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Abstract
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Use of Miconazole for Prevention of Opportunistic Fungal Infection During Treatment of Haematological Malignancies

by Professor J L Michaux, Dr P Jacquemin, Dr G Cornu, Dr G Wauters, Dr J Gigi, Dr H Noel, Dr J B Turine and Dr A Ferrant

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It is widely acknowledged that infection during the treatment of malignant haemopathy is a serious problem. Many infections are due to bacteria. Nevertheless a considerable number have proved to be of fungal origin. Our own studies have shown that of 16 patients who died in the course of malignant blood disease and were autopsied, four (25%) suffered from systemic fungal infection which was the cause of death. Three (18%) had a more localized infection. Thus, 43% of these autopsies were positive for mycosis.

In an attempt to overcome these complications, we initiated a trial with miconazole, a new broad-spectrum antimycotic agent.

Table 1

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males</th>
<th>Females</th>
<th>M+F</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>16</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>11-20</td>
<td>10</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>21-30</td>
<td>3</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>31-40</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>41-50</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>51-60</td>
<td>10</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>61-70</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>71-80</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>54</td>
<td>33</td>
<td>87</td>
</tr>
</tbody>
</table>

Eighty-six patients hospitalized in the Department of Haematology of the University Hospital of Louvain, and all treated with miconazole, were studied. Some patients were hospitalized several times, thus providing information on 100 courses of treatment (Table 1). Most of the patients suffered from haematological malignancies and received potent cytostatic treatment, often associated with corticosteroids and specific or broad-spectrum antibiotics.

Adults were given 1.5 g/day of miconazole in the form of tablets. When high fever led to the suspicion of severe infection resistant to antibiotics, or when the patient was unable to swallow the tablets (e.g. in the case of stomatitis), miconazole was administered intravenously at an average daily dose of 1.2 g in three injections.

Nearly all the patients received oral amphotericin in order to prevent oral mycosis. An oral suspension of miconazole became available after the start of the study. In 10 patients this suspension took the place of amphotericin.

An average miconazole treatment lasted 38 days (range 2-123 days). Evaluation of the results was made by regular checks of the patients' clinical condition and the systemic culture of specimens collected twice weekly from the oropharynx, nose, ears, vagina, feces, urine and if necessary from other sources. The specimens were seeded onto Sabouraud's agar primed with 10 μg of gentamycin and 20 μg of penicillin.

In order to compare the prevalence of mycotic infections with that of a control group, swabs or specimens were taken from patients in different wards of the same hospital. They received neither miconazole nor amphotericin. Three well-established mycotic infections were observed: one stomatitis and two septicemias due to candida. The patient with stomatitis received 1.5 g/day of miconazole orally and from the fifth day of treatment cultures were negative. The first case of candidal septicemia occurred after 31 days of preventive oral miconazole treatment. Intravenous miconazole treatment was successful. The other case was a 5-year-old child admitted with candidal septicemia. Twenty-four hours of intravenous miconazole produced negative blood culture and disappearance of fever.

The results of the swabs and specimens are given in Table 2. Whereas the fraction of positive specimens was 16% in the control group, it was only 6.2% in the group under miconazole and amphotericin. Considering only the results...
Table 2

Number of positive microbiological cultures

<table>
<thead>
<tr>
<th>Group 1 Total samples</th>
<th>Group 2 Total samples</th>
<th>Group 3 Total samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive No.</td>
<td>%</td>
</tr>
<tr>
<td>Blood</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Sputum</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>135</td>
<td>33</td>
</tr>
<tr>
<td>Feces</td>
<td>66</td>
<td>22</td>
</tr>
<tr>
<td>Urine</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Catheter</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>35</td>
<td>0</td>
</tr>
</tbody>
</table>

Total 350 56 16 1725 108 6.2 228 3 1.3

Fisher's two-tailed test

Group 1: control; n = 98 patients
Group 2: miconazole plus mouth-rinsing with amphotericin; n = 86 patients, 100 observations
Group 3: miconazole tablets orally plus mouth-rinsing with miconazole suspension; n = 10 patients

obtained in cultures from the oropharynx, a reduction was also observed, from 24.4% to 12.9%.

A highly significant difference in the faeces is noticeable. When miconazole suspension was substituted for amphotericin for oral washing, the frequency of positive specimens in the oropharynx dropped to 3 in 105. No fungi at all were discovered in the faeces.

Sixteen of the 23 patients who died in the hospital were autopsied. In ten cases (64%) no mycosis could be detected. In six patients (36%) the presence of mycosis was shown either histologically or by post-mortem culture of the organ. Aspergillus was detected in 2 cases, and candida in 4. However, in none of the patients were the mycotic lesions severe enough to have been the cause of death.

Summary

It appears that miconazole is highly effective in reducing the incidence of systemic mycosis in patients suffering from malignant haemopathy and bone marrow failure. Three clinical infections (one stomatitis and two septicaemias due to candida) were easily cured. Autopsy findings never disclosed mycosis as the cause of death. The drug was completely atoxic and seems to offer major help in the treatment of malignant blood disease.
DISCUSSION

Professor Vanbreuseghem (Chairman) asked Professor Michaux what post-mortem techniques had been used to evaluate the presence or absence of fungi.

Professor Michaux said this was done by cultures and by histological study of lesions in different organs – lung, liver, spleen, gastrointestinal tract.

Professor Vanbreuseghem (Chairman) said they did that in 100 cancerous patients in Brussels. They investigated 19 different specimens and that had very much enlarged the number of positive results (1976, *Mykosen* 13, 337).

Dr H B Levine (Oakland) asked what precautions in culturing had been taken to make sure that possible residual miconazole in the tissues did not prevent any growth that might occur. Had Professor Michaux’s team diluted far enough?

Dr A Ferrant (Louvain) agreed that this was very important. They had tried to do the autopsy as rapidly as possible after death and some residual miconazole could have stayed at the site of the lesion. He added that they usually assessed fungal infection from microscopy of the lesions at the time of death. Whenever there were lesions they were quite small, of the order of 0.5 cm.

Dr Z Martinek (Shaffhausen) noted that Professor Michaux’s team had performed 19 autopsies between 1972 and 1974, and 16 autopsies subsequently. He wondered whether miconazole had any influence on the morbidity of their patients.

Dr Ferrant (Louvain) said he believed so because, before initiating their preventive treatment, the cause of death of the patients who died was often systemic mycotic infection. After initiating the treatment, the cause of death was never mycosis. He thought this difference was noticeable but did not pretend that a patient survived longer with miconazole. It was the incidence of systemic mycosis as a cause of death that was lessened.

Dr M Marty (Paris) asked whether the team’s antibiotic policy had been changed when using miconazole or if it had been constant.

Dr Ferrant (Louvain) replied that they had not changed their antibiotic scheme. They had started with newly available antibiotics but their policy of treatment of systemic infections had not changed.

Professor G Gargani (Florence) commented on the candidal septicaemia contracted by one patient during preventive treatment. He asked whether or not the strain was resistant to miconazole *in vitro*.

Dr Ferrant (Louvain) replied that the strain was not resistant.

Professor Vanbreuseghem (Chairman) asked what had been the frequency and duration of the mouth wash.

Dr Ferrant (Louvain) said the patients had been asked to perform a mouth wash four times a day. The duration was only the time of washing the mouth – one or two minutes, not more.

Dr C A L Janssen (Noordwijkerhout) asked for clarification of the fact that they apparently treated 86 patients, but reported 100 treatments.

Dr Ferrant (Louvain) explained that there had been 86 patients who were treated and that for those 86 there were 100 courses of treatment. All the patients now cited had in fact received preventive treatment. Enlarging on this point, he explained that the study had started in an attempt to prevent systemic mycosis and that treatment was initiated in 86 patients. Some patients returned because of a hematological relapse, so they had to start preventive treatment again, which gave 100 courses of treatment altogether.

Dr H Brincker (Odense) said that one objection to their study was that the control group was an historical group and not a simultaneous group. For such reasons he had started a double-blind study using the same kind of patients as a reference group. He asked what was the reason for the Belgian group not having used a comparable control group.

Dr Ferrant (Louvain) said that the main reason was ethical. They had in fact started a control group with oral administration of amphotericin but had to stop because the results were not satisfactory. Afterwards all the patients had been put on oral miconazole treatment.

Professor A Mazzoni (Bologna) enquired about the tolerance of patients to the drug.

Dr Ferrant (Louvain) said that the tolerance was always excellent. There were no problems except for the unpleasant taste.

Professor Vanbreuseghem (Chairman) said that as far as tolerance is concerned the dose used was important. The Louvain team had not used a very large dose, and Dr Ferrant confirmed this.