Volume 30 (2019): Issue 6 (Nov 2019): Conference Special Issue: 2nd International Graduate Student Conference on Pharmaceutical Sciences (IGSCPS) & 2019 International Joint Symposium of the 8th Asia Pacific Pharmacy Education Network and the 2nd Halal Pharmaceuticals and Cosmetics (APPEN-HPC) / Guest Editors: Elida Zairina & Chrismawan Ardianto

in Journal of Basic and Clinical Physiology and Pharmacology

REVIEWS

Pharmacist contributions in the treatment of diabetes mellitus in Southeast Asia: a narrative review

Ayu Wulan Dwiputri, Liza Pristianty, and Andi Hermansyah

Article Category: Review Article | Article Number: 20190322 | Published online: 23 Jan 2020

ABSTRACT

Background

The growing burden of diabetes mellitus (DM) in Southeast Asia puts pharmacists

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The implementation of a chronic disease management program (Prolanis) in Indonesia: a literature review

Sesty Rachmawati, Hanni Prihhastuti-Puspitasari, and Elida Zairina

Article Category: Review Article | Article Number: 20190350 | Published online: 20 Dec 2019

ABSTRACT

Background

The Chronic Disease Management Program or Program Pengelolaan Penyakit Kronis (

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programs in Indonesia. Tuten i

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Synergistic anti-hepatitis C virus activity of *Ruta angustifolia* extract with NS3 protein inhibitor

Tutik Sri Wahyuni, Humairoh Mahfud, Adita Ayu Permatasari, Aty Widyawaruyanti, and Achmad Fuad

Article Category: Research Article | Article Number: 20190348 | Published online: 14 Dec 2019

ABSTRACT

Background

Medicinal plants are known to perform many pharmacological actions due to their

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***In vitro* equivalence of generic and branded amoxicillin tablet by microbiological assay method**

Primadi Avianto, Mahfudz, Suharjono, Isnaeni, and Christopher Paul Alderman

Article Category: Research Article | Article Number: 20190247 | Published online: 11 Jan 2020

ABSTRACT

Background

Indonesian Ministry of Health advocate doctors, especially in government-owned healthcare facility, to prescribe generic drugs including

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Knowledge and attitude: two fundamental factors that determine patient compliance in antibiotic therapy

Liza Pristianty, Vivi Laily Kurniati, and Ika Ratna Hidayati

Article Category: Research Article | Article Number: 20190321 | Published online: 12 Feb 2020

ABSTRACT

Background

With the development of infectious diseases, the use of antibiotics is increasin

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Primadi Avianto[1] / Mahfudz[1,2] / Suharjono[3] / Isnaeni[4] / Christopher Paul Alderman[3,5]

In vitro equivalence of generic and branded amoxicillin tablet by microbiological assay method

[1] Faculty of Pharmacy, Universitas Airlangga, Master Program in Clinical Pharmacy, Department of Clinical Pharmacy, Kampus C, UNAIR, Mulyorejo Rd. Surabaya, Indonesia, E-mail: primadi-a-11@ff.unair.ac.id
[2] Pharmacy Section, Bangka Tengah District Health Office, Bangka Belitung, Indonesia
[3] Faculty of Pharmacy, Universitas Airlangga, Department of Clinical Pharmacy, Kampus C, UNAIR, Mulyorejo Rd. Surabaya, Indonesia
[4] Faculty of Pharmacy, Universitas Airlangga, Department of Pharmaceutical Chemistry, Kampus C, UNAIR, Mulyorejo Rd. Surabaya, Indonesia
[5] School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia

Abstract:
Background: Indonesian Ministry of Health advocate doctors, especially in government-owned healthcare facility, to prescribe generic drugs including amoxicillin. Although BPOM (the National Agency of Drug and Food Control) already guarantees that the generic amoxicillin and the branded one were interchangeable, lack of confidence in generic drugs still remains among patients, pharmacists, and doctors. This issue supported by lack of publication confirmed the therapeutic equivalence of branded and generic drugs. This study aims to evaluate and compare the *in vitro* microbiological assay of different generic and branded amoxicillin that are available in Indonesian market, especially those used in government-owned healthcare facilities.
Methods: Microbiological assays for five samples of amoxicillin tablet containing 500 mg amoxicillin available in Indonesia were determined using a method from Indonesia Pharmacopeia. Samples were coded as Products A to E. The assay was carried out by measuring the diameter of the inhibition zones in the plate agar incubated with *Escherichia coli* and *Staphylococcus aureus*. The obtained data were evaluated to determine the sample potency and compared with the amoxicillin reference standard.
Results: Minor and insignificant differences ($p > 0.05$) were found in the diameters of the inhibition zones. Potency ratio measured both in *E. coli* and *S. aureus* were all between 95% and 105%. The lowest of the tested samples were from Product C, which resulted to ratio potencies of 96.3% and 95.5% in *E. coli* and *S. aureus*, respectively.
Conclusions: All five samples were in the range of the acceptance criteria. Therefore, from the view of the microbiological assay, these products are in equivalence in quality and are interchangeable.

Keywords: amoxicillin, generic substitution, microbiological assay
DOI: 10.1515/jbcpp-2019-0247
Received: September 4, 2019; **Accepted:** November 22, 2019

Introduction

As the Indonesia Ministry of Health advocates doctors to prescribe generic medicine especially in government-owned healthcare facilities such as primary health care centers (PHCCs) and hospitals, pros and cons debate re-emerge [1]. For the pros, generic medicines could benefit patients because of its affordability without affecting treatment outcome (same efficacy). The cons argue that generic medicines are not always clinically equivalent and therefore do more harm than good despite of its low cost [2], [3], [4]. Those that are clinically in-equivalent should be reported because the medicines were substandard (also called out of specification), which, according to WHO, is defined as authorized medical products that fail to meet either their quality standards or specifications, or both [5]. Substandard medicine may have lower quality, therefore resulting in lower efficacy and different safety profile [6]. For substandard antibiotics, it may result in increased mortality, morbidity, and cost because of unmet clinical outcomes (unresolved infection), even the development of resistance bacteria.

Primadi Avianto is the corresponding author.

Beta-lactams were among the most common substandard medicines found. Predominantly, it was amoxicillin, a semisynthetic amino penicillin with bactericidal activity against many Gram-positive and Gram-negative bacteria [7]. This broad spectrum combined with its low cost and well-known safety profile results to its common use in various infections such as in the respiratory tract, ear, skin, and urinary tract.

Antibiotic use profile in Indonesia does not differ from the rest of the world. Beta-lactams was among the most used antibiotic, especially amoxicillin [8], [9], [10]. As one of the district in Indonesia, Bangka Tengah is predicted to have the same antibiotic use profile as the rest of Indonesia.

The present study aims to compare the efficacy of the generic and branded amoxicillin preparations used in PHCC and hospitals across Bangka Tengah district by comparing its antibacterial potency.

Materials and methods

In this study conducted in 2018, three generics and two brand preparations of amoxicillin from various manufacturers were collected from PHCC and a government-owned hospital in Bangka Tengah district. Those five products were all products that were available, circulating, and to be used for the patients in PHCC and the government-owned hospital in Bangka Tengah at the time of the sample collection. Those products then were labeled as products A through E. All samples were kept in manufacturer's original packing and stored as stated in its packaging until testing, that is, in dry and controlled room temperature (<30 °C). The amoxicillin reference standard (equivalent to Indonesian Pharmacopeia Reference Standard) was used for comparison, labeled as F. *Escherichia coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923) were used as the test bacteria in this study. Both *E. coli* and *S. aureus* were obtained from the Clinical Microbiology Department of Dr. Soetomo General Teaching Hospital in Surabaya, Indonesia. Sodium chloride 0.9% (Widatra Pharmaceutical Industry, Pandaan, Indonesia) was used for the preparation of the test bacteria. A spectrophotometer (GENESYS™ 20, Thermo Scientific) was used to measure the optical density of the test bacteria suspension to obtain 25% *T* (transmittance).

Microbiological assay to evaluate the *in vitro* potency comparison was carried out using agar diffusion method by 3 × 3 assay design. Mueller-Hinton agar (Oxoid, USA) was used as the growth media. Mueller-Hinton agar was weighed approximately 3 g, then 150 mL of distilled water (Ikapharmindo Pharmaceutical Industry, Jakarta, Indonesia) was added. The mixture was heated while stirring evenly. Afterward, it was sterilized with an autoclave at 120 °C for 15 min. The agar solution was then poured in Petri dishes at 40–50 °C and then left solid to be used as a base layer. The seed layer media was prepared by inoculating 5 µL 25% T test microbial suspension containing 10^9 CFU of test microbe, poured over the surface of the compacted media layer.

Five tablets of amoxicillin from each sample were randomly selected, weighed, and homogenized. Approximately equivalent to 50 mg amoxicillin was then put in a 10 mL measuring flask, added with 5 mL of DMSO (Merck, Germany) and sonicated. DMSO was added until 10 mL and then filtered with a membrane filter (0.2 µm). Sonification was carried out to ensure all active ingredients were extracted from the tablet matrix (excipients). Furthermore, serial dilution was made to achieve 200, 160, 128, 25, 20, and 16 ppm solutions. The standard solution was made by the same procedure.

Each Petri disk contains wells of each of the product, reference standard, and negative control (only containing diluent). For each product and reference, there were three wells, representing high (H), medium (M), and low (L) test concentrations. For the *E. coli* colony, concentrations used were as follows: 200 (H), 160 (M), and 128 ppm (L). For *S. aureus*, it was 25, 20, and 16 ppm. The zone of inhibition was measured by its diameter using caliper scale in millimeters after 22 h of incubation (Memmert Incubator, Germany).

Statistical analysis was done using one-way ANOVA followed by Tukey's test using the SPSS software (version 22.0, IBM).

Results

The Agar diffusion test using *E. coli* showed that all products were comparable as shown in Table 1. Consistent results were seen in the tests using *S. aureus* as shown in Table 2. Further potency comparisons (Table 3) showed that for *E. coli*, product C had the lowest potency of 96.3 ± 1.7%, and the highest was 98.2 ± 1.3% from product B. For *S. aureus*, product A showed the lowest potency of 96.1 ± 1.1%, and product C showed the highest potency of 97.7 ± 0.2%.

Table 1: Diameter of inhibition zones of amoxicillin against *E. coli* (mm).

Replication	Conc.	Product code					
		A	B	C	D	E	F (STD)
1	High	16.2 ± 1.1	16.6 ± 0.4	16.4 ± 1.1	16.5 ± 0.7	16.4 ± 1.0	16.6 ± 1.1
	Medium	15.2 ± 1.0	15.6 ± 0.6	15.3 ± 0.9	15.3 ± 0.7	15.3 ± 0.9	15.6 ± 1.0
	Low	14.2 ± 0.9	14.6 ± 0.6	14.3 ± 0.7	14.2 ± 0.7	14.3 ± 0.8	14.7 ± 1.1
2	High	16.0 ± 1.0	16.0 ± 0.4	15.9 ± 1.3	16.1 ± 0.6	15.9 ± 1.6	16.6 ± 1.0
	Medium	14.8 ± 0.9	15.3 ± 0.7	14.9 ± 1.3	14.9 ± 1.1	15.1 ± 1.0	15.7 ± 1.1
	Low	13.9 ± 1.0	14.1 ± 0.7	13.5 ± 0.7	13.8 ± 0.9	13.9 ± 1.0	14.6 ± 1.1
3	High	15.6 ± 1.1	16.1 ± 0.3	15.6 ± 1.0	16.3 ± 1.1	16.4 ± 1.1	16.6 ± 1.0
	Medium	14.8 ± 1.2	15.1 ± 0.5	14.7 ± 0.7	15.1 ± 0.5	14.6 ± 1.0	15.6 ± 1.2
	Low	14.3 ± 0.8	14.4 ± 0.9	14.1 ± 0.6	13.9 ± 0.9	13.9 ± 0.7	14.6 ± 1.1
Sum		45.0 ± 2.6	45.9 ± 1.5	44.9 ± 2.7	45.3 ± 2.2	45.3 ± 2.8	46.9 ± 3.0
p-Value		>0.05	>0.05	>0.05	>0.05	>0.05	na[a]

[a] not applicable, F was used as reference standard against product A to E.

Table 2: Diameter of inhibition zones of amoxicillin against *S. aureus* (mm).

Replication	Conc.	Product code					
		A	B	C	D	E	F (STD)
1	High	16.1 ± 0.5	16.2 ± 0.6	15.7 ± 0.6	16.1 ± 0.3	16.0 ± 0.6	16.6 ± 0.2
	Medium	14.6 ± 0.4	14.6 ± 0.5	14.5 ± 0.4	14.7 ± 0.3	14.5 ± 0.5	15.1 ± 0.2
	Low	13.4 ± 0.4	13.5 ± 0.3	13.5 ± 0.5	13.5 ± 0.4	13.3 ± 0.6	13.5 ± 0.3
2	High	15.9 ± 0.7	16.2 ± 0.5	16.0 ± 0.8	16.0 ± 0.9	16.1 ± 0.8	16.7 ± 0.4
	Medium	14.3 ± 0.2	14.4 ± 0.6	14.6 ± 0.6	14.6 ± 0.4	14.8 ± 0.7	15.0 ± 0.3
	Low	12.8 ± 0.5	13.3 ± 0.8	13.2 ± 0.6	13.4 ± 0.5	13.2 ± 0.8	13.3 ± 0.4
3	High	15.6 ± 1.1	16.1 ± 0.3	15.6 ± 1.0	16.3 ± 1.1	16.4 ± 1.1	16.6 ± 1.0
	Medium	14.8 ± 1.2	15.1 ± 0.5	14.7 ± 0.7	15.1 ± 0.5	14.6 ± 1.0	15.6 ± 1.1
	Low	14.3 ± 0.8	14.4 ± 0.9	14.1 ± 0.6	13.9 ± 0.9	13.9 ± 0.7	14.3 ± 0.9
Sums		43.9 ± 1.9	44.6 ± 1.4	43.9 ± 1.6	44.4 ± 1.6	44.3 ± 2.0	45.6 ± 1.7
p-Value		>0.05	>0.05	>0.05	>0.05	>0.05	na[a]

[a]not applicable, F was used as reference standard against product A to E.Add a table footnote here

Table 3: Potency of tested product compared with the standard.

Colony	Product code				
	A	B	C	D	E
E. coli	96.5 ± 0.9%	97.2 ± 1.3%	96.3 ± 1.7%	97.1 ± 0.9%	97.0 ± 1.2%
S. aureus	96.1 ± 1.1%	97.7 ± 0.2%	96.2 ± 0.5%	97.4 ± 0.2%	97.0 ± 0.5%

Indonesian Pharmacopoeia requirements: 95-102%

Discussion

The National Agency of Drug and Food Control (BPOM) has made thorough regulations for medicine manufacturers, often called cGMP (current good manufacturing practices) [11]. This cGMP is applied both for generic and branded medicines. It is requiring the manufacturers to extensively test the products both *in vitro* and *in vivo* before being made available to the public. Even in post marketing situation, BPOM are rigorously testing medicines that are already in the market with random sampling from pharmacies, PHCC, and hospitals from across the country [12], [13]. Therefore, there should be no reason to believe that generic medicines are substandard.

Availability of generic drugs, which are generally lower in cost compared with their branded counterparts, is important especially for developing country such as Indonesia. With low cost and same quality, not only high income people could afford the medicines they needed but also people with middle and low income.

The present study used agar diffusion method, which is also known as cylindrical-plate method. This method is one of the most widely used method to estimate potency/bioactivity of antibiotics [14]. It is very important to have equivalent quality, efficacy, and safety in the various preparations of amoxicillin, as it is the most used antibiotic in the healthcare system in Indonesia. The results shown above revealed that all brands, both generic or branded, that were used for the patients in PHCC and government-owned hospital in Bangka Tengah were comparable in potency. All products were also in the range of acceptance, which is 95%–102% according to the Indonesia Pharmacopoeia.

Various other studies conducted elsewhere show mixed results; some studies show comparable *in vitro* quality between generic and branded medicines, whereas others show that generic medicines were not comparable with the branded ones, especially the innovator brand [15], [16], [17], [18]. Substandard medicine may lead to treatment failure, such as that shown for antimalarial and antitubercular agents. This predominantly occurs in less developed countries in Africa and Asia, in some extent in Europe [7], [19]. Treatment failure means increase in cost, mortality, and morbidity. This suggests that intensive and rigorous manufacturing guidelines and product quality surveillance, as is already done by BPOM, must be kept in pace to prevent substandard medicine from corrupting the quality of health care in Indonesia.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

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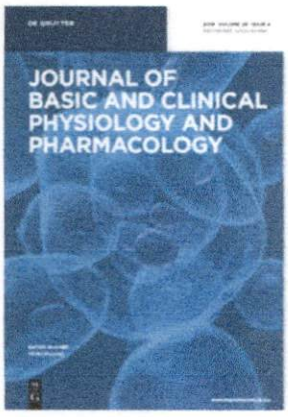

Journal of Basic and Clinical Physiology and Pharmacology

Editor-in-Chief

Michal Horowitz

m.horowitz@mail.huji.ac.il

Editorial Board

Editorial Office

Katharina Appelt

Walter de Gruyter GmbH

Genthiner Str. 13

10785 Berlin

Germany

Tel. +49-30-26005-325

E-mail: jbcpp.editorial@degruyter.com

DETAILS

Online ISSN: 2191-0286

Type: Journal

Language: English

Publisher: De Gruyter

First published: 01 Dec 1986

Audience: researchers and health professionals in the field of clinical physiology and pharmacology