Coccidioidal Meningitis

The Use of Amphotericin B in Treatment

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• **Amphotericin B is the first agent to alter favorably the course of coccidioidal meningitis. The morbidity and toxicity of the drug are at present its chief limiting factors.**

Although no cures were obtained in a series of 11 cases, significant remissions usually followed a course of therapy. Comparison with similar groups showed a significant prolongation of life in adequately treated cases.

THE NEED for an effective therapeutic agent in the deep mycotic diseases has long been recognized. Well over fifty drugs have been given clinical trials,[2,5,7,9] yet until recently none has shown sufficient promise to warrant extensive investigation. The search has continued unabated, however, since in endemic areas the deep mycotic lesions continue as a major cause of morbidity and a minor but significant cause of death.[20,24]

The southern San Joaquin Valley is the most highly endemic area of coccidioidal infection[16,23] with several thousand new cases annually. Of these about 0.2 per cent develop into disseminated disease,[22] usually accompanied by a complement fixation titer of 1:32 or higher.[25] In about 25 per cent of these cases, meningitis,[1,15,19] which has been considered to be universally fatal,[31] will develop. Some of the nonmeningeal disseminated cases also terminate fatally due to generalized dissemination or chronic progressive disease involving bones and viscera.

Amphotericin B, an antifungal agent obtained from a species of *Streptomyces* found on the shores of the Orinoco River in Venezuela,[7,29] is the first extensively investigated drug in the treatment of the deep mycotic infections.

The problems in evaluating the results of therapy in disseminated coccidioidal disease were discussed with great clarity by Fiese.[5] Coccidioidal meningitis is reasonably predictable in its behavior. In view of its invariably fatal outcome the ultimate test of any therapeutic modality is the demonstration of its ability to affect coccidioidal meningitis, since for nonmeningeal disseminated disease there is a high incidence of spontaneous remission and cure. None of the drugs used in the past has affected the course of coccidioidal meningitis.

The present report summarizes our experience in the use of amphotericin B in the treatment of coccidioidal meningitis and is chiefly concerned with our observations of the effectiveness of the drug.

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Supported in part by the Claude Babcock Memorial Fellowship, Kern County Tuberculosis and Health Association.

Submitted March 3, 1961.

METHODS AND MATERIALS

In a period of three years 11 consecutive patients with coccidioidal meningitis have been treated with amphotericin B in essentially the manner described by Winn.[32] Necropsy was performed in all patients who died. Diagnosis was established by the following laboratory criteria:

Spinal fluid findings:

1. Pleocytosis.
2. Elevated protein.
3. Complement fixation titer of 4+ at 1:2 dilution[25] or higher, *on more than one specimen.*

   or

4. Positive culture for *Coccidioides immitis.*

The spinal fluid pressure was usually elevated and a first-zone colloidal gold curve was almost always present, but these findings were not considered essential to the diagnosis.

Amphotericin B was administered intravenously six days each week at a dose of 1 mg. per kilogram of body weight daily. During the first half of the reporting period, amphotericin B was given intravenously only and was temporarily discontinued when azotemia developed. More recently, both intravenous and intraspinal therapy were used in view of the poor transference of the drug across the blood-brain barrier.[6,18,21] During this period treatment was not interrupted because of azotemia; instead, if the blood urea nitrogen rose above 50 mg. per

100 cc. the intravenous dose was temporarily decreased by half and then slowly increased again. Amphotericin B for intravenous use was mixed with 5 per cent dextrose and water to a concentration of 10 mg. per 100 ml. and heparin was added. Early in the study diphenhydramine was added to the intravenous solution as suggested by Winn,[32] and in some instances we added pyridoxine and ascorbic acid. More recently we have added only heparin, 30 mg., as the patients seemed to have less difficulty with chills and fever when other drugs were not added to the solution. Intraspinal amphotericin B was administered three times weekly in doses of 0.5 to 5.0 mg. each with 25 mg. of hydrocortisone.

Rest was stressed only when patients were acutely ill. When elevated, spinal fluid pressure was lowered by tapping and withdrawal daily. Heat lamps and extra blankets were used during the administration of intravenous amphotericin B and seemed to be of some benefit in decreasing the incidence and severity of febrile reactions. Pipamazine, prochlorperazine or chlorpromazine was administered as needed to alleviate nausea. Antihistamines and aspirin were used in an attempt to control febrile reactions.

Planned interval therapy was used during the last year of the reporting period, including weekly, quarterly and semiannual courses. The more prolonged courses of amphotericin B, in most instances, had to be discontinued because of thrombophlebitis which made further intravenous drug administration impossible. In some cases a polyethylene catheter was placed in available veins to facilitate further administration of the drug in very ill patients.

CONTROLS

No truly comparable group was available to act as a control, and placebo therapy was impractical. Therefore, in order to supplement previously published information on life expectancy, the hospital records of all patients with a diagnosis of coccidioidal meningitis during the preceding ten-year period were reviewed. The following criteria were established for inclusion in this "control" series:

1. The diagnosis must have been confirmed in accord with the criteria used for the current series, or necropsy findings had to be conclusive.
2. Some reasonable estimate of duration of meningitis could be established from the records.
3. The patient must not have received amphotericin B.

Sixty consecutive charts were reviewed and 31 were found to meet these criteria. These were analyzed in terms of survival time only (Table 1).

Buss, Gibson and Gifford reviewed 53 cases of coccidioidal meningitis seen in Kern County before 1950.[3] The duration of meningitis was unknown in three of the cases and three patients were still living at the time of their report. Of the remaining 47 patients (Table 1), 15 died within three months of onset, 23 others died within 12 months, seven lived more than one year and two lived almost two years.

TABLE 1.—*Comparative Two-Year Survival in Coccidioidal Meningitis*

	Treated with Amphotericin	No Amphotericin: Cases from Preceding 10-Year Period	No Amphotericin: Tabulated from Buss, et al.[3]
Patients:			
Followed two years or until death	7	31	47*
Living one year after onset	5	2	9
Living two years after onset	5†	0	0

*Fifty-three patients in original report, duration of disease not reported in six of these cases.

†Two of these patients have now lived 3 years, two have died at 27 and 34 months respectively and one is still living but has been followed less than 3 years.

RESULTS

With one exception all patients showed some evidence of clinical and laboratory improvement when amphotericin B was used initially (Table 2). Improvement in spinal fluid findings consisted of decrease of cell count and fall in the complement fixation titer. The spinal fluid pressure decreased and there was clearing of sensorium and relief of headache. Symptomatic improvement was generally significant.

Four patients died while under active therapy. Death in these patients occurred at four and a half, ten, twenty-seven and thirty-four months after onset. In all instances there was evidence of active coccidioidal meningitis at autopsy. In three cases *Coccidioides immitis* was cultured from the surfaces of the brain and meninges. The specimen for culture was inadvertently discarded in the fourth case, but spherules of *Coccidioides immitis* were demonstrated in tissue sections.

The seven surviving patients had lived 7, 7, 9, 18, 21, 36 and 37 months, respectively, at the time of this report. These seven patients had received a total of 15 courses of therapy and had shown improvement during each course. In no instance has a cure yet been obtained in this series. Symptoms usually recur in three to six months after active therapy is terminated. At that time, the spinal fluid shows an increase in pleocytosis and frequently an increase in complement fixation titer. The surviving patients are all carrying on their usual activities except when under active therapy.

TABLE 2.—*Data on Eleven Patients with Coccidioidal Meningitis Treated with Amphotericin B*

Case No.	Identifying Data and Survival	Amphotericin Therapy: Months Treated	Amphotericin Therapy: Total Dose Each Course: Gm. I.V.*	Amphotericin Therapy: Total Dose Each Course: Mg. I.S.*	Spinal Fluid Findings: Cells: B.T.*	Spinal Fluid Findings: Cells: A.T.*	Spinal Fluid Findings: C.F.* Titer: B.T.	Spinal Fluid Findings: C.F.* Titer: A.T.	Blood: C.F. Titer: B.T.	Blood: C.F. Titer: A.T.	Comments
1.	49-year-old white male living 37 months after onset	1	1.5	0	600	488	4+ @ 1:8	N.D.	1+ @ 1:6	N.D.	Treated elsewhere 1 month after onset. Disoriented when admitted to KGH 10 months later; treated I.V. only for 6 months and I.V. and I.S. for 3 additional months. Has worked full time as fireman since except for planned interval therapy.
		9	7.2	25.5	354	34	3+ @ 1:64	4+ @ 1:8	3+ @ 1:64	4+ @ 1:8	
		1½	2.3	7.7	107	50	4+ @ 1:8	4+ @ 1:2	4+ @ 1:16	2+ @ 1:16	
		1½	2.5	10.0	77	57	4+ @ 1:2	4+ @ 1:2	4+ @ 1:8	4+ @ 1:8	
2.	29-year-old white male living 36 months after onset	2	2.1	0	300	110	3+ @ 1:2	N.D.	4+ @ 1:4	3+ @ 1:4	First treated 1 month after onset. Works full time as electrical engineer except for planned interval treatment.
		1	3.2	13.4	162	5	2+ @ 1:16	4+ @ 1:4	3+ @ 1:64	4+ @ 1:8	
		1½	2.05	18.0	119	62	4+ @ 1:4	4+ @ 1:2	4+ @ 1:16	4+ @ 1:8	
3.	26-year-old Negro female living 18 months after onset	3	3.2	15.0	222	5	N.D.	4+ @ 1:4	4+ @ 1:32	3+ @ 1:512	Onset immediately postpartum. First treated 2 weeks after onset. Disoriented when admitted 6 months later. Now working as housewife.
		4	3.5	34.0	198	50	4+ @ 1:8	3+ @ 1:8	4+ @ 1:256	4+ @ 1:128	
4.	15-year-old white male living 21 months after onset	5½	5.1	20	84	8	3+ @ 1:2	0	1+ @ 1:8	4+ @ 1:16	Initial treatment one week after onset. I.S. therapy discontinued at end of 2nd course because of arachnoiditis. Attends school full time except on days treated.
		2	3.5	42.5	115	5	2+ @ 1:4	2+ @ 1:4	4+ @ 1:16	2+ @ 1:16	
		1½	2.3	0	182	34	2+ @ 1:4	N.D.	4+ @ 1:8	N.D.	
5.	41-year-old white male living 9 months after onset	8	5.5	3.2	700	13	2+ @ 1:2	Neg.	4+ @ 1:32	1+ @ 1:16	Initial treatment 1 month after onset, treated in hospital for 2¾ months, and weekly at home since. I.S. therapy discontinued because of arachnoiditis. Works full time as geologist.
6.	19-year-old white male living 7 months after onset	5½	2.0	27	535	74	1+ @ 1:2	1+ @ 1:2	2+ @ 1:16	N.D.	Treated as inpatient for 45 days starting 2 weeks after onset. Since has been treated once weekly. Attends college full time.
7.	29-year-old white male living 7 months after onset	4½	5.4	18	1390	46	3+ @ 1:8	4+ @ 1:16	3+ @ 1:64	4+ @ 1:32	Pneumonia and meningitis on admission. I.V. therapy only for 3 months, then I.V. and I.S.
8.	32-year-old Mexican male expired 34 months after onset	2	1.5	0	18	N.D.	Neg.	Neg.	4+ @ 1:16	N.D.	First treated 22 months after onset. Improved with first course and initially with second course followed by downhill course and death.
		9	7.3	30.0	55	2	2+ @ 1:4	N.D.	4+ @ 1:16	4+ @ 1:8	
9.	44-year-old Negro male expired 27 months after onset	1½	1.9	0	511	173	N.D.	1+ @ 1:32	4+ @ 1:32	1+ @ 1:512	First treated 9 months after onset, disoriented on 2nd admission; treated I.V. for 1 month, then I.V. and I.S. Initially improved during 3rd course followed by downhill course and death.
		5	7.6	39.0	520	2	N.D.	4+ @ 1:8	N.D.	N.D.	
		3	3.8	30.0	154	169	4+ @ 1:8	4+ @ 1:64	4+ @ 1:64	1+ @ 1:64	
10.	41-year-old Negro male expired 10 months after onset	8	4.8	19.0	390	2000	3+ @ 1:4	N.D.	3+ @ 1:16	4+ @ 1:32	I.V. therapy started 1 month after onset. Initial improvement down to 45 WBS in CSF, then relapsed and died despite vigorous I.V. and I.S. therapy for 1 month.
11.	59-year-old Filipino expired 4½ months after onset	1	12	26.0	1090	340	4+ @ 1:64	4+ @ 1:64	4+ @ 1:64	4+ @ 1:64	Moribund on admission 3½ months after onset. No improvement. Died 1 month later.

*I.V.=Intravenous. C.F.=Complement fixation. I.S.=Intraspinal.
B.T.=Before treatment. N.D.=Not done. A.T.=After treatment.

Difficulty in the administration of amphotericin B and drug toxicity was similar to that previously reported.* This has included headache, generalized pain, anorexia, nausea, occasionally vomiting, chills, fever, azotemia, anemia and thrombophlebitis. The latter, in particular, makes very protracted intravenous administration difficult. Paresthesias and transient arachnoiditis occurred during intraspinal administration of the drug, the latter severe enough in two cases to force discontinuance of intraspinal therapy. The more severe reactions were associated with intraspinal doses of 2.5 mg. or greater.

COMMENT

Longevity of patients treated with amphotericin B is compared with that in patients who received no amphotericin in Table 1. Despite the very rare case of chronic coccidioidal meningitis which may follow a very indolent course with survival of five to ten years after onset,[8,14,17] death, in the untreated patient, usually occurs within the first year, and seldom does the patient survive two years.[1,19,30]

In virtually every course of therapy, totaling over 20, the morbidity and toxicity of the drug was the deciding factor forcing discontinuing its use. This may well be the reason for the invariable relapses in the present series. Induced drug resistance has been demonstrated, and it has been speculated that such resistance may emerge in clinical practice.[12,26,28] However, in this series the subsequent courses generally were as effective as the initial one, at times requiring less drug and time to achieve equivalent clinical and laboratory results. This agrees with the observations of Littman.[11] A fungistatic but not fungicidal effect may well explain the drug action in clinical practice.

More effective means of ameliorating the toxicity of amphotericin B are needed so that much more prolonged courses of therapy might be employed. The use of long term intermittent administration may help overcome some of the obstacles. However, the possibility remains that the organism may eventually develop resistance to the drug. The addition of secondary or tertiary antifungal agents may be of value. Some of these avenues are currently being explored, and special studies on the azotemia and anemia so generally observed are in progress.

ACKNOWLEDGMENT

The authors are indebted for the performance of serological studies to C. E. Smith, M.D., University of California School of Public Health, Berkeley, and C. Ross Hampson, Ph.D., Kern County Department of Public Health, Bakersfield. The clinical and anatomical pathology was done in the laboratory of Robert W. Huntington, Jr., M.D., at Kern County General Hospital.

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*References 2, 4, 6, 10, 11, 13, 18, 21, 32.

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Biliary T-Tube Drainage

A Simple Method

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NO FULLY SATISFACTORY METHOD for draining bile into a collection bottle from a T-tube placed in the common bile duct has yet been presented. If it is large, the drainage tube may be so heavy that it pulls the T-tube out of the common duct or out of the abdominal wound; and sometimes a patient's thrashing about in bed immediately after operation will cause the T-tube to become dislodged. To prevent such an occurrence, some surgeons keep a covering of dressings over the T-tube for a day after operation. Usually the dressings become bile-soaked and irritation of the skin of the abdomen results. Some observers have recommended attaching a small bottle directly to the T-tube and keeping it in place with dressings. With this method, however, bile is likely to spill from the bottle onto the bed as the patient turns from side to side. For several years I have used a simple system that serves well yet avoids the dangers and inconveniences mentioned.

After completion of the operation, the T-tube is attached to a plastic intravenous tubing set such as is ordinarily used to administer fluids. The proximal end of the set is detached by cutting the tube with scissors. The distal end, which has a needle adapter, readily fits into the T-tube (Figure 1). After it is attached to the T-tube, which is fixed to the abdominal wall with either sutures or adhesive strapping, the long intravenous tubing is brought out from beneath the dressings and is allowed to hang over the side of the bed to a collecting bottle. Being both light in weight and long enough to permit the patient a good deal of freedom of motion without drawing it taut, the plastic tubing does not put traction on the T-tube. Even should the patient inadvertently pull directly on the plastic tubing, the traction separates it from the T-tube at the point of attachment. When the patient rises to walk about, the plastic tubing can be coiled and the distal end placed into a small collecting bottle pinned to the abdominal dressing, and when he returns to bed it can be uncoiled and the end put into a drainage bottle at the side of the bed again.

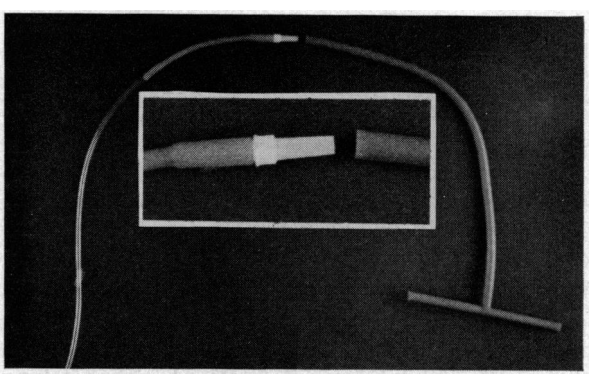

Figure 1.—Plastic intravenous tubing with needle adapter (inset) fits readily into the distal end of T-tube. Tubing photographed (Vacoset V-14) was supplied by Don Baxter, Inc., Glendale.

This work was aided by a grant from the Isaac Brotman Foundation of the Culver City Hospital, Culver City.

Submitted February 23, 1961.

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