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Fighting fake medicines: First quality evaluation of cardiac drugs in Africa

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ABSTRACT

Background: The growing menace of poor quality and falsified drugs constitutes a major hazard, compromising healthcare and patient outcomes. Efforts to assess drug standards worldwide have almost exclusively focused on anti-microbial drugs; with no study to date on cardiovascular drugs.
Our study aims to assess quality of seven routinely used cardiovascular medications (anticoagulants, antihypertensives and statins) in ten Sub-Saharan African countries.
Methods: Drugs were prospectively collected using standardized methods between 2012 and 2014 from licensed (random pharmacies) and unlicensed (street-markets) places of sale in Africa. We developed a validated reversed-phase liquid chromatography with tandem mass spectrometry method to accurately quantify the active ingredient in a certified public laboratory. Three quality categories were defined based on the ratio of the measured to the expected dosage of the active ingredient: A (good quality): 95% to 105%, B (low quality): 85 to 94.99% or 105.01 to 115%, C (very low quality): <85% or >115%.
Results: All expected medicines (n = 3468 samples) were collected in Benin, Burkina-Faso, Congo-Brazzaville, the Democratic Republic of Congo, Guinea, Côte d'Ivoire, Mauritania, Niger, Togo and Senegal. Out of the 1530 samples randomly tested, poor quality (types B and C) was identified in 249 (16.3%) samples. The prevalence of poor quality was significantly increased in certain specific drugs (amlodipine 29% and captopril 26%), in generic versions (23%) and in drugs produced in Asia (35%). The proportion of poor quality reached 50% when drugs produced in Asia were sold in street-markets.
Conclusion: In this first study assessing the quality of cardiovascular drugs in Africa, we found a significant proportion of poor quality drugs. This requires continued monitoring strategies.

1. Introduction

The growing menace of poor quality and falsified drugs constitutes a major hazard, compromising healthcare and patient outcomes [1].

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Despite investments to strengthen enforcement of quality standards in developing countries [2–4], the seizure of counterfeit pills continues to make headlines [5].

Efforts to assess drug standards worldwide have almost exclusively focused on anti-microbial drugs (e.g.: HIV, malarial drugs); other drug categories have been relatively neglected [6–11], with no study to date on cardiovascular drugs [12–14]. A consequence of poor quality drugs is avoidable morbidity and mortality. Developing areas such as Africa have sustained significant loss of human life as a direct result, as per World Health Organization (WHO) figures, nearly 100,000 deaths a year are caused by the menace of counterfeit drugs in Africa [15].

Epidemiological transition in the developing world has resulted in a shift from infectious to non-communicable diseases as leading causes of morbidity and mortality [16]. Since the mid-1970s, while the rate of cardiovascular deaths has declined significantly in several high income countries [17], the incidence of cardiovascular disease has been on the rise in low income countries [18,19]. Thus, >80% of deaths in the world from cardiovascular disease are estimated to occur in low and middle-income countries; [19–21] with a concomitant increase in the consumption of cardiovascular drugs in these areas.

Use of poor quality drugs in cardiology can cause treatment failure leading to increased morbidity/mortality both in the short (drugs such as beta-blockers, anticoagulants) and long (drugs such as statins) terms. Furthermore, unknown variability in the quality of drugs such as anticoagulants can lead to incorrect dosage adjustments resulting in serious adverse events such as thrombosis, stroke, bleeding or death.

The SEVEN study is the first large multinational study to describe quality of cardiovascular drugs in Africa [22]. Hence, in the present study, we carried out accurate testing of seven routinely used cardiovascular medications in ten Sub-Saharan African countries.

2. Methods

2.1. Study design

The SEVEN study was conceived and designed by a multidisciplinary collaborative team of epidemiologists, cardiologists and pharmacists from France and Africa. The study was registered with the French national drug agency (ANSM ID_RCB:2014-A01275-42). This study was exclusively supported by a public grant in order to avoid any conflict of interest with the pharmaceutical industry.

Planning and launching the SEVEN study were aided by the team of SEVEN who has extensive prior research experience and existing collaborations with a network of physician-scientists in Africa such as in the fields of Rheumatic heart disease [23] and sickle cell disease [24].

The SEVEN study was so named because of the number of tested drugs. The research team had chosen seven drugs among the most common cardiovascular medicines used in Africa: an anticoagulant drug (acenocoumarol), a statin (simvastatin) and five antihypertensive drugs: furosemide, hydrochlorothiazide (diuretics), captopril (angiotensin-converting-enzyme inhibitor), atenolol (beta-blocker) and amlodipine (calcium channel blocker).

A pilot study was conducted in November 2012 in Burkina Faso. Samples were collected in two cities (the capital Ouagadougou and a city near the border, Bittou). Five licensed pharmacies were sampled to obtain all seven drugs; cardiovascular drugs were not available in street markets/unlicensed places of sale. Investigator collected 318 samples. According to sampling protocol, 140 samples randomly chosen by drug and place of sale were analysed.

The certified public laboratory of AGEPS (e.g. Agence Générale des Equipements et Produits de Santé, AP-HP, Paris, France) developed and performed the chemical analysis. This is an agency dedicated to the quality control of drugs as per Good Manufacturing Practices [25].

There are important differences regarding public health services and drug supply chain between countries in developing world. Ten African countries participated to the study with one local investigator responsible for sample collection in each country.

2.2. Sample collection

The sampling protocol was developed according to MEDQUARG guidelines [26] that describes how medicine quality surveys should be conducted.

Drug samples were prospectively collected in ten countries: Benin, Burkina Faso, Congo (Brazzaville), the Democratic Republic of Congo, Guinea, Côte d'Ivoire, Mauritania, Niger, Senegal, Togo. The income level of each country was obtained from World Bank data (http://data.worldbank.org/country. assessed 12 January 2015).

Samples were collected by standardized methods between November 2012 and August 2014.

There were no reliable estimates for the prevalence of poor quality medicines or for the proportion of places of sale selling such medicines for any country. Samples were collected from licensed (pharmacy) sources selected randomly and unlicensed (street market) places of sale chosen as per the local investigator's convenience. Lists of licensed outlets were obtained from the Council of the Order of Pharmacists of each country which enabled random sampling; unlicensed markets were identified based on the local investigator's knowledge. If the study medications were not available in the first randomly selected pharmacy, investigators selected another randomly and so on. Medication samples were also collected directly from poor patients who reported that they had purchased medicines from unlicensed places of sale.

Drug samples were purchased in the capital city and when possible in one city located close to the country's border. Medicines were obtained by the study investigator's staff who posed as customers.

After purchase, all drugs were stored at room temperature, in a dry place avoiding direct sunlight. Samples were sent via courier to the coordinating centre in France. Quality assessment tests were completed within 40 days of sample collection.

The project included the collection of at least ten samples of each of the seven drugs at two different places of sale -licensed and unlicensed- (i.e.: 10 samples × 10 countries × 7 drugs × 2 places of sale: 1400 expected samples) in each country.

2.3. Quality analysis

The packaging of each medication was systematically collected and examined. Version of drug (generic or branded), international non-proprietary names and pharmacological class, dates of manufacture and expiry, batch number, place of manufacture (indicated on the packaging or deduced by authors), and the form of the medication (capsule or tablet) were noted.

Chemical analyses of samples were blindly performed by the Department of Laboratories in Paris (AGEPS, AP-HP). A validated reversed-phase liquid chromatography (LC) with tandem mass spectrometry (MS) method was developed [27] to accurately quantify the content of active pharmaceutical ingredient in the sample. Reference standards of active pharmaceutical ingredient were purchased from INRESA Pharma (Bartenheim, France: amlodipine, atenolol, captopril, furosemide, hydrochlorothiazide and simvastatin). Acenocoumarol was kindly provided by Novartis-Pharma (France). The analytical method was validated as per the International Conference on Harmonization recommendations [28] with respect to specificity, linearity, accuracy, precision and limits of detection and quantification. Each drug was identified and then quantified.

For every drug, ten samples randomly chosen by place of sale and country were tested, except in six instances when only 5 samples were available.

2.4. Definition of poor quality

There is no clear and unvarying accepted definition of poor quality medicines encompassing both counterfeit and substandard drugs [2]. The WHO defines a counterfeit drug as "a medication which is purposefully mislabelled, conveying wrong information. Such drugs may either contain other components, deviant from the information stated on the packaging, or vary in the proportion of the actual active ingredient from what is expected. Ingredients other than the actual drug could be inactive substances or potentially, toxic, harmful, compounds [29]. On the other hand, substandard medicines are manufactured by genuine companies, but fall short of expected quality standards which they state [30]."

For the purpose of this study, drugs were classified into three types based on percentage ratio of measured to expected dosage of active ingredient:

- A: Good quality: 95% to 105%,
- B: Low quality: 85 to 94.99% or 105.01 to 115%,
- C: Very poor quality: < 85% or >115%.

Thus, broadly, whenever the active ingredient ratio (measured to expected) was under 94.99% or >105.01% (types B and C), drugs were deemed to be poor quality.

Additional forensic testing of the medications to detect other potentially toxic compounds, in order to determine substandard versus counterfeit drug was not performed in this study.

2.5. Statistical methods

Sample size was estimated using alpha 0.05, power 0.90 with the expected proportion of poor quality drugs at 5%, thus requiring a minimum of 124 samples for each drug.

Data were given in percentages of poor quality and compared using logistic regression in univariate and multivariate analyses, adjusting for factors identified to be relevant in univariate analysis ($P < 0.1$). Interactions were systematically assessed.

To account for intra and inter-group variability, a random effect was used for comparisons (using generalized linear mixed models GLMM; lme4 package of R, http://www.R-project.org/package=lme4).

Analyses were performed using R software (Version 0.98.1103–© 2009–2014 RStudio, Inc). P value of <0.05 was considered as significant.

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