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SULPHONAMIDES AND STREPTOMYCIN IN BACILLARY DYSENTERY

A CONTROLLED TRIAL

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Bacillary dysentery is very prevalent in many warm climates, and in recent years its incidence has greatly increased in temperate climates, especially during the winter and spring. Before the introduction of sulphonamides the course of the illness was not infrequently prolonged, disabling, and sometimes fatal. The use of the poorly absorbed sulphonamides in the early years of the second world war revolutionized treatment, and later the absorbable sulphonamides in smaller dosage were found to be equally effective, although special care must be taken with them, especially in the tropics, to keep the patient free from renal blockage by adequate hydration. The combination of three sulphonamides used in this trial has generally been found to be remarkably free from this defect. In recent years, however, sulphonamide-resistant strains, especially of *Shigella sonnei*, have been met with increasingly, and streptomycin given orally has been widely reported as a satisfactory though expensive substitute, but, again, some strains have become resistant to streptomycin. In some hospitals, therefore, the newer broad-spectrum antibiotics have been employed in moderate or low dosage. Marked success in the control of the dysenteric symptoms has been claimed with these, but there is a risk of side-effects, some very serious. In any case, the high cost

of these drugs makes their massive use out of the question in most tropical and semi-tropical countries.

In order to explore the factors of efficiency combined with cheapness in the mass treatment of bacillary dysentery, a small controlled trial was carried out in Zagreb with (a) sulphonamides alone, (b) tablets containing about 80% sulphonamides and 20% streptomycin, and (c) streptomycin alone. Patients with the acute dysenteric syndrome (abdominal pain, tenesmus, and acute diarrhoea with blood and mucus in the stools), who had had no specific treatment before admission to the hospital, were given the following treatment in successive groups, the dosage being suitably modified in children.

Group 1.—0.5-g. tablets of "sulphatriad" in dosage for adults of 1 g. six-hourly for seven days (total 28 g.). (0.5 g. sulphatriad=0.185 g. sulphathiazole + 0.185 g. sulphadiazine + 0.130 g. sulphamerazine.)

Group 2.—"Streptotriad" tablets (each containing 265 mg. sulphatriad and 65 mg. streptomycin sulphate) in dosage for adults of 2 tablets six-hourly for four days only (total 2.08 g. streptomycin and 8.5 g. sulphatriad).

Group 3.—Streptomycin tablets in dosage for adults of 2 250-mg. tablets six-hourly for four days only (total 8 g. streptomycin sulphate).

A fourth group of patients was started on symptomatic treatment only, but the first two patients remained ill so long that this was, temporarily at least, abandoned.

The numbers in each group are small because so many patients had had some specific treatment before admission and were therefore excluded from the trial. However, before treatment was begun each patient had a careful clinical evaluation, including daily inspection of the stools, a rectal swab, and three stools taken at the bedside, inoculated into desoxycholate medium and incubated immediately; in addition each stool passed during the treatment and for a few days thereafter was bacteriologically examined.

Results

Group 1 consisted of 12 patients—5 *Sh. flexneri* (types I, II, or VI), 5 *Sh. sonnei*, and 2 from whom no shigellae were isolated. In 7 out of 10 proved cases fever after admission ranged from 37.2 to 39.2° C. The treatment was started on the second or third day of disease in 8 of the 10 proved cases. The temperature became normal on the first day of treatment in 6 out of 7 febrile patients. In the proved cases the stools became normal between the first and sixth days of therapy except in two instances. Bacteriologically all the cases were free from shigellae after the fifth day of treatment, the *Sh. sonnei* cases taking longer than the *Sh. flexneri* cases to clear up.

Group 2 consisted of 15 patients—10 *Sh. flexneri* (types I, II, III, or IV), 2 *Sh. sonnei*, 1 *Sh. schmitzii*, and 2 bacteriologically negative. Fever after admission in 8 out of 13 proved dysentery cases ranged from 37.5 to 39.3° C. The treatment was started on the second or third day of disease in 9, on the fourth or fifth day in 2, and on the seventh and ninth days in 2. The temperature became normal on the first or second day of treatment in all 8 febrile cases. The stools became normal in appearance between the third and eighth days, mostly on the fifth or sixth day. Bacteriologically the stools became negative after the first day of treatment

in 7 of the 10 *Sh. flexneri* infections, on the third and fifth days of treatment in 2, and in the remaining case only after a subsequent course of chloramphenicol. The 2 cases of *Sh. sonnei* infection became negative on the first and second days of treatment and the case of *Sh. schmitzii* on the third day.

Group 3 consisted of 21 patients—13 *Sh. flexneri* (types I, II, III, or VI), 4 *Sh. sonnei*, 1 *Sh. etousae*, and 3 bacteriologically negative. Of the 17 confirmed dysentery cases, 14 had fever ranging from 37 to 39.4° C. (11 above 37.5° C.). The treatment was started in 17 cases on the third to fifth day of disease, and in 1 on the sixth day. The temperature became normal in 12 of the 14 febrile

much larger dosage of streptomycin alone. Out of 13 cases of *Sh. flexneri* infections in group 3, 8 were still positive after the first day of treatment, as compared with 3 out of 10 in group 2. The single case of *Sh. etousae* infection also cleared rather slowly after streptomycin treatment.

Conclusions

In countries where *Sh. flexneri* infection is prevalent and where the organism has not yet become resistant to sulphonamides, fairly good results can be obtained by the use of absorbable sulphonamides such as sulphatriad, provided that patients are not allowed to become dehydrated.

Chemotherapy in Successive Groups of Cases of Bacillary Dysentery

Group	Treatment	No. of Cases	Range of Ages	Type of Shigella			Result in Proved Cases	
				Flexneri	Sonnei	Not Isolated	Day of Treatment Stools Normal and No. of Cases	Day of Treatment Stools Negative and No. of Cases
1	Sulphatriad	12	2-66 (av. 27)	5	5	2	2nd-6th (all except 2)	1st-6th (all; but earlier in Flexner cases)
2	Streptotriad	15	17-57 (av. 35)	10	2	2 (1 Schmitzii)	3rd-8th (all, but mostly 5th or 6th)	Flexneri: 2nd, 7 3rd-5th, 1 Later, 1 Sonnei: 1st-2nd, 2 Schmitzii: 3rd, 1
3	Streptomycin	21	18-37 (av. 26)	13	4	3 (1 Etousae)	3rd-7th, 13 Later, 5	Flexneri: 1st-4th, 1 Later, 4 Sonnei: 3rd-8th, 4 Etousae: 5th, 1

cases on the first or second day of treatment, in 1 on the third, and in one on the fourth day. The stools became normal in appearance between the third and seventh days of treatment in 13 cases; in 3 cases (2 *Sh. flexneri* and 1 *Sh. etousae*) the stools remained semi-solid until discharged, bacteriological cure being delayed as well. Bacteriologically the stools became negative between the first and fourth days of treatment in 9 of the 13 *Sh. flexneri* infections, and 3 were still positive on the fifth, sixth, and seventh days respectively; all 4 cases of *Sh. sonnei* infections passed the organism for two to seven days, and the *Sh. etousae* case for four days after the start of treatment. In the 3 bacteriologically negative cases the stools were normal between the fourth and ninth days of treatment (see Table).

Discussion

Although there were some differences in the ages of the patients in the various groups, as well as in the day of disease on which specific treatment was started, the groups on the whole were reasonably comparable. It is clear that a certain therapeutic effect was obtained in each group, and that bacteriological cure was achieved earlier than full clinical cure.

In groups 1 and 2 the *Sh. flexneri* infections responded fairly well; it would seem that sulphonamides were certainly effective in *Sh. flexneri* infections, although in a few the bacteriological cure was delayed. The response of *Sh. sonnei* infections, on the other hand, to sulphatriad treatment in group 1 was poor; 2 of these patients were young children (2 and 6 years of age)—a possible adverse factor—but this finding is in harmony with experience in other longer series of cases. In group 2, on the contrary, the 2 cases of *Sh. sonnei* infection responded rapidly to streptotriad treatment.

On comparing the results in groups 2 and 3 it was somewhat surprising to find that both *Sh. flexneri* and *Sh. sonnei* infections responded better to the streptomycin-sulphonamide combination than to the

Quicker and better results may be obtained with the relatively cheap streptomycin-sulphonamide tablets (streptotriad). This drug appears to be effective also in *Sh. sonnei* infections.

In this trial streptotriad gave better results in both *Sh. flexneri* and *Sh. sonnei* infections than the much more expensive streptomycin treatment, in which nearly four times the amount of streptomycin was used per case.

Summary

The treatment of bacillary dysentery was studied in small groups of cases in Zagreb, using three different chemotherapeutic agents.

A cheap compound consisting of three absorbable sulphonamides and a small amount of streptomycin proved to be superior (a) in Sonne dysentery to the absorbable sulphonamides alone, and (b) in both Flexner and Sonne dysentery to a much larger dosage of streptomycin alone.

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In a pamphlet entitled *Smoking: The Cancer Controversy* Sir R. A. FISHER, Sc.D., F.R.S., sets out his views on the question. They may perhaps be summarily expressed by quoting the following sentence: "The curious associations with lung cancer found in relation to smoking habits do not, in the minds of some of us, lend themselves easily to the simple conclusion that the products of combustion reaching the surface of the bronchus induce, though after a long interval, the development of a cancer." The pamphlet consists mainly of material that has appeared in the *British Medical Journal*, *Centennial Review*, and *Nature*, together with a note of the author's views on some statistics of inhaling tobacco smoke. It is published by Oliver and Boyd for 2s. 6d.