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Original Article

PRELIMINARY SURVEY OF COUNTERFEITING OF ALBENDAZOLE AND METRONIDAZOLE MARKETED IN LUBUMBASHI

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ABSTRACT

Objective: Counterfeit medicines represent a major health risk in the treatment of various pathologies. They are responsible for resistance emergence in the treatment of infectious diseases. This study was conducted in order to identify illegal and legal drugs marketed in the city of Lubumbashi and assess the quality of all samples concerned by this study.

Methods: The study included albendazole and metronidazole for oral administration. Visual inspection of medicines, investigation of the authenticity of drugs from pharmaceutical regulatory authorities, and determination of content were used as study parameters.

Results: A total of 34 samples were collected including 19 of albendazole and 15 of metronidazole. 11 (32%) samples were not permitted to be marketed. 9 (26 %) samples were substandard according to the US Pharmacopoeia in terms of the content of active ingredient: all of them, the active ingredient was found to present in a lower amount (under-dosing). The proportion of non-compliance is highest among medicines not permitted to be marketed (78% vs 8.0%; $p<0.005$).

Conclusion: It is obvious that strengthening the capacity of drug regulatory authority of the DR Congo can reduce the influx of counterfeit/substandard drugs in Lubumbashi.

Keywords: Medicines, Counterfeiting, Antiparasitics, DR Congo, Lubumbashi

INTRODUCTION

Counterfeit drugs represent a huge threat to public health because of the high risk of damage they can cause to patients who consume them [1-3]. It is estimated that over 10% of drugs in circulation in the world are counterfeit, but the rate is much higher in developing countries because of the weakness and lack of drug regulatory systems [4-8]. Indeed, pharmaceutical regulatory authority is a structure which is responsible for the coordination and monitoring the pharmaceutical sector, in order to preserve public health, its deficiency, weakness or ineffectiveness promotes the importation, manufacturing and distribution of drugs without supervision. This causes proliferation of fakes in chain distribution national [9, 10].

Counterfeiting affects all types of medicine, however, the medicines concerned are not the same across countries. In industrialized countries, the targets tend to be lifestyle medicines such as narcotics or treatments for erectile dysfunction [1, 11]. Poor countries are mainly affected by counterfeit anti-infective [1, 11, 12].

It has been reported that in developing countries, counterfeit medicines often involves essential drugs used in life-threatening diseases such as antiparasitics. Albendazole and metronidazole are among the most antiparasitics used in DR Congo (Democratic Republic of Congo) [11, 13, 14]. Albendazole is a broad-spectrum anthelmintic; it is used for the treatment of Threadworm, hookworm and Tapeworm [15]. Metronidazole is very effective in the treatment of amoebiasis, trichomoniasis, giardiasis and many other parasitic diseases [16]. The high demand for these medicines makes them a very attractive target for counterfeiters who benefit from the large amount of products that they easily sell in a short period of time.

Considering all questions above-mentioned, it seemed important to conduct a preliminary study on counterfeiting of albendazole and metronidazole with the objective to identify illegal and legal drugs marketed in the city of Lubumbashi and assess the quality of all samples concerned by this study.

MATERIALS AND METHODS

Geographically this study included drugs obtained in Lubumbashi, the provincial capital of Haut-Katanga, south-eastern province of DR of Congo, the city has seven townships: Lubumbashi, Kampemba, Kamalondo, Kenya, Katuba, Ruashi and Annex. The samples were collected in four types of pharmaceutical establishment: establishment of wholesale, pharmacies opened to public, hospital pharmacies and public market.

Sampling method

Samples were purchased from 15th December 2014 to 10thJanuary 2015. The selection of collecting site was not the same for the types of pharmaceutical structures indicated above. Thus, the establishment of wholesale are twenty-two in Lubumbashi, they are all located in Lubumbashi city center and have been all selected as the collecting site of our samples. Regarding hospital pharmacies, general reference hospitals are eleven (Katuba, Kamalondo, Kenya, Kisanga, Kampemba, Jason Sendwe, Ruashi, Vangu, Munua, Tshiamilemba and Kowe), they were automatically chosen for the collection site of our samples. Concerning pharmacies opened to the public, their selection was made randomly, we randomly selected 5 pharmacies in each township of the city of Lubumbashi. Public markets where medicines are sold are six in Lubumbashi: Kenya, Zambia, M'zee, Texaco, Congo and Katuba, we selected all those markets to collect our samples.

Each sample was collected with his withdrawal slip which contains the necessary information on the traceability of samples collected: active ingredient and strength, brand name, manufacturing and expiring date, batch number, registration number, quantity purchased, date and place of collection and the price of each sample acquired.

Samples which were collected from the same or different pharmaceutical establishment and carrying a label indicating the same mentions: active ingredient, brand name, name and address of the manufacturer or marketer, the number of marketing

authorization, batch number, date of manufacture and expiry, batch number, and having the same pharmaceutical form and strength were considered as one sample. For the purpose of authenticity investigation, the medicines were required to be sold with their outer containers (boxes or plastic bags), or at least with their blisters, providing minimum information about the manufacturer or marketer and the batch/lot number.

Pharmaceutical forms that were involved in this study are those for oral administration, i.e. tablets, capsules, and oral suspensions. All the samples were kept at room temperature until analysis.

The standards (table 1) used in this study have been ordered and obtained from approved suppliers.

Table 1: standard products information

Product	Batch n °	Supplier	Reference
Albendazole	2.0	European pharmacopeia	A0325100
Metronidazole	2.1	European pharmacopeia	M1850000

Observational analysis

Identification of a potentially counterfeit medicine passes first through careful visual inspection of the product. It consisted in examining: the location of mentions on the packaging, the physical aspect of pharmaceutical forms, the bar code, hologram, logo, typography, drawings or pictures, spelling words, language (s) mentioned (s) by the manufacturer, the instructions, the color of the packaging and product etc. [15, 17].

Each sample received a visual inspection questionnaire which incorporated information on samples collected including primary and secondary packaging, the physical appearance of the tablet, capsule, solution for oral drop and powder for suspension, the particle size powders for drinkable suspensions forms.

Investigation of authenticity

Besides complete analytical tests, WHO advises contacting the manufacturer on the label and the pharmaceutical regulatory authorities (PRA) of the country of marketing and manufacturing [15, 17]. In this study, we went to meet the pharmaceutical regulatory authority of D R Congo. The purpose of this investigation was to verify whether medicines collected in the pharmaceutical market were registered and authorized to be marketed in DR Congo. Thus, a formulary was intended for the local pharmaceutical regulatory authority who has the official list of medicines registered and authorized to be marketed in D R Congo.

Chemical analysis

Spectrophotometry was used for determination of the content of albendazole and metronidazole.

Experimental procedure

A Genesys 10S UV-VIS spectrophotometer was used for measurement of the absorbance of solutions.

Preparation standard

Albendazole [18]

In a volumetric flask of 50 ml, weigh exactly 25 mg of albendazole, dissolved in methanol-glacial acetic acid to get a concentration of 500 µg/ml. Prepare (table 2) six different concentrations.

Table 2: Dilutions of standard of albendazole

Prepared solution	Dilution ratio	Concentration(µg/ml)	Absorbance
solution 1	0.5 ml/100 ml	2.5	0.963
solution 2	0.5 ml/50 ml	5	1.986
solution 3	0.75 ml/50 ml	7.5	2.942
solution 4	0.5 ml/25 ml	10	4.028
solution 5	0.5 ml/20 ml	12.5	4.948
solution 6	1.5 ml/50 ml	15	5.875

The absorbance (fig. 1) was measured at 235 nm against the blank and we regenerated a regression line.

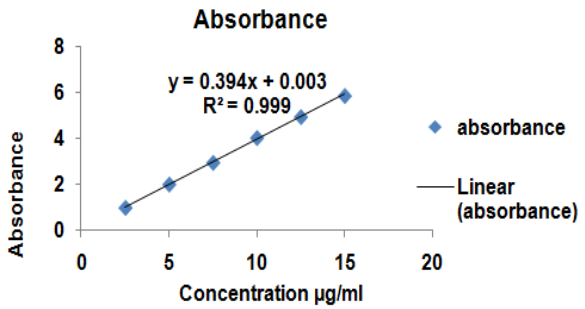

Fig. 1: Calibration curve of albendazole

Metronidazole [14]

In a volumetric flask of 100 ml, weigh exactly 10 mg of metronidazole, dissolved in methanol to get a concentration of 100 µg/ml. Prepare (table 3) six different concentrations.

Table 3: Dilutions of standard of metronidazole

Prepared solution	Dilution ratio	Concentration(µg/ml)	Absorbance
Solution 1	4 ml/100 ml	4	0.1
Solution 2	6 ml/100 ml	6	0.139
Solution 3	8 ml/100 ml	8	0.177
Solution 4	10 ml/100 ml	10	0.216
Solution 5	12 ml/100 ml	12	0.252

The absorbance (fig. 2) was measured at 235 nm against the blank and we regenerated a regression line.

Preparation samples

Samples of albendazole and metronidazole were dissolved and diluted to reach a concentration of 10µg/ml.

Statistical analysis

Data analysis was performed using Epi-info version 7.0

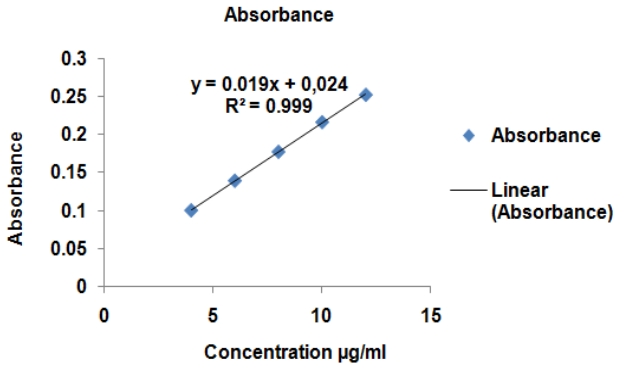

Fig. 2: Calibration curve of metronidazole

RESULTS AND DISCUSSION

Sampling

34 samples were collected from 21 pharmaceuticals establishments: 19 of albendazole and 15 of metronidazole. establishments of wholesale provided about 42% of samples, followed by pharmacies opened to public pharmacies (27%), and respectively 15% and 17% for hospital pharmacies and public market. The predominance of samples provided by establishments of wholesale can be explained by the fact that they supply the majority of other pharmaceutical establishments: pharmacies opened to public, hospital pharmacies and the drugs sold in public markets. The most represented pharmaceutical form is a tablet with 50% and respectively 44% and 6% for oral suspension and capsule form. All samples collected had an identifiable country of origin: 44% of samples collected were manufactured in India, 18 % were from France, 12% for Pakistan and DR Congo, others countries do not exceed 10% (fig. 3). The price of purchased samples fluctuates between 0.08 USD and 5.6 USD for albendazole, and from 0.11 USD to 5.3 USD for metronidazole.

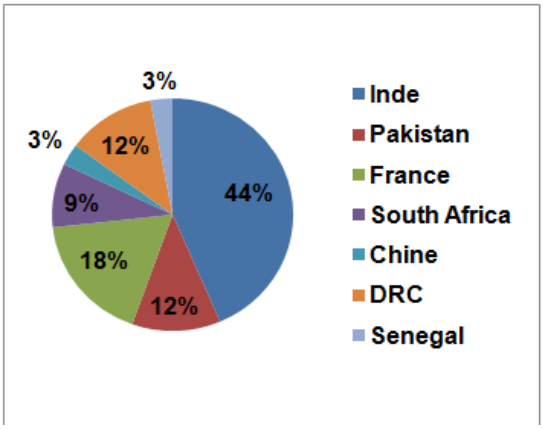

Fig. 3: Distribution of samples collected according to origin country

Authenticity

Investigation of samples authenticity revealed that 11 (32%) samples were not authorized to be marketed in the Democratic Republic of Congo. 6 (55%) cases concerned albendazole, and 5 (45%) for metronidazole. Samples illegally traded in DR Congo are mostly from Asia (fig.4) 91%: 55% for Pakistan and 36% for India, France represents 9%.

The investigation method of drugs authenticity has been practiced rarely and often incomplete, because of the time and budget required for its efficient working. This is the case of Khail *et al.* (2013) [19] who investigated the authenticity of drugs from the medical regulatory authority of manufacturers country and manufacturer, only 3 of 11 medical regulatory authority replied to requests for verification of the legitimacy of manufacturers and samples. Six of 15 manufacturers participated to the study.

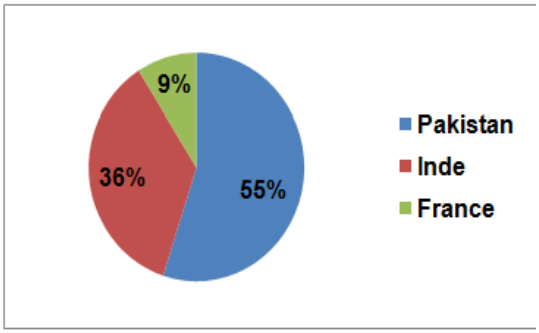

Fig. 4: Distribution of samples illegally marketed in the DR Congo according to origin country

Visual inspection

Of 34 samples collected, 6 (18%) samples were suspected to be counterfeit. We give illustrations of two samples (fig. 5 and 6). Indeed, the medicine suspected to be counterfeited (Ib) reproduce on its primary and secondary packaging information in English and Arabic. This is shown that these products were normally intended exclusively for Arab or English countries. The brand name and the logo of sample Ia are reproduced exactly. The investigation of drug authenticity to pharmaceutical regulatory authority revealed that the authorization and registration of the product Zentel were obtained for France as a country, and there is no Zentel registered in DR Congo which is from Pakistan as it's the case of sample Ib. The two samples were collected in two different establishments of wholesale and the price of the sample Ia is more expensive than sample Ib: 0.11 USD for medicine manufactured in Pakistan (sample Ib) and 4.88 USD for a sample from France (Sample Ia). This corroborates the theory that stipulates that drug prices could serve as a predictor factor to detect counterfeiting in comparisons between genuine products and their copies [20].

Fig. 5: Medicine legally marketed in DR CONGO (Ia)

Content analysis

The percentage content of the samples (table 4) was obtained through calculations using the linear equation obtained from the regression analysis of albendazole and metronidazole.

Fig. 6: Medicine illegally marketed in DR CONGO (Ib)

Of 34 samples collected in this study, 9 (26%) were found to be non-compliant in terms of dosage of active ingredient as specified in the US Pharmacopeia (90%-110%) [21, 22]. The active ingredient was found to present in a lower amount (under-dosing) for all samples non-complaints. Albendazole is the most represented with 5 samples (56%) non-compliant, followed by metronidazole with 4 (44%) samples. The tablet form represents 56 % of non-compliance followed by oral suspension form with 44%. These findings differ from that found by Aka *et al.* (2005) in Cote d'Ivoire, who had found that of 15 samples albendazole, one sample presented an anomaly, this non-compliance was due to a total absence of active ingredient. Musa *et al.* (2011) found that out of 15 samples of metronidazole collected in Nigeria; only one had presented an anomaly of active ingredient content.

Non-compliant samples detected are all from different types of collection site: the establishment of wholesalers are the most represented with 44% of non-compliance, followed by markets publics (33%) and successively 22% and 11% for pharmacies open to public and hospital pharmacies. This shows that substandard medicines problem affects the entire pharmaceutical market in Lubumbashi. Elsewhere, 44% of non-compliance was from Pakistan, followed by India with 33% and respectively 11% for France and DR Congo.

Out of 9 Samples non-compliant, samples illegally marketed in DR Congo represent around 78% (7 samples) of non-compliance. All of them were the case of under-dosing. Among the active ingredient concerned by these non-compliances, albendazole is the most concerned with 57% of non-compliance (table 5). It has been reported that counterfeit drugs are rarely effective and even dangerous and harmful to human health [2, 17, 23]. On the other hand, Aka *et al.* (2005) found that from 44 samples collected in Cote d'Ivoire, 42 were not registered, the determination of content active ingredient revealed that only one sample was not compliant (absence of active ingredient), this sample was not registered in Côte d'Ivoire.

Table 4: Result of determination active ingredient content

N °	Sample	Strenght	Content obtained (90-110%)	Conclusion
1	Alb1	Susp 40 mg/ml	94	Complaint
2	Alb2	Susp 40 mg/ml	108	Complaint
3	Alb3	Susp 40 mg/ml	99	Complaint
4	Alb4	Susp 40 mg/ml	58	Non Complaint
5	Alb5	Susp 40 mg/ml	96	Complaint
6	Alb6	Susp 40 mg/ml	107	Complaint
7	Alb7	Susp 40 mg/ml	102	Complaint
8	Alb8	Susp 40 mg/ml	100	Complaint
9	Alb 9	Susp 40 mg/ml	84	Non Complaint
10	Alb 10	400 mg	95	Complaint
11	Alb 11	400 mg	103	Complaint
12	Alb 12	400 mg	89	Non Complaint
13	Alb 13	400 mg	103	Complaint
14	Alb 14	400 mg	67	Non Complaint
15	Alb 15	400 mg	107	Complaint
16	Alb 16	400 mg	93	Complaint
17	Alb 17	400 mg	96	Complaint
18	Alb 18	400 mg	51	Non Complaint
19	Alb 19	400 mg	92	Complaint
20	Met 1	500 mg	104	complaint
21	Met 2	500 mg	98	complaint
22	Met 3	500 mg	103	complaint
23	Met 4	250 mg	91	complaint
24	Met 5	500 mg	52	non complaint
25	Met 6	500 mg	70	non complaint
26	Met 7	500 mg	106	complaint
27	Met 8	250 mg	99	complaint
28	Met 9	500 mg	100	complaint
29	Met 10	40 mg/ml	31	non complaint
30	Met 11	40 mg/ml	39	non complaint
31	Met 12	25 mg/ml	99	complaint
32	Met 13	25 mg/ml	94	complaint
33	Met 14	25 mg/ml	91	complaint
34	Met 15	25 mg/ml	104	complaint

Legend: Alb: albendazole; Met: metronidazole

Table 5: Results of non-compliant samples illegally marketed in DR Congo

N °	Sample	Strength	Content obtained (%)	Conclusion
1	Alb4	40 mg/ml	58	Non Complaint
2	Alb 9	40 mg/ml	84	Non Complaint
3	Alb 12	400 mg	89	Non Complaint
4	Alb 14	400 mg	67	Non Complaint
5	Met 5	500 mg	52	non complaint
6	Met 10	40 mg/ml	31	non complaint
7	Met 11	40 mg/ml	39	non complaint

From the above, comparing non-complaints between medicines registered and not registered in DR Congo, we found in this study that the proportion (table 6) of non-compliance is the highest among the samples not permitted to be marketed (78% vs 8% %; p<0.005).

Table 6: Conformity of active ingredient content of samples according to their authenticity

	Medicines complaints	Medicines non-compliant	Total
Medicines illegally marketed	2	7	9
Medicines legally marketed	23	2	25

Study limits

Though the purchase of sample was done with discretion so as not to attract the attention of people around, in public markets, the sale of drugs is an activity that is not officially recognized by the authorities, some sellers mobile or fixed have been reluctant to us, that situation did not allow us to obtain some desired samples. It is true that the sample size cannot be generalized to overall pharmaceutical market in Lubumbashi but it reflects the situation of the pharmaceutical market in Lubumbashi and for the first time this study gave interesting information on the quality of legally and illegally medicines marketed in Lubumbashi.

CONCLUSION

This study was undertaken with the aim of detecting drugs illegally and legally marketed in the DR Congo and to assess the quality of all medicines collected. The study showed that drugs marketed illegally in DR Congo represent a potential risk in the treatment of infectious diseases because 78% of non-compliance found in this study concerned medicine illegally marketed in DR Congo.

It is obvious that strengthening the capacity of the pharmaceutical regulatory authority of DR Congo will reduce the influx of counterfeit drug and substandard. It is also essential that a strengthened control at the borders to be permanent in order to reduce the presence of substandard/counterfeit drugs in the pharmaceutical market Congolese.

In the future a further study and extended will allow: (a) to determine the prevalence of counterfeit active ingredients concerned by this study (b) to widen the sample size (c) to add other tests laboratory (galenic tests) to assess the impact of the active ingredients on human health (d) involve manufacturers in study for drug authentication.

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CONFLICT OF INTERESTS

Declared none

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