Pergamon

Oral Oncol, Eur J Cancer, Vol. 30B, No. 3, pp. 196–199, 1994
Elsevier Science Ltd
Printed in Great Britain
0964–1955/94 $7.00 + 0.00

Value of Antifungal Prophylaxis with Antifungal Drugs Against Oropharyngeal Candidiasis in Cancer Patients

Françoise Meunier, Marianne Paesmans and Philippe Autier

This report focuses on the value of antifungal prophylaxis with antifungal drugs in preventing oropharyngeal candidiasis. Randomised trials comparing non-AIDS immunocompromised patients receiving or not an oral antifungal agent were reviewed. Colonisation of the throat with *Candida albicans* is a risk factor, principally when cultures for this species of yeasts remain positive after initiation of the prophylaxis. The results of the trials were meta-analysed and we obtained a combined odds ratio for developing oropharyngeal candidiasis of 0.15 when under antifungal prophylaxis (confidence interval at 95%: 0.10–0.22, χ^2 statistic of 90.77, $P < 0.0001$). We conclude that there is a strong beneficial effect of antifungal prophylaxis against the occurrence of oropharyngeal candidiasis. However, up to now, no study has correctly assessed the value of nystatin as a prophylactic agent against oropharyngeal candidiasis.
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INTRODUCTION

CANDIDIASES are the most common fungal infections in immunocompromised patients. Several clinical entities have been well described and include superficial as well as deep-seated infections..

Among the various presentations of candidiasis, oropharyngeal candidiasis is frequent. During the course of their disease, more than 60% of patients with cancer seem to develop oropharyngeal candidiasis. This infection is usually considered as non-life threatening; however, this complication is painful and significantly alters the quality of life, as well as impairing food and fluid intake. In addition, extension to the oesophagus as well as to the entire gastrointestinal tract may occur, potentially leading to invasion and to haematogenous dissemination resulting in deep-seated infection, particularly among granulocytopenic cancer patients.

During the past decade, numerous attempts have been reported to evaluate various prophylactic modalities against invasive fungal infections among immunocompromised patients; most of the studies have been performed in cancer patients with neutropenia. The definite role of various means used as chemoprophylaxis against all fungal infections is still controversial. Various drugs have been tested including non-absorbable antifungal agents such as nystatin, amphotericin B, clotrimazole or miconazole, as well as more recent systemic antifungal agents such as ketoconazole, fluconazole and intraconazole.

The assessment of the value of those agents may require consideration of several endpoints including fungal colonisation, incidence of all fungal infections (mucocutaneous and/or deep-seated infections), species (*Candida*, *Aspergillus*, new opportunistic pathogens), need for intravenous (i.v.) amphotericin B, and ultimately mortality due to fungal infection. It is well known that it is difficult to eradicate yeasts from the oral cavity of immunocompromised patients. In this report, we analysed the value of antifungal prophylaxis for oropharyngeal candidiasis in cancer patients using available reports from the literature.

MATERIALS AND METHODS

Trials considered in this review come from the medical literature published in English, 1975–1991 and were selected by using the software MEDLINE and the author's library. To be eligible for inclusion in this analysis, a trial had to compare the prophylactic value of a specific antifungal agent vs. a placebo for cancer patients; studies allowing the patients in the placebo group to receive any other antifungal prophylaxis during the trial were not selected. Since there is not yet a consensus about the definitive value of either topical or systemic approach to prevention of fungal infections in cancer patients, we reviewed all studies using antifungal drugs, possessing either systemic or topical antifungal properties. Furthermore, with making separate analyses for topical and systemic antifungal applications, we would have had less patients in each group of studies. Chlorhexidine was not examined since it is a topical antiseptic with an antifungal spectrum, and hence, not an antifungal drug. The trials selected had to be prospective and randomised. Patients entered in the study had to be immunocompromised and not selected according to their fungal colonisation status before study initiation.

Trials concerning AIDS patients were not considered in

Correspondence to M. Paesmans.
M. Paesmans and P. Autier are at the Institut J. Bordet, 1 rue Héger-Bordet, 1000 Brussels; and F. Meunier is at the EORTC Central Office, Data Center, Brussels, Belgium.
Received 7 Apr. 1993; provisionally accepted 22 Apr. 1993; revised manuscript received 18 Aug. 1993.

Table 1. Characteristics of the reviewed trials

	Antifungal prophylactic agent tested	Number (and %) of evaluable patients developing OC		Significance (2-sided) P
		Prophylactic arm	Placebo arm	
Brincker, 1978 [13]	Miconazole 4 × 500 mg/day	1/11(9)	6/14(43)	0.09
Sleijfer *et al.*, 1980 [14]	Amphotericin B 2g/day†	5/53(9)	12/52(23)	0.06
Brincker *et al.*, 1983 [15]	Ketoconazole 400 mg/day	2/19(11)	8/9(42)	0.04*
Owens *et al.*, 1984 [16]	Clotrimazole 3 × 10 mg/day	5/39(13)	21/37(57)	<0.001
Cuttner *et al.*, 1985 [17]	Clotrimazole 3 × 10 mg/day	1/16(6)	11/12(92)	<0.001
Yeo *et al.*, 1985 [18]	Clotrimazole 3 × 10 mg/day	1/101(1)	27/101(27)	<0.001
Hansen *et al.*, 1987 [19]	Ketoconazole 400mg/day	0/27(0)	8/29(28)	0.005
Meunier *et al.*, 1989 [20]	Ketoconazole 200 mg/day	1/23(4)	1/30(3)	1.00
	Amphotericin B 500 mg/day	0/25(0)		
Samonis *et al.*, 1990 [21]	Fluconazole 50 mg/day	1/58(2)	15/54(28)	<0.001

*Nearly all candidiasis reported occurred in the mouth (no more precision in the article). †Sometimes combined with another agent. OC = oropharyngeal candidiasis.

this review. Antifungal prophylaxis among children usually poses many compliance problems and hence data about children were not incorporated in this analysis. Results concerning the development of oropharyngeal candidiasis had to be reported separately for each treatment arm of the trials.

Variables reviewed included the oropharyngeal candidiasis occurrence and the eventual oropharyngeal colonisation status with yeasts. Other prognosis factors for the development of infections were usually not available (e.g. degree and duration of granulocytopenia), or the data reported did not indicate the relationship between the potential prognosis factor and the oropharyngeal candidiasis occurrence.

Statistical analysis was performed using the packages SPSS/PC and GLIM [1, 2] or personally written programs.

To combine the results of the selected trials we used the method developed by Peto and described by Yusuf *et al.* [3]. For each trial, we evaluated the effect of antifungal prophylaxis by calculating an estimated odds ratio of developing oropharyngeal candidiasis (the odds of developing oropharyngeal candidiasis among patients allocated to the treatment arm compared with the odds among patients allocated to the control arm). This estimate is given by the formula $\{\exp[(O-E)/V]\}$ where O is the observed number of patients developing oropharyngeal candidiasis in the prophylaxis arm and E is the expected number of patients who would develop oropharyngeal candidiasis in the prophylaxis arm under the null hypothesis of no prophylaxis effect and V is the variance of $[O-E]$.

The combination method of Peto provides an estimate of the overall odds ratio for prophylaxis effect and its probability distribution.

Before combining the results, a χ^2 test for heterogeneity between the treatment effects among the trials selected was performed.

This methodology does not take into account the heterogeneity of patient populations and drugs from one trial to another but simply provides a global estimate of the impact of prophylaxis on oropharyngeal candidiasis across studies.

RESULTS

We found in the literature 18 papers dedicated to the evaluation of an antifungal prophylaxis vs. a placebo in non-AIDS immunocompromised hosts. Nine publications out of 18 were considered as ineligible for this review [4–12]. In all cases but two, the reason to discard the trial was related to the methodology. Briefly, retrospective design [6], absence of randomisation or unclear randomisation procedure [7, 10–12], topical nystatin to all patients [9], selection of patients without fungal colonisation at study entry [12], and endpoint not appropriate [5]. Two trials [4, 8] were not retained because they did not report specific data about the impact of antifungal prophylaxis on oropharyngeal candidiasis occurrence.

According to our criteria, all trials with nystatin as the prophylactic agent were non-eligible for this review.

Table 1 shows the main features of the nine eligible trials [13–21]. Major heterogeneity was observed among the variables taken into account to describe the characteristics of the patients. The most frequently reported variables for evaluable patients are: sex (3/9 of the reports), underlying disease (8/9 of the reports), age (7/9 of the reports) and the neutrophil count at entry into the trial (6/9 of the reports). The way to display data varies widely among authors, mainly for important variables like age and neutropenia at entry in the trial. For instance, cut-off points to categorise the degree of neutropenia could be indicated as the number of patients with a neutrophil count below 100, 500 or 1000 per μl, or a combination of these boundaries. As a consequence, it was impossible to make indirect comparisons according to these variables.

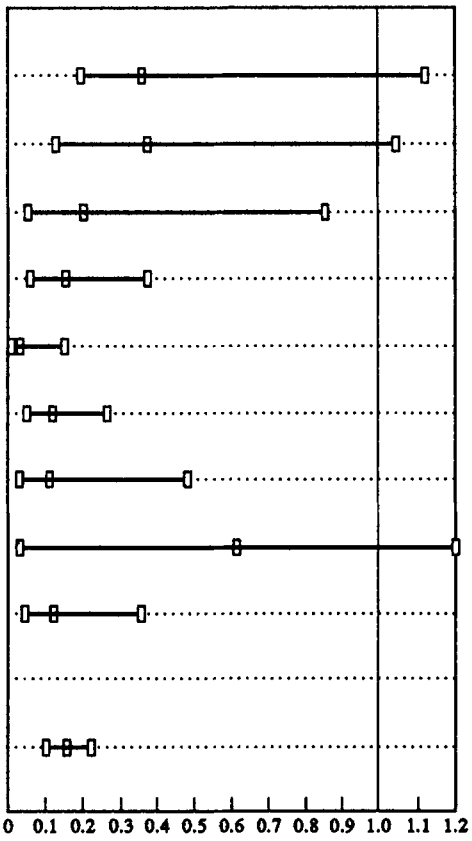
In all selected trials, the proportion of patients developing oropharyngeal candidiasis was lower in the prophylaxis group; six of the nine eligible trials concluded to a statistically significant ($P<0.05$) positive effect of prophylaxis on oropharyngeal candidiasis although the numbers of patients entered into the trials were rather small.

Table 2 shows the results of the meta-analysis. The estimated odds ratio of 0.15 (confidence interval at 95%: 0.10–0.22) indicates a strong beneficial effect of prophylaxis (χ^2 statistic of 90.77, $P<0.0001$). The χ^2 test for heterogeneity had a value of 8.86 with 8 degrees of freedom (non-significant). A separate analysis for clotrimazole and fluconazole prophylaxis confirms these global results (data not displayed).

When looking at the development of oral candidiasis according to the colonisation status with *C. albicans* before antifungal prophylaxis initiation, we obtained an oropharyn-

Table 2. Results for individual trials and combined odds ratio

	O	E	V	OR
Brinckner, 1978 [13]	1	3.08	1.29	0.20
Sleijfer *et al.*, 1980 [14]	5	8.42	3.60	0.39
Brincker, 1983 [15]	2	5.00	1.89	0.20
Owens *et al.*, 1984 [16]	5	13.34	4.33	0.15
Cuttner *et al.*, 1986 [17]	1	6.86	1.74	0.03
Yeo *et al.*, 1985 [18]	1	14.00	6.06	0.12
Hansen *et al.*, 1987 [19]	0	3.86	1.74	0.11
Meunier *et al.*, 1989 [20]	1	1.23	0.47	0.61
Samonis *et al.*, 1990 [21]	1	8.29	3.46	0.12
Overall	17	64.08	24.58	0.15



χ^2 statistic = 90.77, $P < 0.0001$. O = observed number of patients developing oropharyngeal candidiasis in the prophylaxis arm. E = expected number of patients developing oropharyngeal candidiasis in the prophylaxis arm if prophylaxis does not have any effect. V = variance of O–E. OR = estimated odds ratio for prophylaxis effect. The graphic shows the odds ratios (central symbols of the horizontal lines) with their confidence intervals at 95% (extreme symbols of the horizontal lines).

geal candidiasis rate of 25% (45/182) among the patients colonised at entry into the trial and of 8% (15/182) among the patients not colonised at entry (data from [17, 18, 19, 21]).

The summary odds-ratio for colonisation status as risk factor for oropharyngeal candidiasis is 3.66 (95% confidence interval: 1.74–5.18) and the Mantel-Haenszel χ^2 statistic has a value of 17.9 ($P < 0.0001$). Hence, colonisation status is a potential confounder able to distort the relationship between prophylaxis and oropharyngeal candidiasis occurrence.

Three trials out of nine [17, 18, 21] report simultaneously, data about the development of oropharyngeal candidiasis and the presence of positive cultures for *C. albicans* before and during the study. From these data, it was possible to fit logistic regression models with the occurrence of oropharyngeal candidiasis as outcome variable (Table 3). The explanatory variables were the antifungal prophylaxis (clotrimazole troches or fluconazole), and a positive throat culture for *C. albicans* before and during the antifungal prophylaxis course. This analysis shows that a positive throat culture for *C. albicans* during the course of antifungal prophylaxis is a stronger risk factor than a positive culture before initiation of prophylaxis. After adjusting for colonisation status before and during prophylaxis, the preventive effect conferred by either fluconazole or clotrimazole remains highly significant.

DISCUSSION

The beneficial impact of chemoprophylaxis for oropharyngeal candidiasis in cancer patients emerges now as well documented and it seems worthwhile to systematically prevent thrush. Fluconazole or clotrimazole (in troches) appear to be effective drugs for the prevention of oropharyngeal infections caused by *C. albicans*. Although nystatin is mentioned in a large number of studies, according to our review, up to now, no study has correctly addressed the role of this drug in prevention of oropharyngeal candidiasis, even if we take into account a paper by Epstein *et al.* [22] published after the period covered by our review.

Although other yeast species are increasingly detected in the immunocompromised host [23], this review focuses principally on *C. albicans* because data on infections with other fungi are rare in the trials considered.

Clinical researches produced contradictory results about the influence of colonisation status on the development of thrush. Some authors pointed out a possible influence of colonisation status before prophylaxis initiation [15] while others tended to show the opposite [19]. According to this review, a positive culture for *C. albicans* before initiation of prophylaxis is a risk factor for oropharyngeal candidiasis, and the development of thrush is more likely to occur when colonisation of the throat

Table 3. Forward stepwise logistic regression model of oral candidiasis occurrence rate as a function of prophylaxis with clotrimazole troches and throat culture positive for C. albicans *before and during prophylaxis*

Variables	Deviance	df	χ^2	*P*
(A) Prophylaxis with clotrimazole troches (pooled data from [17] and [18])				
Intercept	90.9	7	—	—
+ Positive culture during	34.3	1	56.6	<0.0001
+ Clotrimazole	1.7	1	32.6	<0.0001
+ Positive culture before	1.6	1	0.1	Non-significant
(B) Prophylaxis with fluconazole capsules (50 mg) (data from [21])				
Intercept	46.0	7	—	—
+ Positive culture during	15.3	1	30.7	<0.0001
+ Fluconazole	4.7	1	10.6	<0.0001
+ Positive culture before	0.0	1	4.7	=0.03

χ^2 = difference of deviance between two successive models. df = degrees of freedom of χ^2.

by *C. albicans* persists or occurs after initiation of antifungal prophylaxis.

Some authors have advocated that antifungal prophylaxis is ineffective in patients with leukaemia [24], but the studies on which these assertions are based on were not powerful enough, i.e. their sample size is too small to demonstrate any beneficial effect of antifungal prophylaxis. For instance, in a trial on prophylaxis with clotrimazole among subjects with leukaemia, Owens [16] found that 3 out of 8 patients (37%) under prophylaxis developed thrush whereas 5 out of 8 (62%) in the placebo group developed the disease: this result is not statistically significant although the oropharyngeal candidiasis occurrence rate among leukaemic patients under placebo was 25% higher than for those under clotrimazole. However, at least 140 leukaemic patients would have been necessary to demonstrate a 25% difference in thrush occurrence rate between the placebo and the intervention group (for a power of 80%, a rejection level of 5% and the hypothesis that the theoretical cumulative incidence rates are, respectively, 62 and 37%).

We have not been able to study the effect of neutropenia on the development of oropharyngeal candidiasis because the published data were not suited for this purpose. We believe however, that any future study should take into account both the magnitude and the duration of neutropenia when assessing the benefit of prophylaxis.

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