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8-Hydroxyquinoline analogues for combating difficult-to-treat fungi

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Introduction

The number of patients affected by a fungal infection has grown in recent years and affects about 1.2 billion individuals worldwide[1]. Dermatophytes, they are opportunistic fungi related to infections that are difficult to treat due to resistance, since few drugs in a limited number of classes are available on the market. New therapeutic alternatives are being explored to combat the resistance and recurrence of these fungal infections[2]. 8-Hydroxyquinoline and its analogues, clioquinol and nitroxoline, represent important alternatives since they possess a variety of biological properties such as antibacterial and antifungal, all due to their chelating capacity for metal ions, since these metals have a very important function in biological processes[3]. Therefore, the objective was to evaluate the interaction of the clioquinol and nitroxoline in dermatophyte isolates

Experimental section

A total of 8 isolates were included in this study: *N. gypsea* (early classified *M. gypseum*) (2), *M. canis* (2), *T. mentagrophytes* (2) and *T. rubrum* (2). The minimum inhibitory concentrations (MICs) of the antifungal agents clioquinol and nitroxoline for the all isolates were determined by the broth microdilution method according to protocol M38-A2[4]. Checkerboard method was used to evaluate the interaction between antifungal agents. The concentrations tested varied from MIC/8 to MICx8 for each antifungal compound, resulting in 49 combinations[5,6].

Results and Discussion

The concentration range obtained in the susceptibility test was 1.0 - 2.0 µg/mL for nitroxoline and 0.5 - 2.0 µg/mL for clioquinol. Synergistic interaction was observed in 50% of isolates when clioquinol was associated with nitroxoline as shown in table 1.

Table 1: Minimal inhibitory concentration (MIC) of clioquinol (CQ) and Nitroxoline (NT) tested alone and in combination against dermatophytes.

ISOLATES	MIC (µg/mL)		**MIC combination (µg/mL): Nitroxoline + Clioquinol**			
	NT	**CQ**	**NT**	**CQ**	**FICI**	**INTER**
MCA HCPA 10	1.0	1.0	0.250	0.250	0.500	SYN
MCA HCPA 12	1.0	1.0	0.125	0.500	0.625	IND
MGY ATCC	1.0	2.0	0.125	0.500	0.375	SYN
MGY 42	2.0	2.0	1.0	0.0625	0.53125	IND
TME ATCC	1.0	0.5	0.250	0.250	0.750	IND
TME 2 HCPA	1.0	1.0	0.500	0.500	1.0	IND
TRU ATCC	1.0	1.0	0.250	0.250	0.500	SYN
TRU 45	1.0	1.0	0.250	0.250	0.500	SYN

FICI: fractional inhibitory concentration index; INTER: interaction; IND: indifferent; SYN: synergetic.
TRU: *Trichophyton rubrum*; TME: *Trichophyton mentagrophytes;* MCA: *Microsporum canis*; MGY: *Microsporum gypseum*

Authors have demonstrated in the literature the interactions between different antifungal agents and their benefits.[2,7] Our study demonstrated satisfactory results when antimicrobials are used in combination to treat or prevent dermatophytosis. However, more studies are needed to understand the mechanism of action of this combination. Pippi et al (2019) observed that clioquinol acts on the cell wall of dermatophytes but the mechanism of action of nitroxoline is still unknown.

Conclusions

The use of clioquinol in combination with nitroxoline in the treatment of dermatophytosis has been shown to be an important therapeutic strategy and in this way, problems related to therapeutic failure could be avoided.

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