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Quality of Antiretroviral Drugs Analyzed in the Drug Analysis and Research Unit During 2000-2003

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During the period 2000-2003 the Drug Analysis and Research Unit received and analyzed 33 samples of antiretroviral drugs. Locally manufactured products accounted for 57.6 % of the samples, while the imported drugs constituted 42.4 %. The drugs consisted of single, double and triple component preparations. They were subjected to the identity, assay and dissolution tests. 30 samples (90.9 %) complied with compedial specifications for these tests, while 3 failed. The results obtained show that manufacture of quality generic antiretroviral drugs is achievable.

Key words: Antiretroviral, assay, dissolution, nucleoside reverse-transcriptase inhibitor

INTRODUCTION

The HIV/AIDS pandemic has contributed significantly to social and economic losses in the developing countries, whereby the majority of patients belong to the highly productive age bracket of 15-45 years. Efforts to prevent spread of the disease have not been successful in sub-Saharan Africa where social and religious rituals and beliefs continue to frustrate such endeavors [1,2].

The antiretroviral drugs (ARVs) and drugs for opportunistic conditions are the mainstay of the management of HIV/AIDS patients. Due to resistance of HIV to single component drugs, triple therapy ARVs is the standard practice. For this purpose ARVs are classified as: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). The choice of drugs for triple therapy from the 3 classes is developed by individual countries following WHO guidelines [3,4].

To reduce the cost of ARVs most governments have resorted to compulsory licensing and hence manufacture of generic ARVs [2]. Through such programs, Brazil, India and Thailand have built a well-established system for manufacture, distribution and use of ARVs. However, there have been concerns on the quality of generic ARVs. This can only be ascertained by means of GMP compliance and bioequivalence testing of the products [5-8].

The quality of drugs in the Kenyan market has been shown to vary with the manufacturer (brand/generic) and whether the drugs have been manufactured locally or imported. Published analytical results from Drug Analysis and Research Unit show that almost all classes of products analyzed had quality problems [9-13].

This paper reports on the quality of ARV drugs analyzed at DARU from 2000 to 2003. It is the first report on the quality of antiretrovirals in the East African region.

EXPERIMENTAL

Drug samples

Drug samples and working standards were provided by the clients requesting for analysis. Samples were received from the local industry and importers intending to market the products in Kenya. The protocol for receiving samples at DARU has been described previously [14,15]. The samples analyzed consisted of pharmaceutical specialties only.

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Methods

The drug samples were analyzed using validated high performance liquid chromatography (HPLC) methods. The methods were either developed in DARU or provided by manufacturers of the products. Zidovudine was analyzed using the USP (2002) specifications [16].

Quantitative determination

The active pharmaceutical ingredient (API) content was quantified by comparison with external standards of known potency. Some of the drugs analyzed did not have compendial specifications for the tests carried out especially assay and dissolution. Therefore, the USP limits for assay (90-110 % label claim) have been applied for the results presented in this paper [16]. The dissolution test for the amount of API released into solution at 30 minutes was compared to the 70 % label claim limit.

RESULTS AND DISCUSSION

The drug samples submitted for analysis consisted of single API component and combination specialties in accordance to current trends in HIV/AIDS management. Drugs belonging to the PI category were not presented for analysis. This observation reflects the behavior of ARV prescribers in Kenya, which is PI-sparing mainly due to the adverse effects and rapid resistance to the drugs [17].

The drug samples were subjected to tests for identification, assay and dissolution as requested. The results obtained are summarized in table 1.

Table 1. Antiretroviral drugs analyzed in DARU in the period 2000-2003

Drug(s)	Brand/ Generic	Samples Complied	Samples Failed	Total
Lamivudine 150 mg	Generic	7	0	7
Lamivudine syrup (10 mg/ml)	Generic	5	0	5
Zidovudine 100 mg	Generic	3	0	3
Zidovudine 100 mg	Brand	1	0	1
Stavudine 40 mg	Brand	1	0	1
Stavudine 40 mg	Generic	2	1	3
Stavudine 30 mg	Generic	2	0	2
Nevirapime 200 mg	Generic	2	0	2
Lamivudine 150 mg Zidovudine 300 mg	Generic	2	0	2
Lamivudine 150 mg Stavudine 30 mg	Generic	1	0	1
Lamivudine 150 mg Stavudine 40 mg	Generic	0	1	1
Lamivudine 102.4 mg Stavudine 40 mg	Generic	1	0	1
Lamivudine 150 mg Stavudine 40 mg Nevirapine 200 mg	Generic	1	0	1
Lamivudine 150 mg Stavudine 30 mg Nevirapine 200 mg	Generic	2	1	3
Total number of drugs		30	3	33

A total of 33 samples were analyzed, 22 (66.7 %) of which were single component NRTIs. Among these, lamivudine comprised 12 (54.5 %), zidovudine 4 (18.2 %) and stavudine 6 (27.2 %) samples, respectively. Seven samples of lamivudine submitted were in 150 mg tablet form, while 5 were syrups. The other drugs were presented in the capsule or tablet form. Only 2 samples of nevirapine 200 mg tablets were received, both of which complied with the tests performed.

Generic products accounted for 31 (93.9 %) of the samples while the 2 brands submitted were both single component NRTIs. This reflects the current government policy to encourage marketing of generic ARVs, which are far much affordable than the brands. Since these new generic products require analysis results for registration, it explains why they formed the bulk of samples analyzed in DARU.

The drugs analyzed were both from local (57.6 %) and imported (42.4 %) sources. The analysis results obtained show that 30 (90.9 %) of the samples complied with the USP specifications while 3 generic products derived from the single, double and triple component formulations (one each) failed in the assay test for stavudine.

The multicomponent formulations analyzed were 9 (27.3 %), 5 of which were two component preparations consisting of lamivudine with either zidovudine or stavudine. The triple component formulations contained lamivudine, stavudine and nevirapine (NNRTI). Stavudine occurred in the 30 mg or 40 mg strength depending on the target group of patients [3].

CONCLUSION

As more ARVs enter Kenyan market there is need for continuous market surveillance of these drugs to monitor their quality. Quality assurance during the manufacture of combination ARVs needs to be implemented to minimize cases of formulation problems. Bioequivalence data should be a requirement for the registration of generic products. It is noteworthy that prescription, distribution and dispensing of ARVs in Kenya is not reliable [3]. These problems need to be addressed urgently to make ARVs available to HIV/AIDS patients countrywide. Local manufacture of these drugs will greatly reduce the cost of HIV/AIDS treatment.

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ABBREVIATIONS

Ångström	Å	Gram-molecule	mol	Minimum inhibitory concentration	MIC
Atmosphere	Atm	Hertz	Hz	Molar concentration	M
Atomic weight	at. wt.	High frequency	h.f.	Month	month
Boiling point	b.p.	High pressure liquid chromatography	HPLC	Nanometer	nm
Calorie	cal	Hour(s)	h	Nanomole	nmol
Centimeter	cm	Infrared	i.r.	Normal concentration	N
Central nervous system	CNS	Internal diameter	i.d.	Nuclear magnetic resonance	NMR
Column chromatography	CC	International unit	I.U.	Ohm	Ω
Company	Co.	Joule	J	Outside diameter	o.d.
Corporation	Corp.	Kilocalorie	kcal	Picomole	pmol
Correlation coefficient	r	Kilogram	kg	Probability	P
Coulomb	C	Kilometer	km	Paper chromatography	PC
Counts per minute	cpm	Kilovolt	kV	Proton magnetic resonance	^{1}H-NMR
Counts per second	cps	Kilowatt	kW	Radio-frequency	r.f.
Cubic centimeter	cm^3	Kilowatt-hour	kWh	Relative humidity	r.h.
Cubic inch	in^3	Liter	l	Relative standard deviation	RSD
Cubic meter	m^3	Liquid chromatography	LC	Revolutions per minute	rpm
Cycles per second	c s^{-1}	Logarithm	log	Root mean square	r.m.s.
Day(s)	day(s)	Logarithm (natural)	ln	Second(s)	s
Degrees		Megaelectron volts	MeV	Square foot	ft^2
Celsius	°C	Melting point	m.p.	Square meter	m^2
Centigrade	°C	Meter	m	Standard deviation	SD
Kelvin	K	Microgram	µg	Standard error	SE
Degrees of freedom	df	Microliter	µl	Standard temperature and pressure	S.T.P.
Direct current	d.c.	Micrometer	µm	Thin-layer chromatography	TLC
Disintegrations per minute	dpm	Micromolar	µM	Ultraviolet	UV
Disintegrations per second	dps	Micromole	µmol	Versus	vs
Dyne	dyn	Millicurie	mCi	Volt	V
Electromagnetic force	e.m.f.	Milliequivalent	mEq	Volt-ampere	VA
Electron spin resonance	ESR	Milligram	mg	Volt-coulomb	VC
Electron volt	eV	Milliliter	ml	Volume	vol.
Erg(s)	erg(s)	Millimeter	mm	Volume by volume	v/v
Feet, foot	ft	Millimolar	mM	Watt	W
Freezing point	f.p.	Millimole	mmol	Watt-hour	Wh
Gas-liquid chromatography	GLC	Millisecond	ms	Weight	Wt
Gauss	G	Milliosmolar	mOsM	Weight by weight	w/w
Gram	g	Minute(s)	min	Weight by volume	w/v