Role of Omeprazole as An Antifungal Agent

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Abstract

The antifungal activity of various concentrations of omeprazole (0.1mg/ml, 0.25mg/ml, 0.5mg/ml, 1mg/ml, 2.5mg/ml, 5mg/ml, 10mg/ml, and 20mg/ml) were studied in different pH media (5 and 7) against Aspergillus niger, and Trichophyton urbrum.The laboratory results showed the inhibitory effect of omeprazole against Aspergillus niger at pH 7 and starting from concentration 10mg/ml, and against Trichophyton urbrum starting from 1mg/ml. While its antifungal activity in a medium with pH 5 was extended to reach the lower concentrations 0.25mg/ml against selected fungi. Accordingly, omeprazole is pH dependent.It seems that omeprazole changed cell membrane potential of selected fungal species which led to depolarization of cell membrane as a result of inhibition of the proton pump mechanism. This made the fungal cell not willing to uptake chemicals needed for living.Keywords: omeprazole, proton pump inhibitor, antifungal agent, Aspergillus niger, and Trichophyton urbrum.

دور الامبرازول كمادة مثبطة لنمو الفطريات

الخلاصة

تمت دراسة النشاط المضاد للفطريات في تراكيز مختلفة من الاومبرازول omeprazole (0.1 ملغم/مل و 0.25 ملغم/مل و 0.5 ملغم/مل و 1 ملغم/مل و 2.5 ملغم/مل و 5 ملغم/مل و 10 ملغم/مل و 20 ملغم/مل) في اوساط مختلفة الرقم الهيدروجيني (رقم هيدروجيني 7 و رقم هيدروجيني 5) ضد الانواع الفطرية التالية: Aspergillus niger و Trichophyton urbrum.

كشفت النتائج المختبرية دور الاومبرامزول omeprazole كمادة مثبطة لنمو الفطريات في الوسط المعتدل حيث لوحظ تثبيط نمو Aspergillus niger و ابتداء من تركيز 10 ملغم/مل و تثبيط نمو Trichophyton urbrum ابتداء من تركيز 1 ملغم/مل . في حين ازداد دور الاومبرازول omeprazole في تثبيط نمو الفطريات في الوسط الحامضي. كشفت النتائج تاثير دور الرقم الهيدروجيني على عمل الاومبرازول omeprazole.

اوضحت النتائج ان الاومبرازول omeprazole قد غيّرَ إمكانيةَ الغشاءِ الخلوي في الفطر من خلال إزالةِ إستقطاب غشاءِ الخليةِ كنتيجة لتثبط عمل آليةِ ضخِّ البروتونَ, مما عرقَل مرور المواد الغذائية و العناصر الى داخل الخلية الفطرية.

Introduction

Over the past several years, the medical community has become increasingly concerned over the ability of certain fungi to develop resistance to antifungals [1]. Accordingly, there is a danger of losing the battle against certain pathogens (organisms causing diseases) by using the fungals in the treatment [2].

The development of drug resistance in human pathogens against commonly used antifungals has

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necessitated a search for new antimicrobial substances [3].

Omeprazole is used for the treatment of peptic diseases [4]. Omeprazole increases the intragastric pH by selectively blocking the enzyme H+/K+ATPase in parietal cell [5]. Omeprazole is a proton pump inhibitor [6]. The proton pump system is an integral membrane protein that is capable of grabbing protons from the matrix (the space enclosed by the two membranes) and releasing the protons into the inter-membrane space. The confined protons create a difference or gradient in both pH and electric charge and establish an electrochemical potential [7]. An antibacterial effect of omeprazole had been found as a result of electrochemical potential [8, 9].

Current study has dealt with the role of Omeprazole as an antifungal agent using different concentrations of Omeprazole in different pH media against two tested fungal species, Aspergillus niger, and Trichophyton urbrum.

Materials and Methods

Antifungal Activity of Omeprazole: The antifungal activity of omeprazole against two species of fungi,

Aspergillus niger, and Trichophyton urbrum (the fungal species are obtained from the labs of Biotechnology Department/ School of Applied Science at University of Technology) has been examined by preparing different concentrations of Omeprazole-20 [Ajanta] (0.1mg/ml, 0.25mg/ml, 0.5mg/ml, 1mg/ml, 2.5mg/ml, 5mg/ml, 10mg/ml, and 20mg/ml) that were dissolved in distilled water and stored at -20°C. All the concentrations were added into wells (each plate containing four wells, each well is 3-4mm diameter and takes 50 µl of each concentration) of each of the two fungal cultivated plates containing potato dextrose agar (HIMIDIA) with pH 5 (The test was repeated in plates containing potato dextrose agar with pH 7). All plates were incubated at 25°C for 24-96 hrs. Then the antifungal activity and the MIC (minimum inhibitory concentration which inhibits fungal growth at low concentration) of omeprazole were measured by using a ruler to measure the formed inhibition zone [10].

Results and Discussion

The effect of different pH (pH 7, and pH 5) of the antifungal activity of various prepared concentrations of Omeprazole (0.1mg/ml, 0.25mg/ml, 0.5mg/ml, 1mg/ml, 2.5mg/ml, 5mg/ml, 10mg/ml, and 20mg/ml) against Aspergillus niger, and Trichophyton urbrum were recorded after 24-96 hrs. of incubation.

Table 1 illustrates the effect of pH 7 on omeprazole activity, and shows obvious inhibition zones were formed around the higher concentrations of omeprazole (10mg/ml, and 20mg/ml) against Aspergillus niger and around the concentrations (1mg/ml, 2.5mg/ml, 5mg/ml, 10mg/ml, and 20mg/ml) of omeprazole against Trichophyton urbrum. The inhibitory action of omeprazole was more active in the medium with pH 5 to reach the lower concentrations of the drug (0.25 mg/ml) against the two examined fungi (Table 2).

The results clearly indicated the effect of acidic pH on the action of omeprazole on the tested fungi. It can be suggested that acidic medium had enhanced the binding of omeprazole to proteins of fungal cell [11]. Many studies found that the amount of

omeprazole bound to the microbial proteins was pH dependent and increased with decreasing pH [8, 11].
In current study, after binding of omeprazole to the examined fungal proteins, the study suggested a gradient in electric charge might be created; the concentration of protons inside the fungus was higher than its concentration in the outside [12]. There was no way to restore the balance by pumping the protons outside the cell [13] due to the action of omeprazole as a proton pump inhibitor [14]. Blocking the passage of proton pumping seemed to create a decreasing in cellular membrane potential (Depolarization of cell membrane) [15]. Depolarization of cell membrane might make the fungal species not willing to uptake the chemicals needed for cell living from the medium [16]. Another suggestion could be describing the antifungal effect of omeprazole on the selected fungi which is its effect on microenvironment of tested fungi might change the pH and lead to decrease the fungal growth [14].
The experimental results may reveal the role of omeprazole as an antifungal agent [17]. Accordingly, the MICs of omeprazole is 10 mg/ml for inhibiting the growth of Aspergillus niger, and the MICs of omeprazole is 1 mg/ml needed for inhibiting the growth of Trichophyton urbrum in medium pH 7(Table 1), while the growth of the two tested fungi could be inhibited at concentration 0.25 mg/ml of omeprazole in medium pH 5 (Table 2).
The results of this report are in agreement with the study of (Monk, B. C., et. al., 1995) [18]. They reported the inhibitory effects of the sulfhydryl-reactive reagent omeprazole on cell growth, of Saccharomyces cerevisiae and the human pathogenic yeast Candida albicans in a pH dependent manner. The investigated that the yeast plasma membrane proton pumping ATPase (H+-ATPase) was a potential molecular target for antifungal drug therapy by omeprazole.

Conclusion

The experimental results indicate the antifungal properties of omeprazole against Aspergillus niger, and Trichophyton urbrum, and its inhibitory action is pH dependent. The inhibitory action of omeprazole might be represented by blocking the proton pump system which led to depolarization of cell membrane. This depolarization of cell membrane might make the fungal species not willing to uptake the chemicals needed for cell living from the medium.

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Table 1.Antifungal Activity of Omeprazole at pH 7

Fungal Species	Fungal Growth Susceptibility (Diameter/mm)							
	Concentration of Omeprazole (mg/ml)							
	0.1	0.25	0.5	1	2.5	5	10	20
Aspergillus niger	0	0	0	0	0	0	32	44
Trichophyton rubrum	0	0	0	19	19	25	25	25

Table 2.Antifungal Activity of Omeprazole at pH 5

Fungal Species	Fungal Growth Susceptibility (Diameter/mm)							
	Concentration of Omeprazole (mg/ml)							
	0.1	0.25	0.5	1	2.5	5	10	20
Aspergillus niger	0	19	27	33	32	36	45	45
Trichophyton rubrum	0	13	20	25	25	31	33	34