J HEALTH POPUL NUTR 2003 Mar;21(1):76-78
ISSN 1606-0997 $ 5.00+0.20

LETTER-TO-THE-EDITOR

Tetracycline in the Treatment of Cholera Caused by *Vibrio cholerae* O1 Resistant to the Drug *in vitro*

Sir,

Tetracycline, the most commonly-used antibiotic in cholera, reduces stool volume, duration of diarrhoea, and duration of excretion of *Vibrio cholerae* to about half that seen in patients treated without antibiotics (1). After oral administration, concentrations of tetracycline become relatively high in the intestinal lumen because of partial unabsorption and hepatobiliary excretion (2). It was our clinical impression that conventional dose of tetracycline given orally results in sufficiently high intestinal luminal concentration that much exceeds the minimum inhibitory concentration (MIC), so it might be effective in cholera caused by *V. cholerae* O1 resistant to the drug in *vitro*. If so, this phenomenon would replicate the experience with tetracycline-resistant *Shigella* infection in which tetracycline was thought to be efficacious (3). Pickering *et al*. treated symptomatic shigellosis patients successfully with a single oral dose of 2.5 g of tetracycline hydrochloride even in tetracycline-resistant strains of *Shigella flexneri* and *S. sonnei* (3). Now-a-days, emergence of strains of *V. cholerae* O1 resistant to tetracycline is a global problem (4-6). So, we conducted a pilot study to explore efficacy of tetracycline in the treatment of cholera caused by *V. cholerae* O1 resistant to tetracycline *in vitro*.

This study was carried out at the Dhaka hospital of ICDDR,B: Centre for Health and Population Research during June 1995-December 1996. Both male and female adult patients, aged 18-60 years, with history of watery diarrhoea for ≤24 hours were considered suitable for inclusion in the study, provided females were not pregnant and patients had no other obvious infection or complicating medical illness at the time of entry into the study. No patient who had received any prior antimicrobial therapy for the current episode of diarrhoea was enrolled. Before enrollment, stool samples collected from the selected patients were examined by dark-field microscopy and the results confirmed the provisional clinical diagnosis of cholera. The enrolled patients were severely dehydrated except a few who had moderate dehydration, and rehydration was done within three hours by intravenous polyelectrolyte solution (in mmol/L: Na^+ 133, K^+ 13, Cl^- 98, and acetate 48). They were observed for four hours, during which time hydration was maintained with oral rehydration salts solution (rice-based ORS) or intravenous fluid. After the observation period, each patient was given 500 mg of tetracycline six hourly orally for three days. After initial rehydration, the patients were given normal meals except those containing milk and milk products to avoid chelation of tetracycline. On enrollment, fresh stool sample was taken from each patient for culture (inoculated into tellurite taurocholate gelatin agar, Mackonkey and *Shigella-Salmonella* agar) and sensitivity test. The patients whose stool cultures revealed only *V. cholerae* O1 remained in the study. Microbiological study of stool for *V. cholerae* was done daily until discharge. Drug susceptibility test was done by the disc-diffusion method (Kirby-Bauer) for tetracycline, erythromycin, and ciprofloxacin. For *V. cholerae* O1 resistant to tetracycline, the zone diameter of the disc was considered <15 mm in our laboratory. The patient's history was obtained on admission, and physical examinations were performed at initial screening, on entry into study, and daily. Stool output was recorded six hourly with documentation of its consistency. Simultaneously, ORS intake, other fluid intake, and urine output were recorded six hourly. The patients were discharged after cessation of diarrhoea. Further stool culture was not possible. Weighing of stool and body was done on an electronic scale (Sartorius, Germany) that had a precision of 1 g. Separated urine and vomitus were transferred to a graduated glass cylinder for measurement of volume. All findings were recorded in predesigned case report forms. The results of the susceptibility test for *V. cholerae* were not known by the investigators during the study period. If patients

Correspondence and reprint requests should be addressed to: Dr. Ali Miraj Khan
Clinical Sciences Division
ICDDR,B: Centre for Health and Population Research
GPO Box 128, Dhaka 1000
Bangladesh
Email: miraj@icddrb.org
Fax: 880-2-8823116

had watery stool for more than 72 hours of therapy, the treatment was considered to have failed. The patients were then treated with a suitable antibiotic as indicated by the susceptibility test. We used ciprofloxacin in all failure cases. Patients who developed complications requiring more intensive care were withdrawn from the study and were given standard treatment. The duration of diarrhoea was defined as the time between the administration of the first dose of tetracycline and last watery stool before passage of two soft or one formed stool(s) or occurrence of no stool for 12 hours. Statistical analyses were done using SPSS for Window (SPSS Inc., Chicago III). A two-tailed student's *t*-test was used for comparing the baseline characteristics. Mann-Whitney *U*-test was applied for continuous variables with skewed distribution, and chi-square test was employed for discrete variables.

In total, 157 patients were enrolled into the study. All were infected with the El Tor biotype of *V. cholerae* O1 with either Inaba or Ogawa serotype. Isolates of 130 patients were sensitive to tetracycline, and those of 27 patients were resistant to tetracycline *in vitro*. The two groups of patients were similar with regard to demographic and clinical characteristics, such as age, body weight, duration of diarrhoea, and dehydration on entry into study. Total stool output, total ORS intake as well as intravenous fluid requirement, and duration of diarrhoea between the tetracycline-resistant group and the tetracycline-sensitive group were also similar (Table). Diarrhoea continued for more than 72 hours in four patients—two in the tetracycline sensitive group and two in the tetracycline resistant group. In all of them, diarrhoea resolved on day 4.

In our study, we did not find any significant difference in stool output, rehydration fluid intake, and duration of diarrhoea between the two groups. We admit the limitations of this study. The sample size was not adequate. Moreover, clearance of *V. cholerae* from the stool could not be determined thoroughly for each patient. In addition, antimicrobial resistance could not be graded. We could only classify *V. cholerae* as sensitive or resistant to tetracycline. So, this clinical trial does not yield a good conclusion. However, the results of this study generate the hypothesis that a conventional dose of tetracycline may be clinically efficacious in the treatment of cholera caused by *V. cholerae* O1 resistant to the drug *in vitro*. Such expected clinical response has epidemiological importance. It would be cost-effective, and prompt introduction of tetracycline would be possible during cholera epidemics and for patients in most clinical settings of developing countries where laboratory facilities for sensitivity test are not available. It is also possible that the use of a higher dose of tetracycline could lead to better results. So, further studies are needed in this area, with adequate sample size.

Table. Admission characteristics and clinical outcome

Variable	Tetracycline-sensitive cases (n=130)	Tetracycline-resistant cases (n=27)	p value
Age (years)	26±7	24±5	0.1
Body weight (kg)	45±7	47±9	0.3
Duration of diarrhoea before admission (hours)	10±5	11±4	0.07
Severe dehydration [no. (%)] on admission	118 (90)	26 (96)	0.5
Stool output (g/kg)			
First 24 hours	88 (50-142)	112 (39-192)	0.2
Total	90 (48-165)	142 (44-244)	0.2
Total urine output (mL/kg)	92 (52-154)	72 (26-118)	0.1
Total fluid intake (mL/kg)			
Intravenous fluid	0.0 (0.0-55)	0.0 (0.0-93)	0.3
ORS	143 (77-203)	138 (81-252)	0.5
Water	125 (79-179)	125 (70-217)	0.7
Duration of diarrhoea (hours)	24 (18-36)	30 (18-48)	0.08

Values are mean±SD or median (25th, 75th centiles)

ACKNOWLEDGEMENTS

This research was funded by ICDDR,B: Centre for Health and Population Research which is supported by countries and agencies that share its concern for the health problems of developing countries. Current donors providing unrestricted support include: the aid agencies of the Governments of Australia, Bangladesh, Belgium, Canada, Japan, Kingdom of Saudi Arabia, the Netherlands, Sweden, Sri Lanka, Switzerland, the United Kingdom, and the United States of America.

REFERENCES

1. Greenough WB, III, Gordon RS, Jr., Rogenberg IS, Davies BI, Benenson AS. Tetracycline in the treatment of cholera. *Lancet* 1964;1:355-7.
2. Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, editors. Goodman & Gilman's The pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hall, 1996:1124-31.
3. Pickering LK, DuPont HL, Olarte J. Single-dose tetracycline therapy for shigellosis in adults. *JAMA* 1978;239:853-4.
4. Salam MA, Khan WA, Begum M, Bardhan PK, Islam MR, Mahalanabis D. Antimicrobial treatment of cholera. *Drugs* 1995;49(2 Suppl):466-9.
5. Ferreira E, Costa M, Vaz Pato MV. Resistance to antibiotics of *Vibrio cholerae* strains isolated in Angola. *Pathol Biol (Paris)* 1992;40:561-5.
6. Jain RC, Bhat BD, Basutkar SH. Tetracycline resistant El Tor vibrios in Loni area. *J Assoc Physicians India* 1992 Sep;40:636.

A.M. Khan[1], U. von Gierke[2], M.S. Hossain[1], and G.J. Fuchs[3]

[1]ICDDR,B: Centre for Health and Population Research, Bangladesh GPO Box 128, Dhaka 1000, Bangladesh

[2]Degenfeldstr. 14, 80803 München, Germany

[3]Department of Pediatrics, University of Arkansas for Medical Sciences, 4301 W. Markham, 512-001, Little Rock, AR 72205, USA