Doxycycline in the treatment of cholera*

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Doxycycline was compared with tetracycline in the treatment of cholera. Four types of treatment were compared: Group A was given 200 mg of doxycycline on admission and 100 mg on the second day; Group B was given 200 mg of doxycycline on admission only; Group C was given 300 mg of doxycycline on admission only; and Group D received 500 mg of tetracycline every 6 h for 48 h. Tetracycline showed a slight advantage in respect of duration of diarrhoea and vibrio excretion compared with doxycycline given as a single dose of 300 mg, but fluid intake and output were about the same in these two groups. The other two doxycycline treatment schedules did not compare well with tetracycline treatment.

Doxycycline is a broad spectrum antibiotic of the tetracycline family. It differs from other tetracyclines by virtue of its greater absorption after oral administration and its prolonged antibacterial activity *in vivo*. Oral tetracycline has so far proved to be the best antimicrobial agent in the treatment of cholera patients (*1*) as well as cholera carriers, but it requires to be given in multiple doses for 2 or 3 days (*2–4*). An antibiotic having the same effectiveness when given less frequently would therefore have obvious advantages, and doxycycline was seen to promise these advantages. The present trial was planned with the primary objective of comparing tetracycline in the usual dose with doxycycline in three different dosage schedules.

MATERIALS AND METHODS

One hundred and twenty-seven males between 6 and 70 years of age were studied in four different groups at the Infectious Diseases Hospital, Calcutta from May to September 1975. Only untreated patients showing dehydration according to the criteria published by the World Health Organization (*5*) and with a systolic blood pressure <90 mmHg were included in the study, and these were randomly assigned to one of four different treatment groups (A, B, C, or D).

The patients were first weighed, placed in cholera cots, and examined clinically; rectal swabs were immediately taken, placed in Cary–Blair medium, and sent to the laboratory within 24 h. Intravenous fluid replacement was started with 2 units (540 ml each) of physiological saline and 1 unit of 167 mmol/litre lactate for adults, and with these constituents in the ratio of 1 : 1 for children. The first dose of antibiotics was given orally a little later, generally about an hour after admission. Six patients who regurgitated the capsules were given the same dose later.

The dosage schedules were as follows:

Group A

Adults were given 200 mg of doxycycline (in capsules) on admission and 100 mg on the second day; children under 12 years of age received 4 mg per kg of body weight (in syrup) on admission and 2 mg/kg the following day.

Group B

Adults received 200 mg and children 4 mg/kg of doxycycline on admission only.

Group C

Adults received 300 mg and children 6 mg/kg of doxycycline on admission only.

Group D

Adults were given 500 mg of tetracycline (in capsules) and children 250 mg (in syrup) every 6 h for 48 h.

* These studies were carried out under the joint auspices of the Indian Council of Medical Research (represented by the Cholera Research Centre, Calcutta), the Health Department of the Government of West Bengal, and the World Health Organization.

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Table 1. Fluid output, fluid intake, and duration of diarrhoea in the four groups

	Fluid output (litres)		Fluid intake (litres)		Duration of diarrhoea (hours)	
	mean ± SE	range	mean ± SE	range	mean ± SE	range
Group A	2.45 ± 0.69	0.05 – 10.25	4.38 ± 0.71	0.79 – 11.06	15.03 ± 1.68	3–30
Group B	1.82 ± 0.52	0.15 – 10.40	3.78 ± 1.51	1.62 – 12.34	16.65 ± 1.29	5–26
Group C	1.74 ± 0.52	0.10 – 9.90	3.95 ± 0.60	0.54 – 12.66	9.05 ± 1.45	2–29
Group D	1.78 ± 0.39	0.10 – 6.45	3.65 ± 0.53	1.08 – 9.54	8.33 ± 1.27	1–18

Note: Difference of two means in fluid output and fluid intake between the different groups is not statistically significant ($P>0.05$); difference of two means in duration of diarrhoea between Groups B and C and between Groups B and D is highly significant ($P<0.001$); difference of two means between Groups A and D is highly significant ($P<0.01$); difference of two means between Groups A and C is significant ($P<0.02$).

The patients were allowed plain water *ad libitum* and this was recorded on the fluid intake and output charts, which were kept for every patient from the time of admission up to the time of passing the last liquid stool (i.e., before the appearance of semisolid stools). Intravenous fluid administration was regulated according to the state of dehydration and the systolic blood pressure. Rectal swabs were taken at the time of admission and on the following 4 days. Patients with negative stool reports for *Vibrio cholerae* were taken off the study.

The criteria for comparison of the different doxycycline dose schedules with tetracycline treatment were:

1. Duration of vibrio excretion after the administration of antibiotic.
2. Volume of fluid lost.
3. Volume of fluid intake.
4. Duration of diarrhoea.

The techniques employed for the laboratory diagnosis of cholera were similar to those described earlier (*6*).

RESULTS

There was no mortality in the present series. The patients tolerated doxycycline well and no obvious side effects relatable to it were noted.

Seventy-six patients found to have *V. cholerae* in their stools were considered in the analysis of the results of therapy: 18 were in group A, 22 in group B, 20 in group C, and 16 in group D. The results of therapy are shown in Tables 1 and 2, which indicate that tetracycline in conventional doses was the best overall treatment. Of the doxycycline-treated groups, Group C compared closely with the tetracycline-treated Group D. The mean fluid output in Group C was 1.74 ±0.52 litres, with a range of 0.10–9.90 litres, as compared with 1.78 ±0.39 litres with a range of 0.10–6.45 litres in Group D. The fluid intake in Group C was 3.95 ±0.60 litres with a range of 0.54–12.66 litres, as compared with 3.65 ±0.53 litres with a range of 1.08–9.54 litres in Group D. The mean duration of diarrhoea in Group C was 9.05 h and in Group D 8.33 h. Effectiveness against vibrio excretion after 24 h was highest in Group D (58.8%), but after 72 h the results in Group C (90.0%) and Group D (94.1%) were almost identical (Table 2). Groups A and B were inferior in respect of all the criteria compared with Groups C and D.

Table 2. Duration of vibrio excretion and the effectiveness of treatment in the different groups

Group	Percentage effectiveness after:				Mean duration in hours (± SD)
	24 h	48 h	72 h	96 h	
A	5.9	58.8	82.4	94.1	34 ± 2.2
B	19.1	52.4	76.2	81.0	40 ± 1.7
C[a]	30.0	65.0	90.0	95.0	34 ± 1.6
D[b]	58.8	94.1	94.1	100.0	29 ± 1.9

[a] The treatment given to Group C was more effective than that given to Groups A and B ($P<0.05$).

[b] The treatment given to Group D was more effective than that given to any other group ($P<0.05$).

DISCUSSION

Tetracycline has long been the antimicrobial of choice in the treatment of cholera. Its addition to

fluid replacement therapy constitutes the cornerstone in the treatment of this disease, and helps in reducing the volume of fluid loss, the amount of replacement fluid necessary, and the duration of vibrio excretion. Since tetracycline has to be administered over a minimum period of 48 h in several doses, it was felt that an equally effective antimicrobial given in a single dose would be a definite advantage in the face of an outbreak. Doxycycline in a single dose of 300 mg proved almost as effective as tetracycline therapy, and has the additional advantage of being less expensive.

ACKNOWLEDGEMENTS

The authors wish to express their gratitude to the Superintendent, Infectious Diseases Hospital, Calcutta for his help and cooperation and to Dr D. Barua, Bacterial Diseases, World Health Organization, Geneva, for his encouragement and guidance. The active and valuable assistance of Sri Kamal Sadhu in carrying out the study and of Mr S. N. Sikdar with the statistical analyses is gratefully acknowledged. Thanks are also extended to the Pfizer Chemical Co. for supplying the Vibramycin brand of doxycycline used in the present study. The work was supported by a grant from the World Health Organization.

RÉSUMÉ

LA DOXYCYCLINE DANS LE TRAITEMENT DU CHOLÉRA

On a comparé la doxycycline à la tétracycline pour le traitement du choléra. A cet effet, 4 types de traitements ont été appliqués: dans le groupe A, les malades ont reçu 200 mg de doxycycline lors de l'admission et 100 mg le deuxième jour; ceux du groupe B, 200 mg de doxycycline lors de l'admission uniquement; ceux du groupe C, 300 mg de doxycycline lors de l'admission uniquement; et ceux du groupe D, 500 mg de tétracycline toutes les 6 heures pendant 48 heures. Le traitement par la tétracycline s'est montré légèrement supérieur, en ce qui concerne la durée de la diarrhée et de l'excrétion des vibrions, au traitement par la doxycycline à la dose unique de 300 mg, mais l'absorption et les pertes liquidiennes étaient à peu près identiques dans ces deux groupes. Les deux autres schémas de traitement par la doxycycline ne donnaient pas de résultats comparables à ceux du traitement par la tétracycline.

REFERENCES

1. KOBARI, K. C. ET AL. *Bulletin of the World Health Organization*, **37**: 751-762 (1967).
2. GREENOUGH, W. B. ET AL. *Lancet*, **1**: 355-357 (1964).
3. CARPENTER, C. C. J. ET AL. *Bulletin of the Johns Hopkins Hospital*, **118**: 174-196 (1966).
4. CARPENTER, C. C. J. ET AL. *Bulletin of the Johns Hopkins Hospital*, **118**: 230-242 (1966).
5. *Principles and practice of cholera control*. Geneva, World Health Organization, 1970 (Public Health Papers, No. 40).
6. JOINT ICMR-GWB-WHO CHOLERA STUDY GROUP, CALCUTTA, INDIA. *Bulletin of the World Health Organization*, **43**: 379-387 (1970).