Trimethoprim-Sulphamethoxazole (Bactrim) in the Treatment of Typhoid Fever


SUMMARY

Ninety-two patients with proven typhoid fever were treated with trimethoprim-sulphamethoxazole. There were 3 failures and the side-effects noted were minimal. The average time taken for the temperature to return to normal was 4.1 days and there were no relapses or persistent carriers detected after 3 weeks' treatment.


Chloramphenicol has been the cornerstone of treatment for typhoid fever since its accidental discovery as an effective bacteriostatic agent by Smadel et al. in 1948. His findings were confirmed by many workers. Chloramphenicol has been shown to have a number of disadvantages, including a high relapse rate, a minimal effect on the carrier state, and the serious possibilities of bone marrow depression. Furthermore, Chakraborty showed that the period of time taken for defervescence to occur following the administration of chloramphenicol appeared to be increasing progressively each year. Subsequent observations have tended to confirm this. Because of these disadvantages many other drugs have been assessed in typhoid fever.

Of the drugs which promised to be of value from in vitro testing, ampicillin proved generally disappointing in vivo, especially in the larger trials, although in a number of the smaller series the authors gave more encouraging reports. Furfazolidone has been extensively employed in India, but has not been shown to be superior to chloramphenicol, although it is a useful additional antibiotic in the treatment of typhoid fever.

Numerous other drugs have also been investigated, including cephaloridine, chlorotetracycline and chloramphenicol, penicillin in large doses with probenecid, and tetracycline, all of which have proved clinically inferior to chloramphenicol.

The introduction of trimethoprim (a powerful inhibitor of the enzyme which reduces dihydrofolate acid to tetrahydrofolic acid) in combination with a medium-long-acting sulphonamide, sulphamethoxazole, has resulted in a potent bactericidal agent. Preliminary reports of in vitro testing against Salmonella typhi were encouraging and small pilot studies supported these findings.

On the basis of these findings it was decided in October 1969 to carry out a trial with trimethoprim-sulphamethoxazole in a larger number of patients than had been reported up to that time. However, during the course of the trial, a large series of cases was reported by Kamat with findings similar to our own.

Methods

In order to avoid controversy over the diagnosis, only patients who had Salmonella typhi isolated on blood culture were included in the series, and one carrier found on routine urine testing in another hospital (case 3, see below).

All patients suspected of having typhoid fever on admission were started on trimethoprim-sulphamethoxazole after a blood culture had been done. Those patients who were bacteriologically negative on blood culture were discarded. This left a total of 92 patients in the series.

All patients were treated in the Salisbury Municipal Infectious Diseases Hospitals. A large number of the African patients were first seen at Harari Hospital and once the diagnosis of typhoid fever had been established, they were transferred to the isolation hospital. Any patients receiving antibiotic therapy other than trimethoprim-sulphamethoxazole before a positive diagnosis was made were excluded.

As the effectiveness of trimethoprim-sulphamethoxazole had, at that time, been proved in only a small number of cases, it was considered unreasonable to carry out a double-blind clinical trial. In the early stages of the series some seriously ill patients, especially those with nausea and vomiting, were treated with intramuscular chloramphenicol. These patients were excluded, but, as the series progressed and more confidence was gained with trimethoprim-sulphamethoxazole, this type of seriously ill patient was included where possible.

In the first 59 patients the following tests were carried out at the commencement of treatment: haemoglobin, white cell count, erythrocyte sedimentation rate, blood urea, cholesterol, bilirubin, SGOT and SGPT, while blood, urine and faeces culture for Salmonella typhi were taken before starting therapy. The tests for haemoglobin, blood urea, SGPT and SGOT were repeated at the end of 3 weeks' treatment.

All patients were bacteriologically assessed at the end of treatment by examinations of the urine and stool for Salmonella typhi on 3 consecutive days, beginning a minimum of 48 hours after the last treatment. In the early stages of the trial, trimethoprim-sulphamethoxazole was supplied in drapsule form and later as tablets, each containing 80 mg trimethoprim and 400 mg sulphamethoxazole. Paediatric tablets contained a quarter of the above...
dose, namely 20 mg trimethoprim and 100 mg sulphamethoxazole. This variation in presentation led to some difficulties in identification for the staff, which is reported more fully later.

Dosage

Severely ill patients were initially given 2 tablets (or capsules) 3 times daily until a clinical improvement was noted, this being on an average after 4 days. Otherwise the dosage was 2 tablets twice daily for adults. Children between 3 - 8 years were given 1 tablet twice daily, and in the under-3 age group, 2 paediatric tablets twice daily. All patients were treated for a total of 21 days and were observed for at least 3 weeks following defervescence at the Infectious Diseases Hospital.

Results

Of the 92 patients admitted to the series, 53 were male and 39 female, and their ages ranged between 2 - 70 years with a mean average of 15 years. Eighty-eight were indigenous Africans, 3 were Europeans and 1 was of mixed race. Eleven patients were afebrile at the commencement of therapy. We are satisfied that these were true cases of typhoid fever and not carriers, as they all had symptoms consistent with an acute Salmonella infection and 7 patients had been pyrexial before starting treatment.

The time taken for the remaining 81 patients to defervescence varied between 1 - 9 days with an average of 4.1 days. There were 3 failures. In 1 patient we failed to eliminate the organism (case 2), and the other 2 died 3 days after starting treatment, with acute gastro-intestinal bleeding.

For the first 17 cases, sensitivity discs were not available, but in the remainder we were able to carry out in vitro sensitivities. Two of these cases showed in vitro resistance, one of whom responded well clinically to trimethoprim-sulphamethoxazole with no evidence of a carrier status, and the other was one of our abovementioned failures.

Side-Effects

Apart from three cases, all children, with temporary depression of the neutrophil series, showed no serious side-effects on the recommended regimen. Nausea and vomiting were seen in 1 patient and dizziness in another. In no case was it necessary to discontinue treatment because of the side-effects. However, 1 patient was inadvertently given 4 times the recommended dosage; 16 tablets each containing 80 mg of trimethoprim and 400 mg of sulphamethoxazole for 7 days. On the 8th day, the patient was markedly icteric with minimal elevation of the SGOT and SGPT. Despite this minor setback, she made an uneventful recovery and was well on discharge 4 weeks later. Subsequent follow-up with liver function tests 4 months later were perfectly normal.

Case 2

A 19-year-old woman in the 36th week of gestation was admitted to Harari Central Hospital with a POU. She was treated empirically with trimethoprim-sulphamethoxazole but unfortunately treatment was discontinued 5 days later, as blood cultures were negative. She was discharged but admitted a week later to the Municipal Infectious Diseases Hospital in a very toxic state. Trimethoprim-sulphamethoxazole was recommenced with 2 tablets twice a day. Her temperature initially responded, but a week later she again had a high temperature with urinary symptoms and pyuria. At this point an E. coli resistant to trimethoprim-sulphamethoxazole, ampicillin and chloramphenicol was isolated, and the patient was given a course of gentomycin 40 mg intramuscularly every 6 hours. Her pyrexia subsided but in accordance with our practice the trimethoprim-sulphamethoxazole was continued for a total of 21 days. She delivered normally the following week a 2.04 kg infant who was apparently normal, and whose cord blood culture was negative for Salmonella typhi. At no time did the child show any evidence of typhoid infection. The patient, however, had a puerperal pyrexia lasting 10 days. Trimethoprim-sulphamethoxazole was stopped and a variety of combined antibiotic therapies tried. Administration of trimethoprim-sulphamethoxazole was re-instituted on the isolation of Salmonella typhi from the urine at the end of the 10th day, but the pyrexia failed to respond and subsequent determination of the sensitivity of the organism indicated resistance in vitro to trimethoprim-sulphamethoxazole, among other drugs. The patient was finally successfully treated with a combination of iodochlorhydroxyquinoline, chloramphenicol and cloxacillin.

Case 3

A 32-year-old woman of mixed race was transferred to the Municipal Infectious Diseases Hospital, subsequent to a hysterectomy operation, because Salmonella typhi was cultured from a routine urine sample prior to operation. Further urinalysis confirmed the presence of Salmonella typhi in 1 out of 6 subsequent midstream specimens of urine. The patient was symptom-free.

A course of 21 days' trimethoprim-sulphamethoxazole was exhibited with apparently successful elimination of the organism from the urine. Spot checks of the urine at 3, 6 and 9 months after treatment failed to isolate evidence of Salmonella typhi excretion.
DISCUSSION

We are satisfied from the results of the above series that trimethoprim-sulphamethoxazole is an effective treatment for typhoid fever. The average time taken for the temperature to return to normal in 81 patients was 4.1 days. This compares favourably with the 6 patients reported by Akinkugbe et al., where the time taken for the temperature to settle was 6 days, and 6.7 days in 13 patients reported by Kamat et al. The largest series reported so far is by Kamat, who treated 110 patients with trimethoprim-sulphamethoxazole and where the temperature on average returned to normal in 4 days.

The so-called 'toxic' crisis commented upon by Kamat in his group of patients treated with chloramphenicol but not with trimethoprim-sulphamethoxazole, is a clinical feature not found in Rhodesia. Contrary to Kamat's findings of no failures with trimethoprim-sulphamethoxazole, we had 3 failures. In 1 patient (case 2), the organism was not eliminated, and treatment had to be changed to a combination of other antibiotics, while 2 patients died from severe sudden gastro-intestinal tract bleeding 3 days after starting treatment.

One of the most important features elicited in this series, apart from therapeutic effectiveness, was the small number of side-effects on the recommended dosage. The first 59 patients (64%) had repeat liver function tests, blood urea, and haemoglobin estimations carried out after 3 weeks' treatment, and no abnormalities were detected, except where the patient inadvertently received 4 times the recommended dosage and developed jaundice, but on follow-up made an uneventful recovery.

Five patients were pregnant during therapy and of these, 3 delivered full-term normal babies. One patient delivered a normal premature baby at 36 weeks' gestation and in the other, abortion occurred at 16 weeks. Little conclusion can be drawn from the latter case, as abortion is not uncommon in typhoid fever during pregnancy.

Two patients were admitted with evidence of hepatocellular damage. Both cases were treated with trimethoprim-sulphamethoxazole and no adverse effects were noted, both patients making a full recovery after the correction of their hepatic failure by standard methods of therapy.

We have found it is important to use an adequate therapeutic dose, as was exemplified by a proven case of typhoid fever in a 4-year-old child who was not included in this series. He was given a quarter of the recommended effective dosage and although he was discharged clinically well, and with a negative stool culture, he was readmitted 3 weeks later with a positive blood culture. This subtherapeutic dosage has been commented upon by other workers.

Although trimethoprim-sulphamethoxazole was very effective during the acute stage of typhoid fever in this series, the effect on the carrier state is just as important an aspect of 'total' treatment. We were concerned to exclude as far as possible the return to the community of typhoid carriers. Post-treatment assessment failed to demonstrate a carrier status even in the case who failed to respond to trimethoprim-sulphamethoxazole, but the problems of long-term follow-up in a large indigenous population are considerable.

The carrier state in Rhodesian Africans would appear to be very low, and this may well be related to the observation that gall bladder disease is rare in the indigenous African. However, renal disease is common, and one would have expected to have found more urinary carriers than is the case. During the period this series was carried out, 3,500 food handlers were screened for the carrier state by the Salisbury City Health Department, but none were found.

Preliminary results with trimethoprim-sulphamethoxazole in the carrier state have been encouraging especially as most antibiotics to date have been of limited value in eradicating the persistent cases. Case 3 is considered a successfully treated urinary carrier, who has remained bacteriologically negative for Salmonella typhi in the urine for a year.

In summary, this series confirms the favourable reports of trimethoprim-sulphamethoxazole in the treatment of enteric fever for the following reasons:

1. The standard treatment, chloramphenicol, regularly produces clinical improvement, but the relapse rate is not uncommon. By contrast, in this series, only 1 relapse was recorded and this was probably related to interrupted therapy.

2. The post-treatment carrier rate is not apparently altered by chloramphenicol treatment and the mortality not eliminated. However, recent studies suggest that both of these factors may be improved by trimethoprim-sulphamethoxazole. The success in the treatment of the carrier case in this series, and the occurrence of only 2 deaths (2%), compared with a local mortality of 7%, on conventional chloramphenicol treatment alone, appears to support this contention.

3. Several reports indicate that Salmonella typhi is becoming more resistant to chloramphenicol, which, it has been suggested, may be related to its bacteriostatic action. As trimethoprim-sulphamethoxazole is bactericidal, it is considered to be therapeutically superior, especially as Salmonella typhi causes septicaemia.

4. Chloramphenicol has the added risk, albeit small, of severe bone marrow depression. Trimethoprim-sulphamethoxazole has the advantage that few serious side-effects have been reported, and this series has not produced any previously unrecognized side-effect.

The crucial factor in the use of trimethoprim-sulphamethoxazole in the treatment of typhoid fever may be the cost when compared with chloramphenicol or furazolidone. This will be particularly relevant (in developing countries) where the budget for drugs may be limited.

We were not confident that a shorter period of treatment was adequate to eliminate the organism. However, if, as this series seems to indicate, the incidence of carrier status is significantly less, then initial cost is not such an important factor. A limiting factor in the treatment of trimethoprim-sulphamethoxazole is that a parenteral form is as yet not generally available. This is a serious drawback, especially in those patients who have marked gastrointestinal disturbances.
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REFERENCES

Books Received: Boeke Ontvang


