane Municipality, Lao PDR. As a measure of quality, a representative sample of phenobarbital was examined for the concentration of the active compound.

Patients and Material

The study was performed between February and March 2004, in 4 central districts (Chanthabuli, Saysetha, Sikhot Tabong and Sisathanak; n = 308,767 people) of Vientiane Municipality, capital of Lao PDR. The prevalence of active epilepsy in Vientiane is not known. However, a prevalence of 7.7‰ was found in 2004 [4] in a nearby rural district.

In Lao PDR, there are 3 categories of pharmacies according to the variety of drugs sold and the qualifications of the holder. Pharmacies of the first category have the largest variety of drugs and category III pharmacies are restricted to few drugs. The latter pharmacies may be operated by a person with only paramedical training.

The Ministry of Health (MOH) provided the addresses of all 277 (public and private) pharmacies registered in the study districts. 208 (75.1%), 45 (16.2%) and 24 (8.7%) pharmacies were of category III, II and I, respectively. Pharmacies of category III are not allowed to sell AEDs and were therefore excluded from the study. Eight hospital pharmacies (included in category I) are present in the 4 districts: pharmacies of the 4 district hospitals and the 4 central (university) hospitals (Mahosot, Mitaphap, Seththathirat and the Military Hospital 103).

The drugs were procured from Lao pharmaceutical companies or were imported. Six generics of AEDs (phenobarbital, clonazepam, diazepam, carbamazepine, phenytoin and valproic acid) are listed in the essential drug list of Lao PDR (13th edition, April 2003, MOH).

We visited all registered pharmacies of categories I and II and all 8 hospital pharmacies. General information on age, gender and training of the pharmacy holders was obtained. Subsequently, they were interviewed about the availability of all AEDs in the store (brand name, dosage) and their (direct) purchasing costs. Medicine prices were obtained in Lao Kip (LAK) and converted to USD (mean conversion rate of March 2004: 10,420 LAK per 1 USD). Information on the selling practices (requirement of prescription) and the number of PWE who frequented the pharmacies was collected as well.

Where available, a sample of 10 phenobarbital tablets was purchased regardless of the brand name (speciality) and dosage. If several phenobarbital categories were available, samples of each were obtained. The country of origin, purchase and expiry dates of the medicine were recorded.

Assays of phenobarbital tablets were performed at the Department of Pharmacology-Toxicology of Limoges’ University Hospital using high-performance liquid chromatography with ultraviolet detection [16]. The chromatographic separation in the isocratic mode was performed using a pump (Model 510, Waters) on a Nucleosil C18, 150 × 4.6, 5-μm (Macherey-Nagel) column; 40 μl of solution was injected (injector type 712 Wisp, Waters) and the detection done using a detector SPD-6AV (Shimadzu) at 220 nm. One tablet was randomly chosen from each pharmacy sample.

The content of phenobarbital was defined as correct if the amount did not deviate by 15% or more from the indicated strength [14].

Data were entered in Excel spreadsheets in which frequency calculations were done.
Results

Coverage

Two hundred and seventy-seven pharmacies were registered in the 4 study districts. Taking into account that only 24.9% of the pharmacies dispense AEDs, there were an average of 4,475 persons per pharmacy. Given a prevalence of 7.7‰ observed in the district, this means that there is 1 pharmacy per 34 PWE.

Availability of AEDs

Out of 69 registered pharmacies, 66 (95.7%) were operational during the survey period and we were able to interview the pharmacy owner as well (13 and 45 of categories I and II, respectively; 8 hospital pharmacies). The pharmacies were located mainly in the city center and along the main roads of the districts.

Table 1 reports AEDs sold in the pharmacies. All 6 generics of AEDs of the essential drug list of Lao PDR were found.

The 2 most widely available drugs were diazepam (5 mg) and phenobarbital (100 mg) present in 87.9 and 53.0% of the pharmacies, respectively; 60- and 50-mg tablets of phenobarbital were found in 4 and 1 pharmacies, respectively. Gardenal, diazepam and Valium were available in preparations for injection.

Table 1. Availability, costs and origin of AEDs sold in 66 pharmacies in Vientiane Municipality, Lao PDR

<table>
<thead>
<tr>
<th>AED</th>
<th>Availability and pricea</th>
<th>Total number of pharmacies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lao products</td>
<td>USD/tablet</td>
</tr>
<tr>
<td>Phenobarbital&lt;br&gt;Phenobarbital 100 mg</td>
<td>29</td>
<td>0.07</td>
</tr>
<tr>
<td>Phenobarbital 60 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Phenobarbital 50 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gardenal 100 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gardenal (injection)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Carbamazepine&lt;br&gt;Tegretol 200 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Covalin</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Phenytoin&lt;br&gt;Di-Hydan 100 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ditoin 100 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Valproic acid&lt;br&gt;Depakin 200 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Clonazepam&lt;br&gt;Rivotril</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Diazepam&lt;br&gt;Diazepam 5 mg</td>
<td>41</td>
<td>0.06</td>
</tr>
<tr>
<td>Diazepam (injection)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Valium 5 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Valium 10 mg</td>
<td>24</td>
<td>0.09</td>
</tr>
<tr>
<td>Valium 10 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Valium (injection)</td>
<td>6</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate percentages.

a Commercial price obtained in Lao Kip (LAK) and converted to USD; mean conversion rate, March 2004: 10,420 LAK per 1 USD.
b Imported from Thailand.
c Imported from France.
d In 10 pharmacies, generics from France.
e In 1 pharmacy, generic from France.
Information on the Pharmacy Holders and PWE

Most of the pharmacy holders were women (79%). Twenty-one percent (n = 14) of the pharmacy holders were trained pharmacists and 50% (n = 33) were assistant pharmacists. The remaining pharmacy holders were medical doctors (n = 8, 12%), medical assistants (n = 2, 3%), nurses (n = 2, 3%) or other professionals (n = 7, 11%).

Forty-nine pharmacy holders (75.4%) reported selling AEDs without a prescription. None of the 8 hospital pharmacies did so. The proportion of this practice was not different between the pharmacies of the first (83.3%) and second category (86.7%, p = 0.217). Twelve reported 1 (and only 1) PWE regularly purchasing AEDs. Ten of the 12 patients were on phenobarbital, and obtained the AED in pharmacies of the second category. The remaining 2 patients were reported by the pharmacies of the first category. The pharmacies of the central hospitals did not report any regular customers. Three quarters of the 12 regular customers had been buying AEDs for more than 6 months already. All but 3 bought their drugs once per month, the remaining patients purchased the drug every fortnight. All of the 12 PWE were reported to possess a valid prescription for the drug.

Results on the Phenobarbital Content

We analyzed samples from 34 pharmacies, corresponding to 81.0% of pharmacies where phenobarbital tablets are sold. 67.6% of phenobarbital tablets (23 of 34) were Lao products, while 20.6% (7 of 34) and 11.8% (4 of 34) were imported from France and Thailand, respectively. Thirty samples were phenobarbital 100 mg tablets, while 4 samples were phenobarbital 60 mg tablets which were all imported from Thailand. None of the drug samples had expired.

All 34 samples of phenobarbital contained an accurate concentration of the active compound. Tablets of 100 mg contained on average 95.6 mg (range 89.6–103.7 mg). On average, the Lao tablets contained 94.7 mg phenobarbital (n = 23) – significantly less (p = 0.005) than the imported samples (n = 7, mean = 99.7 mg). All imported samples of 100 mg tablets were from France. On average, 60-mg tablets of phenobarbital had a content of 58.5 mg (range 57.3–59.7 mg), which is not significantly different from 60 mg (p = 0.07).

Costs of AEDs

The costs of the drugs varied substantially by brand name and origin (table 1). Phenobarbital (100 mg) originating from Lao PDR was sold for an average price of 0.07 USD per tablet, 30% cheaper than the imported equivalent. The direct drug costs for an adult person (100 mg per day) per month and per year would reach approximately 2.1 USD and 25.2 USD, respectively.

Discussion

In Vientiane Municipality, AEDs are available in only a few pharmacies and restricted to higher-category pharmacies concentrated in the city center. The quality of phenobarbital sold was satisfactory in terms of the active substance content. The commercial costs were high compared to the general per capita income in Lao PDR.

Our study benefited from the cooperation of the pharmacy owners. All registered and operational pharmacies participated. The MOH identified the pharmacies in the planning phase of the study and informed us that the distribution of AEDs was not permitted in category III pharmacies. These include three quarters of the pharmacies in Vientiane Municipality, and virtually all in rural Lao PDR, which is, hence, a major limitation for the accessibility of AEDs in Vientiane Municipality and, more importantly, in the rural part of the country.

In Vientiane, in all pharmacies of the first or second category, at least 1 AED could be found. A variety of drugs were available and all AEDs named in the essential drug list of the MOH (13th edition, April 2003, MOH) could be found. The same was true for the drugs of the diazepam group, found in almost all pharmacies. However, phenobarbital, the recommended first-line drug for long-term treatment of epilepsy in developing countries [17], was only available in less than 60% of the pharmacies. Hence, treatment of epilepsy is in principle available in Vientiane, however, to a rather limited extent.

Whether or not the presently available AEDs are sufficient to cover the current local demand remains an open question. Little information is available on demand. However, there is evidence that presently only a small portion of PWE is actually seeking treatment. In our study, only 12 PWE were reported by pharmacists to be under regular treatment compared to the expected number of PWE in the study districts. Furthermore, findings in the nearby Hinheub district (120 km north of Vientiane), from a door-to-door household survey in 8 villages, support this observation and showed that only 1 of 33 identified PWE was under treatment [4].
Hence, the gap between existing and treated PWE is tremendous and reasons for not seeking help might be various, including quality of care, awareness of patients and their close family and stigma associated with this pathology.

Based on the prevalence of 7.7‰ obtained in a nearby district [4] and population numbers of the study districts, it is reasonable to assume that approximately 2,350 PWE are currently living in the study area. Although the rural district where the prevalence data have been obtained differs from our study setting regarding socioeconomic, cultural and environmental factors, it is the best current estimation. It is doubtful that the current supply provides sufficient treatment opportunity. The most frequently reported AEDs are diazepam and Valium. They are not used for chronic epilepsy treatment but rather in acute situations such as status epilepticus. Phenobarbital (100 mg) and Tegretol (200 mg) mainly used in chronic epilepsy treatment were found in only half (53.0%) and one quarter (25.8%) of the pharmacies, respectively.

However, more information would still be required to come to a final conclusion, e.g. the exact amount of sold medicine and stock-keeping practices of the pharmacies. The latter has been an important factor in Vietnam where not maintaining a stock of AEDs in pharmacies was a problem for long-term treatment of PWE [18]. This may or may not become a decisive issue in the treatment of PWE in Vientiane.

In Lao PDR, curative and preventive health services are not used sufficiently. In particular, chronic diseases are concerned and the proposed causes are various. The costs of treatment may explain to a large extend why so few PWE were taking medications. Based on our calculations, an annual treatment course of around 25 USD is required for the phenobarbital drug costs alone. This calculation does not include any additional indirect costs such as transport to health services, or loss of income. These additional costs might be considerable as currently pharmacies with AEDs are mainly found in the city center. Given the annual per capita income of an average Lao of 331 USD in 2002 [19], the medicine costs are equivalent to about 13% of the annual income which is certainly difficult to sustain by PWE. Hence, the medicine costs represent a major challenge to overcome for PWE. In this context, it is interesting to note that none of the pharmacies of the central hospitals reported a regular customer of AEDs. This might be due to the fact that their prices are on average higher than in pharmacies of the first and second category. In neighboring Vietnam, a recent study in a southern urban setting revealed similar drug prices ranging from 39.3 to 290 USD per annual treatment [18]. However, epilepsy treatment for considerably lower prices is available in other settings. In Mali, for example, the annual phenobarbital treatment costs reach only 7 USD [20]. Therefore, cost-effective treatment options should be explored in order to address this issue.

Analysis of the concentration of active compounds in phenobarbital revealed a satisfactory quality. Given the problem of counterfeit drugs in Southeast Asia [11] and the previously reported low quality of drugs produced in Lao PDR [13], this is an encouraging finding. However, we found that the phenobarbital tablets produced in Lao had on average a significantly lower content level of the active substance than the imported equivalent, although it was perfectly within the evaluation criteria of 15%. Further monitoring of this issue might be of importance as well as expanding the sampling to potentially existing parallel markets.

An interesting finding was that most of the pharmacy owners reported to sell AEDs without a prescription. This is in contrast to the relatively high training standard of the owners of the enrolled pharmacies. Inappropriate selling procedures of retail pharmacies is a well-known problem [21]. Our study documents that it is also an issue for AEDs and the PWE. Furthermore, it shows that the policy of selling restriction to higher-category pharmacies is justifiable, given the existing selling practices. However, further studies on the selling practices, e.g. in relation to self-medication of PWE and access to AEDs, are necessary in order to understand their importance for the treatment of PWE.

Although the public health importance of epilepsy is acknowledged at a global scale [22], at a local level data are frequently scarce and insufficient to start targeted interventions. Our study documents the present situation in an urban setting of Southeast Asia, similar to many settings in the region. It showed that policy guidelines restrict the authorized distribution to first- and second-category pharmacies where phenobarbital is rather limited. The medicine cost associated with long-term treatment is a serious financial burden to an average Lao resident. The quality of phenobarbital available on the market in Vientiane was found to be satisfactory, although the selling practices need to be addressed.

Future interventions will need to take these findings into account. Furthermore, they will have to be combined with the relative low knowledge level and inappropriate attitudes and practices of the general population concerning epilepsy and PWE. A study conducted recently in
Lao PDR identified a series of misconceptions such as the belief in transmission of epilepsy by saliva, which resulted in stigmatizing behavior [23].

A national control program on epilepsy will need to address a large set of issues. Our study has identified a part of them.

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