PUBLIC HOSPITAL SETTING IN RURAL ANGOLA: MEDICINE QUALITY AND MEDICATION ADHERENCE

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Abstract

The *A.P.P.A.*® Project focuses on Galenic Laboratories (GLs) established in medical structures in Developing Countries . The first laboratory in Angola was set up in 2011.
In this context, the objectives of the study carried out in 2016 were: to update the handbook of the GL in view of locally endemic pathologies and the widespread infiltration of counterfeit medicines; to curb the use of counterfeit medicines within the health structure through the implementation of a monitoring programme and to identify an effective method for monitoring and increasing the medication adherence by patients with non-communicable diseases. All objectives have been achieved.

Il progetto *A.P.P.A.*® ha come scopo la realizzazione di laboratori galenici (GLs) in strutture mediche di Paesi in via di sviluppo. Il primo laboratorio in Angola è stato istituito nel 2011. In questo contesto, gli obiettivi dello studio condotto nel 2016 erano: aggiornare il formulario del GL in considerazione delle patologie endemiche e della presenza diffusa di medicinali contraffatti; ridurre l'uso di medicinali contraffatti all'interno della struttura sanitaria attraverso l'implementazione di un programma di monitoraggio, identificare un metodo efficace per monitorare ed incrementare l'aderenza alla terapia da parte dei pazienti con malattie non trasmissibili. Tutti gli obiettivi sono stati raggiunti.

Keywords

Galenic medicines, developing Countries, countefeit medicines, non-communicable-diseases, *A.P.P.A.*® Project

Introduction

Aid Progress Pharmacist Agreement *(A.P.P.A.®)* is a non-profit association (*A.P.P.A.®* website, 2019) whose main activity is the *A.P.P.A.®* Project (Baratta, 2014). The Project began in 2004 and is the result of the cooperation between the University of Turin (Department of Drug Science and Technology) and Italian Community Pharmacists. The Project focuses on Galenic Laboratories (GLs) established in medical structures located in Developing Countries (DCs).

The project involves undergraduate students of the Degree Course in Pharmacy as part of their experimental thesis. Community Pharmacists and University Researchers are usually involved in supervision missions of on-site activities. The Project complies both with European and the guest country's legislation while safeguarding the quality of medicinal products. The Project is structured in different steps following which an effective and functional lab can be set up: only if a real need for the GL is demonstrated, can the subsequent steps be carried out. The pharmaceutical forms proposed are liquid preparations, capsules, ointments, pessaries, suppositories and multi-dose parenteral solutions. For each laboratory, a specific handbook has been designed: each of these complies with the different local needs taking into account the medicinal products that, based on our studies on site, are more often counterfeit (WHO website, 1999; Di Giorgio, 2010; Baratta,2012). After ten years, several Projects have been established: two in Cameroon, Madagascar and Angola; one in Chad and one in Haiti (*A.P.P.A.®* website, 2019).

The first *A.P.P.A.®* laboratory in Angola was set up in 2011 at the Nossa *Senhora da Paz* Hospital (NSPH) (*A.P.P.A.®* website, 2019). The NSPH is in Cubal, a city located in a rural zone in the south of the country; this large region covers an area of 4.794 km^2. The territory is made up of small towns with a total population of about 500.000 inhabitants. The NSPH offers many services among which are: Accident and Emergency, Paediatrics department, Malnutrition department, Adult medicine, AIDS department, Vaccination department, Paedology clinic, Paediatrics clinic and General Medicine. It has also one of the most important centres in Angola for the treatment of tuberculosis (NSPH website, 2019).

In this context, medicines are supplied by various sources. Firstly, the Ministry of Health provides some medicines free of charge, especially for the treatment of malaria, AIDS and tuberculosis. Other medicines are produced directly in the *A.P.P.A.®* GL or purchased on the local market. These purchases regard, in particular, medicines in which the active ingredient is impossible to ship in pure form for compounding in the GL. However, the use of medicines of industrial origin, purchased independently of the hospital or acquired through the Ministry of Health, gives rise to a

significant problem: as shown in previous studies, a large part of the products available on the local market in DCs and even in Angola are counterfeit (Baratta, 2012).

In addition to the problem of counterfeit medicines described above, it is necessary to consider the growth of Non-Communicable-Diseases (NCDs): cardio-vascular and respiratory diseases, tumours and diabetes, which have reached epidemic proportions in low-income countries owing to factors such as ageing populations, urbanisation and the spread of unhealthy lifestyles. DCs are facing a double blow from disease as they are under attack from both communicable and non-communicable diseases entailing a growing demand for new services and high costs for medical treatment: costs, in large part, borne directly by the patient. This situation calls for a multi-sector healthcare programme aimed at the prevention and control of the principal risk factors - smoking, unhealthy diet, sedentary lifestyle and alcohol abuse - and addressing the underlying social drivers. In the near future, in line with the global strategies of the WHO, the fight against NCDs will be extended to many countries, contributing to achieving target 3.4 of the Sustainable Development Goals of the United Nations (WHO website, 2018; UN website, 2015).

This is a fundamental goal considering that, according to the WHO in 2015, the African region had the highest rate of mortality from NCDs. Angola, in particular, ranks ninth in the world and third in the region, with 823 deaths per 100,000 inhabitants, just after Cote d'Ivoire and Sierra Leone (WHO, 2016).

Given this background, the aims of the study performed in 2016 at the *Nossa Senhora da Paz Hospital* in Cubal in collaboration with *A.P.P.A.*® non-profit association, University of Turin (Department of Drug Science and Technology) and local healthcare staff were:

To update the handbook of the GL in order to meet the requirements of the hospital in view of the spread of endemic pathologies in the area (the updating of the handbook takes place periodically in order to ensure that it matches the real current needs) and, furthermore, to keep up with changes in the availability of industrial products on the local market as well as to prevent the infiltration of counterfeit products.

To curb the use of counterfeit medicines at the health structure through the implementation of a monitoring programme for industrial products purchased locally and used in the various departments of the hospital with the goal of detecting immediately any counterfeit products;

To identify an effective methodology for monitoring and increasing the medication adherence amongst patients affected by NCDs and treated in out-patients' clinics in a rural setting in a DC such as NSPH.

Methods

The implementation of an *A.P.P.A.*® project normally takes place through missions involving qualified pharmacists and undergraduate students from the Degree Course in Pharmacy (Baratta,2014). To satisfy the objectives of the project in this current study, a physician was also involved. The involvement of a physician was justified as:
It facilitated the rapport with local healthcare personnel, eased the way for the updating of the handbook of the GL and led to the rapid identification of potentially counterfeit medicines.
The local healthcare personnel required training for the monitoring of adherence to therapy project.
The physician mission was funded as part of a cooperation project of the University of Turin called UNIto for international COOperation (UNI.COO).

Updating the galenic formulations handbook

In order to increase the synergies between the diagnostic and treatment activities and the production of the GL, a number of meetings were held with the participation of the *A.P.P.A.*® volunteers (qualified pharmacists and undergraduate students of the University of Turin) as well as the stakeholders in medicine management within the NSPH: the general director of the hospital, the health director, heads of departments and the out-patients' clinics, nursing staff and the GL staff.
During these meetings, the details of the project were outlined and all staff were asked to co-operate with the project team in order to achieve the goals of the project.
Regarding the updating of the handbook of the GL, based on the actual requirements of the hospital, the following procedure was applied:
an assessment was made of the frequency of prescription for all the galenic formulations in the existing handbook of the GL;
the reasons for a reduction in the number of prescriptions for particular medicines were investigated;
proposed new medicines to be inserted into the handbook of formulations were put forward based on the clinical requirements;
each proposed new medicine was evaluated based on cost-effectiveness and feasibility in terms of laboratory capabilities;
the selected preparations were introduced into the handbook of the GL;
a year later, a follow up mission was carried out to check the progress of the project.

Monitoring of Counterfeit Medicines

The investigation of the presence of counterfeit medicines within the hospital commenced with a random sampling of the industrial medicines available in the NSPH. The objective was to ensure the performance of tests in compliance with those specified by European standards for pharmaceutical quality control (EDQM,2017). In addition, tests were also performed on any product whose efficacy was suspect, based on reports by the local health personnel, as patients had not responded to the therapy to the degree expected.

Monitoring of Medication Adherence

In order to monitor in the out-patients' clinic the levels of medication adherence amongst patients affected by NCDs in a rural setting of a PVS, an observational study was conducted involving all adult patients who were examined at the out-patients' clinic at the NSPH in the months of March and April 2016. The study was designed as follows:

Inclusion criteria: all patients with a declared age over 14 years were included in this study provided that it was possible to make a diagnosis and prescribe a therapy.

Exclusion criteria: patients suffering from tuberculosis or HIV were excluded from this study as the NSPH utilises a different diagnostic-therapeutic procedure for these patients.

Diagnosis, enrolment and consent: The diagnosis was made through medical records, examination, radiological tests (traditional x-ray and echotomography), laboratory and microbiological tests. In the specific cases of arterial hypertension, dyslipidemias and type 2 diabetes mellitus (DMT2), the diagnostic criteria specified by WHO guidelines were adopted (WHO, 2003; WHO, 2006; WHO, 2009). The diagnosis of communicable diseases was confirmed through radiological tests of the thorax for pneumonia and microbiological test for other infections. At the moment of the diagnosis, the patient was informed of the study and asked to participate. The patient then signed a consent form.

Prescription: insofar as possible, medicines prepared in the GL at the NSPH were prescribed to patients. The reason for this was to avoid prescribing industrial medications that may be falsified.

Subdivision of patients into comparative groups: the participating patients were divided into two groups: group 1 comprised those patients diagnosed with one or more chronic non-communicable diseases such as arterial hypertension, DMT2 or dyslipidemias; group 2 was made up of those patients diagnosed with other pathologies: mainly communicable diseases (CDs). The patients

diagnosed with more than one type of pathology were inserted in the former group when at least one of these was a non-communicable disease.

Follow-up: each patient was given a follow-up appointment at a date distant enough from the date of diagnosis to enable a clear evaluation of the effectiveness of the therapy. In order to assess the adherence to therapy, it was decided to utilise an objective assessment scale - pill-count- as well as a subjective scale-the Morisky Medication Adherence Scales with 8 items (MMAS-8)-. Upon enrolment in the study, each patient was asked to retain the blister pack so that the pill-count could be performed during the follow-up examination. A ratio equal to or greater than 85% between observed pill-count and expected pill-count was taken as the cut-off point indicating a high adherence to therapy (Krueger, 2003). During the follow-up examination, each patient was surveyed using the MMAS-8. The scale was in Portuguese, the official language of Angola, and also in Umbundu, often the only language spoken by the patients. Given the high rate of illiteracy among the population, the questions were read aloud to the patients by a member of the nursing staff. A value of 8 on the MMAS-8 scale corresponded to a high adherence to therapy; values between 6 and 8 indicated a fair adherence to therapy while any value below 6 was interpreted as poor adherence to therapy. Finally, it was also recorded whether the patient had been prescribed industrial, galenic or both types of medication in order to assess whether the type of medication had any influence on the outcome (Morisky, 2008; Morisky, 1986).

Statistical methods: A chi-squared test and a multi-variate logistic regression was employed for the study of dichotomous variables. The level of significance of the test was set at 95% (α=0,05). The calculations were performed using STATA® software package.

Results

Updating the galenic formulations handbook

The meetings to review the handbook of the GL created a useful dialogue between all the stakeholders involved in the production, prescription and dispensation of medicines at the NSPH. This permitted the *A.P.P.A.*® volunteers to assess rapidly and efficiently the current needs of the hospital and, hence, to review and purchase the necessary supplies of raw materials as well as, in agreement with the laboratory staff, to draw up a monthly production schedule for galenic medicines. The following preparations have been added: paediatric formulations for the treatment of tuberculosis, promethazine cream, promethazine capsules, metronidazole oral suspension and carbocisteine syrup.

Monitoring of Counterfeiting

In order to monitor the extent of medicines which were suspected of being counterfeit, a range of drugs was tested based on the two following criteria: (a) they had been specifically reported as being ineffective in the treatment of patients by the local medical staff or (b) they were part of a random sample of medicines stocked in the hospital. The results obtained, summarised in table 1, highlight the dramatic nature of the problem of counterfeit medicines in Angola.

Table 1 – Quality control results

A.P.I.[1] and DOSAGE	DOSAGE FORM	ORIGIN	RESULT	EUR. PH. UNSATISFIED TESTS
Albendazole 400 mg	Tablets	UAE	Unsuitable	2.9.1. Disintegration of tablets and capsules 2.9.7. Friability of uncoated tablets 2.9.8. Resistance to crushing of tablets
Artemeter 20 mg Lumefantrine 120 mg	Tablets	USA	Suitable	/
Artemeter 20 mg Lumefantrine 120 mg	Tablets	India	Suitable	/
Ciprofloxacin 500 mg	Tablets	India	Unsuitable	2.9.8. Resistance to crushing of tablets
Ciprofloxacin 500 mg	Tablets	United Arab Emiratesi	Unsuitable	2.9.6. Uniformity of content of single-dose preparations 2.9.8. Resistance to crushing of tablets
Cotrimoxazole 480 mg (sulfamethoxazole 400 mg + trimethoprim 80 mg)	Tablets	India	Unsuitable	2.9.6. Uniformity of content of single-dose preparations 2.9.8. Resistance to crushing of tablets
Cotrimoxazole 480 mg (sulfamethoxazole 400 mg + trimethoprim 80 mg)	Tablets	India	Unsuitable	2.9.8. Resistance to crushing of tablets
Doxycycline 100 mg	Capsules	Mauritius	Suitable	/
Doxycycline 100 mg	Tablets	Brazil	Unsuitable	2.9.7. Friability of uncoated tablets
Ethambutol 400 mg Isoniazide 150 mg	Tablets	India	Unsuitable	2.9.8. Resistance to crushing of tablets
Ethambutol 400 mg Isoniazid 150 mg	Tablets	India	Unsuitable	2.9.8. Resistance to crushing of tablets
Ethionamide 250 mg	Tablets	India	Suitable	/
Isoniazid 100 mg	Tablets	India	Unsuitable	2.9.7. Friability of uncoated tablets
Isoniazid 100 mg	Tablets	India	Unsuitable	2.9.7. Friability of uncoated

[1] A.P.I.: Active Pharmaceutical Ingredient

				tablets 2.9.8. Resistance to crushing of tablets
Isoniazid 300 mg	Tablets	India	Suitable	/
Lamivudine 150 mg Zidovudine 300 mg	Tablets	India	Unsuitable	2.9.8. Resistance to crushing of tablets
Efavirenz 600 mg	Tablets	India	Unsuitable	2.9.8. Resistance to crushing of tablets
Lamivudine 30 mg Nevirapine 50 mg Zidovudine 60 mg	Tablets	India	Unsuitable	2.9.6. Uniformity of content of single-dose preparations 2.9.7. Friability of uncoated tablets 2.9.8. Resistance to crushing of tablets
Lopinavir 100 mg Ritonavir 25 mg	Tablets	Switzerland	Unsuitable	2.9.1. Disintegration of tablets and capsules 2.9.7. Friability of uncoated tablets 2.9.8. Resistance to crushing of tablets
Dapsone 100 mg	Tablets	Portugal	Unsuitable	2.9.7. Friability of uncoated tablets
Ofloxacin 400 mg	Tablets	India	Unsuitable	2.9.8. Resistance to crushing of tablets
Paracetamol 500 mg	Tablets	India	Unsuitable	2.9.7. Friability of uncoated tablets
Pyrazinamide 400 mg	Tablets	India	Unsuitable	2.9.7. Friability of uncoated tablets
Prothionamide 250 mg	Tablets	India	Suitable	/
Rifampicin 150 mg Isoniazid 75 mg Pyrazinamide 400 mg Ethambutol 275 mg	Tablets	India	Unsuitable	2.9.6. Uniformity of content of single-dose preparations 2.9.8. Resistance to crushing of tablets
Rifampicin 150 mg Isoniazid 75 mg Pyrazinamide 400 mg Ethambutol 275 mg	Tablets	India	Unsuitable	2.9.6. Uniformity of content of single-dose preparations 2.9.8. Resistance to crushing of tablets

Monitoring of Medication Adherence

To monitor the adherence to therapy, a total of 82 outpatients were enrolled in the study. The two most representative age groups were patients between the ages of 40 and 49 (28%) and patients between the ages of 20 and 29 (22%). 23% of the studied subjects were over 50 years of age. In terms of gender, females accounted for 60% of the total number of subjects. 26% of the subjects were affected by NCDs. The most common NCDs, often in co-morbidity, were arterial hypertension, type 2 diabetes mellitus and dyslipidemias (mainly mixed dyslipidemias and hypercholesterolemia). The communicable diseases most commonly found during the study period

were in descending order: malaria, pneumonia, tuberculosis, urinary tract infections and intestinal parasites.

Out of the 82 patients enrolled in the study, 27 (33%) returned to the hospital for a follow-up examination. 30% of these returning subjects had NCDs.

As regards the tests utilised for the evaluation of adherence to therapy, the results for the patients who returned for the follow-up examination are as follows: 78% brought back the empty packaging necessary to conduct the pill-count. 76% of these patients were in the high adherence category after the pill count test. The results of the MMAS-8 test are that 33% of patients belong in the high adherence category, 37% in the intermediate category and 30% in the poor adherence category.

The results obtained from the MMAS-8 test were, therefore, compared with those of the pill-count test; from this comparison, good values for sensitivity (80%) and specificity (81%) emerged even for the MMAS-8 test. Furthermore, the MMAS-8 test showed a good negative predictive value (93%). In other words, if a high or intermediate adherence to therapy (MMSA ≥ 6) results from the MMAS-8 test, this indicates with a good degree of certainty that one can rule out the possibility that a patient is not following the prescribed course of medication.

Finally, it can be affirmed that there is no link between that prescription of Galenic medication at the time of diagnosis and the successive return of the patient for the follow-up examination in that no patient received a prescription solely for galenic medication. For this reason, it is not possible to evaluate whether the use of galenic preparations had any influence in terms of treatment effectiveness and, hence, return for follow-up examination.

Discussion

Updating the galenic formulations handbook

The most pressing clinical requirement identified in the meetings to review the handbook of the GL was the complete lack of medicines for paediatric tuberculosis therapy. The Angolan Ministry of Health provides the NSPH with medicines suitable for the treatment of TB in adults, but nothing that can be used for the treatment of paediatric cases. In the past, the only way to provide therapy for such cases was to break the tablets used for adults. However, this practice has obvious risks; the tablets were split without using scales and, hence, the dosage could not be accurate or precise. Moreover, an excipient or, worse yet, an active ingredient, such as ethambutol, contained in the tablet may not be suitable for paediatric use. To overcome the above issues and to satisfy the demand for paediatric medicines for tuberculosis, the GL started production of capsules containing

the active ingredients at suitable dosage levels for paediatric therapy as specified by the WHO (WHO, 2017).

Monitoring of Counterfeiting

Compared to a study carried out in 2011 (Baratta, 2012), in the same area and employing the same study criteria, the situation has worsened drastically. In the 2011 study, 54% of the sampled medicines turned out to be counterfeit; by 2016, the figure had risen to 77%. In accordance with WHO assessments, India was the first exporting Country, with 19 samples (about 79% of which were counterfeits). This prominent role of India in the production of counterfeits could be a result of several causes, among which is the permissive legislation and inefficient judiciary system, absence of qualified supervising staff, and widespread corruption (Swaminath, 2008).

Monitoring of Medication Adherence

The low return rate of patients for the follow-up examination (27 patients) can, in part, be explained by the probable improvement in their clinical condition for those patients treated for communicable diseases. As far as patients affected by NCDs are concerned, the low return of patients may be a consequence of their difficulty in understanding the concept of a non-communicable disease. In particular, the course of a chronic disease. As often happens, even in high-income countries, patients have difficulty in understanding that some pathologies can be asymptomatic for long periods of time and that they are not cured by the therapy, but simply under control.

In order to explain the pill-count test results, it can be affirmed that given the low purchasing power of the local population and the high cost of medicines *in loco*, the patients enrolled in the study did effectively take the prescribed medicine.

The MMAS-8 test encountered two obstacles: firstly, the effectiveness of the interview format. Despite being asked to respond to the questions honestly, some patients may have given inaccurate answers which skew the results of the test in favour of a higher adherence to therapy; secondly, although the test had been translated into both Portuguese and Umbundu, some patients displayed difficulty in the comprehension of the questions as they lacked the necessary socio-cultural background for a task of this complexity. Taking all of the above into account, the pill-count test was deemed to be the benchmark for reliability against which to evaluate the results of the MMAS-8 test.

Conclusions

The excellent collaboration between the staff responsible for prescribing medication, the staff of the GL and the team of volunteers from *A.P.P.A.*® led to a series of decisions, shared by all stakeholders, of great importance for the treatment of patients availing of the NSPH.

In the first place, it enabled the updating of the handbook of the GL and ensured the production of high-quality galenic medicines in line with the effective local demand. Furthermore, thanks to the constant surveillance of industrial products, it is possible to quickly detect counterfeit industrial products. Another advantage of the GL is the capability to produce tailor-made medicine to fit the specific needs of the patient e.g. based on the age of the patient. In particular, a new line of medicines for paediatric patients suffering from tuberculosis has been introduced; products that, in the context of the NSPH, would not normally be possible to obtain.

Concerning the monitoring of medication adherence, despite the low number of subjects in the sample population enrolled, it is still possible to draw some interesting conclusions from the observational study conducted at the NSPH. Firstly, given the widespread presence of NCDs, even in areas such as Cubal and its environs, and taking into account the results obtained, it is clear that a fundamental priority is the development of a health education programme for the local population, which, in view of the low educational levels, lacks an understanding of chronic diseases and is unable to conceive an asymptomatic disease. Hence, in this setting, the forthcoming missions to the NSPH will focus on providing patients affected by NCDs with a formal counselling programme available through the out-patients' clinics of the general medicine department or the pharmacy where the medicine is dispensed to the public. It will be interesting to evaluate the effectiveness of this method on a population availing of this service for the first time and it will be a useful pilot scheme for larger-scale programmes at a regional level in the future.

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Acronyms

A.P.P.A.®: Aid Progress Pharmacist Agreement
CDs: communicable diseases
DCs: Developing Countries
DMT2: type 2 diabetes mellitus
GLs: Galenic Laboratories
MMAS-8: Morisky Medication Adherence Scales with 8 items
NCDs: Non-Communicable-Diseases
NSPH: Nossa *Senhora da Paz* Hospital
WHO: World Health Organization