ORIGINAL ARTICLE

Evaluation of the Quality of Fixed Dose Combination Anti Tuberculosis Drugs in Public and Private Health Institutions in Lusaka District

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ABSTRACT

Background: Counterfeit and substandard medicines are a threat to health and the risks they pose have been largely underestimated to date.[13] Almost all areas of the world are affected by the availability of substandard and counterfeit medicines, but mounting evidence shows that the problem is disproportionately severe in developing and emerging market countries, which also have a high burden of infectious diseases.[5,12] In poor countries, essential and life-saving drugs used to treat infectious diseases such as tuberculosis and malaria are often the drugs under threat. [3]

Methodology: This was a cross sectional study whose objective was to determine the quality of 3 types of fixed dose combination (FDC) anti TB drugs namely 4FDC, 3FDC and 2FDC tablets available in Lusaka District by assessing the presence of active ingredients and the percentage content of these active ingredients according to the British pharmacopoeia 2008 using Spectrophotometric method. The drug samples analyzed had a shelf life of at least one year.

Results: For presence of active ingredient, all the seventeen samples that were tested gave a positive result indicating that each sample had the correct active ingredients as indicated by the label claim. However, 20% (1/5) of the 4FDC samples and 14% (1/7) of the 2FDC samples were none compliant to the BP 2008 specification for percentage content. One sample of 4FDC had a percentage content of 106.3% for Isoniazid that was above the BP 2008 specification of 95% to 105% and one sample of 2FDC had a percentage content of 105.6% for Isoniazid that was also above the BP. 2008 specification of 95% to 105%.

All the 3FDC samples were compliant to the BP 2008 specification for percentage content of 95% to 105%.

Conclusion: The results from this study have established that substandard fixed dose combination anti TB drugs are present in Lusaka District. These results confirm the urgent need to have a national quality control laboratory that is supported by satellite mini laboratories at the points of entry for drugs and also to strengthen post marketing surveillance of all Pharmaceutical products that are imported into the country or manufactured locally. This will ensure safety and efficacy of the drugs that are used in the country.

INTRODUCTION

Drug quality is currently receiving renewed international attention. Counterfeit and substandard drugs have been increasingly reported in developing countries where drug regulations are ineffective. Many factors contribute to the increased prevalence of substandard and counterfeit medications such as poor quality control during manufacture.[1,2,14]

Fixed dose combination (FDC) anti TB Drugs used in Zambia come as imports from other countries and

access to these drugs is through the public institutions such as the Government run hospitals and clinics, the private institutions (hospitals and clinics). What is of much concern is that there is inadequate post – marketing surveillances on these drugs. The consequence of using counterfeit and substandard FDC drugs is a high burden of the disease leading to toxicity or multi drug resistance tuberculosis, high mortality and morbidity.[13]

Almost all areas of the world are affected by the availability of substandard and counterfeit medicines, but mounting evidence shows that the problem is disproportionately severe in developing and emerging market countries, which also have a high burden of infectious diseases. In poor countries, essential and life-saving drugs used to treat infectious diseases such as tuberculosis and malaria are often the drugs under threat.[3] Counterfeit and substandard medicines present an enormous public health challenge.[11]

According to WHO, Substandard drugs do not meet official standards for strength, quality, purity and / or labeling, and these drugs result in serious health implications such as lacking therapeutic effect and causing treatment failure, severe adverse effects, increased morbidity and mortality, development of drug resistance and in the case of TB multi drug resistance TB and waste of resources.[12]

It is quite clear from above that the problem of counterfeit and substandard anti TB drugs is a growing threat to global health and has not spared Sub Saharan Africa as shown by studies conducted in South Africa and Botswana.[6,7,9]

Substandard drug preparations are present throughout the world.[11] A study that involved the screening of single and fixed dose combination (FDC) anti TB drugs from selected TB programs from Colombia, Estonia, India, Latvia, Russia and Vietnam was done using a method called Thin Layer Chromatography (TLC). The results from this study showed that a substantial number of anti Tuberculosis drugs from several countries, in particular FDC were found to be substandard. 10% (4/40) of all samples contained less that 85% of stated content, 13% (4/30) Rifampicin samples contained less than 85% of stated content. The study also showed that more FDCs (5/24, 21%) than single drug samples (2/16, 13%) were substandard. Such drugs may contribute to the creation of drug resistant Tuberculosis.[8]

In 2001 a study was done in Nigeria to check the quantity of active ingredients in anti TB drugs and the results showed that more than 50% of the anti TB drugs failed to comply with the official monographs. The tested drugs had low quantities of the active ingredients.[10] In 1999, a study was also conducted in South Africa that involved screening of FDC formulations and the results showed that 70% (7/10) of the samples had Rifampicin being non bioequivalent to the official monograph and this had serious implications on treatment outcomes for TB hence the moderately high rate of multi drug resistance (MDR) cases that were recorded in the country.[9]

Another study was done in Botswana in 1999 that involved quantitative analysis of 13 FDC anti TB samples and the results obtained showed that 31% (4/13) of the samples were substandard with 15% (2/13) having less than 85% Rifampicin as active ingredient, 8% (1/13) having more than 115% of Rifampicin and 8% (1/13) of the samples having more than 115% Pyrazinamide. The gold standard used was Ultra Violet Spectrophotometry with a sensitivity of 100% and specificity of 90%.[6,7]

In Zambia there is no documented evidence about any research done to determine the existence of substandard FDC anti TB drugs. However, the Government of the Republic of Zambia has shown its commitment to fight the scourge by establishing institutions such as the Pharmaceutical Regulatory Authority (PRA) and the Drug Enforcement Commission (DEC). Furthermore, on 11th November 2008, the government formed the Drug Taskforce to fight counterfeiting of drugs in the country.

The aim of this study was to evaluate the quality of fixed dose combination anti TB drugs in Lusaka district so as to find ways of strengthening the fight against the use of substandard drugs.

MATERIALS AND METHODS

The drugs that were used in the study were anti tuberculosis drugs that are used in the treatment of TB according to the national tuberculosis treatment guidelines for Zambia. These were all fixed dose combination drugs that were collected from the points of distribution to the patients. Three fixed dose combination drugs were used in this study and their details are indicated in table 1.

Table 1: Details of drugs used in the study

Drug Class	Name of Drug	Drug Combination	Formulation
Antibacterial	4FDC	Pyrazinamide Ethambutol Rifampicin Isoniazid	Tablet
Antibacterial	3FDC	Ethambutol Rifampicin Isoniazid	Tablet
Antibacterial	2FDC	Rifampicin Isoniazid	Tablet

Drug quality was assessed by measuring the level of active ingredient content as a percentage of stated content in the tablet samples in compliance to the official monograph. The acceptable levels for each drug according to the official monograph (BP 2008) are indicated in table 2.

Table 2: Specifications for acceptable levels of each drug according to BP. 2008

Drug	Acceptable % content of active ingredient in Official monograph (BP 2008)
Pyrazinamide	95 – 105%
Ethambutol	95 – 105%
Rifampicin	92.5 – 107.5%
Isoniazid	95 – 105%

RESULTS

4FDC

All the four drugs that were contained in 4FDC drug samples tested positive to the identification tests and the results for the identification tests done on the individual drugs contained in 4FDC samples are indicated in table 3.

Table 3: Results of identification tests done on 4FDC samples

Drug Code	Pyrazinamide	Ethambutol	Rifampicin	Isoniazid	Result
1A	+	+	+	+	Pass
1B	+	+	+	+	Pass
1C	+	+	+	+	Pass
1D	+	+	+	+	Pass
1E	+	+	+	+	Pass

+= Positive identification test

For percentage content of active ingredient, one sample out of five (20%) was not compliant to the BP 2008 specification for content of active ingredient as a percentage. Sample 1E had 106.3% of Isoniazid and fell above the BP 2008 specification of 95 – 105%. Values of the percentage content of active ingredient of the four drugs in the assayed 4FDC drug samples are indicated in table 4.

Table 4: Percentage content of four drugs in 4FDC samples

Drug Code	Pyrazinamide	Ethambutol	Rifampicin	Isoniazid	Result
1A	103.1%	96.3%	94.4%	103.3%	Pass
1B	101.4%	95.0%	95.9%	102.9%	Pass
1C	103.8%	97.7%	94.9%	102.9%	Pass
1D	103.3%	97.6%	98.9%	104.6%	Pass
1E	101.2%	97.7%	105.0%	**106.3%**	**Fail**

3FDC

All the three drugs contained in 3FDC gave a positive identification test result for all the five samples tested and the identification results of the three drugs that were contained in 3FDC samples are indicated in table 5.

Table 5: Drug identification test results for the drugs in 3FDC samples

Drug Code	Ethambutol	Rifampicin	Isoniazid	Result
2A	+	+	+	Pass
2B	+	+	+	Pass
2C	+	+	+	Pass
2D	+	+	+	Pass
2E	+	+	+	Pass

+= Positive identification test

All the five samples of 3FDC were found to be compliant to the specifications of the BP 2008 for percentage content and the values for percentage content of the three drugs contained in 3FDC samples tested are indicated in table 6.

Table 6: Values of percentage content of the three drugs in 3FDC samples

Drug Code	Ethambutol	Rifampicin	Isoniazid	Result
2A	95.6%	98.9%	104.6%	Pass
2B	95.0%	101.0%	103.7%	Pass
2C	97.7%	100.5%	104.2%	Pass
2D	95.6%	106.8%	104.2%	Pass
2E	96.3%	100.5%	103.3%	Pass

2FDC (Rifinah)

The identification tests on the seven samples of 2FDC drugs showed a 100% positive identification test result for all the samples that were tested and the test results are indicated in table 7.

Table 7: Identification test results for individual drugs in Rifinah drug samples

Drug Code	Rifampicin	Isoniazid	Result
3A	+	+	Passed
2B	+	+	Passed
3C	+	+	Passed
3D	+	+	Passed
3E	+	+	Passed
3F	+	+	Passed
3G	+	+	Passed

+ = Positive identification test

However, one out of seven samples (14%) of 2FDC was not compliant to the BP 2008 specifications for percentage content of active ingredient. Sample 3D had 105.6% of Isoniazid and fell above the accepted range of 95% - 105%. The results are indicated in table 8.

Table 8: Values of percentage content of the two drugs in Rifinah samples

Drug Code	Rifampicin	Isoniazid	Result
3A	94.9%	103.3%	Passed
2B	95.9%	103.3%	Passed
3C	95.9%	104.6%	Passed
3D	97.9%	**105.6%**	**Fail**
3E	96.4%	104.2%	Passed
3F	97.9%	103.8%	Passed
3G	99.4%	104.2%	Passed

DISCUSSION

This cross sectional study that was conducted in Lusaka District to assess the quality of fixed dose combination anti Tuberculosis drugs from the clinics which are the points of distribution to the patients provides vital information on the quality of drugs that are being used for the treatment of Tuberculosis in the national TB programme. The results of the study (table 3 to table 8) provide objective information on the quality of drugs in terms of presence of active ingredient as well as the actual percentage content of each active ingredient for each sample that was tested.

Quality can be defined as a combination of attributes of a product which determine its degree of acceptability as the right product for the intended use and is capable of exerting the correct pharmacological action when used correctly. The quality of a pharmaceutical product will therefore depend on the degree of adherence to the general manufacturing practices and the packaging materials used to package the product as well as the storage conditions that the pharmaceutical product is subjected to after manufacture. When any one of the above is not addressed adequately the result is a pharmaceutical product that is none compliant with the official monographs that provide guidance on the specifications for quality.

The identification tests for individual drugs that were contained in the fixed dose combination formulations yielded positive results for all the samples that were tested. This means that all the

samples that were tested yielded a 100% positive identification test for the individual components of the fixed dose combination formulations in line with the label claims of each category of the fixed dose combination formulation. All the 4FDC samples contained the four drugs indicated on the label and these included Pyrazinamide, Ethambutol, Rifampicin and Isoniazid. All the 3FDC samples contained the three drugs indicated on the label for 3FDC and these drugs comprised Ethambutol, Rifampicin and Isoniazid and the 2FDC samples also contained the two drugs as indicated on the label which included Rifampicin and Isoniazid.

The findings of the study on the percentage content of active ingredients confirmed the existence of substandard fixed dose combination anti TB drugs. 20% (1/5) of the 4FDC samples and 14% (1/7) of the 2FDC samples were found to be none compliant to the BP 2008 specification for percentage content. Isoniazid was found to fall above the BP specification of 95 – 105% with a percentage content of 106.4% in one sample of 4FDC and 105.6% in one sample of 2FDC. All the 3FDC samples were found to be compliant to the BP 2008 specifications for percentage content.

The findings that 20% (1/5) of 4FDC and 14% (1/7) of 2FDC did not comply with the BP 2008 specifications for percentage content entails that there is urgent need to strengthen post marketing surveillance of all pharmaceutical product with a view of improving quality control of for these products before they are released to the general public for use. The basic aim of these monitoring activities is to ensure that all drugs meet the required specifications for quality as stipulated in the official monographs.

CONCLUSION

This study has established that substandard anti Tuberculosis drugs are present in Lusaka district. The results have shown that 20% (1/5) of the samples for 4FDC and 14% (1/7) of the samples for 2FDC were none compliant to the BP 2008 specifications for percentage content for Isoniazid.

These results confirm the urgent need to strengthen the capacity of the Pharmaceutical Regulatory Authority (PRA) to carry out post marketing surveillance on all pharmaceutical products that are either sold or distributed for free to the general public. There is also need for the Ministry of Health to establish a national quality control laboratory that should be supported by satellite mini laboratories at the points of entry for drugs so that quality control on drugs can be enhanced. This will ensure safety and efficacy of the drugs that are used in the country.

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