Trimethoprim-Sulphamethoxazole in Enteric Fevers

Z. FARID,* M.D., D.T.M. & H. ; A. HASSAN,|| D.M. ; M. F. A. WAHAB,¶ D.M., D.T.M. & H. ; W. R. SANBORN,† M.SC.
D. C. KENT,‡ M.D. ; A. YASSA,§ ; S. E. HATHOUT,** D.M.

British Medical Journal, 1970, 3, 323-324

Summary: Clinical improvement was rapid in all 13 patients with enteric fever and one with Brucella abortus infection treated with trimethoprim-sulphamethoxazole. There were no side-effects of the treatment and it was found easy to administer to toxic and delirious patients.

Trimethoprim-sulphamethoxazole has been successfully used in the treatment of urinary tract infections (Gruneberg and Kolbe, 1969; Reeves *et al*, 1969), gonorrhoea (*British Medical Journal*, 1969), chronic bronchitis (Hughes, 1969), and Gram-negative septicaemia (Noall *et al.*, 1962). Except for one report from Nigeria by Akinkugbe *et al.* (1968) there have been few well-controlled studies on its use in typhoid fevers. We report here on use of the substance in the treatment of 13 patients with enteric fever and one patient with proved *Brucella abortus* septicaemia.

Materials and Methods

The study was conducted during the last three weeks of February 1970. Of the 14 patients included in the study 7 were males and 7 were females; all lived in Cairo. Their ages ranged from 5 to 16 years. All were very sick and toxic before treatment was started, and all had a temperature of 104°F. (40°C.) or above. In every case examination revealed a thickly-coated white tongue, abdominal distension with tympanitis, and a soft tender palpable spleen.

Blood cultures were performed on double-phase Castaneda bottles (Castaneda, 1947) and on ox bile (Kaye *et al.*, 1966), and urine and stool cultures were made on selective media on selenite broth. Three blood specimens, one urine, and one stool specimen were obtained before starting treatment. Subsequentiy, blood, urine, and stool cultures were performed twice weekly during treatment and for three weeks after treatment.

* Head of Department.
† Head of Bacteriology Department.
‡ Director, U.S. Naval Medical Research Unit No. 3.
§ Senior Technician.
Tropical Medicine Department, U.S. Naval Medical Research Unit No. 3, Cairo, Egypt.

|| Director, Abbassia Fever Hospital.
¶ Senior Physician.
**Assistant Director, Abbassia Fever Hospital.
Abbassia Fever Hospital, Ministry of Public Health, Cairo, Egypt.

Treatment was started 24 hours after admission to hospital. Patients 12 years of age and over were given two tablets of trimethoprim-sulphamethoxazole (80 mg. of trimethoprim and 400 mg. of sulphamethoxazole) every 12 hours, and those under 12 years of age one tablet every 12 hours. Treatment was continued for 10 days for all patients.

Results

The clinical, serological, and bacteriological data are given in the Table. Twelve patients had positive blood cultures; eight had *salmonella typhi* infection, two a *Salm. paratyphi B*, one a *Salm. paratyphi C*, and one a *Br. abortus* infection. The two remaining patients had rising Widal titres with positive stool cultures—one for *Salm. paratyphi B* and one for *Salm. typhi*.

Clinical improvement was rapid in all patients, and within 36 to 48 hours abdominal distension, tympanitis, and toxicity had practically disappeared. All the patients became afebrile within two to six days of starting treatment. None complained of nausea or vomiting, and no other side-effects were noted.

Comment

Akinkugbe *et al.* (1968) treated six patients with *Salm. typhi* infection with trimethoprim-sulphamethoxazole, and considered their results to be superior to those produced by chloramphenicol. The present study confirms the remarkable effectiveness of trimethoprim-sulphamethoxazole in the treatment not only of *Salm. typhi* but also of *Salm. paratyphi B* and *C* infections and in one patient with *Br. abortus* infection. The response to treatment in all 14 patients was rapid—toxicity was relieved within 48 hours and all the patients became afebrile within six days.

Though blood, urine, and stool cultures were performed twice weekly during treatment and for at least three weeks after the end of treatment, no positive cultures were obtained once treatment was started, and none of the patients relapsed clinically. The patient with proved *Br. abortus* infection was followed up for two months and had not relapsed at the time of writing.

No side-effects to the drug treatment were noted and the

Clinical, Serological, and Bacteriological Data on 14 Patients Treated with Trimethoprim-Sulphamethoxazole

Case No.	Sex	Age (Years)	Days Febrile Before Treatment	Highest Widal Titre	Blood Culture	Stool Culture	No. of Days to Become Afebrile	Comments
1	F.	11	6	N	*Br. abortus*	N	4	Brucella aggl. 1/640
2	M.	12	7	1/640	*Salm. typhi*	N	4	
3	F.	15	4	1/640	*Salm. typhi*	N	2	
4	M.	5	9	1/640	*Salm. typhi*	N	5	
5	F.	12	6	1/640	*Salm. paratyphi B*	N	4	Delirious, very toxic
6	F.	11	6	1/640	*Salm. typhi*	N	5	
7	F.	5	7	1/640	*Salm. typhi*	N	5	
8	M.	13	7	1/640	*Salm. typhi*	N	3	
9	F.	6	7	1/640	*Salm. paratyphi B*	N	6	Delirious, very toxic
10	M.	10	6	1/640*	N	*Salm. paratyphi B*	2	
11	M.	16	7	1/640	*Salm. typhi*	N	2	
12	M.	13	10	1/640	*Salm. typhi*	N	2	Delirious, very toxic
13	F.	10	5	1/640*	N	*Salm. typhi*	2	
14	M.	11	3	1/640	*Salm. paratyphi C*	N	3	

*Admission Widal was negative. Cases 5, 9, and 10 were siblings. N = Negative.

ease of its administration made it very acceptable to the delirious and toxic patients.

We are grateful to Dr. A. Sallam, Minister of Health, for allowing us to carry out this study. We are indebted to the Roche Company and to Burroughs Wellcome and Co. for free supplies of Bactrim and Septrin used in the clinical trial.

This research forms part of research project No. MR.005.20.01-0094A of the Bureau of Medicine and Surgery, Navy Department, Washington, D.C., U.S.A.

Addendum

Two additional patients were treated with trimethoprim-sulphamethoxazole (two tablets every 12 hours for 10 days). The first patient was a young man aged 15 who was admitted to hospital acutely sick, with a temperature of 104°F. (40°C.); his blood culture was positive for *Salm. paratyphi A*. The second patient was a woman aged 16 years who gave a history of recurrent febrile attacks of one year's duration. Her brucella agglutination titre was 1/1640 and her blood culture was positive for *Brucella melitensis*. Both patients responded promptly to treatment, were asymptomatic and afebrile within five days of starting therapy, and have remained well up to the time of writing, three weeks after the end of treatment.

REFERENCES

Akinkugbe, O. O., Lewis, E. A., Montefiore, D., and Okubadejo, O. A. (1968). *British Medical Journal*, **3**, 721.
British Medical Journal, 1969, **3**, 578.
Castaneda, M. R. (1947). *Proceedings of the Society of Experimental Biology and Medicine*, **64**, 114.
Grüneberg, R. N., and Kolbe, R. (1969). *British Medical Journal*, **1**, 545.
Hughes, D. T. D. (1969). *British Medical Journal*, **4**, 470.
Kaye, D., Palmieri, M., Eyckmans, L., Rocha, H., and Hook, E. W. (1966). *American Journal of Clinical Pathology*, **46**, 408.
Noall, E. W. P., Sewards, H. F. G., and Waterworth, P. M. (1962). *British Medical Journal*, **2**, 1101.
Reeves, D. S., Faiers, M. C., Pursell, R. E., and Brumfitt, W. (1969). *British Medical Journal*, **1**, 541.

Preliminary Communications

Simple Method for Determining Isoniazid Acetylator Phenotype

British Medical Journal, 1970, **3**, 324-325

Summary: Methods have been developed for estimating acetylisoniazid and isoniazid in urine without a spectrophotometer. In experiments with volunteers the ratio of acetylisoniazid to isoniazid in urine samples collected the morning after three spaced oral doses each of 100 mg. was bimodally distributed.

INTRODUCTION

The rate at which administered isoniazid disappears from the circulation is genetically determined. The two major phenotypes, rapid and slow inactivators (Hughes *et al.*, 1954; Harris *et al.*, 1958), differ in the rate of hepatic acetylation of the drug (Evans and White, 1964; Goedde *et al.*, 1964). The acetylator phenotype does not affect the outcome of tuberculosis treatment with standard dosage regimens (Evans *et al.*, 1960). Rapid inactivators, however, respond less well to a once-weekly dosage regimen (Menon, 1968), and develop isoniazid resistance sooner, than slow inactivators (Tripathy, 1968). Thus there is increasing interest in determining acetylator phenotype. Some new methods have been proposed (Evans, 1969; Tiitinen, 1969) but simpler techniques suitable for routine screening in developing countries are still required.

The ratio of acetylisoniazid to isoniazid (A:I) in the urine after an oral dose of the drug distinguishes rapid from slow inactivators (Peters *et al.*, 1965). A method is here described for estimating this ratio by simple colour tests. The ratio is bimodally distributed in volunteers receiving isoniazid daily. On the basis of these results a simple method for acetylator phenotyping is proposed.

SUBJECTS AND METHODS

Healthy adult volunteers swallowed 100 mg. of isoniazid three times daily after meals for five days. On the second and following days morning urine was collected and analysed.

Analysis for Acetylisoniazid.—The method used was adapted from that of Venkataraman *et al.* (1968). Urine (4 drops) was placed in a test-tube, internal diameter 0·8 cm., and treated with 10% w/w potassium cyanide (4 drops), followed after mixing by 10% w/w chloramine T (9 drops). After one minute the contents were again mixed. One minute later acetone (0·2 ml.) was added. After remixing, the concentration of acetylisoniazid was determined by comparison with standards of acetylisoniazid in normal drug-free urine (320, 160, 80, 40, 20, and 0 μg./ml.) which were treated in the same way. To each sample was allotted a nominal acetylisoniazid concentration equal to that of the standard which it matched or immediately exceeded in depth of colour. Thus a sample intermediate in colour between the 80 and 160 μg./ml. standards was allotted a nominal concentration of 80 μg./ml. The actual colour varied between pink and orange, depending on the concentration of the urine; comparison was made with respect to depth of colour rather than hue.

Analysis for Free Isoniazid.—The method used was adapted from that of Dymond and Russell (1970) for determining isoniazid in blood. The sample (20 drops) was treated with 50% (w/w) dipotassium hydrogen phosphate (10 drops) followed by a solution (1·25%) of 2,4,6-trinitrobenzene-sulphonic acid in methyl isobutyl ketone (0·25 ml.) The contents were mixed *vigorously* for 10 seconds, allowed to stand for two minutes, mixed again *vigorously* for 20 seconds, and briefly centrifuged. The concentration of isoniazid in the sample was determined by comparison with standards of isoniazid in normal drug-free urine (64, 32, 16, 8, 4, 2, and 0 μg./ml.), which were treated in the same way. The orange colour due to isoniazid was in the upper phase; the lower phase was ignored. To each sample a nominal isoniazid concentration was allotted in the same way as for acetylisoniazid.

Notes on the Methods.—Aqueous reagents were measured from Pasteur pipettes held at an angle of approximately 45°. One pipette was used for all urine samples and standards and one for each aqueous reagent. For organic liquids a graduated pipette was used. Mixing was done with a Vortex Genie mixer (Scientific Industries, Springfield, Mass., U.S.A.). For each sample a "nominal A:I ratio" was calculated from the nominal concentrations.