Research Journal of Medical Sciences 2 (3): 159-162, 2008
ISSN: 1815-9346
© Medwell Journals, 2008

Assessment of the Drug Storage Facilities and Quality of Generic Co-Formulation Tablets (Stavudine, Lamivudine, Nevirapine) at HIV/AIDS Treatment Centers in Uganda

[1]Musoke David, [2]Obua Celestino and [2]Waako Paul John
[1]Department of Pharmacology, Gulu University P.O. Box 166, Gulu, Uganda
[2]Department of Pharmacology and Therapeutics, Makerere University,
P.O. Box 7072 Kampala, Uganda

Abstract: This study investigated the storage facilities and the quality of Co-formulation tablets containing stavudine, lamivudine and nevirapine at four treatment centers in Uganda. A cross-sectional survey of drug storage conditions at four distribution centers randomly selected from four regions of Uganda was done using a checklist developed from the guideline for good drug storage practices. Drug batches were sampled at the time of the survey and one month after storage and analyzed for quality using appearance, uniformity of weight, dissolution rate and drug content. All treatment centers had satisfactory storage design but lacked facilities for monitoring temperature and humidity. Air-conditioning facilities were also lacking. Batches investigated had average weight deviation of less than 5%; content of active pharmaceutical ingredients lay between 90-110% and the dissolution rate was greater than 80% in 45 min both on delivery and after one month of storage. The quality of co-formulation tablets containing stavudine, lamivudine and nevirapine was of good quality. However, the storage facilities at the HIV/Aids treatment centers were inadequate. They need to be provided with facilities to monitor temperature and humidity as the antiretroviral programme expands to cover a broader spectrum of drugs.

Key words: HIV/Aids, antiretrovirals, drug quality, co-formulation tablets, drug storage and tropical countries

INTRODUCTION

HIV/Aids is a leading global health challenge and combating of HIV/Aids is one of the United Nations Millennium Development Goals. The use of Antiretroviral drugs (ARVs) is a major strategy for the reduction of morbidity and mortality due to the disease (Palella *et al*., 1998; Kumarasmy *et al*., 2003). In Uganda, ARVs have been introduced to further ameliorate the condition of people living with HIV and Aids with a view of increasing both the quality and quantity of life. This initiative is supported by a number of partners including the Global Fund for Malaria, Aids and Tuberculosis (GFAMT), The Presidential Emergency Fund for Africa and the Gates Foundation among others. This has resulted in the upscale and expansion of Antiretroviral Therapy (ART) services in the country. ARVs are currently dispensed at the level of district hospital and there are plans to extend the services to health centers with health workers that include at least Medical Doctors, Nursing officers and Pharmacy Technicians. It is envisaged that mainly generic brands will be used since they are more affordable but concerns about the quality of generics remain a threat to the intervention.

A number of studies have reported incidences of sub-standard drugs (Shakoor *et al*., 1997; Ogwal-Okeng *et al*., 2003; Kayumba *et al*., 2004; Ahmed *et al*., 2000). While, counterfeiting has been implicated in many of these studies, transportation practices and storage conditions are also known to affect quality of pharmaceuticals. Tropical conditions (high temperatures coupled with humidity) are known to have undesirable effects on the biopharmaceutical properties of drugs (Hogerzeil *et al*., 1992; Helm *et al*., 2003). Similarly for ARVs quality concerns have been raised as an issue in the implementation of ART programs (Houston, 2002). Treatment with antiretroviral drugs is life long; therefore, possibility of poor quality drugs causes genuine fears of treatment failure and emergence of resistance to the drugs.

This study set out to assess the storage facilities and the quality of co-formulation tablets containing stavudine, lamivudine and nevirapine at selected

Corresponding Author: Musoke David, Department of Pharmacology, Gulu University P.O. Box 166, Gulu, Uganda

HIV/AIDs treatment centers in Uganda at the time of receipt and after storage period of one month at these centers.

MATERIALS AND METHODS

Study design and setting: This was a cross-sectional survey of drug storage facilities at 4 ARVs distribution centers accredited by the Ministry of Health, Uganda and experimental evaluation of ARVs. Baseline evaluation of the tablets containing the ARVs was done at the time of receipt and repeated after one month of storage. The study was carried out between the month of June and August. These centers are situated at regional hospitals, staffed by clinical specialists and a resident pharmacist. Antiretroviral drugs supplied from the National Medical Stores. The quantities supplied are determined according to estimated number of patients attending the health facility for ART. Each treatment center is responsible for the storage of antiretroviral drugs till they are dispensed to the patients. Study hospitals had between 200 to 300 HIV/AIDs clients. Experimental analysis of the ARVs was performed in the Department of Clinical Pharmacology and Therapeutics at Makerere University, Kampala Uganda.

Sampling procedures: Study hospitals were randomly selected with help of a list of centers accredited to offer antiretroviral therapy in the country obtained from the AIDS control program of the Ministry of Health, Kampala, Uganda. The sampling of the drugs was carried out using the WHO guidelines (WHO, 1997). The packs of the tablets sampled were picked at the time of delivery and the same batches sampled again after a period of one month of storage in the hospital stores. The storage duration was limited to one month only due to regulations that require the centers to restock after one month. The samples were carried to the laboratory for analysis in the packing patients ordinarily use for carrying them.

Data collection and outcome measures

Storage conditions: The drug storage conditions were assessed by direct observation using the checklist developed from the WHO guidelines on Good Storage Practices of pharmaceuticals (WHO, 2003). Key outcome variables included cleanliness, ventilation, availability and usage of shelves and pallets, protection from direct sunlight and the availability and usage of thermometers and hygrometers to monitor temperature and humidity in the drug storage facilities.

Quality of drugs

Physiochemical evaluation: Tablets were *i*nspected for color changes, shape obliterations, presence or absence of stains and any other evidence of contamination.

From each batch twenty tablets were picked randomly and weighed individually using an electronic balance (Metler, AJ 100). The weight for each tablet was recorded and the average weight (g) for each batch determined. The *in-vitro* Dissolution rate was determined as described in the United States Pharmacopoeia (2000). The instrument used was Eureka. Nine hundred milliliter of 0.1 mol L^{-1} Hydrochloric acid (Dissolution medium) adjusted to 37°C was placed in 6 amber colored dissolution flasks. One tablet was placed in each flask at a paddle speed of 50 rpm and allowed to run for 45 min. About 50 mL of the mixture was withdrawn and filtered through a whatman filter paper no. 41. Ten milliliter of the filtrate was then diluted to 25 mL with the mobile phase and then 20il injected into the HPLC system.

Mobile phase and standard solution: In the quantification of stavudine, lamivudine and nevirapine, the mobile phase consisted of a buffer (pH 2.5), methanol HPLC grade and Acetonitrile (HPLC grade) in a ratio of 65: 15: 20, v/v/v, respectively. The buffer was prepared by dissolving 2.0 g of Octane sulfonic acid sodium salt AR and 1.36 g of potassium dihydrogen phosphate AR in 1.8 l of water filtered through 0.45 um filters. Two milliliter of Triethylamine AR was added to the solution and pH adjusted to 2.5 with Orthophosphoric acid and then made up to 2.0 L with water.

Standard solutions were prepared from 3.75 mg of stavudine, 25 mg of nevirapine and 18.75 mg of lamivudine all USP reference standards using a 25 mL volumetric flask to which 10 mL methanol AR and 10 mL of water were added to dissolve the powders and the volume made up to mark. Two milliliter of the solution was then diluted to 25 mL with the mobile phase. Twenty microlitre of the above solutions were injected in to the HPLC system.

Quantification of active ingredients in the tablets: Five tablets were weighed and transferred into a 500 mL volumetric flask. Fifty milliliter of distilled water were added to the flask followed by swirling of the flask to disintegrate the tablets. Two hundred milliliter of methanol AR were added to the flask to dissolve the active ingredients. The solution was then made up to 500 mL with distilled water. About 10 mL of the above mixture was centrifuged at 5000 G for 15 min. One milliliter of the filtered supernant was then diluted to 25 mL will mobile phase from which 20 μL was loaded on to the High Performance Liquid Chromatography system.

The HPLC system was a SHIMADZU model; with a ultra-violet detector set at wavelength 266 nm. The column used was Waters Spherisorb 5 micro, 4.6 mm internal diameter and 250 mm long maintained at a temperature of 30°C in an oven. A run time of 15 min was used at a flow rate for the mobile phase at 1.0 mL min^{-1}. The peak areas of the concentrations from the calibration curves of the stavudine, lamivudine and nevirapine USP reference standards were used to calculate the amount of drug. Linearity of the assay method was examined by replicate analysis (n = 5) of a series of concentrations corresponding to 80-120% of the amounts claimed on the label. The following correlation co-efficient (r^2) were obtained: stavudine, 0.9994; lamivudine, 0.9976; nevirapine, 0.9981. Stavudine separated at 3.512 min., lamivudine at 4.221 min. and nevirapine at 10.666 min.

Data analysis: Data on storage conditions and visual inspection of the drugs was analyzed descriptively. The means and standard deviation were used to establish weight uniformity among the drug batches. The uniformity of weight was considered to be acceptable if the standard deviation of the average weight of the tablets did not exceed 0.05. The content of the active ingredients was deemed to be acceptable if it lay between 90-110% of the label claim. The mean dissolution rate was deemed to be acceptable if 80% or more of the drugs were released into solution in 45 min.

Ethical considerations: Approval to carry out this study was granted by the Makerere University, Faculty of Medicine, Ethics and Research Committee and The National Council of Science and Technology (NCST). The AIDS Control Programme granted the permission to collect the samples from the various distribution centers. The samples used where from buffer (excess) stock and no patient was deprived of treatment.

RESULTS

Storage facilities: The storage facilities in all the four hospitals were found to be clean, had good ventilation and well placed shelves and pallets. The storage facilities were all protected from direct exposure to direct sunlight. However, thermometers and hygrometers to monitor temperature and humidity, respectively were absent. Air conditioning facilities were also lacking.

Quality of drugs

Tablet visual appearance: All the batches of the co-formulation tablets containing stavudine, lamivudine and nevirapine investigated were found to be of uniform shape, uniform color and with no visible sign of staining or contamination.

Table 1: Chemical content of seven batches of stavudine/lamivudine/nevirapine co-formulation tablets sampled at time of survey and after one month

	Chemical content % label claim (%mean/SD)					
Sample code	Stavudine on receipt	At 1 month	Lamivudine on receipt	After 1 month	Nevirapine on receipt	After 1 month
1	103.5(0.92)	101.3(3.25)	96.1(3.32)	95.2(4.54)	104.0(4.29)	102.2(6.22)
2	103.7(3.20)	101.3(3.25)	103.0(3.24)	101.2(4.17)	101.1(3.56)	102.7(5.8)
3	99.1(0.42)	100.4(1.48)	92.2(0.01)	91.7(0.71)	97.9(0.10)	98.0(0.07)
4	106.0(0.0)	101.4(0.07)	100.5(1.63)	90.9(0.14)	99.6(0.14)	97.7(0.14)
5	95.6(0.28)	97.5(0.21)	92.6(0.14)	96.9(0.57)	103.4(0.07)	102.9(0.07)
6	106.9(1.20)	105.7(0.49)	97.5(4.03)	98.3(2.33)	105.0(4.10)	102.9(3.39)
7	106.6(0.35)	95.6(0.64)	95.8(0.21)	94.3(2.76)	103.4(0.14)	102.3(0.07)

Limits of assay: The tablet is deemed to be of acceptable quality if the content of the tablet is found to be 90-110% label claim. The results obtained were for analysis of five tablets and the experiment repeated twice. In the brackets is the standard deviation

Table 2: Dissolution test of 7 batches of stavudine/lamivudine/nevirapine co-formulation tablet formulations sampled at the time of survey and after storage for one month

	Dissolution test (45 min). Dose released as % label claim (%mean/SD)					
Sample code	Stavudine on receipt	Lamivudine At 1 month storage	Nevirapine on receipt	After 1 month	on receipt	After 1 month
1	99.8(6.13)	103.4(5.32)	92.2(5.45)	95.7(5.12)	102.1(7.02)	104.5(7.58)
2	106.0(0.62)	103.5(5.55)	104.5(2.80)	101.5(5.56)	101.1(3.69)	105.9(6.69)
3	105.3(4.05)	103.2(5.85)	97.1(4.32)	95.6(5.92)	103.1(4.33)	104.3(7.14)
4	101.6(3.13)	104.7(1.23)	94.1(2.72)	97.3(3.38)	101.5(3.96)	106.4(.89)
5	101.3(3.10)	95.0(1.87)	96.0(1.97)	96.3(1.72)	103.8(3.14)	99.4(1.54)
6	103.1(4.95)	101.2(4.21)	94.1(3.36)	94.8(4.02)	99.4(5.62)	100.1(3.64)
7	106.3(1.24	97.2(3.39)	95.0(0.32)	93.6(3.55	102.5(0.58)	99.7(2.48)

Limits: The results for the dissolution test are interpreted on average values from 6 tablets: whereby the amount of stavudine, lamivudine and nevirapine in solution should be more than 80% of the amounts claimed on the label

Test for uniformity of weight: All the batches of the tablets investigated had a standard deviation from the average weight of less than 5% (0.47-1.57), which is well within the acceptable pharmacopoeia limits.

Chemical content: The Active Pharmaceutical Ingredients (API) were within the acceptable limits required, that is 90-110% of label amount claimed for all the tablets sampled from the hospitals at the time of delivery and after storage for one month. (Table 1). There was no significant change in the content of the tablets at the time of receipt and after storage for a period of one month in the hospital storage facilities ($p>0.05$).

Dissolution rate: All the seven samples at the time of delivery and after 1 month of storage had an average of over 80% dissolution rate within 45 min. There was no significant change in the dissolution rate at the time of receipt and after storage for a period of one month in the hospital storage facilities ($p>0.05$) (Table 2).

DISCUSSION

This study reports inadequate storage facilities for ARVs in four facilities in Uganda with lack of thermometers and hygrometers for monitoring temperature and humidity, respectively. Air condition facilities are also lacking. However most of storage buildings were found to be clean and structurally in good condition. It was also found that despite these inadequacies, the quality of antiretroviral drugs was not affected after one month of storage at the health facility. Drug quality has been reported to be adversely affected by poor manufacturing processes (Shakoor *et al*., 1997), transport and storage conditions (Hogerzeil *et al*., 1992; Helm *et al*., 2003). The quality of essential antimicrobial and antimalarial drugs assessed in Rwanda and Tanzania established that some drugs were sub-standard at the time of purchase and that they deteriorated during storage under simulated tropical conditions (Kayumba *et al*., 2004).

Our study is in agreement with reference to inadequate storage conditions for drugs in Uganda and perhaps in central African region (Ogwal-Okeng *et al*., 2003). This state of affairs becomes important with the ongoing expansion in scaling up of antiretroviral therapy programmes. These drugs are generally new and whose properties may not be well established under tropical conditions. While workload and limited resources are considered key factors affecting effective monitoring of storage conditions, the risk of poor quality drugs is enormous and it is important that these contributory factors are addressed. Our study did not show that the quality of the drugs was affected. This could be because the duration of storage investigated was only one month. It is envisaged that drugs will be stored for longer times with expansion of ART services. Our study was also limited as it investigated only one co-formulation. There is need for studies that will provide information on conditions storage at household level.

The storage facilities are inadequate and need to be improved to facilitate the expansion and up scaling of antiretroviral drugs use in the country implementing antiretroviral therapy.

ACKNOWLEDGEMENT

We wish to extend our thanks to Sida/ SAREC and the World Bank funded programme, I@mak, for providing financial support to carry out this research study. We are also profoundly grateful to Mr. Lyazi Ivan for his help in statistical matters.

REFERENCES

Ahmed Abdo-Rabbo, Amal Bassili and Hoda Ata, 2004. Malar J., 4: 28.

Hogerzeil, H.V., A. Battersby, V. Srdanovic and N.E. Stjermstrom, 1992. BMJ., 304 (6821): 210-212.

Helm, M., T.H. Castner and L. Lamp, 2003. Acta Anaesthesiol. Scand., 47: 425-429.

Houston, S., 2002. Physicians AIDS care (Chic 111). J. Int. Assoc., 1 (2): 78-83.

Kumarasamy, N., S. Solomon, T.P. Flanigan, R. Hemalatha, S.P. Thyagarajan and K.H. Mayer, 2003. Clin. Infect. Dis., 36: 79-85.

Kayumba, P.C., P.G. Risha, D. Shewiyo, A. Msami, G. Masuki, D. Ameye, G. Vergote, J.D. Ntawukuliryayo, J.P. Remon and C. Vervaet, 2004. J. Clin. Pharm. Ther., 4: 331-338.

Ogwal-Okeng, J.W., E. Owino and C. Obua, 2003. Afr. Health Sci., 3 (1): 2-6.

Palella, F.J., K.M. Dalaney, A.C. Moorman *et al*., 1998. N Engl. J. Med., 338: 853-860.

Shakoor, O., R.B. Taylor and R.H. Behrens, 1997. Trop. Med. Int. Health, 2 (9): 839-845.

World Health Organisation, 1997. Quality assurance of pharmaceuticals. A compendium of guidelines and related materials, Vol. 1.

World Health Organisation, 2003. Technical report series 908.WHO expert committee on specification for pharmaceutical preparations.