# Trimethoprim and Sulphamethoxazole in Typhoid

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**Summary: Six patients with proved typhoid fever were treated with a combination of trimethoprim and sulphamethoxazole; four others were treated with chloramphenicol. All ten patients made an uneventful recovery.**

**Though the numbers are small it appears that the patients treated with the combined drugs did just as well as those treated with chloramphenicol, and fever seemed to subside quicker with the combined drugs.**

**Trimethoprim and sulphamethoxazole have low toxicities, so further studies of their use in the treatment of typhoid are justified.**

## Introduction

Over the past few years evidence has steadily been accumulating regarding the efficacy of trimethoprim (2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine) used in combination with sulphonamides in various bacterial infections.

Trimethoprim inhibits dihydrofolic acid reductase, thus blocking the metabolic pathway leading to purine (and hence deoxyribonucleic acid) synthesis. The prior step in the same metabolic pathway, the conversion of para-aminobenzoic acid to dihydrofolic acid, is blocked by the sulphonamides. The two drugs in combination show marked synergism in their antibacterial activity (Bushby and Hitchings, 1968).

There have been a number of recent reports of the therapeutic use of trimethoprim in combination with a sulphonamide: proteus septicaemia (Noall *et al.*, 1962; Cooper and Wald, 1964), urinary tract infections (Schneider *et al.*, 1965), gonorrhoea (Csonka and Knight, 1967), and chest infections (Drew *et al.*, 1967; Fowle *et al.*, 1967) are among the conditions in which satisfactory results have been reported.

The fact that trimethoprim appears to be concentrated in the tissues, and the fact that there is a very marked synergistic action, in vitro, of trimethoprim and a sulphonamide on *Salmonella typhi* (Bushby and Hitchings, 1968) led us to investigate its therapeutic use in typhoid infections.

We report here our findings in six patients with typhoid fever treated with trimethoprim and sulphamethoxazole (Gantanol) combination. The findings in four patients treated with chloramphenicol are also reported for comparison.

## Materials and Methods

*Patients.*—The patients included in the trial have been drawn from a large group presenting with pyrexias of undetermined origin and features suggestive of typhoid fever. Patients were excluded from the study only if they were *in extremis*, had the complication of haemorrhage or perforation, were pregnant, or if subsequent bacteriological tests failed to confirm the diagnosis of typhoid fever by isolation of *Salm. typhi*. From the day of admission observations—recorded on a special card—were made for temperature, pulse, spleen size, and other relevant features. Blood, stool, and urine samples were taken for bacteriological examination, and tests were repeated on alternate days. Other investigations included white cell count, erythrocyte sedimentation rate, packed cell volume, and chest *x*-ray examination. Patients eligible for inclusion in the trial were randomly allocated either to the chloramphenicol group or to the trimethoprim and sulphamethoxazole group.

*Drugs.*—Patients on chloramphenicol received 2 g. daily in divided doses for 14 days. Patients on trimethoprim and sulphamethoxazole received two tablets six-hourly for 14 days. Each tablet contained 80 mg. of trimethoprim and 400 mg. of sulphamethoxazole. For the purposes of this preliminary study drugs were not given "blind," since it was felt to be important to know immediately if it seemed that a patient was not doing well while on treatment with a new drug.

*Bacteriology.*—Stools and urine samples were inoculated on to bismuth sulphite agar (Oxoid Single Pack) freshly made plates; deoxycholate citrate agar; MacConkey agar; and into Selenite F broth. Subcultures were made from the Selenite F broth and bismuth media on to MacConkey and deoxycholate citrate agar plates for further tests and identification of colonies. For blood cultures two 120-ml. "medical flat" bottles containing the following media were inoculated. One bottle contained broth plus 0.5% sodium taurocholate, with nutrient agar slope, and the other contained thioglycollate broth (Cruickshank, 1965) with methylene blue instead of resazurin indicator.

In-vitro sensitivity tests were carried out with Oxoid Multodiscs in the case of antibiotics, and separate discs containing sulphonamides, trimethoprim, and a sulphonamide-trimethoprim combination (trimethoprim 2.5 μg., sulphamethoxazole 50 μg.; chloramphenicol 10 μg. per disc). Tests were done with Oxoid sensitivity agar.

## Results

The age, sex, and presenting clinical features of the patients are set out in the Table. All patients had comparably severe illnesses on admission.

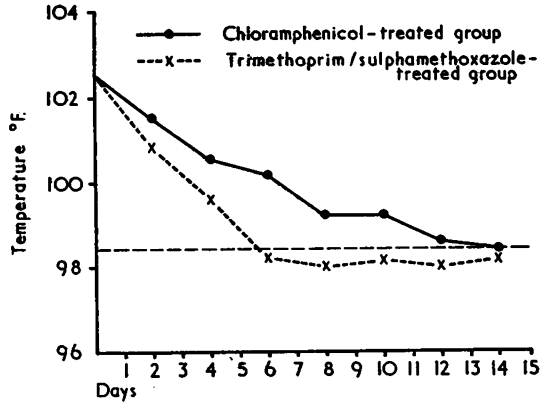
*Progress.*—In the six patients treated with trimethoprim the temperature fell to normal by the 6th, 8th, 4th, 8th, 4th, and 6th days respectively (mean duration of fever, six days). In the four patients treated with chloramphenicol fever subsided by the 14th, 12th, 10th, and 5th days respectively (mean duration of fever 10 days). The Chart shows the means of the daily maximum temperatures for the patients in each treatment group, and illustrates the more rapid defervescence among those treated with trimethoprim and sulphamethoxazole. Headache was a presenting feature in three of the six patients in the trimethoprim group, and in these it lasted an average of 3.5 days. Two of the patients in the chloramphenicol group complained of headache, and in both it lasted one day only. Other symptoms, such as abdominal pain, vomiting, diarrhoea, cough,

*Findings at Time of Admission*

| Case No. | Age | Sex | Drug | Temp. °F. | Temp. °C. | Headache | Backache | Abdominal Pain | Diarrhoea | Vomiting | Cough | Mental Changes | Chest Signs | Meningism | Dehydration | Enlarged Spleen | W.B.C. | *Salm. typhi* in Blood | *Salm. typhi* in Stool |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 30 | M | C | 105 | 40·6 | − | − | − | + | + | − | + | − | + | + | − | 5,500 | + | − |
| 2 | 24 | M | C | 102 | 38·9 | − | − | + | + | + | − | − | − | − | + | + | 5,600 | + | − |
| 3 | 14 | F | C | 104 | 40·0 | + | − | − | + | − | + | + | − | + | + | + | 5,700 | + | − |
| 4 | 11 | F | C | 102·5 | 39·2 | + | − | + | + | + | − | + | − | − | − | + | 3,150 | + | − |
| 5 | 17 | F | TS | 105 | 40·6 | + | − | − | + | − | + | + | + | − | − | + | 6,600 | + | − |
| 6* | 23 | M | TS | 103 | 39·4 | + | + | + | − | − | + | − | − | − | − | − | 3,000 | − | + |
| 7 | 25 | M | TS | 99·7 | 37·6 | + | + | + | − | − | − | − | − | + | − | − | 2,600 | + | − |
| 8 | 12 | F | TS | 100 | 37·8 | − | + | + | + | − | − | − | − | − | − | − | 4,700 | + | − |
| 9 | 12 | M | TS | 104 | 40·0 | − | − | + | + | + | + | − | − | − | − | − | 2,500 | + | − |
| 10 | 24 | M | TS | 102 | 38·9 | − | − | − | + | − | − | − | − | − | − | − | 4,700 | + | − |

C = Chloramphenicol. TS = Trimethoprim and sulphamethoxazole.
* Patient complained of illness for three to four weeks before attending hospital

and mental changes occurred in one or other of the patients; all resolved within a few days, irrespective of the drug treatment given. There were no complications, and all patients made a very satisfactory and uneventful recovery.




Mean daily maximum temperature.

*Laboratory Findings.*—On admission white cell counts were generally low, between 2,500 and 6,600/cu. mm. These values did not materially alter in any patients during the period of observation. E.S.R.s were raised on admission and fell slowly as the patients recovered. Chest *x*-ray examination showed that one patient in the chloramphenicol group had a mild pneumonitis of the left lower lobe: this resolved uneventfully during treatment. *Salm. typhi* was isolated on admission from the blood of all patients except one in the trimethoprim group in whom the organism was isolated from the stool. *Salm. typhi* was not isolated from any urine sample. In one patient in the trimethoprim group blood cultures were positive up to the sixth day of treatment, and thereafter became sterile. In all other patients *Salm. typhi* was isolated on the day of admission only; except in the case mentioned above, all stool samples proved negative for *Salm. typhi*.

Though the duration of illness before admission could not be exactly determined, all patients except the one with a positive stool culture complained of feeling definitely unwell for less than one week. The one patient with a positive stool culture on admission gave a three- to four-week history of illness. It would seem, therefore, that the absence of *Salm. typhi* from the stools of all except the one patient reflects the early stage of their illness, during which faecal excretion of the organism is rare. *Salm. typhi* was isolated from the stool of the one faecal excreter on the day of admission only; subsequent stool samples were all negative. Long-term follow-up was not undertaken during this preliminary study, so no information is available regarding the possible later development of a carrier state in any of the patients.

All strains of *Salm. typhi* showed in-vitro sensitivity to chloramphenicol, sulphamethoxazole, and trimethoprim, with evidence of synergistic activity of the trimethoprim and sulphamethoxazole combination (Darrell *et al.*, 1968).

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REFERENCES

Bushby, S. R. M., and Hitchings, G. H. (1968). *Brit. J. Pharmacol.*, 33, 72.
Cooper, R. G., and Wald, M. (1964). *Med. J. Aust.*, 2, 93.
Cruickshank, R. (1965). *Medical Microbiology*, 11th ed., p. 756. London.
Csonka, G. W., and Knight, G. J. (1967). *Brit. J. vener. Dis.*, 43, 161.
Darrell, J. H., Garrod, L. P., and Waterworth, P. M. (1968). *J. clin. Path.*, 21, 202.
Drew, C. D. M., Hughes, D. T. D., and Jenkins, G. C. (1967). *Proceedings of V International Congress on Chemotherapy*, Suppl., p. 107.
Fowle, A. S. E., Drew, C. D. M., Hughes, D. T. D., and Cassell, M. A. (1967). *Proceedings of V International Congress on Chemotherapy*, 1, 293.
Noall, E. W. P., Sewards, H. F. G., and Waterworth, P. M. (1962). *Brit. med. J.*, 2, 1101.
Schneider, M., Schwarzenberg, L., Cattan, A., Schlumberger, J. R., Amiel, J. L., and Mathé, G. (1965). *Presse méd.*, 73, 893.

# *Medical Memoranda*

## Paraquat Poisoning in a Pregnant Woman

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At least eight deaths are known to have resulted from paraquat poisoning. Seven subjects died after oral ingestion of the liquid suspension and one after subcutaneous administration of 1 ml. of a 20% suspension. Survival has been reported after the ingestion of granules in one case. All eight patients appear to have passed through a phase of renal and hepatic insufficiency before expiring from respiratory failure associated with a specific type of pulmonary proliferative lesion (Bullivant, 1966; *Brit. med. J.*, 1967; Almog and Tal, 1967; Campbell, 1968; Duffy and O'Sullivan, 1968; Oreopoulos *et al.*, 1968). We wish to report the case of a 27-year-old pregnant woman who died 20 days after ingestion of paraquat. The antimetabolite fluorouracil was used in an attempt to depress the proliferative lesion, but without success.

CASE REPORT

On 4 March 1968 a married woman accidentally swallowed a teaspoonful of paraquat mixture from an old wine bottle. Pharyngitis and oesophagitis developed, and she was treated with antibiotics and corticosteroids. On 14 March she was transferred to a Dublin hospital, where initial studies showed renal- and hepatic-cell damage without evidence of respiratory involvement, as follows: haemoglobin 90%; serum sodium 163, potassium 4.8, chlorides 119 mEq/l.; blood urea 490 mg./100 ml.; urine volume at this stage exceeded 1 litre a day; the electrocardiogram was normal. Serum lactate dehydrogenase 700 units, alanine aminotransferase 80 units, aspartate aminotransferase 83 units, alkaline phosphatase 26 K.A. units, and serum bilirubin 1.1 mg./100 ml. indicated low-grade liver-cell damage. Over the next seven days the renal function improved, as shown by a fall in blood urea to 103 mg./100 ml. and a return of serum electrolytes to normal. On 19 March, some 14 days after the ingestion of paraquat, the patient complained of dyspnoea, and a repeat chest *x*-ray examination showed a diffuse miliary mottling pattern. In spite of hydro-