The evidence suggests that the aplasia of the erythron can itself account for the clinical presentation of an anaemic crisis. In that case why the aplasia?

It has been considered that the crises in spherocytic anaemia are often precipitated by infection (Murray-Lyon, 1935; Scott, 1935; Dameshek, 1941; Horne, Lederer, Kirkpatrick, and Leys, 1945), and recently it has been recognized that certain infections, notably diphtheria and infectious mononucleosis (Gasser, 1950; Chernoff and Josephson, 1951), may be associated with a transient hypoplasia of the erythron.

In spherocytic anaemia we have to consider the effect of an infection upon a bone marrow in a state of prolonged and profound compensatory hypertrophy and therefore especially liable to a conditioned nutritional deficiency. The diversion of essential protein which is thought to be responsible for the anaemia of infection (Cartwright and Wintrobe, 1952), could thus be exaggerated in effect, and a relatively acute deficiency could occur, with resulting aplasia.

Such an explanation would seem to us more likely than the postulation of a hypothetical hypersplenism, and would also account for the apparently increased tendency to crises during pregnancy.

Summary

Four crises in three children with spherocytic haemolytic anaemia were studied.

All crises were associated with reticulocytopenia and with hypoplasia of the erythron in the bone marrow.

Recovery from crises was associated with the reformation of the usual hypertrophic marrow.

No evidence of increased haemolysis was seen in the crises.

It is suggested that the marrow aplasia is the primary cause of the anaemic crises and that the aplasia is due to conditional deficiency states induced by the presence in the body of an infection on a marrow undergoing prolonged compensation hypertrophy.

We are indebted to Dr. T. Colver and Professor R. S. Illingworth, the paediatricians in charge of the cases reported here.

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The C.W.S. Retail Co-operative Society of Manchester was fined £120, with 10 guineas costs, at Hastings, Sussex, on March 18 on five summonses in respect of the condition of premises used for food storage at St. Leonards. The society pleaded guilty to summonses accusing them of (1) failing to provide a sufficient supply of water for persons employed there; (2) failing to see that the walls, ceilings, and doors of the room had been purified; (3) failing to give notice that an infestation of rodents was present in the room; (4) failing to protect food stored in the room; and (5) failing to see that the walls, ceilings, floors, and windows were kept in a proper state of repair. The premises were used for the storage of cereals, rice, and beans in sacks and packages. A spokesman for the society said they deplored this matter and now had very good premises.

FURTHER TRIAL OF AUREOMYCIN IN THE TREATMENT OF CHOLERA*

BY

S. C. SEAL, Ph.D., M.B., B.S., D.P.H., F.A.P.H.A.
Professor of Epidemiology (Offg.), All India Institute of Hygiene and Public Health, Calcutta

M. M. GHOSH, M.B., B.S.

Honorary Visiting Physician, Infectious Diseases Ward, Nilratan Sircar Medical College Hospitals, Calcutta

AND

S. C. GHOSAL, M.B., B.S., D.P.H., D.B.†

Lately Professor of Bacteriology, School of Tropical Medicine, Calcutta

In a previous communication (Seal, Ghosal, and Ghosh, 1951) the results of a preliminary trial of aureomycin, administered intravenously, in the treatment of cholera cases were reported. These being unsatisfactory it was suggested that the oral route might be chosen for the administration of the drug if further trial was undertaken in future. Accordingly a trial was organized in the same institution at Calcutta, this time during the prevalence of cholera epidemic in the city between April 30 and July 20, 1951. Only frankly typical cases were chosen at random and were divided into three groups: experimental, sulphaguanidine control (control 1), and saline control (control 2), the number of cases treated in each group being 50, 35, and 35 respectively, total 120. The subjects were all males and were admitted in a stage of collapse, generally within 24 hours of the onset of symptoms, and had received little or no treatment prior to admission to hospital.

Treatment

Dosage.—The drug was supplied in capsules, each containing 250 mg. In the previous study the dosage used for intravenous administration was 100 mg. every six hours, and in a few cases 50 mg. every three hours, the total quantity used being generally 300 mg. Some untoward symptoms were noted with 100 mg., but not with 50 mg. per adult dose. With this experience, and in the absence of any previous knowledge of the dose which would be suitable for oral administration in cholera patients, it was tentatively decided to try one capsule of 250 mg. every three hours. This amount was easily retained with no untoward effect referable to the drug. A few cases which showed complications during the course of the disease will be discussed later. Of the 43 cases which recovered 8 were clinically severe, 23 moderately severe, and 12 were mild, the average doses received by these groups being 6.65 g., 5.5 g., and 4.875 g. respectively. From the nature of response obtained by oral administration of the drug it appears that 500 mg. every three hours or 250 mg. every one and a half hours may be tried as an initial dose, whichever is found convenient, and if the drug is effective at all the total amount actually needed for recovery may be much less than has been used in the present investigation, perhaps about 3 to 5 g., depending upon the severity.

Other Treatments.—As in the previous trial, all cases brought to the hospital in a state of dehydration and collapse were given intravenous saline and glucose in varying

*Presented before the Medical and Veterinary Section of the Indian Science Congress Association at its annual meeting held at Lucknow in January, 1953.

†Dr. S. C. Ghosal has died since the paper was written.

doses before the administration of the experimental drug. In severe cases, this treatment was further supplemented by alkaline saline, coramine, and atropine whenever necessary.

Treatment of Controls.—Two groups of control cases were simultaneously treated, one receiving sulphaguanidine in place of aureomycin and the second receiving no specific drug, the "other treatments" being the same in all the three groups. The initial dose of sulphaguanidine was 4 g., the total doses varying from 4 to 36 g. (average 25 g.) in the cases which recovered.

Laboratory Examinations

Examination of Stool Samples.—The procedures adopted by Chaudhuri *et al.* (1950) were followed for the collection and examination of stool samples, and only specimens collected by means of a sterile rectal rubber catheter or on a burnt earthenware vessel and removed to the laboratory in sterile borate-buffered salt solution were accepted for cultural examination. This had twofold advantages. It eliminated the use of a bed-pan, which could give spurious results due to imperfect washing and sterilization or to the presence of some residual antiseptics; secondly, it gave more reliable

data about the period of excretion owing to the greater chance of isolating *V. cholerae*, if present, by this method than by others. A case was considered bacteriologically negative when at least three consecutive stool samples inoculated into the enriched medium proved negative to *V. cholerae*. Seventy-five or 62.5% of the patients were vibrio-positive, yielding Inaba type in 64 cases, Ogawa in 10 cases, and both Inaba+Ogawa in one case. The vibrio-positive cases were equally distributed in the three groups (see Table II).

Examination of Blood Samples for Non-protein Nitrogen.

—As in the previous trial the examination of blood samples from the cholera patients for non-protein nitrogen was carried out in the Biochemistry Section of the Calcutta Medical College. The estimation could be made only in 28 patients, 12 from the aureomycin group and 8 each from the two control groups; these tests were done mostly in the earlier period of the investigation; the difficulty arose out of the gas-workers' strike in Calcutta during the months of May to July, 1951. The amount and distribution of non-protein nitrogen in different groups of cases, according to the nature of complications, are given in Table I.

TABLE I.—Amount and Distribution of NPN (mg./100 ml.) in the Blood of Cholera Patients According to the Nature of Complications in Different Experimental Groups.

Group Treated With	Uraemic Cases		Lung Complication		Tymanitis		Jaundice		Vasomotor Failure		Without Complication	
	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)
1	2	3	4	5	6	7	8	9	10	11	12	13
Aureomycin	5	95 (D), 86 (D), 60, 38	2	25 (D)	—	—	2	56	—	—	41	15, 16, 20 (D), 22 (D), 39.2, 42
Sulphaguanidine	4	90 (D), 72.8 (D), 53	—	—	1	18 (D)	1	—	1	39.2	28	24, 28, 45
Saline	1	86 (D)	—	—	1	—	—	—	—	—	33	25, 25, 26 (D), 28, 34, 24, 62 (D)
	10	8	2	1	2	1	3	1	1	1	102	16

The letter D in parentheses stands for death.

TABLE II.—Showing the Clinical States and Progress of the Three Groups of Cholera Patients Treated with Aureomycin (Oral), Sulphaguanidine, and Saline Respectively.

Clinical States	Aureomycin (Oral)-treated Group	Sulphaguanidine-treated Group (Control 1)	Saline-treated Group (Control 2)
Number of cases treated	50	35	35
Age distribution (in years)	10-50 (average 30.5 years)	12-60 (average 31.2 years)	14-80 (average 31 years)
Duration of illness before admission (hours)	1½-48 ¹ (average 9.6 hours)	3½-48 ² (average 15 hours)	4-72 ³ (average 17.2 hours)
Sp. gr. of blood on admission	1062 (3), 1062 (14), 1063 (3), 1064 (10), 1065 (3), 1066 (9), 1067 (1), 1068 (7); average 1064.2	1061 (1), 1062 (8), 1063 (1), 1064 (8), 1065 (1), 1066 (11); 1068 (3); average 1064.5*	1062 (7), 1063 (2), 1064 (5), 1065 (4), 1066 (10), 1067 (3), 1068 (4); average 1065
Clinical types	Severe 15 (30%); Mod. 23 (46%); mild 12 (24%)	Severe 8 (22.9%); Mod. 16 (45.7%); mild 11 (31.4%)	Severe 11 (31.4%); Mod. 16 (45.7%); mild 8 (22.9%)
Condition of urine on admission	Suppressed 32 (64%); scanty 18 (36%)	Suppressed 16 (45.7%); scanty 19 (54.3%)	Suppressed 19 (54.3%); scanty 16 (45.7%)
Duration of suppression of urine (hours)	6-36 (average 16.0 hours, SD 2.219)	3-34 (average 16.3 hours, SD 2.103)	11-36 (average 22.75 hours, SD 2.207)
Complications	Uraemia 5; lung complications 2; jaundice 2; total 9 (18%)	Uraemia 4; tymanitis 1; vasomotor failure 1; jaundice 1; total 7 (20.0%)	Uraemia 1; tymanitis 1; total 2 (5.7%)
Blood NPN (mg./100 ml.)	Done in 12 patients (15, 16, 20, 22, 25, 38, 39.2; 42, 56, 60, 86, and 95 mg.—average 42.85 mg.)	Done in 8 patients (18, 24, 28, 39.2, 45, 53, 72.8, and 90 mg.—average 46.25 mg.)	Done in 8 patients (25, 24, 25, 26, 28, 34, 62, and 86 mg.—average 38.75 mg.)
Vibrio positive or negative	Vibrio+31 (62%); Vibrio-19 (38%); Inaba 27; Ogawa 3; In.+Og.=1	Vibrio+22 (63%); Vibrio-13 (37%); Inaba 20; Ogawa 2	Vibrio+22 (63%); Vibrio-13 (37%); Inaba 17; Ogawa 5
Excretion of vibrios (average duration)	2.75 days (SD 0.132)	3.2 days (SD 0.164)	3.72 days (SD 0.271)
Average number of stools during the first 5 days of admission	10.9 (SD 0.919)	12.3 (SD 1.611)	14.1 (SD 1.902)
Average duration of illness (acute stage)	37.1 hours, SD 1.611 (average of 43 cases); 37.4 (including the dead)	39.7 hours, SD 2.249 (average of 29 cases); 39 hours (including the dead)	47.3, SD 3.530 (average of 29 cases); 43 hours (including the dead)
Average amount of saline used (pints)	6.0 (average of all cases); 5.96 (excluding the dead)	6.0 (average of all cases); 5.7 (excluding the dead)	6.2 (average of 34 cases); 6.3 (excluding the dead)
Specific drugs	4 to 36 capsules (250 mg. each); average 23 capsules (excluding dead)	4-36 g.; average 26 g. (excluding the dead)	Nil
Number died	7† (14.0%)	5 (14.3%)	5 (14.3%)
Period between admission and death or cessation of acute stage	28.3 hours (excluding the dead); 28.8 hours (all cases)	28.0 hours (excluding the dead); 28.4 hours (all cases)	30 hours (excluding the dead); 27.2 hours (all cases)
Average length of stay in hospital (days)	5.5 (excluding the dead); 6.2 (all cases)	6.5 (excluding the dead); 6.2 (all cases)	5.9 (excluding the dead); 6.8 (all cases)

* Sp. gr. of two cases not estimated.

† One case had only 1 capsule and died within 3 hours of admission and another had 2 capsules and died within 4 hours of admission. Fatality rate excluding the first case=12.2%.

¹ 48 hours—1 case; ² 48 hours—3 cases; ³ 48 hours—3 cases, and 72 hours—1 case.

Reactions after Oral Administration of Aureomycin

Five cases in the aureomycin-treated group developed uraemia, two cases lung complications, and two cases jaundice, total nine cases (18%). Similarly in the sulphaguanidine-treated group four cases developed uraemia, one case tympanitis, one case vasomotor failure, and one case jaundice with pain in the abdomen, total seven cases (20%). In contrast with this only two cases (5.7%) in the saline-treated group showed complications. It is thus a question whether these complications were in any way the results of drug treatment. Though the appearance of jaundice in two cases and uraemia in five cases treated with aureomycin may be considered as some evidence for the toxic action of the drug it is doubtful whether the latter was directly responsible for the complications: not only did the amounts of the drug administered to the patients who developed complications vary widely—namely, 1, 1.75, 4.5, 4.75, and 7.25 g. in the uraemic cases, 3.5 and 4.75 g. in the jaundiced cases, and 5.25 and 6 g. in cases with lung complications—but also all those who received as much as 9 g. each (two severe, three moderate, and one mild), recovered without any complication. This question will be discussed again later.

Results

The data relating to the clinical states and the progress of the patients in the aureomycin-, sulphaguanidine-, and saline-treated groups are summarized in Table II. As will be seen, the cases in the three groups are fairly well distributed in regard to age, clinical stage at the time of admission, specific gravity of blood, condition of urine, and positive isolation of *V. cholerae*. In so far as the end-results are concerned there is no appreciable difference between the three methods of treatment, but in regard to certain minor points aureomycin treatment showed some advantages.

Unlike the previous trial by the intravenous route the blood non-protein nitrogen was generally within the normal range in the majority of cases treated by aureomycin, being high only in two of the twelve cases examined. The same was true of the control groups. The average duration of the suppression of urine in the aureomycin group was significantly less than that of the saline-treated group by 6.8 hours ($t=2.099$ with 41 d.f., as against 2.021 with 40 d.f. at 5% point of t), but there was very little difference between the aureomycin and the sulphaguanidine groups in this respect ($t=0.105$ with 39 d.f. and 90% point of t with 40 d.f.=0.126).

So far as complications, such as uraemia, lung symptoms, jaundice, and tympanitis, are concerned, the advantage was definitely in favour of the saline controls, there being hardly any difference between the aureomycin and the sulphaguanidine groups. However, a significant advantage of the aureomycin group over the saline controls is found in respect of the duration of excretion of vibrios. Although the difference is small it is statistically significant ($t=3.514$ with 43 d.f., as against 3.551 with the same d.f. at 0.1% point of t). The same advantage is found over the sulphaguanidine group ($t=2.417$ with 45 d.f. and 2% and 5% point of t with the same d.f. are 2.423 and 2.021 respectively). Similarly the average duration of the acute stage was curtailed by 10 hours in the aureomycin group compared to the saline group ($t=2.919$ with 69 d.f. and 1% point of t with 60 d.f.=2.660). In this respect the sulphaguanidine group gave nearly the same results as the aureomycin group. The average number of stools during the first five days of hospital treatment was also less in the aureomycin-treated group than in the sulphaguanidine- or the saline-treated group, though the difference is not statistically significant. Some difference was also noted in the average length of stay in hospital of patients in the three groups, the advantage being in favour of the aureomycin group, but the discharge of the patients from the hospital was not strictly guided by the condition of the patient. There was no difference, however, in the fatality rates of the three groups of patients.

Comments

Although no appreciable reduction in the fatality rate of patients treated with oral aureomycin was obtained, the findings of this investigation are nevertheless interesting. Firstly, the toxicity seen after intravenous administration was practically eliminated, the toxicity being no greater than was observed in the cases treated with sulphaguanidine. It is true, complications were much less without any chemotherapy, but treatment with aureomycin had certain advantages. For instance, there was a significant reduction in the average period of suppression of urine as well as of the acute stage of the disease. Perhaps more important than this, from the point of view of epidemiology and international quarantine laws, is the fact that the patients became vibrio-free earlier than with sulphaguanidine or saline treatment. However, judging from the fatality rates and from the average amount of saline used in each group it is difficult to avoid the impression that the drug had no influence upon the course of the disease. This would appear to support Lahiri's (1951) view that no specific drug has yet been found in cholera. We do not, however, fully subscribe to this. In the experience of one of us (S. C. S.) in the field trial of sulphaguanidine (Seal, 1947) it became quite clear that the secret of success in the treatment of cholera cases lay in their early treatment; once dehydration and collapse set in, the administration of a vibrio-static drug is of no help without saline treatment; and treatment with a vibriocidal drug becomes sometimes positively harmful owing to the release of a large quantity of endotoxin at a stage when the patient is already at a serious disadvantage owing to the extreme loss of fluid.

Another difficulty is the great individual variation in the behaviour of patients against cholera infection. Some people are more apt to develop vasomotor failure or uraemic symptoms than others, and such cases generally do not respond easily to treatment. Again, the fatalities mostly occur in the earlier part of the epidemic and there is proportionately greater chance of recovery in cases occurring after the peak period. Thus, in the present study, deaths in all the three groups occurred during the first two weeks of May, 1951—that is, the early weeks of this investigation. In fact no fatality occurred amongst 35 patients treated with another antibiotic during the period between May 22 to July 18, 1951. The failure of any drug in the advanced stages of cholera does not necessarily mean that it has no action on the cholera vibrio. Aureomycin is vibriocidal *in vitro*, and the quicker disappearance of the organism from the convalescent cases indicates that the drug is also effective *in vivo*. The dose of aureomycin capsules used in the present investigation was probably high. A lower dose of 3 to 5 g. according to the stage of the disease may be found sufficient.

Summary

1. In a trial of oral aureomycin for the treatment of cholera, 50 patients were treated with aureomycin capsules, 35 with sulphaguanidine, and 35 with saline, the last two groups acting as controls.

2. There was no difference in the fatality rates among the three groups, which were all about 14%. In the group receiving aureomycin the acute stage was shorter, and the duration of suppression of urine and the period of excretion of vibrios were reduced. There were no serious toxic effects.

3. The results are discussed.

Thanks are due to Dr. A. K. Dutta Gupta, Principal, Nilratan Sircar Medical College, for kindly providing facilities for this investigation and to Dr. M. Chakrabarti, Professor of Physiology, Medical College, Calcutta, for carrying out the blood examinations for the estimation of N.P.N.

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