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Triple-Action Antifungal Topicals, Microbiologist's Alarm

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Author's contribution

The sole author designed, analysed, inteprted and prepared the manuscript.

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ABSTRACT

Today, we are witnessing the development and marketing of triple action antifungals for the treatment of superficial mycoses. It is a mixture of antifungals, antibiotics and anti-inflammatory. The problem of this research was to verify the effects of this mixture as to its effectiveness on superficial mycoses. Thus, we set ourselves the following objectives: to identify the antifungals in the pharmacies of the cities of Likasi, Lubumbashi and Kolwezi, to determine their composition and to discuss this composition with the existing literature.

Through a cross-sectional study, we identified thirty-four different antifungals in 588 pharmacies, of which 16 or 47.05% are triple action and made up of Azoles as antifungal, the antibiotic gentamicin, and corticosteroids as anti-inflammatory, alongside polyene, Echinocandins and flucytosine. It is the combination of antifungals with conventional non-antifungal agents reoriented for their action on the growth of fungi. They consist of antibacterial drugs and steroidal anti-inflammatories. This reorientation was supposed to have excellent antifungal activity and could prevent resistance. However, the presence of the antibiotic will reduce the composition of the colonizing microbiota and promote fungal growth and enhance fungal pathogenicity indirectly and the corticosteroid component may interfere with the therapeutic actions of the antifungal agent and may accelerate fungal growth, due to a decrease in the host's local immunological reaction, so that the underlying

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infection may persist, and the dermatophytes may even acquire the ability to invade the deeper tissues. So, in support, it would be interesting to favor antifungals without combinations than those combining antibiotics and anti-inflammatory which has an extremely high rate of recurrence.

Keywords: Topical; antifungal; triple action; alarm; microbiologist.

1. INTRODUCTION

Fungal infection has become a significant event resulting in more than 1.5 million deaths per year worldwide [1] and fungi are a diverse group of organisms, different enough from other life forms to be considered a universe of their own. The similarity of their metabolic pathways with those of humans makes the development of selective antifungal agents difficult.

antifungal therapy represents a difficult problem for clinicians [2] because Conventional antifungal agents have limitations due to the presence of drug-resistant strains, current antifungal options have become more restricted [3]. “It is important to note that some of these infections are resistant to all current antifungal agents” [4].

Besides the synthesis of new substances, the use of extracts of organisms, the modification of methods of administration or the forms of old drugs to treat fungal diseases, and a combination between known antifungal drugs and non-antifungal agents [5], the redirection of drugs , due to the excellent antifungal activity of these drugs, proves to be one of the solutions for the treatment of fungal infections [1]. “This is the combination of antifungals with non-antifungal excitatory agents consisting of antibacterial drugs, immunosuppressants, statins, antiarrhythmics, antipsychotics, antidepressants, and nonsteroidal anti-inflammatory drugs (NSAIDs)” [6].

The antifungal association on the one hand with antibacterials will reduce the composition of the colonizing microbiota and promote fungal growth and improve fungal pathogenicity indirectly [7]. And on the other hand, the use of immunosuppressants can inhibit the immune response of the host, which increases the risk of fungal infection [8].

Faced with this worrying situation, we considered it urgent to make an inventory of the composition of antifungals in the pharmacies of the cities of Likasi, Lubumbashi and Kolwezi.

2. METHODOLOGY

This survey involves a cross-sectional observation of 588 pharmacies in the city of Lubumbashi, Likasi and Kolwezi using a questionnaire to identify antifungals and their composition in local pharmacies. in addition to the composition of the antifungals, we have in this questionnaire evaluated the qualification of the staff of the pharmacies. All pharmacies that accepted our investigators and offered at least one antifungal on their shelves were included comprehensively in this study. Statistical analysis of the data was done using Epi info 7.3 and Office Excel 2013 and the results are presented in the form of pie charts and histograms.

3. RESULTS AND DISCUSSION

The inventory of antifungals (Fig. 1) in the three cities allowed us to count 34 different brands of antifungals in our local pharmacies; Clotrimlazole was the most produced (29.41%) followed by Tolnaftate (17.64%), Isoconazole, Xetoconazole and Nystatin (8.82%), Ketokonazole, Luliconazole and Clioquinol (5.88%) and finally Sertaconazole, Fluconazole and Terbinajine (2.94%). Sixteen of these antifungals, or 47.05%, were triple action.

The World Health Organization, and most public health organizations, do not have a surveillance program for fungal infections, even though invasive fungal infections have a high mortality rate worldwide, often exceeding 50% [9].

“Currently, a multitude of antifungal agents have been used clinically. Polyenes, azoles, echinocandins, and flucytosine are currently the main treatments for invasive fungal infections in clinical settings” [10]. The representative polyene drug is amphotericin B, which can bind ergosterol from lipid bilayers and form large extramembrane aggregates [11]; Azoles can be used against the majority of fungi, as they inhibit the enzyme 14α demethylase dependent on cytochrome P450 (Cyp51) [12] and have excellent therapeutic effects on molds as well as yeasts [13]; Echinocandins primarily involve the inhibition of

cell wall synthesis by inhibiting β-1,3-D-glucan synthase, a key component of the fungal cell wall [14]; Flucytosine is also an important antifungal agent which inhibits DNA and RNA synthesis and is mainly used to treat cryptococcosis and candidiasis [15].

"Conventional antifungal agents have limitations due to the presence of drug-resistant strains through several mechanisms: in azoles, reduced antifungal efficacy is due to their ability to bind to the human cytochrome P450 (CYP450) enzyme system" [16]. Echinocandins rarely cause resistance, have a good safety profile, have better clinical outcomes and have been used for two decades [17], flucytosines have low efficacy as monotherapy due to the prevalence of inherently resistant strains [18].

Thus, these possibilities of resistance justify the use of non-antifungal drugs that function as antifungal agents in various ways towards different targets, have been shown to be effective antifungal strategies.

From Fig. 2: Betamethasone, clobetasole and diffucortolone are the combined anti-inflammatories respectively at 69%; 25% and 6% in triple action antifungals; which are associated with gentamicin (64%), Neomycin (22%), polymyxin (7%) and Metronidazole (7%) as antibiotics.

"The above antibiotics are part of the list of antibacterials with antifungal activity and Venturini et al believe that they should be commonly used alone or in combination to regulate the gene expression levels of adhesion, hyphae, or biofilm formation, to decrease the level of extracellular glycan and the hydrophobicity of the cell surface, and even to inhibit efflux pump activity" [19].

"Gentamicin on the other hand, its major complex moieties (C1, C1a, C2, C2a) possess weak antifungal activity and one of the minor components (A, A1-A4, B, B1, X), gentamicin B1 has been shown to be a potent antifungal agent" [20]. "The gentamicin B1 moiety of the gentamicin complex possesses a novel robust antifungal effect expanding the spectrum of previously known antibacterial, anti-protozoal and anthelmintic gentamicin, reflecting a family of growth controlling compounds. It exerts its selective fungistatic activity on filamentous phytopathogenic fungi, moderately inhibiting the growth of dermatophytes. With respect to yeasts, Candida albicans is tolerant but Cryptococcus is sensitive to gentamicin B1" [21]. This antibacterial to antifungal conversion of aminoglycosides dates to the alkyl modification of old drugs [22], it is the cyclic moiety with amino-modified sugar glycoside (purpuroseamine) responsible for binding to ribosomes and inhibiting protein synthesis [23].

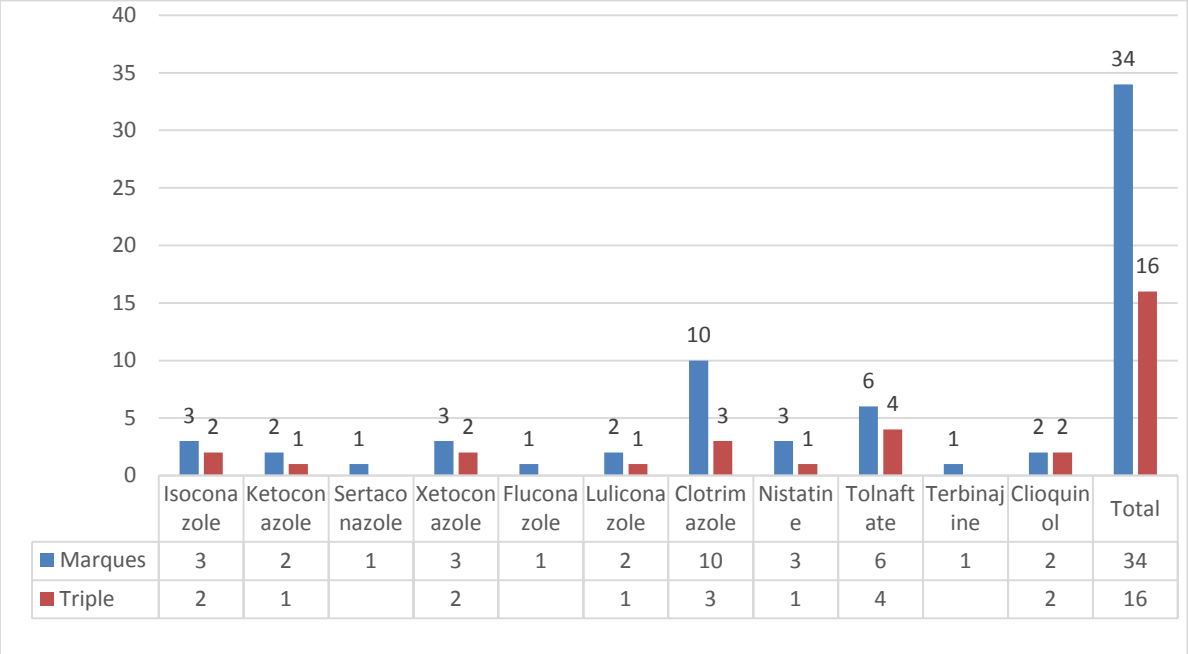

Fig. 1. Distribution of antifungals listed in pharmacies in the cities of Lubumbashi, Likasi and Kolwezi

Polymyxin B is a cationic lipid oligopeptide antibiotic that was identified in an approved drug screen for activity against Aspergillus nidulans [24]. However, upon further investigation, it was found to have trivial effect on the fungal pathogens assessed, except for Cryptococcus neoformans, on which it had a strong fungicidal effect and showed synergistic activity with fluconazole. Polymyxin B possesses a species-specific mechanism, suggesting that the characteristic polysaccharide capsule of Cryptococcus, an important virulence factor, is the target of polymyxin B activity [25].

In general, antibacterial drugs have potential antifungal value due to their good antifungal activity. However, human health depends on the balance of the microbiota [26,27] and antibiotic treatment will reduce the composition of the colonizing microbiota and promote fungal growth and improve fungal pathogenicity indirectly [6].

“The proven efficacy of antifungals and their positioning in the treatment of fungal skin infections is reinforced by high patient compliance, especially when appropriate vehicles such as creams, ointments and gels are used. However, inflammation resulting from a fungal infection can often interfere with treatment, especially when combined with pruritus (itching), an unpleasant sensation that causes an urge to scratch. The scratching that occurs in response to pruritus frequently accelerates skin damage, aggravating and spreading the fungal infection. To help overcome this problem, a topical antifungal-corticosteroid combination is used. Due to their inherent benefits, these topical antifungal-corticosteroid combinations can simultaneously and effectively reduce inflammation, relieve pruritus, and treat fungal infections” [28].

“The addition of a corticosteroid to local antifungal treatment may be useful in reducing the local inflammatory reaction and thus has the theoretical advantage of rapid symptom relief in acute dermatophyte infections associated with significant inflammation. However , evidence from well-controlled studies suggests that the use of a combination of steroids and antifungals is not superior to a single antifungal agent and has lower mycological and clinical cure rates in the management of dermatophytosis. showed a mycological cure rate of 73% with naftifine and only 43% with steroid FDC, at 4 weeks of treatment” [29,30].

“Thus, the use of such combinations requires caution as they have certain risks, especially during long-term use under occlusive conditions, the corticosteroid component may interfere with the therapeutic actions of the antifungal agent, or fungal growth may be accelerated due to a decrease in the host's local immunological reaction, so that the underlying infection may persist, and dermatophytes may even acquire the ability to invade tissues further Deep” [31,32].

There is no doubt that we need new antifungal agents. Drug redirection is less expensive, takes less time, and is more likely to be successful than new drug discovery. Critical questions that will need to be addressed are those related to *in vitro/in vivo* correlation, for which the efficacy of key repositionable compounds will need to be tested in clinically relevant models of fungal

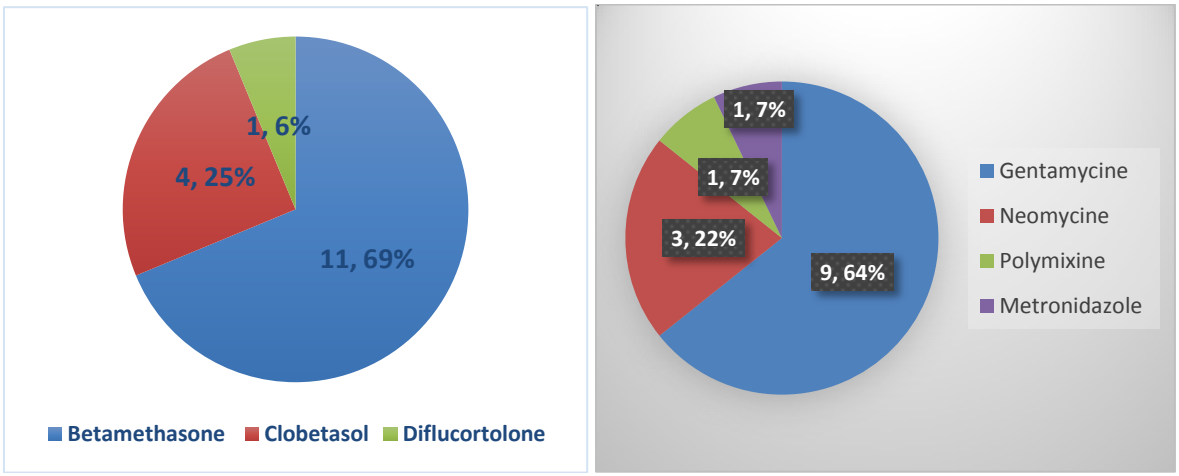

Fig. 2. Distribution of anti-inflammatories and antibiotics in the triple action antifungals identified in pharmacies

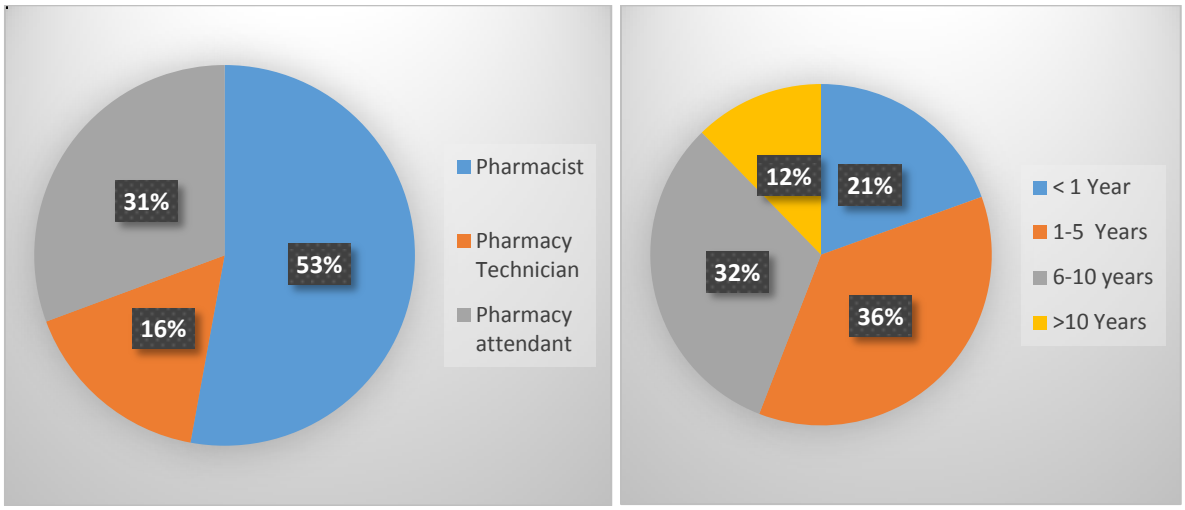

Fig. 3. Pharmacy staff and years of experience

infections, as well as those dealing with key toxicological and pharmacokinetic/ pharmacodynamic principles of site of action exposure, target binding, and expression of functional pharmacological activity. Moreover, must be considered, the potentially undesirable side effects associated with the reused drug. Although the route is theoretically facilitated for reused drugs, it is imperative that the antifungal efficacy of these drugs, in their new indications, be demonstrated.

Regarding the pharmacy staff, it is mainly composed of trained pharmacists (53%), pharmacy attendants and pharmacy technicians complete the staff. 36% of the members of this staff had professional experience ranging from one year to five years and 32% between 6 and ten years, 20% had less than one year of experience while 12% had more than ten years. It is obvious that the situation described above is indeed catastrophic and the role of the pharmacist is crucial in this process, because indeed, the profession of pharmacist has the fundamental responsibility to ensure the safe and effective use of drugs [33]. And Training in infectious diseases and knowledge of the principles of responsible prescribing and use of antimicrobials need to be improved. To change practice, health professionals must be made aware at all levels of their training [34], pharmacists, infectiologists and clinicians must be added microbiologists [35] for responsible management of antimicrobials.

4. CONCLUSION

It is known that the signs and symptoms of fungal infection appear during antibiotic therapy, especially due to opportunistic fungal agents. Invasive fungal infections affect patients with weakened immune systems. Thus, the topical antifungal treatment administered to a patient must be specific and adapted according to individual needs and especially to the etiologic agent. It should be based on standard treatment guidelines. It would be interesting to favor antifungals without combinations than those combining antibiotics and anti-inflammatory which has an extremely high rate of recurrence.

A team approach involving all stakeholders such as drug regulatory authorities, pharmaceutical industry, physician, pharmacist, and patients is needed to ensure rational use of topical corticosteroids.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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