PEG-15-hydroxystearate non-ionic surfactant enhances amphotericin B activity against Mucorales in vitro

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Background

• The first-line treatment of mucormycosis is based on the use of liposomal amphotericin B, but despite this treatment, mortality remains high.

• It has been shown that the activity and toxicity of AmB vary according to its aggregation state. Non-ionic surfactants, which are low toxicity molecules used in parenteral preparations, could control the aggregation state of AmB and thus modulate its efficacy and toxicity.

➢ The aim of this study was therefore to evaluate the effect of various non-ionic surfactants on the anti-Mucorales activity of AmB, its toxicity on eukaryotic cells and its aggregation state.

Materials and methods

• Checkerboards were performed on five genera (12 strains) of Mucorales to determine the MIC of AmB in the presence of different surfactants (Brig6, PEG-15-hydroxystearate (PEG15HS)) concentrations and data were analyzed by an Emax model.

• The effect of surfactants on the potentialization of AmB cytotoxicity was assessed by hemolysis measurement and by propidium iodide internalization in monocyctic (THP1) and lung epithelial (A549) cell lines.

• The effect of PEG15HS on the aggregation state of AmB was evaluated by UV-visible spectrometry.

Results

• PEG15HS was the surfactant that most increased the efficacy of AmB on 4 of the 5 genera of Mucorales, with MICs decreased up to 68 times and this with high potency (EC50 < 2.5 mg/L) (Figure 1).

• For concentrations up to 100 mg/L, PEG15HS was the only surfactant not to increase the hemolytic activity of AmB (Figure 2). The cytotoxic effect of AmB on THP-1 and A549 cells was not increased by PEG15HS.

• The UV-visible spectra showed that the control of the efficacy and toxicity of AmB by PEG15HS is related to an increase of the monomeric and polyaggregated forms of AmB at the detriment of the dimeric form (Figure 3).

Conclusion

PEG15HS increases the efficacy of AmB (up to 68 times) against Mucorales at concentration that do not increase its cytotoxicity on human cells. This combination could be considered in the treatment of mucormycosis.