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Preliminary Communications

Comparative Trial of Tetracycline, Chloramphenicol, and Trimethoprim / Sulphamethoxazole in Eradication of *Vibrio cholerae* El Tor

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Summary: A comparison of tetracycline, chloramphenicol, and trimethoprim/sulphamethoxazole showed that all hasten the eradication of Vibrio cholerae from the stools of patients with cholera.

A four-day period of tetracycline or trimethoprim/sulphamethoxazole was adequate for eradicating V. cholerae from the stools of all patients, but three days, as suggested by the W.H.O. Expert Committee, was not. Four days of chloramphenicol therapy was sufficient for most patients, but a minority required up to seven days' therapy.

Purging produced reappearance of V. cholerae in the stools of one-eighth of the patients who had had three successive daily negative stool cultures; such patients are a potential danger to the population.

INTRODUCTION

The efficacy of suitable antibiotics both for eradication of *Vibrio cholerae* from the intestinal tract and for reducing the intravenous fluid requirement has been well established (Carpenter *et al.*, 1965; Gordon *et al.*, 1965; Wallace *et al.*, 1965). From the epidemiological standpoint it is vitally important that cholera patients should not leave hospital until free from *V. cholerae*. According to the recommendation made by the World Health Organization Expert Committee, administration of a suitable antibiotic in a proper dose for three consecutive days is sufficient to abolish *V. cholerae* from the stools (W.H.O., 1967). Tetracycline and chloramphenicol have been used widely and reported to be quite effective for treatment of cholera and for eradication of the organism (Carpenter *et al.*, 1965; Kobari, 1966; Felsenfeld, 1967; W.H.O. 1967).

This study was carried out to compare the therapeutic value of a combination of trimethoprim/sulphamethoxazole with that of tetracycline and chloramphenicol, and to determine whether a three-day period of therapy is adequate to eliminate *V. cholerae* from the intestinal tract. We also studied the effect of purging on the reappearance of *V. cholerae* in the stools of patients who had had a negative stool culture on three consecutive days.

METHODS

The study was carried out in the infectious diseases ward of the Pahlavi University Hospital in Teheran during an outbreak of cholera. Stool specimens were cultured before treatment was begun and on each day of the stay in hospital. Only those patients from whose stools *V. cholerae* had been cultured were taken into the trial.

Therapy.—The patients were divided randomly into four groups, who received one of the following treatment regimens: chloramphenicol, tetracycline, trimethoprim/sulphamethoxazole, or a placebo (dextrose). A dose of 40 and 50 mg/kg. body weight to a maximum of 2 g./day was given for tetracycline and chloramphenicol respectively in four equally divided doses. Trimethoprim/sulphamethoxazole was given in a dose of 10 mg. of trimethoprim and 50 mg. of sulphamethoxazole per kg. of body weight to a daily maximum of 390 mg. of trimethoprim and 1·6 g. of sulphamethoxazole (4 tablets) in two equal doses. Dextrose tablets were given to the placebo group twice a day. All the medications were given orally and were well tolerated. Each drug, or dextrose, was given for a minimum of three days or until a negative stool culture was obtained. After three consecutive daily stool cultures had proved negative magnesium sulphate was given as a purge in doses of 10 g. for children and 20 g. for adults. If the stool culture remained negative after the purge the patients were discharged. Those patients with previously negative stools who showed a positive culture after the purge were given three more days of antibiotic therapy and then discharged.

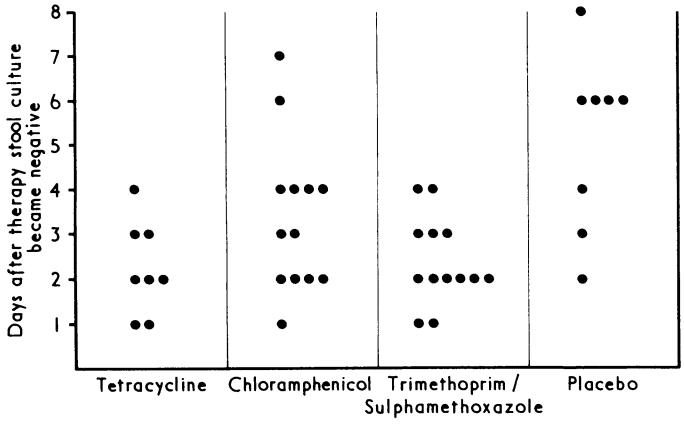
Bacteriological Studies.—Stool specimens were placed immediately in alkaline peptone water, pH 8·6, and on one-half of a thiosulphate citrate bile salt sucrose agar plate (T.C.B.S.) (Kobayashi, *et al.*, 1963). They were incubated at 37°C. for six to eight hours and then the other half of the T.C.B.S. plate was streaked from the growth obtained in liquid medium. After overnight incubation the suspicious colonies were tested with polyvalent cholera antiserum and if positive were then retested with Ogawa and Inaba type-specific antisera. If the suspicious colony failed to react with the polyvalent serum a sweep from the confluent area was similarly tested before discarding the culture as negative. When agglutination was positive the remnants of the colony were transferred on to a Kligler iron agar slant. The growth was serologically confirmed and then subjected to the following tests: the Voges-Proskauer reaction, indole test, haemagglutination of chicken erythrocytes, sensitivity to a disc containing 50 units of polymyxin B and to cholera phage group IV at normal test dilution, plate and tube haemolysis of sheep erythrocytes, the oxidase test, and sucrose, mannitol, and arabinose fermentation tests (Felsenfeld, 1967; W.H.O. 1967).

RESULTS

Bacteriology.—All the strains isolated were *V. cholerae* El Tor, type Inaba. They were insensitive to Mukerjee's phage IV, insensitive to polymyxin B, gave haemolysis on plates but none in tubes, and agglutinated chicken erythrocytes. They

all gave positive Voges-Proskauer and indole tests. They did not ferment arabinose, but fermented sucrose and mannitol and were oxidase-positive.

Elimination of V. cholerae from the Stool.—Of the 92 patients investigated a complete follow-up was possible in only 42. Of these, 13 were treated with chloramphenicol and 13 with trimethoprim/sulphamethoxazole. Eight received either tetracycline or the dextrose placebo. The time required for the first negative stool culture is given in the Chart. All three antimicrobial agents were clearly effective in shortening the length of excretion of *V. cholerae* from the stool when compared with placebo, but tetracycline and trimethoprim/sulphamethoxazole were somewhat more effective for rapid eradication of the organism than was chloramphenicol. No patient receiving tetracycline or the trimethoprim/sulphamethoxazole mixture required more than four days for the stool culture to become negative, whereas of the 13 patients receiving chloramphenicol, one patient required six days and another seven days of therapy (see Chart).



Effect of chloramphenicol, tetracycline, and trimethoprim/sulphamethoxazole as compared with placebo in eliminating *V. cholerae* from the intestinal tract.

Effect of Purging.—Forty of the 42 patients who were completely followed up were purged, and as a result five were converted to positive. One of these had been treated with tetracycline and one with trimethoprim/sulphamethoxazole. Three had received the placebo (see Table).

Effect of Purging on Detection of V. cholerae *in the Stools of Patients who had had Three Consecutive Negative Stool Cultures*

Group	No. of Patients Purged	No. of Patients Converted to Positive
Tetracycline	8	1
Chloramphenicol	13	0
Trimethoprim/sulphamethoxazole	11	1
Placebo	8	3

Discussion

Patients with cholera often recover clinically before the *V. cholerae* is eliminated from their intestinal tract. These patients, if discharged, may infect others in the community. It is therefore of vital importance that the patient not only recovers clinically but becomes free of *V. cholerae* (Felsenfeld, 1967). The W.H.O. Expert Committee (1967) suggested that three days of therapy with tetracycline or chloramphenicol at a dosage of 2 g./day would eliminate the *V. cholerae* from the stools of most patients. From our results it appears that three days is not sufficient, but four days of therapy with a dose of 2 g. of tetracycline/day or four tablets of trimethoprim/sulphamethoxazole eliminates the *V. cholerae* from all patients, whereas seven days of therapy at 2 g./day is required in the case of chloramphenicol for complete confidence that the patient's stools will become negative.

Of 40 patients who had three consecutive daily negative stool cultures and then received a purge, five once more showed a positive stool culture. It has been postulated that the normal intestinal flora act as a filter for *V. cholerae* among carriers, but that when such patients develop diarrhoea, either from another infection or from taking a purge, this barrier breaks down and vibrios can be isolated from the stool in greater numbers (Gangarosa *et al.*, 1966). Our results appear to lend weight to this hypothesis. This may well contribute to the maintenance of the *V. cholerae* among a population and its appearance when an opportunity arises. It is also interesting that none of the patients who became positive after purging was in the chloramphenicol group. One could postulate that because elimination of *V. cholerae* by chloramphenicol is delayed, the drug has to be given for a longer period, and thus has a greater chance of eliminating the organism completely from the intestinal tract.

The present results were obtained in a relatively small group of patients and require confirmation on a larger series.

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