GENTIAN VIOLET, KETOCONAZOLE AND NYSTATIN IN OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS IN ZAIRIAN AIDS PATIENTS

by

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Summary. — A randomized un-blinded study on the treatment of oropharyngeal and esophageal candidiasis was conducted in Kinshasa (Zaire), among 141 inpatients with AIDS and oropharyngeal candidiasis, of whom 136 also had esophageal candidiasis. The study compared the efficacy of gentian violet mouth washes (1.5 ml 0.5% aqueous solution b.i.d.), oral ketoconazole (200 mg/day, after a meal) and nystatin mouth washes (200,000 U oral suspension q.i.d.). Patients treated with mouth washes swallowed their medication after mouth washing.

Patients enrolled in this study had a very high mortality (probability of death: 41.6% after 14 days). After 14 days, 72 patients could be evaluated. At that time, oropharyngeal lesions had disappeared in similar proportions of patients treated with gentian violet (11/26, 42%) and ketoconazole (10/23, 43%), and in a lower proportion of patients treated with nystatin (2/23, 9%; p < 0.05). In esophageal candidiasis, ketoconazole seemed more efficient than both other treatments: esophageal lesions had disappeared in 5 (24%) of the 21 patients on ketoconazole, compared to less than 10% of patients on both other treatments (p = 0.07). The suboptimal results observed with all 3 treatments could be explained by the profound immunosuppression of patients enrolled in the study.

This study suggests that gentian violet is effective treatment for oropharyngeal candidiasis. As it is very cheap (0.5 US$/treatment course in Kinshasa), we suggest that its use should be assessed in larger studies.

KEYWORDS: Oral thrush; Candida; HIV; AIDS; Gentian violet; Ketoconazole; Nystatin; Clinical trial.

Introduction

Oropharyngeal candidiasis is the most frequently diagnosed opportunistic infection in African AIDS patients. In Mama Yemo Hospital (Kinshasa, Zaire), 30 to 63% of HIV seropositive adult medical inpatients had oropharyngeal candidiasis (5, 17). The prevalence of esophageal candidiasis among African AIDS patients has been reported to be 21 to 27% (4, 20).

Though rarely fatal, oropharyngeal and esophageal candidiasis are a source of significant morbidity in HIV seropositive patients. If left untreated, no spontaneous cure occurs and, after successful treatment, maintenance therapy is necessary to prevent relapses. Unfortunately, the medications most often used to treat candidiasis in Zaire (nystatin and ketoconazole) are too
costly (13-20 US$/treatment course) to be within reach of the average African patient. As gentian violet is very cheap (0.5 US$/treatment course in Zaire), and has been used successfully in oral thrush (15), we evaluated its use in oropharyngeal and esophageal candidiasis among adults inpatients with AIDS in a randomized study. The study could not be blinded given the characteristics of the trial drugs, of which one was a dye. A placebo-controlled trial was felt to be unethical, because effective treatment for the condition was available.

**Methods**

*Patient evaluation*

Adult inpatients in the medical wards of Mama Yemo Hospital (Kinshasa, Zaire), who had not taken any antifungal treatment in the previous 2 weeks, and who had a clinical diagnosis of oropharyngeal candidiasis, confirmed by microscopy of oral scrapings, were eligible for entry in the study. After written informed consent to participate was obtained, a clinical examination, esophagoscopy with a flexible endoscope, and HIV serology were performed.

Patients were re-evaluated 14 days after starting treatment. This re-evaluation included a clinical assessment of oral lesions and microscopy of oral scrapings. Esophagoscopy was repeated if the patient had esophagitis at enrolment, and esophageal biopsies were obtained from any lesions detected.

*Treatments*

Patients were stratified into patients with oropharyngeal candidiasis only, and patients with both oropharyngeal and esophageal candidiasis. Within these strata, consecutive patients received an unique incremental study number, which had been randomized beforehand to one of the 3 treatments. A listing of study numbers and treatments was kept by one of the authors (Joseph Perriëns), who was not involved in the initial assessment of the patients. The treatment to be given was disclosed only after the patient was enrolled in the study.

The treatments were oral ketoconazole 200 mg/day, mouth washes with nystatin oral suspension (200,000 U q.i.d.), or mouth washes with gentian violet 0.5% aqueous solution (1.5 ml b.i.d.). Treatment was prescribed for 10 days, or longer, until complete clearance of symptoms. When mouth washes were given, patients were instructed to continue mouth washing for at least 2 minutes, and to swallow the medication afterwards. Patients were not supervised when taking their treatment.

*Laboratory methods*

Light microscopy of oral scrapings, obtained after the patient had rinsed his mouth with tap water, were carried out after clearing the preparation with 10% KOH.
Esophageal biopsies were fixed in 10% buffered formalin and processed by standard methods. Sections were stained by Hematoxylin and Eosin for routine examination and Periodic-Acid Schiff for detection of fungal elements.

HIV serology was performed using an ELISA test (Vironostica anti-HTLV III microelisa system, Organon Technica, Boxtel, Holland), and reactive samples were confirmed by Western Blot (Dupont de Nemours, DE, USA). A Western Blot was considered positive if antibodies against p24 and gp41 and/or gp120/160 were present.

Data analysis

Patients with oropharyngeal lesions only and patients with both oropharyngeal lesions and esophageal lesions were included in the assessment of oropharyngeal lesions under therapy.

Treatment groups were compared using the Chi-square (with Yates' correction in 2 x 2 tables) or the Fisher Exact Test. The actuarial life-table method was used to describe mortality. Null hypotheses were rejected at a two-tailed significance of 0.05.

Results

Patient population (Table 1)

Between May 9, 1989 and May 31, 1990, 150 patients were entered in the study. Of those 150 patients, 141 (94%) were included in the analysis. Three (2% of 150) patients with negative and 6 (4% of 150) patients with missing HIV serology results were excluded from analysis. One hundred thirty six patients (97% of 141) had, in addition to oropharyngeal candidiasis, esophageal candidiasis.

There were no significant differences between treatment groups for age, sex, extent of the lesions and the proportion of patients taking antibiotics.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Characteristics of the patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gentian violet (n = 49)</td>
</tr>
<tr>
<td>Age (Mean ± SD)</td>
<td>34.5 ± 8.0</td>
</tr>
<tr>
<td># and (%) on antibiotics</td>
<td>26 (53)</td>
</tr>
<tr>
<td>Extent of lesions (# and % of n)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Oropharyngeal only</td>
<td>47 (96)</td>
</tr>
<tr>
<td>Oropharyngeal and esophageal</td>
<td></td>
</tr>
<tr>
<td>Type of oropharyngeal candidiasis (# and % of n)</td>
<td>43 (88)</td>
</tr>
<tr>
<td>Pseudomembranous</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Atrophic</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hyperplastic</td>
<td></td>
</tr>
<tr>
<td>Mortality and losses to follow-up</td>
<td>22</td>
</tr>
<tr>
<td>Died</td>
<td>1</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td></td>
</tr>
<tr>
<td>Probability of death</td>
<td>45.4</td>
</tr>
<tr>
<td>After 14 days (%)</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05 compared to gentian violet and ketoconazole.
Mortality and losses to follow-up (Table 1)

The probability of death of the entire study population was 41.6%. There were no significant differences in mortality between treatment groups.

In the nystatin group more patients (9/47) were lost to follow-up than in the ketoconazole group (3/45, p < 0.05) or the gentian violet group (1/49, p < 0.005). Patients lost to follow-up were similar to patients who remained in the follow-up for age, sex, and extent of disease.

Oral lesions (Table 2)

After 14 days, 72 patients were available for evaluation. The oral lesions had disappeared in 11 (42%) of 26 patients on gentian violet, in 10 (43%) of 23 patients on ketoconazole, and in 2 (9%) of 23 patients on nystatin (p < 0.05). Oral scrapings of patients on nystatin were less often negative for mycelia (p < 0.001).

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Treatment results</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Oral lesions</td>
<td>Gentian violet</td>
</tr>
<tr>
<td># Patients evaluable after 14 days</td>
<td>26</td>
</tr>
<tr>
<td>Lesions:</td>
<td></td>
</tr>
<tr>
<td>Disappeared</td>
<td>11 (42)</td>
</tr>
<tr>
<td>Improved</td>
<td>10 (39)</td>
</tr>
<tr>
<td>Same or worse</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Oral scrapings negative for mycelia</td>
<td>16 (62)</td>
</tr>
<tr>
<td>B) Esophageal lesions</td>
<td>Gentian violet</td>
</tr>
<tr>
<td># Patients endoscoped after 14 days</td>
<td>22</td>
</tr>
<tr>
<td>Lesions:</td>
<td></td>
</tr>
<tr>
<td>Disappeared</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Improved</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Same or worse</td>
<td>13 (59)</td>
</tr>
<tr>
<td># With positive biopsy / # biopsies</td>
<td>6/3 (46)</td>
</tr>
</tbody>
</table>

* p < 0.05 compared to gentian violet group and ketoconazole.
** p = 0.07 compared to the combined results of both other treatment groups.

Esophageal lesions (Table 2)

Of the 136 patients with esophageal candidiasis, 70 were available for re-evaluation after 14 days. Repeat endoscopy was refused by 7 patients: 3 in the gentian violet group, 2 in the nystatin group and 2 in the ketoconazole group.

Of the 63 endoscoped patients, 32 (51%) had unchanged or worse lesions, 23 (37%) had improved lesions, and in 8 (13%) lesions had disappeared. The proportion of patients whose lesions had disappeared tended to be higher in the ketoconazole-group, but this difference was not significant (p = 0.07).
Esophageal biopsies were available in 40 of the 55 endoscoped patients, who had visible lesions. In 15 patients no biopsies were taken, because of technical problems. The proportion of biopsies positive for candidiasis was similar in all treatment groups. Other esophageal conditions were diagnosed on biopsy in 8 patients, of whom 7 (17% of 40) had no associated esophageal candidiasis. In the gentian violet group 1 had chronic intestinal metaplasia, and 3 had non-specific esophagitis. In the nystatin group, 1 patient had, in addition to esophageal candidiasis, an esophageal ulcer. In the ketoconazole group, 2 patients had non-specific esophagitis, and 1 had acute herpes simplex esophagitis.

Concomitant therapy and treatment outcome

The proportion of patients treated with antibiotics was similar in all treatment groups. The use of antibiotics was not associated with poor response to antimycotic treatment. None of the patients received corticosteroids at any time during the study.

Side effects and acceptability

Two patients treated with gentian violet developed irritation, accompanied with small superficial ulcers of the oral mucosa, within 24 hours of the start of therapy. These were rapidly reversible after a temporary dose reduction of gentian violet. No side effects were observed with ketoconazole or nystatin.

Of the patients evaluated at 14 days, 3 patients in the nystatin group indicated that they would refuse to take the same drug again, because they found it inefficient. All patients treated with ketoconazole or gentian violet would accept retreatment with the same drug.

Discussion

In this study, gentian violet mouth washes appeared as effective as ketoconazole in the treatment of oropharyngeal candidiasis in AIDS patients, and nystatin appeared less effective than gentian violet or ketoconazole. Ketoconazole tended to be more efficient in esophageal candidiasis, than gentian violet and nystatin. However, results of this study should be interpreted with caution, because its sample size limited its power to detect a 30% difference in efficacy to 50%. In addition, more nystatin-treated patients were lost to follow-up, and treatment with this unpleasant tasting drug was not supervised. On the other hand, all but 2 (3, 10) of the studies on oral and oesophageal candidiasis, cited below, suffered from similar limitations in sample size, and data on nystatin in this study are in line with comparative studies of nystatin and ketoconazole in the prophylaxis of oropharyngeal candidiasis in neutropenic patients (9, 18) and on the treatment of oral thrush in newborns and infants (1).

Compared to other studies, treatment for candidiasis was inefficient in this study. Studies on the treatment of oropharyngeal candidiasis with ketocona-
zole reported clinical cure rates of 75% (12/16) in patients receiving 200 mg/day (6), and of 79% (15/19) to 100% (34/34) in patients receiving 400 mg/day respectively (16,19). Cure rates of 78% (14/18) to 100% (48/48) were reported in patients with esophageal candidiasis receiving 400 and 200 mg ketoconazole/day respectively (3,8). Studies with fluconazole reported cure rates of 80 to 100% in both oropharyngeal and esophageal candidiasis (2,6,7,8,10,14,16,21). Impaired gastric acid secretion may have contributed to the lower than anticipated efficacy of ketoconazole in the present study (12). The low doses of ketoconazole and nystatin used in this study are not thought to be the most likely explanation for the suboptimal treatment results, as similar doses had been much more effective in previous studies (3,6,11). In our view, the low cure rates in this study can be explained by the inclusion of end-stage patients with profound immunosuppression. The severity of immunosuppression of patients in this study is illustrated by their high prevalence (97%) of esophagitis (though a few may not have been of candidal origin), and by findings of a previous study in the same wards, in which the mean T-helper cell counts of 21 AIDS patients was 92/mm³ (range 0-164/mm³) (J. Perriëns, unpublished). As in other studies (13,15), the side effects of gentian violet therapy were local irritation and ulceration, but these were infrequent and reversible. Its acceptability was good, in spite of staining of teeth and gums.

The finding that, in this patient population, gentian violet was as effective as ketoconazole in oropharyngeal candidiasis is encouraging, as gentian violet is much cheaper (0.5 US$/30 ml) than ketoconazole (13-17 US$/10 tablets) and nystatin oral suspension (of which 4 bottles of 2.4 million units are necessary per treatment course, at 4-5 US$/bottle) (Kinshasa prices at the time of the study). Therefore, we suggest that gentian violet (and other cheap anti-mycotic drugs) to treat oropharyngeal candidiasis should be assessed in larger studies. Pending their results, we suggest to use gentian violet to treat oropharyngeal candidiasis in patients who otherwise could not afford treatment.

Acknowledgements. — The writers thank Dr. M. M. Gerniers, who signalled the possibility of treating oral candidiasis with gentian violet, and the Belgian Administration for Development and Cooperation, Brussels, Belgium, which funded this study.

Violet de gentiane, kétôconazole et nystatine dans la candidose oropharyngée et oesophagienne chez des patients sidéens zaïrois.

Résumé. — Une étude randomisée portant sur le traitement de la candidose orale et oesophagienne a été menée à Kinshasa chez 141 patients sidéens, dont 136 présentaient en outre une candidose oesophagienne. L’étude avait pour but de comparer l’efficacité du violet de gentiane (1,5 ml de solution à 0,5% 2 fois par jour en bain de bouche, suivi de déglutition), le kétôconazole (200 mg/jour par voie orale, à la fin d’un repas) et la nystatine (200.000 U en solution buvable, 4 fois par jour en bain de bouche, suivi de déglutition).

Les patients enrôlés dans cette étude ont présenté un taux de mortalité très élevé : la probabilité de décès au cours des 14 jours de suivi était de 41,6%. En conséquence seulement 72 patients pouvaient être réévalués après 14 jours. A ce moment, la candidose orale avait disparu dans une proportion similaire chez les patients traités au violet de gentiane (11/16, 42%) et au kétôconazole (10/23, 43%), mais dans une proportion moins élevée chez les patients traités à la nystatine (2/23, 9% p < 0.05). Vis à vis de la candidose oesophagienne, le kétôconazole semblait plus efficace que les deux autres traitements : 5/21 ou 24% de guérisons, contre moins de 10% pour les autres traitements (p = 0.07). Les résultats médicoces, obtenus avec les 3 médicaments, pouvaient être expliqués par l’immunodépression profonde des participants.

La présente étude suggère que le violet de gentiane est un traitement efficace de la candidose orale. En outre, ce médicament est très bon marché (0.5 US$ pour une cure complète). Nous suggérons donc de l’évaluer dans des études portant sur des effectifs plus importants.
Gentiaanviolet, ketoconazole en nystatine in orofaryngeale en esophageale candidiasis bij Zairese AIDS patiënten.

Samenvatting. — 141 AIDS patiënten met orofaryngeale candidiase, waarvan er 136 bovendien slokdarmcandidiase hadden, namen in Kinshasa deel aan een gerandomiseerde niet-blinde studie over de behandeling van candidiase van de orofarynx en de slokdarm. In deze studie werd de effectiviteit van gentiaanviolet (mondbaden met 1,5 ml 0,5% waterige oplossing 2 maal daags) vergeleken met die van ketoconazole (200 mg per os, na een maaltijd) en van nystatine (mondbaden met 200.000 U 4 maal daags). Patiënten behandeld met mondbaden slikten hun medicatie na het mondbad door.

De patiënten hadden een zeer hoge mortaliteit; de sterftekans was 41,6% na 14 dagen. Hierdoor waren na 14 dagen slechts 72 patiënten beschikbaar voor herevaluatie. Op dat ogenblik bleken de orofaryngeale letsebloemen bij 11 (42%) van de 26 patiënten, behandeld met gentiaanviolet, bij 10 (43%) van de 23 patiënten, behandeld met ketoconazole, en bij slechts 2 (9%) der 23 patiënten, behandeld met nystatine (p < 0,05). Ketoconazole leek efficiënter dan de andere behandelingen bij slokdarmcandidiase: de letsebloemen verdwenen in 5 (24%) van de 21 geëvalueerde patiënten behandeld met ketoconazole, in vergelijking met minder dan 10% der patiënten die andere behandelingen kregen (p = 0,07). De minder goede resultaten, behaald met alle drie de behandelingen, konden worden verklaard door de ver gevorderde immuunsuppressie der patiënten.

Deze studie suggereert dat gentiaanviolet een effectieve behandeling is voor orofaryngeale candidiase. Daar het bovendien zeer goedkoop is (0,5 US$ voor een volledige kuur) stellen we voor gentiaanviolet verder te evalueren in grotere studies.

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REFERENCES


