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Tetracycline Prophylaxis in Families of Cholera Patients*

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The evaluation of tetracycline as a chemoprophylactic agent for cholera is described. Families of cholera patients were divided into 4 groups by strict rotation. The first group received multivitamin preparations and served as the control. The second received 1.0 g of tetracycline, divided into 4 doses, daily for 5 days, the third received 1.0 g of tetracycline in a single dose daily for 5 days, and the fourth received a single dose of 1.0 g of tetracycline. All families were visited daily for 10 days, a rectal swab being taken from each family member on each occasion. Tetracycline given daily for 5 days, either in divided doses or in a single daily dose, was effective in preventing subsequent infection. A single dose of tetracycline was less effective. The indications for chemoprophylaxis in cholera are discussed.

Greenough et al. (1964) and Carpenter et al. (1964) demonstrated that tetracycline, when combined with fluid and electrolyte replacement in the treatment of cholera, effectively reduces the volume and duration of diarrhoea as well as the intravenous fluid requirement. Tetracycline also rapidly eliminates the cholera vibrio from the stool of cholera patients.

The discovery of the value of tetracycline led to the use of various antibiotics as chemoprophylactic agents. Mackenzie (1965) reported that oral streptomycin given to proven cholera carriers in 1.0-g doses hourly for 8 hours eliminated the vibrio within 24 hours from 96% of the subjects. He emphasized the important part persons with unrecognized infections play in spreading cholera and suggested that antibiotic prophylaxis might be of value for selected high-risk groups, such as contacts of known cholera patients.

During the 1965 cholera epidemic in Iran, mass chemoprophylaxis was employed in an attempt to keep the disease from spreading from the involved eastern provinces to the cholera-free western provinces. All persons entering the western provinces were given chloramphenicol, 500 mg every 6 hours for 3 days. This regimen had previously been used in Japan as prophylaxis for contacts of cholera patients (Gangarosa et al., 1966a).

The present study was designed to evaluate the relative efficacy of various tetracycline dosage schedules in cholera prophylaxis for family contacts of cholera patients.

METHOD

The study population was drawn from families of patients admitted to the Pakistan-SEATO Cholera Research Laboratory (PSCRL) hospital in Dacca from December 1966 to February 1967. We attempted to select families with more than 3 members in which the index patient was the first in the family to have cholera. Seven families with 2 index patients each were selected. Convenience of geographical location as well as willingness to co-operate was considered. Families were selected before a definitive bacterio-

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logical diagnosis of cholera could be made in the index patient. Families in which the index patient was subsequently found not to have cholera were dropped from the study.

Once selected for the study, families were assigned by strict alternation to one of 4 groups:

(*a*) placebo (multivitamin preparation)—1 dose 4 times a day for 5 consecutive days;

(*b*) tetracycline hydrochloride—250 mg 4 times a day for 5 consecutive days;

(*c*) tetracycline hydrochloride—1.0 g in a single dose daily for 5 consecutive days;

(*d*) tetracycline hydrochloride—1.0 g in a single dose on the first day only.

Children under the age of 10 years were given half the amounts stated above. Thus, the total daily dose of tetracycline in the treated groups was 1.0 g for those 10 years of age or older and 500 mg for those under 10 years of age.

The study of each family began as soon as possible after the onset of illness in the index patient. Immediately after selection, a field team (consisting of a man and a woman) visited the family, recorded demographic data, collected a rectal swab from each family member, and administered the first dose of drug. The team visited each family daily for a total of 10 days. On each visit, the team inquired as to the presence of diarrhoea, obtained a rectal swab from each family member, and administered medication as appropriate.

The initial daily dose of medication was administered by the field team; subsequent doses, if any, were left each day with verbal instructions. During the month of Ramadan, the dosage schedule was modified for Muslim subjects observing the sunrise-to-sunset fast; those given 4 doses daily were instructed to take 2 doses at sunset, the third at bedtime, and the fourth with the meal taken just before sunrise, while the others were instructed to take their entire daily dose at sunset. For individuals not at home when the field team came, the indicated drugs and the material necessary for collecting a rectal swab were left with a responsible family member.

All rectal swabs were collected with a tellurite-impregnated swab, which was placed after collection in bile peptone transport medium and delivered daily to the bacteriology section, PSCRL. There, after overnight incubation, they were plated on gelatin and TTGA media and examined for *Vibrio cholerae* by the method described by Monsur (1963).

RESULTS

In all, 92 families with 655 members were studied; most of them resided in the crowded older areas of Dacca and Narayanganj cities along the banks of the Buriganga and Lakhya rivers: Table 1 lists, by group, characteristics of the index patients in these families. (For the 7 families with 2 index patients each, only the index patient with the earliest onset on symptoms was included in this tabulation.) All four groups had similar distributions with regard to sex, age, and serotype of vibrio isolated.

TABLE 1
CHARACTERISTICS OF INDEX PATIENTS

Drug	Dosage [a]	No. of index patients	Age-group (years)				Sex		Serotype		
			0-4	5-9	10-14	>15	M	F	Inaba	Ogawa	Inaba and Ogawa
Placebo		23	6	6	3	8	11	12	20	3	0
Tetracycline hydrochloride	4×250 mg daily for 5 days	20	4	7	1	8	11	9	17	2	1
	1.0 g daily for 5 days	26	9	9	4	4	16	10	24	2	0
	1.0 g once only	23	10	7	0	6	10	13	20	3	0
Total		92	29	29	8	26	48	44	81	10	1

[a] The amounts given refer to adult doses; the doses for children were one-half of the adult dose.

TABLE 2
CHARACTERISTICS OF FAMILY CONTACTS OF INDEX PATIENTS

Drug	Dosage [a]	No. of families	No. of contacts	Mean No. of contacts per family	No. of contacts in age-group (years)				Mean time between onset in index patient and first visit to family (hours)	No. of families with contact positive on day 1
					0-4	5-9	10-14	>15		
Placebo		23	143	6.2	28	33	25	57	25.1	8
Tetracycline hydrochloride	4 × 250 mg daily for 5 days	20	105	5.2	20	13	14	58	26.5	2
	1.0 g daily for 5 days	26	173	6.7	31	27	20	95	28.9	3
	1.0 g once only	23	135	5.9	23	25	25	62	26.0	7

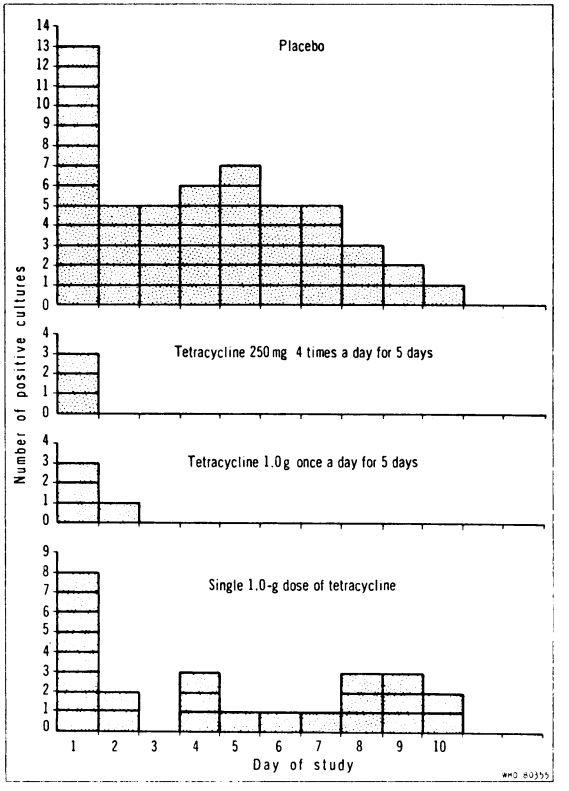
[a] The amounts given refer to adult doses; the doses for children were one-half of the adult dose.

Table 2 presents some characteristics of the study families, excluding index patients. In all groups, an average of 25–29 hours elapsed between the onset of symptoms in the index patient and the first field-team visit to the study family. The proportion of positive stool specimens taken at this time (day 1), before any drugs had been administered, would be expected to be about the same for all groups, but more families in the groups given placebo or one single dose of tetracycline hydrochloride had at least 1 member (other than the index patient) infected with *Vibrio cholerae* on day 1. This distribution could have resulted from chance alone ($\chi^2 = 6.53$ with 3 degrees of freedom; $0.1 > P > 0.05$). Because of this uneven distribution, data for families without an infected member (other than the index patient) on day 1 were tabulated separately.

The total number of documented positive cultures is shown by group and by day of collection in Fig. 1. The number of families and the number of persons who were found to be infected with *V. cholerae* after the initiation of drug prophylaxis, i. e., after day 1, are listed in Tables 3 and 4, respectively. Because of the uneven distribution of infections before drug administration had begun, data for families without an infection on day 1 are tabulated separately. By both methods of tabulation, a dosage of 1.0 g for adults or 0.5 g for children daily (in a single dose or divided doses) for 5 days appears to have been effective in preventing subsequent infections.

Fig. 2 shows the day of the first positive culture for those given placebo or one single dose of the drug who were found to be infected after the initiation of treatment. Among those given placebo, 17 of the 18

FIG. 1
NUMBER OF CULTURES POSITIVE FOR *VIBRIO CHOLERAE* IN FAMILY CONTACTS OF CHOLERA PATIENTS, BY DAY OF STUDY AND DRUG DOSAGE [a]



[a] The amounts given refer to adult doses; the doses for children were one-half of the adult dose.

TABLE 3
CONTACT INFECTIONS IN FAMILIES AFTER INITIATION OF CHEMOPROPHYLAXIS (AFTER DAY 1)

Drug	Dosage [a]	All families			Excluding families with an infected contact on day 1		
		No. studied	No. infected	Percentage infected	No. studied	No. infected	Percentage infected
Placebo		23	13	56.5	15	8	53.3
Tetracycline hydrochloride	4 × 250 mg daily for 5 days	20	0	0	18	0	0
	1.0 g daily for 5 days	26	1	3.8	23	1	4.3
	1.0 g once only	23	10	43.5	16	6	37.5

[a] The amounts given refer to adult doses; the doses for children were one-half of the adult dose.

infected individuals (94%) became positive during the first 6 days of observation. Among those given one dose of the drug, infection first became apparent before day 6 in only 7 of the 11 positives (64%).

DISCUSSION

The families of cholera patients were selected for this study because family contacts are a known high-risk group. Family studies involving classic endemic cholera in Dacca (Oseasohn et al., 1966) and epidemic El Tor cholera in the Philippines (Tamayo et al., 1965) have shown that about 20% of household contacts of cholera patients can be shown to be infected with *V. cholerae*.

Authorities have recommended various ways of reducing the importance of the role of these individuals in the transmission of the disease. Some have suggested that infected households be evacuated and all members observed in a quarantine station. Others have suggested that the family contacts of cholera patients be quarantined at home under close observation (Pollitzer, 1959).

The findings of the present study indicate that 1.0 g (500 mg for children) of tetracycline administered daily for 5 days either in a single dose or in divided doses considerably decreases detectable secondary infections within the families of cholera patients. The single daily dose is a more convenient form of administration and appears to be just as effective as divided doses.

The administration of a single dose of tetracycline to contacts as soon as possible after onset in the index patient reduces the number of subsequent

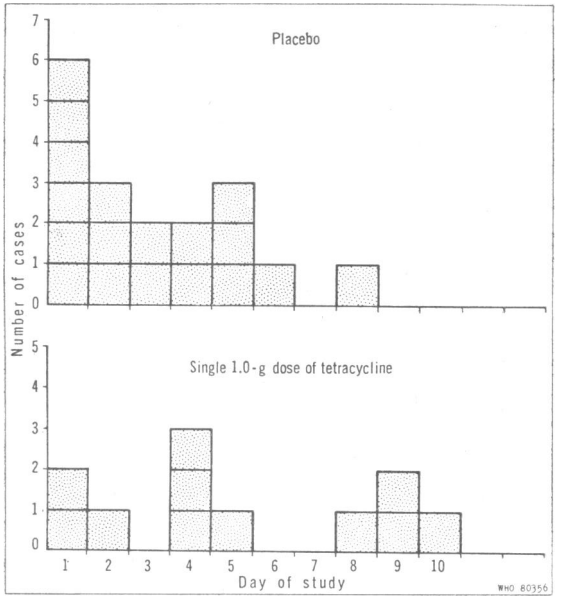
TABLE 4
INFECTIONS IN INDIVIDUAL CONTACTS AFTER INITIATION OF CHEMOPROPHYLAXIS (AFTER DAY 1)

Drug	Dosage [a]	All contacts			Excluding contacts in families with an infected contact on day 1		
		No. studied	No. infected	Percentage infected	No. studied	No. infected	Percentage infected
Placebo		143	18	12.6	86	11	12.8
Tetracycline hydrochloride	4 × 250 mg daily for 5 days	105	0	0	88	0	0
	1.0 g daily for 5 days	173	1	0.6	153	1	0.7
	1.0 g once only	135	11	8.1	95	6	6.3

[a] The amounts given refer to adult doses; the doses for children were one-half of the adult dose.

FIG. 2

DAY OF FIRST ISOLATION OF *VIBRIO CHOLERAE* FROM FAMILY CONTACTS GIVEN PLACEBO OR A SINGLE DOSE OF TETRACYCLINE [a]



[a] The amount given refers to the adult dose; the dose for children was one-half of the adult dose.

infections. There is also some indication that it delays the appearance of the infections that do occur. However, a single dose of tetracycline is obviously *not* a satisfactory prophylactic measure.

Tetracycline was used in this study because it is known to be effective against *V. cholerae* and is relatively non-toxic. Other agents to which the cholera vibrio is sensitive *in vitro* might be just as effective.

In clinical cholera, the duration of antibiotic therapy appears to be more important than the amount of drug given. A recent study of childhood cholera in Dacca compared the usual children's dose of tetracycline (500 mg daily) with a reduced dose (100 mg daily) and with furazolidone, each given in divided doses for 5 days. The different dosages were equally effective in modifying the clinical course of the disease. Rectal swabs for culture were obtained daily for about 2 weeks and a purged stool from each individual was examined before the patient was discharged. Only one of the approximately 75 antibiotic-treated subjects suffered a bacteriological relapse.[1]

Treatment with the usual dosage of tetracycline (1.0 g daily for adults, 500 mg daily for children) for 3 days effectively terminated diarrhoea but failed to eliminate the organism from 11 out of 58 children (18.9%) and 7 out of 59 adults (11.8%) studied by Lindenbaum et al. (1967a, 1967b).

Gangarosa et al. (1966b) reported 8 convalescent cholera patients with repeatedly negative stool cultures in whom purging with magnesium sulfate revealed the cholera vibrio. Five of these 8 patients had received 2.0 g of chloramphenicol daily for 3 days. Antibiotic treatment of clinical cholera for less than 3 days results in clinical as well as bacteriological failures (Carpenter et al., 1966).

Thus, the duration of antibiotic therapy for clinical cholera must be more than 3 days if elimination of the vibrio from the stool is desired. Presumably, this also applies to chemoprophylaxis, and although reduction of the prophylactic antibiotic administration period would be of considerable practical benefit, it cannot be recommended on the basis of the evidence now available.

Chemoprophylaxis is indicated for all household contacts of cholera patients and for other close contacts. To be effective, however, drug administration should be initiated as soon as possible after the onset of the disease in the index patient, as most subsequent infections can be expected to become apparent within a few days (Oseasohn et al., 1966).

Beyond this, the indications are less clear. Isolation of travellers from cholera-affected areas and administration of tetracycline to them would probably prevent the introduction of cholera into an area, assuming that all travellers can be controlled. Unfortunately, those individuals who are most likely to be carriers of cholera vibrios from one area to another are least likely to fall under such a chemoprophylaxis programme. It would be difficult to endorse such programmes if they could not reach those most at risk.

[1] Curlin, G., Karchmer, A. W. & Hirschhorn, N.—in preparation.

RÉSUMÉ

Les auteurs ont procédé à une évaluation de l'action chimioprophylactique de la tétracycline sur le choléra, à Dacca, Pakistan oriental. A cet effet, ils ont étudié des familles, de plus de trois personnes, de malades atteints de choléra, car on sait que la fréquence des infections secondaires est élevée dans cette catégorie de contacts. Les familles ont été réparties entre quatre groupes, par simple alternance. Au premier groupe, qui servait de témoin, on a administré un placebo sous forme de préparations vitaminées. Le deuxième groupe a reçu 250 mg de tétracycline quatre fois par jour pendant cinq jours. Le troisième a été traité pendant cinq jours au moyen d'une dose unique de 1 g et le quatrième n'a pris qu'une seule dose de 1 g de tétracycline le premier jour de l'observation. Les doses administrées aux enfants de moins de dix ans étaient réduites de moitié. Les équipes chargées de l'enquête se sont rendues quotidiennement dans chaque famille pendant dix jours, s'informant de l'apparition éventuelle de diarrhée, prélevant un échantillon de selles sur chaque membre de la famille par écouvillonnage rectal, et administrant la médication prescrite.

Il est apparu que la tétracycline donnée quotidiennement pendant cinq jours, soit en doses fractionnées, soit en une seule fois, prévenait pratiquement toute infection secondaire décelable chez les contacts familiaux. Administrée en une dose unique le premier jour seulement de l'observation, elle réduisait le nombre des infections secondaires ou en retardait l'apparition, mais cette méthode ne constituait pas, de toute évidence, une mesure prophylactique efficace.

La chimioprophylaxie semble particulièrement indiquée pour les membres de la famille de malades cholériques et pour toutes les personnes qui se trouvent en contact étroit avec ceux-ci. Elle devrait être entreprise dès l'apparition des signes cliniques de choléra chez le sujet témoin, car les infections secondaires apparaissent le plus souvent dans les quelques jours qui suivent. En isolant tous les voyageurs en provenance de régions infectées par le choléra et en leur administrant de la tétracycline, on parviendrait probablement à empêcher la propagation de la maladie aux régions indemnes.

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