Title page

Quality of antiepileptic drugs in sub-Saharan Africa: a study in Gabon, Kenya and Madagascar

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Key Point Box

- Epilepsy is a chronic neurological disorder with a high burden in deprived settings. Availability and accessibility of antiepileptic drugs is critical, but may be complicated by poor drug quality. There are few studies examining this issue.
- 3782 tablets of AEDs gathered in three sub-Saharan African countries, revealed that 32.4% of AEDs were of poor quality (26.5% in Gabon, 37.0% in Kenya and 34.1% in Madagascar; p=0.7). The overall substandard proportion was estimated at 22.6%. No counterfeit drugs were identified.
- Storage in places without temperature and humidity control, and un-packing practices generate improper and dangerous drugs, enhancing avoidable distrust in conventional medicines.

Abstracts

Objective: Epilepsy is a major public health issue in resource poor settings. Availability and accessibility of antiepileptic drugs (AEDs) remain important issues, which may be aggravated by poor drug quality. Primary objective was to measure the quality of AEDs through official and unofficial supply chain.

Methods: This was a cross-sectional study carried out in Gabon, Kenya and Madagascar. The official and unofficial supply chain have been investigated in urban and rural areas. Oral pharmaceutical forms were collected in structures where a patient could buy or obtain AEDs. Pharmacological analytical procedures were used to assess quality. Medicine Quality Assessment Reporting Guidelines were used.

Results: In total, 102 batches were sampled representing 3782 units of AEDs. Overall 32.4% of the tablets were poor quality, but there was no statistical difference across the sites: 32.4% (26.5% in Gabon, 37.0% in Kenya and 34.1% in Madagascar; p=.7). Carbamazepine had the highest proportion of poor pharmaceutical features in 38.7% (p=.01). Sodium valproate and phenytoin had the poorest quality (p<.001). Phenobarbital (94.5%) and diazepam (100.0%) had better quality (p<.001). Facilities from the public system were associated with presence of substandard (OR, 9.9; p<.04) as well manufacturing in China (OR, 119.8; p<.001). Phenytoin and exposure to atmosphere were associated with a risk of encountering drugs with bad quality (OR, 3.3; p<.007 / OR, 5.4; p<.03).

Significance: Even if countries import good and efficient drugs on their market, they might become ineffective and dangerous by inappropriate storage conditions.

Introduction

Epilepsy is a chronic neurological disorder affecting more than 70 million people worldwide, and nearly 80% of them live in low and middle-income countries (LMICs)[1]. Primary healthcare is limited in LMICs, where availability of antiepileptic drugs (AEDs) and accessibility remain important issues[2]. This is particularly relevant in rural areas. Poor quality of the AED would aggravate this problem, but there are few studies examining this issue. Two studies have shown a proportion of poor quality drugs ("genuine drug products which do not meet the quality specifications set for them") ranging from 14% (for phenobarbital in Mauritania) to around 65% (for major AEDs in Vietnam)[3,4]. A recent counterfeiting ("deliberately and fraudulently mislabelled, may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging") alert has been observed for phenobarbital in Guinea-Bissau and Nigeria[5].

Consistent drug quality is ensured by undertaking stability studies, to establish an expiration date under specific storage conditions. These studies take into account the influence of environmental factors (temperature, relative humidity (RH), light), duration of storage, in the area where the drug is supplied. For tropical areas, the World Health Organization (WHO) provides guidelines for storage of pharmaceutical products[6]. WHO proposes a categorization for tropical areas by climate zone, three categories have been established: i) dry and hot climate (stability at 30°C and 35% RH); ii) hot and humid climate (30°C and 65% RH); iii) hot and very humid climate (30°C and 75% RH). Storage outside these limits is unfavourable and may damage the quality of medicines, leading to ineffective or dangerous medication. In many resource poor settings, a common practice is to unpack supplied tablets/capsules with only primary packaging (e.g. blister packs) and sometimes in bulk. Even aluminium blisters are not

completely effective protecting the drugs in inadequate storage conditions[7,8]. Previous studies on quality of AEDs were focused on one country[3,4]. Differing methods of analysis and sampling complicated comparison. The differences in AED quality between urban and rural areas have not been investigated.

Primary objective of the study was to measure the quality of AEDs through various delivery structures of the supply chain, including official and illegal ones. Secondary objective was to determine the variables associated (climatic, storage, manufacturing origin, etc.) with the quality of AEDs.

Furthermore, an ancillary study has been performed to assess the specific role of climatic conditions representative of sub-Saharan Africa on the quality of AEDs.

Method

Settings

This was a multicentre study carried out in three countries (Gabon, Kenya and Madagascar) using an identical data and sample collection protocol.

The official supply chain and the unofficial systems have been investigated in urban and rural areas of each setting. The sources of the AED used by the patient were classified as: public (e.g. public hospital); registered private for profit (e.g. private pharmacies, clinics, supermarkets); and informal meaning outside the approved distribution chain (e.g. kiosks, street sellers, street market, grocery shops).

Inclusion criteria

All the drugs belonging to N03 Anatomical Therapeutic Chemical group from the classification system of the WHO Collaborating Centre for Drug Statistics Methodology and registered on the 19th WHO essential medicines list were considered. Only oral pharmaceutical forms were collected with the packaging when present.

Endpoints

An AED was considered good quality if it met several endpoints from different analytical methods, were fulfilled: mass uniformity, homogeneity of the appearance and organoleptic features, identification and assay of the active ingredient (AI), impurities screening, dissolution test, friability test (only for uncoated tablets). Sufficient amount of unit (tablets/capsules) to perform all analytical tests was sometimes not possible, since insufficient material was available. A prioritization of analyses was decided: i) identification and assay of AI and impurities screening; ii) dissolution/disintegration; and iii) friability. A degree quality scale has been established (Figure 1). The overall raw result of the quality has been dichotomized into two main categories: i) good (combining categories good quality with caution and good quality, Figure 1) and ii) poor quality (both substandard categories and bad quality).

To assess the quality of the packaging and the quality of the patient leaflet WHO, guidelines were used[9,10]. Data for climatic conditions were recorded daily during the month prior the sampling phase, by the climate and research department of Météo-France. Data on storage conditions were collected in each delivery structure through a questionnaire filled by the investigator. These data were compared to reference mentioned in WHO guidelines[6].

Sampling method

In each urban and rural settings of countries included, public and private system from the official supply chain have been considered. Facilities from all health levels [*primary level (centre of primary health care, primary point of contact for patients with a health professional), secondary (district referral hospital, the first level hospital of a district or a defined geographical area containing a defined population) and tertiary (general and specialized hospitals*)] were investigated. For unofficial system, investigation was made by word of mouth in both urban and rural settings.

Urban setting: Study area considered as urban has to be a developed location and autonomous in terms of health services**.** The urban study areas of each country was considered as the politic and/or economic capital of the country. For the public system, we investigated all hospitals (tertiary and/or secondary level) and other type of public facilities (dispensaries, depots, etc.) where a drug supply to patient was provided. For private system, we investigated all hospitals (clinics) able to provide a drug supply for out-patient. For pharmacies, a random selection of six facilities from a list of official and registered facilities was selected.

Rural settings: The study area considered as rural has to be located outside a city or metropolitan district and considered underdeveloped in terms of infrastructure and specialized services. For this study area, all accessible facility was investigated.

For each delivery structure, the sampling comprised of two stages performed on the same day

by two investigators (*A* and *B*). Stage one consisted on collection of AEDs, performed as a patient by investigator A. In that stage the seller/owner of the facilities was not aware that the purchase was for a study. In stage two, variables of interest were collected by investigator B using a questionnaire.

A sample (statistical unit) corresponded to a collected item at a specific collection site and each unit (tablets, capsules) of a sample must be from the same manufacturing batch. This meant that the same product (same name, AI, strength, batch and produced by the same manufacturer) collected in two different sites represented two different samples.

Analytical testing

For standardization, all analyses were performed in France in a WHO prequalified laboratory. Assays were performed by high-performance liquid chromatography (HPLC, Waters 2695) with diode array detection (Waters 2996). Pharmacopoeias (British, BP 2015; American USP38 and 39; International Pharmacopoeia 5th edition) were used as reference for all samples. For sodium valproate film-coated scored, modified-release tablets the manufacturer analytical procedure was used. Standardized pharmaceutical tests (mass uniformity, dissolution, disintegration, friability) were performed according to the European Pharmacopoeia, 8th edition, 2014. For unknown impurity detected, an identification procedure[11] was performed using high resolution mass spectrometry with a liquid chromatography/quadrupole Orbitrap mass spectrometer (LC/MS), tandem mass spectrometry (MS/MS) and/or one/two-dimensional nuclear magnetic resonance (NMR).

Samples included in the ancillary study were those which did have an out of specification (OOS): deviation(s) of parameters compared to predetermined compendial acceptance criteria) on assay of AI and/or on dissolution test. Samples and authorized drugs for export

used as reference products were exposed during three months to stress conditions: i) 45°C + 75.0%RH; and ii) 45°C + 99.9%RH in a climatic chamber (Memmert HP108) with and without primary packaging. Assay of AI (HPLC-DAD, Thermo scientific Dionex Ultimate 3000), dissolution, disintegration tests and chemical stability (studied by total attenuated reflection - Fourier transform infrared spectroscopy (ATR-FTIR, Perkin Elmer Spectrum 65 FT-IR module ATR) and differential scanning calorimetry (DSC, Mettler Toledo DSC822)) were performed at T0 (baseline), one (T1) and three months (T3).

Data cleaning and processing of variables were done using Stata (version 14.1 StataCorp, College Station, Texas, United States). Datasets are stored on secured servers at Limoges University. Chi-square and Fisher exact tests (where appropriate) have been used for descriptive analysis. To quantify the strength of association between independent variables and the dependent variable (quality of the drug), bivariable and multivariable analysis were performed using multinomial logistic regression. The final model was obtained by a downward stepwise method. The independent variables included in the initial model of the multivariable analysis were those with a $p \leq 0.25$ in the bivariable analysis. The significance level was fixed at 5%.

The study received approval from African countries authorities as part of their ongoing epilepsy studies. All samples shipped in France received authorization for importation from the French National Security Agency of Medicines and were declared to customs.

The MEDQUARG (Medicine Quality Assessment Reporting Guidelines) statement was used as a guide in the reporting of this study[12].

Results

In total, 102 batches have been sampled representing 3782 units of AEDs.

- In Gabon, only the urban area (Libreville) has been assessed due to the inaccessibility to the rural study area during field operations. A number of 34 batches have been sampled. The main public hospital did not have any AEDs. A number of 19 unofficial points of sale have been investigated but none sold AEDs. Only one (5%) has proposed a combination of ibuprofen-caffeine-paracetamol to treat epilepsy.
- In Kenya, 27 batches were collected. The urban area was Mombasa where 22 batches have been sampled. The rural area was the district of Kilifi, and 5 batches were collected.
- In Madagascar, 41 batches have been sampled. The urban area was Antananarivo where 24 batches have been collected. The rural area was the region of Bongolava where 16 batches were collected.

Overall, drug quality was poor across the sites: 32.4%, and there was no significant differences between the sites (26.5% in Gabon, 37.0% in Kenya and 34.1% in Madagascar; p=.7; Table 2).

Carbamazepine had the highest proportion of poor pharmaceutical features (mainly due to dissolution failure) in 38.7% (p=.01). VPA and PHY were drugs with the poorest quality (p<.001). PB (94.5%) and DZ (100.0%) were AEDs with the better quality (p<.001). (Table 2)

There was a statistically significance difference between the proportion of substandard AED between the brand (11.8%) and generic formulations (27.9%), p<.001, in contrast to

proportion of bad quality categories for the brand (22.0%) and that for the generics (2.3%), p<.001.

Analysis of the drugs manufactured in the European Union, 64.6% were of good quality, 12.5% of substandard while 22.9% were of bad quality (p<.001). Drugs manufactured in Africa (Senegal, Madagascar and Kenya) were 90.0% of good, none bad, 5.0% of substandard and 5.0% of good quality with caution (p=.034). Samples from India were 38.1% in good quality, 14.3% in bad quality, 9.5% with poor pharmacotechnical features and 38.1% categorized as good but with caution due to not sufficient unit for complete analyses (p<.001). For AEDs manufactured in China, 23.1% were good and 76.9% with poor pharmaco-technical features (p<.001).

In each study areas, the average RH was above the threshold of 65% recommended by WHO (each country belongs to WHO category IVA [30 °C/65% RH]), ranging from 70.7% (+/- 5.4%) in Madagascar to 80.1% (+/- 14.5%) in Kenya and 85.2% (+/- 9.7%) in Gabon. As for the temperature, only in Gabon and Kenya the threshold of 30°C was surpassed, for daytime maximal temperature (Gabon: 31.7 (+/- 2.2); Kenya: 27.7 (+/- 4.9) in Mombasa, 28.0 (+/- 5.0) in Kilifi).

Concerning the quality for sample exposed to over 65% RH, PHY (83.3%) and VPA (32.1%) had the worst quality (p<.001), and CBZ (38.7%) the poorest pharmacological properties (p=.01).

All samples from Gabon were sold with conformed primary and secondary packaging. AEDs were sold without secondary packaging in 100.0% (27) in Kenya and 24.4% (10) in Madagascar (p<.001). In Kenya, 22.2% (6) of samples were sold without any packaging.

For the patient leaflets, in Gabon 100.0% (34) of samples were sold with an appropriate leaflet in French. In Kenya, none of the samples were sold with the leaflet. In Madagascar, 58.5% (24) were sold with appropraite patient leaflet in French.

The multinomial logistic regression identified that facilities from the public supply chain system were associated with presence of substandard (Odds Ratio [OR], 9.9; 95% confidence interval [CI], 1.2-84.1; p<.04) and manufacture in China (OR, 119.8; 95% CI, 8.7-1651.9; p<.001). PHY and exposure to atmosphere were associated with a risk of bad quality drugs (OR, 3.3; 95% CI, 1.4-7.9; p<.007 / (OR, 5.4; 95% CI, 1.2-24.1; p<.03). No association with urban or rural zone has been established, nor to presence or not of packaging, exposure to dust and moisture and unofficial sector (Table 3).

Environmental factors influence

Carbamazepine

This study has been performed on 8 batches of 200 mg-CBZ manufactured in China and India. One sample manufactured in EU has been purchased directly from the manufacturer as a reference. Breaks in the shell for coated tablets without packaging and red/brown spots in uncoated tablets with and without packaging were observed.

Assays of active ingredient were successful for all the samples and no chemical degradation has been observed between T0, T1 and T3. ATR-FTIR spectrum and DSC thermograms at T0 for all samples showed the presence of the anhydrous polymorphic form III of CBZ. At T1 and T3, a dihydrate polymorphic form was observed in samples from China and India but not in reference product. The Figure 2 shows the dissolution profiles of the reference product and 5 samples that failed the dissolution test (3 samples manufactured in India were not assessed for dissolution because of lack of quantity). The dissolution profile was unsatisfactory for all samples from India and China. At 20 min, the dissolution rate ranged on average from -31.2% (+/-14.0; max: -48.6) of the lowest limit of the acceptance criteria threshold for samples exposed to 75% RH during 3 months, up to -98.5% at 99.9% RH. The final proportion of active ingredient released at 60 min was for all batches under 73.3% to 3.2% (USP min. 75%).

Sodium Valproate

Analyses were performed on 14 batches of 200 mg-VPA and 10 batches of 500 mg-VPA enteric-coated (manufactured in EU and India). One sample manufactured in EU was purchased directly from the manufacturer as a reference. Without packaging, after two days, for all sample the pill coating was cracked and melted at 45°C and 75.0% RH. All VPA samples

were enteric-coated, hence the disintegration test was performed with two conditions (acidic: hydrochloric acid solution, 0.1M; buffer: pH 6.8 +/-0.5). The result showed a loss of enteric resistance for 200 mg-VPA after only ten days of exposure.

Analyses on sample of PHY with OOS were not be possible due to lack of quantity of sample gathered at the sites.

Discussion

This study revealed that a third (32.4%) of AEDs in three sub-Saharan African countries are of poor quality. The overall substandard prevalence was estimated to be at 22.6%. Compare to Otte[5] in Guinea Bissau and Nigeria, no counterfeit samples were identified, probably because of under-diagnosis and stigma. PB had the best quality, with no poor quality drug and only 5.9% of substandard. This is less than the proportion of 13.7% found by Laroche[3] in Mauritania in 2005, who found mostly under-dosed samples. AEDs manufactured locally in Africa was a better quality than AEDs manufactured in China and India. This results should be weighted by observed attitude consisting in falsely indicated as manufactured from EU, when indeed they may have been done locally. In several situations, AEDs quality was satisfactory for the active ingredient assay. However, tablet properties which condition the *in-vivo* behaviour (releasing of active ingredient at the right amount, the right kinetic, the right stage of the gastrointestinal tract, etc.) are an important issue. CBZ and VPA were had the most issues. In Gabon with its equatorial monsoon climate (Köppen-Geiger classification[13]), VPA sample was unsealed, although sold with the primary packaging and polypropylene tube with a desiccant. In Kenya (tropical savannah climate) we found the highest proportion of poor quality. Un-packing was a common practice in Kenya and might be the main cause of deterioration. The exposure to the atmosphere diminishes the quality, probably by acceleration of oxidation reaction and/or overexposure to humidity. Madagascar has a warm temperate climate with dry winter, and the sampling was done during winter period. The high frequency of substandard CBZ is likely to be caused by inhomogeneity of manufacturing process, rather than quality. The stress study has confirmed that CBZ tablets may be unable to correctly release the active ingredient. The modification of dissolution behaviours might be due to the polymorphism of the CBZ[14,15]. Kobayashi[16] in 2000 has shown significant differences between areas under the curve (AUC)

of different polymorphs, with the lowest AUC for the dihydrate. Thus, the presence of the dihydrate modifies the dissolution, which might disturb active ingredient release in the gastrointestinal tract. Lake[17] in 1999 showed an in *vitro/in vivo* correlations of dissolution data of CBZ tablets with *in vivo* pharmacokinetic data. The proportion of AI release at 20 min is correlated to C_{max} and $AUC_{0-\infty}$ of CBZ with a correlation coefficient of 0.99. Our study has shown that at 20 min, all the batches manufactured in China and India do not comply with Pharmacopoeias specification. The consequence is a bio inequivalence between brands and in the same brand. Issues concerning coating of VPA remain also problematic. The bioavailability of enteric-coated tablets is similar to that of the regular tablet[18]. However, peak plasma levels occur at 1-2 hours for regular tablets compared to 3-8 hours for enteric-coated tablets[19,20]. A loss of coating may lead to a heterogeneity of the VPA absorption, with fluctuations in the blood level, which may finally impact on effectiveness and tolerability. Storage without temperature and humidity control, un-packing are practices leading to improper and dangerous drugs, more so for the hot and humid areas, enhancing avoidable distrust in conventional medicines.

This study has several strengths such as the multisite comparison which provides a more representative picture of the situation in sub-Saharan Africa, a standard methodology of data collection, the laboratory analysis was robust and followed worldwide recommended guidelines. The main limitation was the cross-sectional design providing only a snapshot of the situation and the results may differ if another time-frame was chosen. The representativeness of the results cannot be established. Furthermore, causal inference of variables on the AEDs quality could not be established with this type of study design. A degradation may occur during the period between the sampling in Africa and analysis in France. To minimise this confounder, the time between the sampling phase and the analysis has been reduced as much as possible,

sample were cautiously packed, and stored in a closed temperature-controlled location before shipment to France. Another limitation is the difficulty to check the relevance of the labelling on the packaging of the drug (if present) with regard to origin of manufacturing.

Conclusion

Governments and health care professionals should be aware that even if they import good and efficient drugs on their market, they might become ineffective and dangerous by inappropriate storage conditions. Awareness and advocacy on this issue needs to be done, the poor quality issue highlighted here for AEDs is the same for other types of drugs in LMICs such as cardiovascular drugs with major health consequences[21].

Declaration of interests

The authors declare that they have no competing interests.

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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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