Effect of sulfadoxine on transmission of *Vibrio cholerae* infection among family contacts of cholera patients in Calcutta*

B. C. DEB,[1] P. G. SEN GUPTA,[2] S. P. DE,[3] J. SIL,[3] S. N. SIKDAR,[4] & S. C. PAL [5]

Sulfadoxine, a long-acting sulfonamide, and tetracycline were compared as regards their effectiveness in reducing transmission of cholera infection among the contacts of cholera patients in Calcutta. A total of 109 healthy family contacts of confirmed hospitalized cholera patients were treated with a single oral dose of sulfadoxine graded according to age. Another similar group of 101 contacts received 6 divided doses of oral tetracycline over a period of 3 days. All these contacts were bacteriologically examined for 15 days. Results showed that tetracycline was effective in significantly reducing the load of cholera infection from the 2nd to 6th day, while sulfadoxine was effective from the 3rd to the 6th day. The advantages and disadvantages of the two drugs as chemoprophylactic agents in cholera are discussed.

Several attempts have been made in the past to control inapparent cholera infection among contacts of cholera patients by using various antibiotics as chemoprophylactic agents. Streptomycin given orally in hourly doses of 1.0 g for 8 consecutive hours eliminated the infection in 96% of known cholera carriers in Hong Kong (*6*). Chloramphenicol has been effectively employed for treating the contacts of cholera patients entering Japan and also Iran when given orally in 500-mg doses every 6 hours for 3 days (*3*). When treated with oral tetracycline in doses of 500 mg twice daily for 3 days, the number of cholera carriers in Calcutta was significantly reduced up to a period of 5 days (*5*). In a similar study conducted in Dacca tetracycline was found to be effective in carriers, but it had to be given for 5 days (*7*). In all the above trials it was necessary to administer the medicament to each patient about 6 to 12 times.

Gangarosa et al. (*3*) tested sulfadoxine, a long-acting sulfonamide, in a single-dose therapy trial, since it had been found effective against *Vibrio cholerae* in *in vitro* sensitivity tests. Earlier, sulfadoxine was found to be effective as a single-dose therapeutic agent against meningococcal meningitis (*5*). However, Gangarosa et al. (*3*) observed that sulfadoxine was less effective than other chemotherapeutic agents and this has been attributed to rapid excretion and poor absorption of the drug in acute cholera patients.

The objective of the present study was to determine the duration of effectiveness, if any, in controlling inapparent cholera infection among contacts of cholera cases, of a single dose of sulfadoxine [a] in comparison with multiple doses of tetracycline. It was presumed that sulfadoxine might be more effective for the treatment of cholera carriers having formed stools.

MATERIALS AND METHODS

As soon as patients with gastroenteritis were admitted to the Infectious Diseases Hospital, Calcutta, their stool samples were collected and

* From the Cholera Research Centre, 3 Kyd Street, Calcutta-700016, India. These studies were carried out under the joint collaboration of the Indian Council of Medical Research, the World Health Organization, and the Health Department, Government of West Bengal.

[1] Assistant Director.

[2] Research Officer.

[3] Senior Research Officer.

[4] Assistant Statistician.

[5] Director.

[a] Sulfadoxine is the International Nonproprietary Name for this compound. In some countries the approved name is sulformethoxine.

examined for the presence of *V. cholerae* by the standard bacteriological technique (*4*). The affected families were visited within 24 hours of the onset of symptoms of the index cases and samples of stools/rectal swabs were collected from all family members. All family contacts were then treated according to one of the schedules described below, and stool samples were tested every day for 15 consecutive days for *V. cholerae*.

The study population was divided into groups who received either sulfadoxine, tetracycline, or multivitamins (placebo). The contacts of the first index case received sulfadoxine, those of the second tetracycline, and those of the third placebo, and then the cycle was repeated maintaining the same sequence. The contacts of the index cases who were subsequently reported to be bacteriologically negative for *V. cholerae* were dropped from the study. In this way, of the 148 families initially investigated, the results were analysed for the contacts in 75 families (50.7%) for which the index cases were bacteriologically confirmed. A total of 322 family contacts, excluding index patients, were studied, 109 in the sulfadoxine group (25 families), 101 in the tetracycline group (25 families), and 112 in the placebo group (25 families). The composition of the groups was very similar as regards age, approximately 14% being aged under 4 years, 18% 5–9 years, 16% 10–14 years, and 52% over 15 years. About half the contacts were male and half female in each treatment group.

The dosage schedules in the different treatment regimens are shown in Table 1. Sulfadoxine was given as a single-dose treatment in graded doses as shown in the table. Tetracycline, on the other hand, had to be given in 6 divided doses, as this dosage schedule was found to be effective in an earlier trial (*5*). Persons in the placebo group also received 6 doses of multivitamins to match the dosage schedule of tetracycline. Infants below 1½ years were not included in the study. Repeated visits were made in order to administer the prescribed doses directly to the persons concerned. Any adverse reactions such as skin rash, fever, or diarrhoea were looked for amongst the study population following medication.

Table 1. Dosage schedule used in the study [a]

Age group (years)	Dose
	sulfadoxine
1½–4	0.5 g once only
5–14	1.0 g once only
> 14	2.0 g once only
	tetracycline
1½–12	0.25 g every 12 h for 3 days
> 12	0.5 g every 12 h for 3 days

[a] Two doses of multivitamins daily for 3 days were administered to the placebo group.

The strains of *V. cholerae* isolated during the study were preserved in soft agar containing 5 μg of chloramphenicol per millilitre to prevent loss of R-factors. These strains were finally tested by Professor O'Grady [a] for drug-sensitivity.

RESULTS

The effects of treatment of the contacts on vibrio positivity on different days of follow-up is shown in Table 2. Of the expected total of 4830 stool samples from 322 persons in the 15-day period, 4733 were collected, giving an overall coverage of 98.0%. The daily coverage ranged from 96.9% to 100.0%. It may be observed from Table 2 that the infection rate in all three treatment groups was almost the same on the first day before the treatment was started. As in earlier studies, tetracycline reduced the number of infections from the second day. Sulfadoxine, on the other hand, did not reduce the number of infections until the third day. Though Table 2 shows that the number of infections in the sulfadoxine group on day 4 is not statistically different from that in the placebo group, the χ^2 value was not far from significance at the 5% probability level. The level of *V. cholerae* infection remained lower in both groups receiving chemotherapy until the sixth day; subsequently no significant difference in infection between these two groups and the placebo group was observed.

Table 3 shows the number of carriers detected during the 15-day follow-up, by age group. A total of 108 contact carriers (33.6%) were detected in the three groups, of whom 19 were found to excrete *V. cholerae* only once on the first day before the treatment was started. In addition to these 19 carriers, there was another group of 13 carriers who, after being positive for *V. cholerae* on the first day, were also found to excrete the organism during the later part of the study, in spite of receiving treatment.

[a] Department of Bacteriology, St Bartholomew's Hospital, London, England.

Table 2. Isolation of *Vibrio cholerae* from cholera contacts, by treatment group and day of follow-up

Day of follow-up	Treatment groups						Sampling coverage (%)
	Sulfadoxine		Tetracycline		Placebo		
	No. sampled	No. found *V. cholerae* positive	No. sampled	No. found *V. cholerae* positive	No. sampled	No. found *V. cholerae* positive	
1	109	11	101	10	112	11	100.0
2	109	7	101	2[a]	112	10	100.0
3	108	3[a]	100	1[a]	112	11	99.4
4	107	3	101	1[a]	111	10	99.1
5	104	1[a]	99	2[a]	111	10	97.5
6	106	2[a]	98	2[a]	110	9	97.5
7	107	3	100	3	109	5	98.1
8	106	1	101	2	106	3	97.2
9	107	2	100	1	108	3	97.8
10	106	1	98	2	110	5	97.5
11	104	1	98	2	111	4	97.2
12	106	2	100	2	108	3	97.5
13	105	2	98	2	109	5	96.9
14	107	1	98	3	108	1	97.2
15	102	1	101	4	109	1	96.9

[a] Statistically significant difference with placebo group ($P < 0.05$).

Table 3. Number of carriers detected in the 3 treatment groups by age

Age group (years)	Sulfadoxine			Tetracycline			Placebo			Total		
	No. sampled	No. of carriers detected	%	No. sampled	No. of carriers detected	%	No. sampled	No. of carriers detected	%	No. sampled	No. of carriers detected	%
1½–4	15	1	6.7	17	3	17.6	14	6	42.9	46	10	21.7
5–9	20	5	25.0	18	5	27.8	21	6	28.6	59	16	27.1
10–14	17	4	23.5	15	4	26.7	19	7	36.8	51	15	29.4
> 15	57	11	19.3	51	9	17.6	58	28	48.3	166	48	29.5
All ages	109	21	19.3	101	21	20.8	112	47	42.0	322	89[a]	27.6

[a] This does not include 19 carriers who were detected once only on the first day of the follow-up before any treatment was given. Total no. of carriers = 89 + 19 = 108; male = 53, female = 55.

The table indicates that the maximum effectiveness of both sulfadoxine and tetracycline as compared with placebo, was observed in children below 4 years and adults above 15 years of age. There was no difference in effectiveness between males and females.

Seventeen (22.7%) of the 75 bacteriologically confirmed index cases were found to re-excrete *V. cholerae*, 3 of them repeatedly, during the later part of the follow-up after their return from hospital. All these 75 cases received standard antibiotic treat-

ment in hospital, but no other treatment was given to them after their return home. A similar observation was made during earlier studies (*7*), when 35% of such index cases were found to re-excrete *V. cholerae* after their discharge from hospital.

Most (71.3%) of the carriers excreted vibrios on only one day and the numbers of one-day excretors were similar in the three treatment groups. However, in addition to these one-day excretors 7, 3, and 19 subjects were detected in the sulfadoxine, tetracycline, and placebo groups, respectively, who excreted vibrios on more than one day. These figures indicate the ability of sulfadoxine and tetracycline to control these multiple excretors who may be responsible for spreading the infection to other family contacts. Analysis of the pattern of *V. cholerae* excretion of these 29 multiple-excretors on different days of follow-up in the 3 groups showed that the smallest number (3) of these multiple-excretors occurred in the tetracycline group. None of these 3 carriers were found to excrete *V. cholerae* during the 7-day period following treatment, while 6 of the 7 in the sulfadoxine group, and 17 of the 19 in the placebo group continued to excrete vibrios during that period.

All the strains of *V. cholerae* isolated during the study were *V. cholerae*, biotype *eltor*. Approximately 85% of these strains belonged to the Ogawa serotype. As reported by Professor O'Grady, 248 of the *V. cholerae* strains isolated in the study and tested by him, failed to grow on plates containing ampicillin 2 μg/ml, chloramphenicol 0.5 μg/ml, furazolidone 0.03 μg/ml, sulfadoxine 16 μg/ml, sulfafurazole 4 μg/ml, sulfamethoxazole 2 μg/ml, and tetracycline 2 μg/ml. Two other strains required a concentration of 64 μg/ml of sulfadoxine to inhibit their growth. The results did not show any indication of the emergence of resistant strains when sulfadoxine was used a single dose.

The numbers of subjects who showed certain adverse reactions following medication are shown in Table 4. During the period from day 2 to day 6 when the two chemotherapeutic agents were effective, none of the treated subjects presented any skin rash, and there was little difference in the incidence of fever and diarrhoea between the sulfadoxine and placebo groups. A smaller proportion of the patients receiving tetracycline, however, presented fever and diarrhoea.

Table 4. Assessment of reactions in the study population after treatment between 2nd and 6th day of follow-up in the 3 groups [a]

Symptoms looked for	No. of persons having symptoms in groups			Total
	sulfadoxine	tetracycline	placebo	
Skin rash	nil	nil	nil	nil
Fever	5 (4.6)	2 (2.0)	4 (3.6)	11 (3.4)
Diarrhoea	17 (15.6)	10 (9.9)	22 (19.6)	49 (15.2)

[a] Figures in parentheses indicate the percentage of the total in the group.

DISCUSSION

In order to prevent the spread of cholera by healthy carriers it is essential to find an effective chemoprophylactic agent. Ideally such an agent should be effective in a single, safe, and preferably long-acting, oral dose. It should not produce cross-resistance to any other antimicrobial drugs. Tetracycline has been found effective but as it is necessary to administer divided doses for 3–5 days it is not very suitable for use in developing countries. Sulfadoxine was shown in this trial to be effective in a single dose but it did not become effective until the third day. This lag period may be vital in relation to dissemination of cholera infection since a significant proportion of carriers will be actively excreting vibrios during this period.

In this study no significant adverse reactions were seen, but sulfadoxine has been reported to produce skin reactions in some African countries (*1*). As in the earlier trial (*5*) the present study again indicated the limited usefulness of chemoprophylaxis in high cholera endemic areas.

RÉSUMÉ

EFFET DE LA SULFADOXINE SUR LA TRANSMISSION DE L'INFECTION À *VIBRIO CHOLERAE* PARMI LES CONTACTS FAMILIAUX DES CHOLÉRIQUES À CALCUTTA

Un essai de chimioprophylaxie a été entrepris à Calcutta à l'aide de sulfadoxine, qui est un sulfamide retard, et de tétracycline en vue de comparer l'efficacité relative de ces médicaments en ce qui concerne la transmission de l'infection cholérique parmi les contacts des malades. Un total de 109 sujets en bonne santé apparente, contacts familiaux de cholériques hospitalisés, ont été traités avec une dose unique de sulfadoxine par voie buccale. Dans un autre groupe similaire, 101 contacts ont reçu 6 doses fractionnées de tétracycline, par voie buccale, pendant 3 jours. Tous ces contacts ont été examinés bactériologiquement pendant 15 jours. Les résultats ont montré que les deux médicaments entraînaient une réduction significative de l'infection cholérique, la tétracycline étant efficace du deuxième au sixième jour et la sulfadoxine du troisième au sixième jour. Les avantages et les inconvénients de l'application de ces deux médicaments comme agents chimioprophylactiques dans le choléra sont examinés.

ACKNOWLEDGEMENTS

Authors are grateful to Dr D. Barua and Dr Y. Watanabe of Bacterial Diseases, World Health Organization, Geneva, for their helpful suggestions and cooperation in the study. They also thank Professor O'Grady, who kindly performed the antibiotic sensitivity tests on the strains of *V. cholerae* isolated during the trial. The cooperation of Dr J. Nath, Superintendent, Infectious Diseases Hospital, Calcutta, is gratefully acknowledged, and the authors wish to thank Dr A. Mondal who, as previous Director of the Cholera Research Centre, showed keen interest in the study. They also express their gratitude to the authorities in the Health Department of the Government of West Bengal for their continued cooperation. Finally, the authors thank the field and laboratory staff for their valuable assistance.

REFERENCES

1. BERGOEND, H. ET AL. *Ann. Dermatol. Syph.*, **95**: 481-490 (1968).
2. FAUCON, R. ET AL. *Méd. trop.*, **24**, Suppl. 1: 1-61 (1964).
3. GANGAROSA, E. J. ET AL. *Bull. World Health Organ.*, **35**: 669-674 (1966).
4. JOINT ICMR-GWB-WHO CHOLERA STUDY GROUP, CALCUTTA. *Bull. World Health Organ.*, **43**: 379-387 (1970).
5. JOINT ICMR-GWB-WHO COLERA STUDY GROUP, CALCUTTA. *Bull. World Health Organ.*, **45**: 451-455 (1971).
6. MACKENZIE, D. J. M. Proceedings of the Cholera Research Symposium, Honolulu. Washington DC, US Government Printing Office, 1965, pp. 341-346.
7. MCCORMACK, W. M. ET AL. *Bull. World Health Organ.*, **38**: 787-792 (1968).