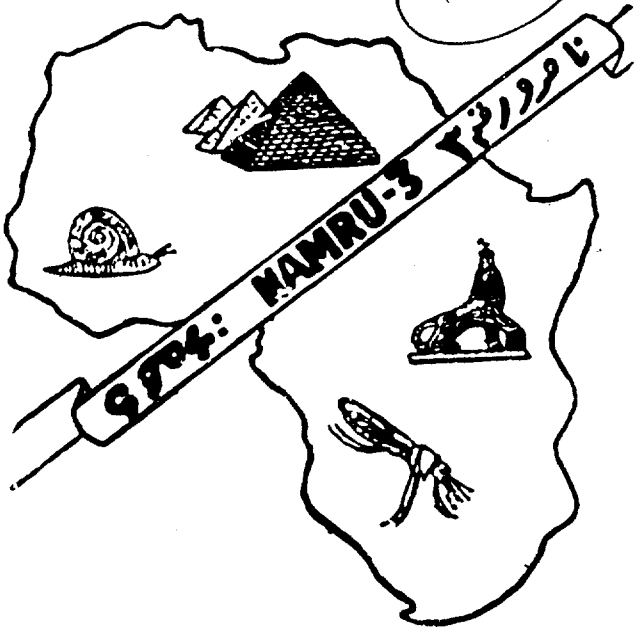

TECHNICAL/SCIENTIFIC REPORT

11-75

RIFAMPIN CONCENTRATIONS IN CEREBROSPINAL FLUID OF PATIENTS WITH TUBERCULOUS MENINGITIS

By

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RIFAMPIN CONCENTRATIONS IN CEREBROSPINAL FLUID OF PATIENTS WITH TUBERCULOUS MENINGITIS[1, 2]

Summary

Rifampin was administered orally in one dose of 25 mg per kg of body weight to 6 patients with tuberculous meningitis who had received no previous antituberculous chemotherapy and to 7 control subjects. There was no significant difference in rifampin absorption at 3 hours between patients and control subjects; however, no rifampin could be detected in the 3-hour cerebrospinal fluid (CSF) specimens taken from control subjects. Significant concentrations were reached in patients' CSF within 3 hours and were maintained for 24 hours.

D'Oliveira (1) recently reported that rifampin promptly diffuses into the cerebrospinal fluid (CSF) of patients with tuberculous meningitis who are receiving antituberculous chemotherapy. Detectable concentrations were obtained within 2 hours and were maintained for 12 hours when 300 mg was administered orally.

In the present study, a single dose of 25 mg per kg of body weight (maximum: 600 mg) of rifampin (Rifadin®, Lepetit Pharmaceutical, Milan, Italy) was given orally to 6 patients whose symptoms were compatible with tuberculous meningitis but who had not previously received antituberculous therapy (table 1), and 7 control subjects who were elective surgery patients with no infectious disease. The purpose for giving the rifampin and for taking the CSF specimen was fully explained to each control patient. The antimicrobial agent was given to the surgical patients 3 hours before spinal anesthesia was administered, and a spinal tap was performed when the anesthetic agent was given.

The diagnosis was confirmed in 4 patients with tuberculous meningitis by acid-fast *Bacillus* stain or by culture. Because it could not be determined on admission that the patients had tuberculosis, ampicillin was administered in a dose of 160 mg per kg of body weight 6 times per day commencing at the time of rifampin administration in Patients 1 through 5, and 24 hours before rifampin administration in Patient 6.

Rifampin concentrations in serum and CSF were bioassayed by the agar-well diffusion method (2) using simultaneous parallel comparison with standard. One milliliter of a broth suspension of *Sarcina lutea* (ATCC 9341) with an absorbance of 0.35 at 550 nm was added to 300 ml of sensitivity test medium (Oxoid) containing 0.1 per cent penicillinase concentrate (BBL) to inactivate the ampicillin that was given to the patients. The agar was poured to a thickness of 2.7 mm, and wells 4.5 mm in diameter were cut.

A rifampin stock solution of 1,000 μg per ml was prepared in dimethyl formamide. Working standards were prepared in pretested normal human serum at concentrations of 0.25, 0.5, 1, 2, 4, 8, and 16 μg per ml. Standards and clinical specimens were stored at −70° C until use. Each assay involved triplicate samples of test serum, test CSF, and rifampin standards. Results were analyzed by the second method recommended by Bennett and associates (2).

The serum and CSF rifampin concentrations in test patients and control subjects are listed in table 2. No

(*Received in original form November 16, 1973 and in revised form February 11, 1974*)

1 The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department, the naval service at large, or the Egyptian Ministry of Health.

2 This study was supported by the Bureau of Medicine and Surgery, Department of the Navy, Washington D.C. Work Unit No. M4305-01-10005-BFG6.

TABLE 1

CLINICAL AND LABORATORY DATA FOR PATIENTS WITH TUBERCULOUS MENINGITIS

Patient	Age (years)	Sex	Weight (kg)	Days of Illness (Approx.)	CSF Values: Protein (mg/100 ml)	CSF Values: Glucose (mg/100 ml)	CSF Values: Lymphocytes (cells/ml)	Acid-Fast Bacilli in CSF: By Microscopy	Acid-Fast Bacilli in CSF: By Culture
1	29	F	50	30	168	36	220	Negative	Negative
2	23	M	60	10	75	70	200	Positive	Negative
3	25	F	40	30	210	2	260	Negative	Negative
4	30	M	60	21	151	42	480	Positive	Negative
5	35	F	48	19	105	54	240	Positive	Negative
6	3	M	10	30	414	12	770	Negative	Positive

TABLE 2

RIFAMPIN CONCENTRATION IN SERUM AND CEREBROSPINAL FLUID (CSF) OF PATIENTS WITH TUBERCULOUS MENINGITIS AND CONTROL SUBJECTS

	Rifampin (μg/ml) (Serum/CSF)		
	0 Hour	3 Hours	24 Hours
Patient			
1	0/0	4.90/0.33	0.88/0.22
2	0/0	6.90/0.24	0.00/0.00
3	0/0	8.70/0.31	0.00/0.26
4	0/0	4.40/0.24	0.00/0.21
5	0/0	9.30/0.23	0.19/0.20
6	0/0	ND*/ND	0.30/0.40
Control Subject			
1	–	5.75/0.00	–
2	–	4.70/0.00	–
3	–	5.30/0.00	–
4	–	1.07/0.00	–
5	–	12.00/0.00	–
6	–	5.70/0.00	–
7	–	5.30/0.00	–

*ND = Not done.

zones of inhibition were produced with the CSF and serum specimens from Patient 6 when he was receiving only ampicillin, thereby confirming that the amount of penicillinase used was sufficient to annul ampicillin activity. All 3-hour serum specimens from patients contained significant concentrations of drug, the average value being 6.84 μg per ml; however, only 3 of 6 patients had detectable rifampin in their serum 24 hours after administration. The 3-hour rifampin CSF concentrations in the 6 patients ranged from 0.23 μg per ml to 0.33 μg per ml. Five of these patients had detectable CSF rifampin after 24 hours, with concentrations ranging from 0.20 to 0.40 μg per ml. Although all of the serum specimens taken from control subjects at 3 hours contained significant concentrations of rifampin, with values ranging from 1.07 to 12.00 μg per ml, no antimicrobial agent was detected in any of the control CSF specimens. Apparently, rifampin did not easily diffuse through normal meninges.

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High CSF concentrations were obtained within 3 hours and maintained for at least 24 hours when 25 mg of rifampin per kg of body weight was administered orally to patients with tuberculous meningitis who had not received previous antituberculous chemotherapy.

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UNCLASSIFIED

Security Classification

DOCUMENT CONTROL DATA - R & D

U.S. Naval Medical Research Unit No. 3 FPO New York 09527	UNCLASSIFIED

REPORT TITLE

RIFAMPIN CONCENTRATIONS IN CEREBROSPINAL FLUID OF PATIENTS WITH TUBERCULOUS MENINGITIS.

DESCRIPTIVE NOTES (Type of report and inclusive dates)

Technical/Scientific report.

AUTHOR(S) (First name, middle initial, last name)

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REPORT DATE	TOTAL NO. OF PAGES	NO. OF REFS
February 11, 1974	2	2

CONTRACT OR GRANT NO.

PROJECT NO.

M4305-01-1005BFG6

ORIGINATOR'S REPORT NUMBER(S)

NAMRU-3-TR-11-75

OTHER REPORT NO(S) (Any other numbers that may be assigned this report)

Acc.989

DISTRIBUTION STATEMENT

Distribution of this report is unlimited

SUPPLEMENTARY NOTES

Published in Am. Rev. Resp. Dis. 109:579-580,1974

SPONSORING MILITARY ACTIVITY

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ABSTRACT

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DD FORM 1 NOV 65 1473 (PAGE 1)

UNCLASSIFIED

Security Classification

14 KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Tuberculous meningitis						
Rifampin concentrations						
Cerebrospinal Fluid						
Patients						
Chemotherapy						