Treatment of Mycotic Infections: Hydrocortisone in the Control of Amphotericin-B Toxicity

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The pulmonary mycoses were considered of little importance until recent years when a better understanding of some of these diseases and newer diagnostic techniques enabled physicians to become more aware of their presence and to make the diagnosis more readily. Some of the mycoses such as histoplasmosis, blastomycosis, coccidioidomycosis, have assumed greater importance in the United States because of endemic areas plotted out within the continent combined with reports of localized epidemics. Cases of histoplasmosis have been reported sporadically from most countries and such reports may become more widespread with better dissemination of knowledge now available.

This increase in mycotic infections could be a result of wider experience in this field, acquired through research and better laboratory facilities, or it could be related to the extensive use of wide spectrum antibiotics and corticosteroids in recent years. On this background the problem of effective therapy presented itself. Louria et al., Steinberg et al., and others, demonstrated the high in vitro activity of the amphotericins against many pathogenic fungi. Numerous agents have been tried, but none found as effective as one of the more recent of these, namely amphotericin-B. The problem of amphotericin-B toxicity has received considerable attention and some physicians go as far as recommending its use only sparingly and in selected cases. In our experience with the treatment of 22 cases, we have found hydrocortisone extremely useful in counteracting most of the toxic symptoms encountered in this series of patients. On the other hand, no deleterious effects from its use have been noted even when hydrocortisone is discontinued simultaneously with amphotericin. It is therefore apparent that the dosage necessary to control these toxic symptoms is below the level at which steroid complications may be expected from a short-term administration.

Material and Method

Over a period of two and one-half years, 22 patients have received amphotericin-B intravenously for varying periods of time. The recommended course usually extends over four months. A diagnosis of pulmonary histoplasmosis was made in 19 cases and that of primary or secondary aspergillosis in three. The presence of histoplasmosis was established by sputum culture in 12 cases, by tissue studies in five, and it was a presumptive diagnosis in two cases because of a positive complement fixation reaction and deteriorating x-ray lesions when other investigations were non-contributory. Aspergillosis was diagnosed by sputum and histopathology in one case, sputum and intracavitary aspiration of material in the second, and by histopathology in the third. Some patient statistics are found in Table 1, where a preponderance of men

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-29</td>
<td>30-49</td>
</tr>
<tr>
<td>Men</td>
<td>2</td>
</tr>
<tr>
<td>Women</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2</td>
</tr>
</tbody>
</table>

over women patients is pointed out, as well as a majority of cases among the white race. Farming was the predominant occupation in these cases. Chronic cavitary pulmonary disease was present in all but two of the histoplasmosis cases and in all aspergillosis cases.

Therapy was of some benefit in most of the histoplasmosis patients, but results were

*From District Two State Tuberculosis Hospital.
questionable in the case of aspergillosis as more experience in this field is needed. All patients with a positive sputum for histoplasmosis who completed the prescribed course of antifungal treatment had achieved sputum conversion in the first few weeks of therapy. In most cases, decrease in cough and sputum was noted, as well as weight gain and improvement in the general condition. Concomitant active tuberculosis was proved culturally in one case only in this series. This patient's sputum converted satisfactorily with regard to both diseases under combined effective anti-tuberculosis and amphotericin-B therapy. Surgery was recommended for residual cavitation, but the patient declined to accept. Eighteen months following discharge. Histoplasma capsulatum has again been isolated from sputum, though there is no obvious radiographic deterioration and as yet no evidence of recurrence of tuberculosis. It is quite likely that the organism may now be resistant to amphotericin-B. This patient is receiving a second course of this drug and surgery is again being considered. It is to be noted that on commencement of treatment, toxic reactions consisting mainly of chills were observed and these were controlled satisfactorily with the introduction of hydrocortisone. This was the experience with the previous treatment on this patient.

Amphotericin-B has been administered intravenously three times a week and the recommended dose is calculated at 1 mg. per kilo body weight. Thus a patient weighing 60 kg. would receive 60 mg. amphotericin-B with each treatment; however therapy is started at approximately a quarter of this dose and is then increased gradually to the final dosage depending on patient's tolerance. The antibiotic is dissolved in 5 per cent dextrose in water at least 10 cc. per mg., and the infusion is usually given over a period of four to eight hours, alternating veins whenever possible.

**Observations on Toxicity**

Toxic reactions of varying degrees were observed in all cases following institution of amphotericin-B and in order of frequency these reactions were as follows:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disturbance</td>
<td>10</td>
</tr>
<tr>
<td>Chills and/or fever</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>7</td>
</tr>
<tr>
<td>Malaise</td>
<td>6</td>
</tr>
<tr>
<td>Vertigo</td>
<td>3</td>
</tr>
<tr>
<td>Maxillary &quot;Pressure&quot;</td>
<td>2 (one of these was combined with epistaxis)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>1</td>
</tr>
</tbody>
</table>

As has been observed by other investigators, certain abnormal laboratory results have been obtained in this series. Repeated data are available in 17 of these 22 patients. A decrease in hemoglobin and hematocrit was noted in eight cases, and a significant increase in BUN, NPN and BSP was not uncommon (Table 2), and mostly this change occurred in the first two to four weeks of treatment. These values usually returned to normal, sometimes following temporary interruption of therapy or decrease in dosage.

**Table 2—Relevant Laboratory Data (17 cases only)**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of Cases Showing Increase Above Initial Value</th>
<th>Per cent Aver. of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By 25-50 per cent</td>
<td>By more than 50 per cent</td>
</tr>
<tr>
<td>BUN</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>NPN</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>BSP</td>
<td>Elevated in 9 Cases</td>
<td></td>
</tr>
</tbody>
</table>

*Return to normal has been the rule after decrease in dosage or cessation of therapy.*

Measures to counteract toxic effects at first consisted of acetylsalicylic acid, antihistamines, chlorpromazine (Thorazine), with no marked benefit. It was then decided to try hydrocortisone in 20 mg. dosage with the infusion, and a great improvement in toxic reactions was noted immediately. On the other hand, no untoward effect from the use of hydrocortisone was observed on either the mycotic or concom-
tant tuberculous infections. It is well known that corticosteroid therapy has a definite place in selected cases of tuberculosis, severe toxemia or hypersensitivity phenomena being such indications. This form of therapy has been carried out safely under effective antimicrobial coverage. It is fair to assume that the same applies to corticosteroids when used in conjunction with amphotericin-B. In patients with no associated proved tuberculosis, high isoniazid (600-900 mg daily) with pyridoxine is usually used simultaneously on a prophylactic basis.

In 19 cases of the present series antifungal therapy was started without hydrocortisone, but the latter was subsequently introduced because of persisting significant reactions in all cases. Twelve patients (63 per cent) experienced practically complete control of symptoms, and in seven cases some symptoms persisted though of a minor degree (Table 3). In 11 instances, hydrocortisone was introduced in the first two weeks of treatment and in five cases in the second two weeks. The remaining three had received longer periods of amphotericin-B with persisting side effects, and the decision to try hydrocortisone was made following a conference which dealt with the subject of toxicity.

In one patient, hydrocortisone was introduced with the first treatment and in spite of this therapy was poorly tolerated and was discontinued approximately one month later. This was a 48-year-old colored woman in a debilitated state who was being prepared for left pneumonectomy, following which a histopathologic diagnosis of aspergillosis was made. In three cases, no hydrocortisone was used: one of these tolerated amphotericin-B very poorly and reactions persisted on and off until treatment was discontinued after a total dosage of 911 mg. The second patient, a 51-year-old white woman, tolerated amphotericin-B rather well and received a course of 38 treatments with a total dose of 1298 mg. with only minor headaches. This was the only patient in our series who showed no significant toxic effect. The third patient with a diagnosis of aspergillosis, received only three treatments.

The total dose of amphotericin-B in these cases varied from 67.5 mg. to 2700 mg. Twelve patients received over 1200 mg. No relationship was observed between dosage reached and toxicity, most of the reactions were quite marked within the first two weeks of treatment. Improvement after the introduction of hydrocortisone was noted both when it was used early and late in treatment.

**Discussion**

A number of agents have been used in the past in the treatment of mycotic infections such as ethyl vanillate, nystatin, stilbamidine, MRD 112, amebacide, iodides, and sulphonamides. One of the more recent, amphotericin-B, has definitely produced superior therapeutic results at least in some of the deep mycoses. Divergent

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**Table 3—Patients Receiving Amphotericin-B with Hydrocortisone**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>No. of Treatment Hydrocortisone Started</th>
<th>Total Dosage (Mg.)</th>
<th>Relief of Toxic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hydrocortisone+ Amphotericin</td>
<td>Marked</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>1435</td>
<td>640</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>246</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>800</td>
<td>480</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>840</td>
<td>200</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>2555</td>
<td>800</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>445</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>1480</td>
<td>300</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>745</td>
<td>200</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>2037</td>
<td>860</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>1980</td>
<td>680</td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>2700</td>
<td>1140</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>1343</td>
<td>220</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>273</td>
<td>260</td>
</tr>
<tr>
<td>14</td>
<td>6</td>
<td>2132</td>
<td>860</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>1865</td>
<td>660</td>
</tr>
<tr>
<td>16</td>
<td>13</td>
<td>1544</td>
<td>520</td>
</tr>
<tr>
<td>17</td>
<td>6**</td>
<td>830</td>
<td>280</td>
</tr>
<tr>
<td>18</td>
<td>20</td>
<td>2326</td>
<td>580</td>
</tr>
<tr>
<td>19</td>
<td>2</td>
<td>512</td>
<td>300</td>
</tr>
</tbody>
</table>

*Second course of therapy.
**Part of the time received I.M. cortisone instead of hydrocortisone.
†Number of days of actual hydrocortisone administration per patient is the total dosage divided by 20.
views have been presented with regard to
the effect of ethyl vanillate; on the other
hand MRD 112, nystatin, amebacides
have generally proved disappointing. Lehan
et al.\textsuperscript{3} obtained some favorable results from
stilbamidine in blastomycosis, but not in
histoplasmosis. These investigators have
screened several antifungal agents and have
reported the most promising results with
amphotericin-B, although toxic manifes-
tations with this drug were frequent. Larsh
et al.\textsuperscript{4} working with tissue cultures suggest-
et that combined therapy may be necessary
because of its additive activity, as was the
experience in the early days of antituber-
culosis chemotherapy.

Furcadow and Rubin\textsuperscript{5} found amphotericin-
B definitely helpful in histoplasmosis and
cryptococcosis where other forms of
treatment had proved disappointing. Blas-
tomycosis had proved amenable to other
forms of therapy, but again amphotericin-B
was found superior in this regard. Seabury
et al.\textsuperscript{6} in evaluating amphotericin-B re-
marked that this antibiotic may prove un-
acceptable to patients and physicians be-
cause of its toxic effect. In meningitic cases
they found small doses of amphotericin
intragranally were tolerated when injected
slowly and when preceded by 20 mg. of
hydrocortisone. They also observed numer-
ous toxic effects, particularly chills and fe-
ver and when these reactions were severe
they resorted to concomitant hydrocorti-
sone which they found highly effective.
However, there was no indication as to
how often they used this procedure. Yates
et al.\textsuperscript{7} have also observed numerous toxic
reactions to amphotericin-B and have used
ancillary medications to counteract them,
but hydrocortisone was used only in an oc-
casional case. The most prevalent side ef-
te effects in their hands were anorexia and
chills, and this is comparable with our ex-
perience. Some of their cases apparently
could tolerate the drug without reactions,
whereas all but one of our cases developed
significant degrees of toxicity.

Conrad and co-authors\textsuperscript{8} feel that corti-
sone is contraindicated in histoplasmosis
and they cite as proof of this two patients
who received steroid therapy and died of
progressive disease. However, it is impor-
tant to note that these patients were ap-
parently not receiving effective antifungal
therapy concomitant with the steroid ther-
apy. Our experience tends to show a paral-
el in the role of steroids in histoplasmosis
and in tuberculosis, namely that a definite
indication exists for the use of steroids on a
short term basis, under cover of adequate
therapy. In the case of histoplasmosis, such
an indication is the all-too-frequent inci-
dence of toxic manifestations following
amphotericin-B. This has been shown to be the
best antymycotic agent currently available
and the proper use of steroids may make it
more acceptable to patients. Boland and
Headley\textsuperscript{9} reported fewer adverse effects from
hydrocortisone than from cortisone
and this they attributed to the fact that
smaller doses of hydrocortisone achieved
the desired effect.

A marked increase in morbidity and
mortality in untreated cases of histoplas-
mosis, compared to treated ones, has been
demonstrated in a follow-up study,\textsuperscript{10} and
it would therefore appear that amphoteri-
chin-B may be indicated in all proved histo-
plasmosis cases. We have also shown that
surgery for chronic cavitary histoplasmosis
without amphotericin-B coverage has re-

tited in a higher incidence of complica-
tions than in those patients receiving simul-
taneous amphotericin-B therapy.\textsuperscript{11} This
would make efforts to reach a diagnosis
important from the point of view of insti-
tution of therapy prior to surgery. The
problem of coexisting pulmonary diseases
is sometimes forgotten\textsuperscript{12} and an example of
this is the presence of active pulmonary
histoplasmosis and active tuberculosis.
Thus, the treatment of the tuberculous con-
dition when the presence of histoplasmosis
goes unsuspected, can obviously produce
unsatisfactory results. In such cases ade-
quate treatment of both disease entities is
indicated.

In a recent paper on nocardiosis, Mur-
ray et al.\textsuperscript{13} refer to the association of this
condition with other diseases particularly those requiring long-term steroid therapy. They point out cases of bronchial asthma, leukemia and Hodgkin's disease in whom the development of nocardial infection appeared related to therapy with steroid and antineoplastic drugs. This again highlights the caution necessary in this form of treatment. Small doses of steroids for short periods may have definite value, and are indeed indicated as has been shown in the management of histoplasmosis in this series where amphotericin-B was instituted. Thorn et al.\textsuperscript{14} presented in tabular form some of the changes in urine and serum analyses observed in a fasting normal subject receiving 12 mg. of hydrocortisone intravenously per hour. These changes were less marked than those seen in a normal subject receiving intravenous cortisone 12 mg. per hour. The above dosage of hydrocortisone is considerably higher than the 2.5 - 5 mg. per hour our patients receive by the time the amphotericin-B infusion is completed. In certain conditions, in medical practice the recommended dose of hydrocortisone for the first few days may be as high as 100 to 300 mg. daily. After a clinical response is established, this is then gradually reduced until the lowest possible maintenance level is reached which is compatible with therapeutic effect.

Hydrocortisone is, in some way, thought to facilitate function in every system in the body and it is believed that the undesirable effects of this drug are always those of prolonged overdosage. The dosage used in this study has produced the desired result with no untoward symptom, and because of toxic reactions to amphotericin-B it is more likely that treatment would have been discontinued in a large number of cases if hydrocortisone had not counteracted these manifestations. Recently Utz et al.\textsuperscript{16} reported on studies with x-5079c, another antifungal drug, apparently well tolerated and effective against a number of deep mycotic infections. Further research may yet come up with an antifungal agent easier to administer, with a much lower spectrum of toxicity, and thus more acceptable generally.

\textbf{SUMMARY}

Nineteen cases of pulmonary aspergillosis mosis and three of pulmonary aspergillosis were treated with intravenous amphotericin-B. This study deals particularly with the use of hydrocortisone in the infusion to counteract the all-too-frequent toxic manifestations of this antifungal agent. This has been done successfully in the majority of cases and with no apparent untoward effect from hydrocortisone when used in this manner.

It is concluded that, as amphotericin-B is considered the best antymycotic drug currently available, such a procedure makes it more acceptable to patients.

\textbf{Resumen}

Diecinueve casos de histoplasmosis pulmonar y tres de aspergillosis se trataron con Amfotericina B, intravenosa. Este estudio se refiere al uso de hidrocortisona en la infusión para contrarrestar las manifestaciones tóxicas demasiado frecuentes de este agente fungídico. Esto se ha logrado con éxito en las mayoría de los casos y sin efectos contraproducentes de la hidrocortisona.

Se concluye que la amfotericina B es de considerarse la mejor droga antibiótica actualmente disponible, el procedimiento aquí descrito la hace más aceptable para los enfermos.

\textbf{Resume}

Dix-neuf cas d'histoplasme pulmonaire et trois cas d'aspergillose pulmonaire furent traités par l'amphotéricin B intraveineuse. Cette étude s'applique particulièrement à l'emploi de l'hydrocortison en perfusion, pour contrer les trop fréquentes manifestations secondaires de ce produit antifongique. Ceci a été obtenu avec succès dans la majorité des cas et sans effet secondaire apparent imputable à l'hydrocortison lorsque elle fut utilisée de cette façon.

Les auteurs concluent que, puisque l'amphotéricin B est considéré comme le meilleur produit antymycosique que l'on puisse utiliser actuellement, le procédé qu'ils ont employé le rend plus facilement acceptable pour les malades.

\textbf{Zusammenfassung}

Erfolg und mit keinem augenfälligen ungünstigen Effekt von Seiten des Hydrocortisons bei Verwendung in dieser Form.

Es wird gefolgt, daß das Amphotericin-B als das gegenwärtig beste der zur Verfügung stehenden antymykotischen Mittel angesehen wird, ein solches Vorgehen, das Mittel für den Kranken günstiger gestaltet.

References

MARFAN'S SYNDROME

A peculiar development anomaly characterized by a triad of symptoms is described: 1) pathologic changes of the skeleton (extraordinarily large stature, long, thin limbs, kyphoscoliosis, deformation of the chest, etc.); 2) changes of the eyes (dislocations of the crystalline lens, cataracts, irregular coloring of the iris, etc.); 3) pathology of the cardiovascular system (aplasia of the interventricular septum, tetralogy of Fallot, patent ductus arteriosus, etc.). At the basis of this malady lies defective development of the connective tissue, in the first place of elastic fibers. Defective development of the vascular wall, predominantly of its media, may serve as the principal cause of development of severe vascular disturbances (dilatation of the aortic ostium with insufficiency of its valves, dissecting aortic aneurysm, dilatation and dissecting aneurysm of the pulmonary artery, etc.). Changes of the cardiovascular system were noted in 20-25 per cent of patients suffering from Marfan's syndrome.