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ANTIBIOTICS IN THE TREATMENT OF SHIGELLA AND SALMONELLA ENTERITIS

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Gastroenteritis is the most common illness requiring admission to the paediatric wards at Baragwanath Hospital. In 1956 over 1,000 children suffering from this illness were admitted to the wards[1] and for every one admitted at least 20 others were treated in the out-patients department. It is estimated that in 1951 every tenth child in the African population of Johannesburg succumbed to an attack of diarrhoea before reaching the age of one year.[2] In Cape Town, 45% of all deaths in non-European children under one year of age were due to gastroenteritis.[3]

It was stated at one time that, in the United States and elsewhere, most cases of diarrhoea and enteritis were due to bacillary dysentery.[4] This would appear, even today, to apply to certain sections of the South African non-European population. In the summer of 1954-55, shigella and salmonella organisms were isolated from 71 (29%) of 241 consecutive patients with gastroenteritis admitted to one of our wards.[5] The mortality rate among patients with these infections was considerably higher than among those suffering from 'non-specific' gastroenteritis. In an unselected series of 100 paediatric out-patients at this hospital, suffering from gastroenteritis during the summer months, 23 were found to be due to these infections.[6] In another investigation carried out at this hospital, shigella and salmonella organisms were isolated from 37·5% of 200 consecutive paediatric admissions for gastroenteritis.[2] It was estimated that under ideal conditions for investigation, approximately 50% of all severe cases of gastroenteritis would be shown to be caused by shigella or salmonella infection.[2]

In view of the high morbidity and mortality associated with shigella and salmonella enteritis in the African population of Johannesburg, it is of great importance to determine the most efficacious antibiotics for the treatment of this group of diseases. From our investigation in 1954-55, chloramphenicol* emerged as the most effective antibiotic for these infections, as compared with sulphonamides and oxytetracycline†. However, chloramphenicol is expensive and has certain side-effects and is therefore not an ideal drug for out-patient use. In addition, we have gained the impression over the past few years that the efficacy of chloramphenicol against shigella and salmonella was diminishing. It was therefore considered important to reassess the place of this antibiotic in the treatment of these infections, and if possible, to find a safer and less expensive antibiotic.

* Used as chloromycetin (Parke, Davis).
† Used as terramycin (Pfizer).

MATERIAL AND METHODS

This study was done in two parts:

1. *In Vitro Testing*

During a 4-month period of the summer of 1957-58, all cultures of shigella and salmonella organisms isolated from patients in our paediatric wards and out-patients department were subjected to *in vitro* sensitivity tests. The antibiotics tested were chloramphenicol, streptomycin, neomycin, tetracycline and sulphatriad (sulphamerazine 1 part, sulphathiazole 1·4 parts, sulphadiazine 1·4 parts). There was a total of 145 positive cultures, 92 of which were shigella organisms and 53 were salmonella; of the shigella sub-groups, 64 were Flexner, 13 Sonne, 8 Newcastle and 7 Schmitz. The methods of culture and testing were as follows:

Rectal swabs were emulsified in tubes of saline and of selenite F as soon after collection as possible. The saline tubes were plated on 'SS' and desoxycholate citrate agar after approximately 20 minutes, the selenites being treated in the same way after 24 hours incubation. Suitable colonies were picked off and finally identified biochemically and serologically. Blood agar plates were flooded with a 24-hour pure culture of the organism in nutrient broth, so obtaining a uniform inoculum. Any excess fluid was poured off. The petri dishes were then incubated at 37°C, with lids ajar until dry. The antibiotic sensitivity discs were placed on the surface of the plates by means of sterile forceps at intervals of 1½ to 2 inches. These discs contained the antibiotics in strengths of 50 μg. The inverted plates were then incubated overnight at 37°C. The sensitivity of the organism was assessed as follows: Zone of inhibition of growth less than 2 mm.—'resistant'; 2-4 mm.— 'slightly sensitive'; 4-6 mm.—'moderately sensitive'; greater than 6 mm.—'highly sensitive'.

2. *Clinical Trials*

Concurrent with the commencement of *in vitro* testing, all ward patients with shigella and salmonella enteritis were treated with chloramphenicol (chloromycetin palmitate) in a dose of 40-50 mg. per lb. body weight per day, for a period of 10 days. This was done regardless of the results shown in the *in vitro* tests. In all, 56 patients with shigella dysentery and 31 patients with salmonella enteritis, were so treated.

After *in vitro* testing had been carried out for about 2 months, it became apparent that streptomycin might also be effective in shigella and salmonella infections. Thus 19 patients with shigella dysentery and 10 patients with salmonella enteritis were treated with oral streptomycin sulphate in a dose of 40-50 mg. per lb. body weight per day, for a period of 10 days. Streptomycin sulphate was freshly made up out of ampoules in our dispensary on alternate days.

All the patients included in this trial were under 2 years of age; all were very ill, 94% requiring intravenous therapy. Relapses were assessed on the basis of increased frequency of stools, recurrence of pyrexia, and principally on a recurrence of clinical dehydration, requiring intravenous therapy. Where relapses occurred, change of therapy was made to the most effective antibiotic as indicated by the *in vitro* tests. When each course of treatment was complete, or when changes of treatment were made, rectal swab cultures were repeated to ascertain whether the original infecting organism was still present in the patient's stools. This was done immediately after a course of therapy was complete. In only a few cases could rectal swab cultures be repeated several days after completion of treatment, since shortage of hospital accommodation forced us to discharge most patients immediately after clinical cure had been effected.

RESULTS OF INVESTIGATION

1. *In Vitro Tests*

The results of the *in vitro* tests with shigella organisms are shown in Table I, and with salmonella organisms in Table II. These tests show that of the 92 shigella cultures tested, the great majority (80%) were highly sensitive to chloramphenicol, 32 (35%) were highly sensitive to streptomycin and 23 (25%) were highly sensitive to neomycin. A high proportion (53% and 68% respectively) were moderately sensitive to streptomycin and neomycin. The sensitivity to tetracycline was poor; 20 cultures (22%) were resistant and only 1 was highly sensitive to this antibiotic. 88 (96%) of the cultures were completely resistant to sulphatriad. Analysis of the *in vitro* tests of the various shigella sub-groups (Flexner, Sonnei, Newcastle and Schmitz) show no significant differences in sensitivity (Table III).

TABLE I. IN VITRO ANTIBIOTIC SENSITIVITY RESULTS OF SHIGELLA ORGANISMS

Sensitivity	*Antibiotic employed*				
	Chloramphenicol	*Streptomycin*	*Neomycin*	*Tetracycline*	*Sulphatriad*
Highly sensitive ..	74	32	23	1	2
Moderately sensitive	14	49	63	41	1
Mildly sensitive ..	0	4	3	30	1
Resistant	4	7	3	20	88
Total No. of cases..	92	92	92	92	92

TABLE II. IN VITRO ANTIBIOTIC SENSITIVITY RESULTS OF SALMONELLA ORGANISMS

Sensitivity	*Antibiotic employed*				
	Chloramphenicol	*Streptomycin*	*Neomycin*	*Tetracycline*	*Sulphatriad*
Highly sensitive ..	26	26	32	0	0
Moderately sensitive	26	25	19	3	0
Mildly sensitive ..	0	1	1	12	0
Resistant	1	1	1	38	53
Total No. of cases..	53	53	53	53	53

TABLE III. IN VITRO ANTIBIOTIC SENSITIVITY RESULTS OF SHIGELLA SUBGROUPS

	Sensitivity	*Antibiotic employed*				
		Chloramphenicol	*Streptomycin*	*Neomycin*	*Tetracycline*	*Sulphatriad*
Flexner 64 Cases	Highly sensitive	50	16	16	1	2
	Moderately sensitive	10	38	43	33	1
	Mildly sensitive	0	4	3	19	0
	Resistant	4	6	2	11	61
Sonnei 13 Cases	Highly sensitive	10	9	2	0	0
	Moderately sensitive	3	3	10	2	0
	Mildly sensitive	0	0	0	5	1
	Resistant	0	1	1	6	12
Newcastle 8 Cases	Highly sensitive	7	5	4	0	0
	Moderately sensitive	1	3	4	0	0
	Mildly sensitive	0	0	0	5	0
	Resistant	0	0	0	3	8
Schmitz 7 Cases	Highly sensitive	7	2	1	0	0
	Moderately sensitive	0	5	6	6	0
	Mildly sensitive	0	0	0	1	0
	Resistant	0	0	0	0	7

Of the 53 salmonella cultures tested, 32 (60%) were highly sensitive to neomycin and 26 (49%) in each case were highly sensitive to chloramphenicol and streptomycin. Most cultures (72%) were resistant to tetracycline and all were resistant to sulphatriad. One culture was resistant to all the antibiotics tested.

2. *Clinical Trials*

In the clinical trials (Table IV) 56 patients with shigella infection were treated with chloramphenicol; of these, 41 patients (73%) had an uneventful recovery on one course of treatment; 8 patients died, all within the first 5 days of treatment, while dehydration and electrolyte balance were being corrected; 7 patients relapsed, but ultimately recovered. In one patient relapse was due to staphylococcal enterocolitis and septicaemia.

Nineteen patients with shigella dysentery were treated with

TABLE IV. CLINICAL TRIAL (TOTAL 116 CASES)

A. GROUP TREATED ON CHLORAMPHENICOL (87 CASES)

Infection	*No. of cases*	*Relapses*	*Deaths*	*Uneventful recovery*
Shigella	56	7	8	41 (73%)
Salmonella	31	2	6	23 (74%)
Total	87	9	14	64 (74%)

B. GROUP TREATED ON STREPTOMYCIN (29 CASES)

Infection	*No. of cases*	*Relapses*	*Deaths*	*Uneventful recovery*
Shigella	19	7	4	8 (42%)
Salmonella	10	3	3	4 (40%)
Total	29	10	7	12 (41%)

oral steptomycin; of these 8 (42%) recovered uneventfully, 4 died and 7 relapsed. Relapses were treated with the antibiotic to which the particular infecting organism was most sensitive by *in vitro* tests. In 5 of these cases the antibiotic employed was chloramphenicol and in the other 2, neomycin. One of the cases in which a change was made to chloramphenicol therapy died during the course of treatment, the others recovered.

31 patients with salmonella infection were treated with chloramphenicol, of whom 23 (74%) recovered uneventfully, 6 died and 2 relapsed but responded to a second course of treatment. Deaths in this group all occurred within the first 6 days of treatment. One of the 2 patients with salmonella infection who relapsed while on chloramphenicol therapy was the only case in the whole series in which on rectal swab culture an organism was found after a complete course of therapy. The rectal swab from this patient produced the only culture of salmonella showing complete resistance to chloramphenicol *in vitro*.

10 patients with salmonella enteritis were treated with oral steptomycin; 4 (40%) of these recovered uneventfully, 3 died, and 3 relapsed. Neomycin therapy was used in 2 of the relapses and chloramphenicol in the third case. All three recovered.

The group of patients treated with oral streptomycin was relatively small and the trial of this antibiotic was abandoned as it was soon apparent that the death and relapse rate in this group was considerably higher than in the group treated with chloramphenicol.

DISCUSSION

Chloramphenicol emerged from *in vitro* tests as the most potent agent against shigellae and one of the most potent against salmonellae. These findings correlated well with the results of the clinical trials, where 73% and 74% of patients with shigella and salmonella enteritis respectively, treated with this antibiotic, made an uneventful recovery. These results compare well with those obtained in our previous series dealing with similar cases.[5] Thus our fears that chloramphenicol was losing its efficacy in patients with these infections, was not substantiated. One case developed a staphylococcal enterocolitis and septicaemia, but no haematological complications were seen in the 87 cases treated with this antibiotic. This low incidence of complications of chloramphenicol therapy is a reflection of what we have found over several years in using it in the treatment of hundreds of cases of severe gastro-enteritis.

In vitro tests showed that the majority of shigella and salmonella cultures were sensitive to streptomycin. However, the use of this antibiotic in the clinical trials was disappointing; only 42% and 40% of patients suffering from shigella and salmonella enteritis respectively recovered uneventfully on treatment with it. Sangster[7] found streptomycin to be very efficacious in the treatment of a large series of adults and children suffering from shigella dysentery. However, his cases, as contrasted with ours, were not severely ill; less than 1% required intravenous therapy for dehydration. The series are thus probably not comparable. The discrepancy between our *in vitro* and *in vivo* results with streptomycin may be partly explained by the work of Forbes,[8] who showed that *in vitro* streptomycin kills shigella Sonne in lower concentration than chlortetracycline, oxytetracycline or chloramphenicol, but that this organism acquires resistance to streptomycin earlier than to the other antibiotics. Brown and Bailey,[9] discussing the use of streptomycin in B. coli gastroenteritis in infants, also state that resistance is rapidly acquired to this antibiotic by intestinal organisms.

In vitro tests showed that shigellae were slightly less sensitive to neomycin than to chloramphenicol, but that salmonellae were more sensitive to neomycin than to any of the other antibiotics. Neomycin was not included in the clinical trials, but will be tested at some future time. This antibiotic is too toxic for parenteral administration, but is not absorbed when given orally and is safe when administered this way. At present, it is too expensive to allow its routine use, but it is possible that a shorter course of therapy than we have employed in using chloramphenicol may be sufficient.

Tetracycline and its derivatives have been disappointing in the treatment of shigella and salmonella enteritis. In our previous series[5] oxytetracycline was less effective than chloramphenicol in treating these infections. In the present *in vitro* tests, the majority of cultures were very poorly sensitive to tetracycline, especially the salmonellae, 72% of which were completely resistant to this antibiotic. These findings have been in contrast to those of other workers[10, 11] who found chlortetracycline, oxytetracycline and tetracycline effective particularly in the shigella dysenteries.

Sulphatriad did not inhibit the growth of shigellae and salmonellae in our *in vitro* tests, 96% and 100% of these cultures, respectively, being completely resistant. Sulphonamides are still very commonly used in the treatment of gastroenteritis, but it appears rather pointless to do so where a high proportion of these cases are due to shigella and salmonella infections, particularly in view of the not inconsiderable toxic effects of these chemotherapeutic agents.

It thus appears from this investigation that chloromycetin is the antibiotic of choice in the treatment of shigella and salmonella enteritis and that neomycin warrants further investigation in their treatment.

SUMMARY

In vitro sensitivity tests were carried out on 92 cultures of shigellae and 53 of salmonellae, using chloramphenicol, streptomycin, neomycin, tetracycline and sulphatriad.

The findings of the *in vitro* tests are contrasted with the results of treatment of 116 patients with shigella and salmonella enteritis, using chloramphenicol and oral streptomycin.

Chloramphenicol was effective, both *in vitro* and *in vivo*. Streptomycin was effective *in vitro* but relatively ineffective *in vivo*. *In vitro* shigella and salmonella sensitivity to neomycin was good, but was very poor to tetracycline and sulphatriad.

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