CHEMOTHERAPY OF INTESTINAL INFECTIONS TREATED WITH SULPHONAMIDE COMPOUNDS

BY

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Sulphaguanidine was originally discovered by Buttle in 1938, but little attention was paid to it until the further researches of Marshall *et al.* in 1940 emphasized its solubility yet poor absorption from the gastro-intestinal tract, and thus presented a new principle in the treatment of intestinal infections somewhat analogous to the use of sulphanilamide derivatives as urinary antiseptics. This was confirmed by Roblin and Winnek (1940). It was used with success by Marshall and his colleagues (1941) in the treatment of acute bacillary dysentery in children in the Harriet Lane Home, New York; and Lyon (1941) described his findings in a group of 23 cases, which were compared with a similar number of controls. Subsequently Anderson and Cruickshank (1941) reported the successful treatment of 41 adult cases of Flexner dysentery, which were compared with a series of 55 control cases in the same epidemic. Fairley and Boyd (1942, 1943) published their observations on some 500 cases treated in the Middle East, the bulk of which were Shiga infections, although a number of cases of Flexner, Schmitz, and Sonne infections were also successfully treated. Bulmer and Priest (1942) and Brewer (1943) have also reported their findings in 76 and 77 cases respectively in the same sphere of military operations. Hall (1941) recorded the successful treatment of 20 cases of typhoid fever with sulphaguanidine, while Levi and Willen (1941) reported the successful treatment with sulphaguanidine of a typhoid carrier who had remained positive after cholecystectomy. Canizares and Morris (1941) made a study of 6 patients with proctitis due to lymphogranuloma venereum in whose condition some improvement was effected by means of sulphaguanidine prior to surgical intervention; while Firor and Jonas (1941) suggested that it might be successfully used in chronic ulcerative conditions of the bowel. Firor and Poth (1941) used it pre-operatively to reduce coliform organisms in the large intestine of patients submitted to colonic surgery. Henderson (1943) has recently recorded the excellent results achieved with sulphaguanidine in epidemic gastro-enteritis of the newborn.

Clinical Findings

During 1941 and the first six months of 1942 there were treated in the City Hospital, Aberdeen, 273 cases of bacillary dysentery, all of which were proved bacteriologically. Of these, 140 were given no chemotherapy but saline treatment only, 83 were treated with sulphaguanidine, and 50 were treated with sulphanilamide. Unfortunately, it was not possible to run the three series concurrently. Specimens of stool were examined twice weekly for organisms, and the blood sedimentation rate was taken on admittance to hospital and at the completion of the course in those receiving drug therapy. The cases under review comprise Flexner and Sonne infections, and were, on the whole, of a mild character, with seldom more than 5 or 6 stools a day, some of which contained blood and mucus and others merely mucus, while some were simply loose. All cases showing blood and mucus in the stools were classified as "acute," while those with loose stools were classified as "convalescent carrier cases." Low-grade pyrexia with minor signs of dehydration and occasional vomiting was observed in the 140 cases receiving no chemotherapy. Of 24 who on admission could be described as acutely ill 6 died, two of the deaths being attributable to intercurrent disease. Where necessary, parenteral fluid was given intravenously in the form

of 5% glucose-saline, but, so far as was possible, patients were encouraged to take fluid by mouth, the quantity aimed at being 8 to 10 pints in 24 hours for adults and proportionately less for children. Throughout, the customary general nursing measures were employed.

Dosage

Sulphaguanidine.—The dosage used was an initial loading dose of 0.5 g. per kilo of body weight for the first 24 hours, followed by a maintenance dose of 0.1 g. for the next 4 days. The tablets were powdered, and were administered in milk 4-hourly for the first 24 hours and thereafter 3 times daily for 4 days.

Sulphanilamide.—The following doses were given 4-hourly for the first 4 days and 3 times daily for a further 4 days, each tablet containing 0.5 g.:

0-3 months	..	..	..	..	1/4	tablet
3 months-2 years	..	..	..	..	1/2	"
2-5 years	..	..	..	..	3/4	"
5-10 "	..	..	..	..	1	"
10-15 "	..	..	..	..	1 1/2	tablets
Over 15 years	..	..	..	..	2	"

No Chemotherapy.—Adult patients were given 2 drachms of sodium sulphate night and morning, and child patients 1 drachm night and morning.

At the end of the first 24 hours the drug content in faeces and blood was estimated and the blood sedimentation rate was also determined. Similarly, when a patient became bacteriologically negative the blood sedimentation rate was again taken. Specimens of stool were examined twice weekly until three consecutive negative results were obtained. In no case were rectal swabs taken; nor were the faeces mixed before obtaining specimens, these being taken purely at random.

Analysis of Flexner Cases

Flexner Cases treated with Sulphaguanidine.—Forty-seven cases were treated; the average duration of stay in hospital was 13.4 days and the average number of days before becoming bacteriologically negative was 6.6. These were subdivided into 13 acute cases and 34 convalescent carriers.

Flexner Cases treated with Sulphanilamide.—Twenty-one cases were treated; the average duration of stay in hospital was 30.4 days and the average number of days before becoming bacteriologically negative was 20.9. Eleven cases were regarded as acute and 10 as convalescent carriers.

Flexner Cases—No Chemotherapy.—Eighty-three cases were treated without chemotherapy; the average duration of stay in hospital was 22.7 days, while the average number of days before becoming bacteriologically negative was 13.3. These were subdivided into 63 acute cases and 20 convalescent carriers.

Analysis of Sonne Cases

Sonne Cases treated with Sulphaguanidine.—Thirty-six cases were treated; the average duration of stay in hospital was 17.1 days and the average number of days before becoming bacteriologically negative was 10.3. These were divided into 16 acute cases and 20 convalescent carriers.

Comparative Results of Chemotherapy

Treatment		Flexner			Sonne		
		Acute	Conv. Carr.	All Cases	Acute	Conv. Carr.	All Cases
Sulphaguanidine	No. of cases	13	34	47	16	20	36
	Average days in hospital	12	13.9	13.4	12.1	21	17.1
	Average days bacteriologically positive	4.6	7.4	6.6	5.9	14.3	10.3
Sulphanilamide	No. of cases	11	10	21	9	20	29
	Average days in hospital	28.8	32.2	30.4	26.1	22.8	23.8
	Average days bacteriologically positive	19	23.1	20.9	16.3	13.4	13.9
No chemotherapy	No. of cases	63	20	83	18	39	57
	Average days in hospital	23.4	20.5	22.7	19.4	18.8	19
	Average days bacteriologically positive	14	10.5	13.3	9.9	9.4	9.5

Sonne Cases treated with Sulphanilamide.—Twenty-nine cases were treated; the average duration of stay in hospital was 23.8 days, while the average number of days before becoming bacteriologically negative was 13.9. These cases were divided into 9 acute cases and 20 convalescent carriers.

Sonne Cases—No Chemotherapy.—Fifty-seven cases were treated; the average duration of stay in hospital was 19 days, while the average number of days before becoming bacteriologically negative was 9.5. These were divided into 18 acute cases and 39 convalescent carriers.

Biochemical Findings

Sulphaguanidine.—Blood concentrations usually varied from 3 mg. per 100 c.cm. to a trace, but in one case 9 mg. was found, in 2 cases 8 mg., in 1 case 7 mg., and in one other case 6 mg. per 100 c.cm. The concentration in faeces varied from a trace to as high as 10,000 mg. per 100 c.cm. At the beginning of the series leucocyte counts were done as a routine in each case, but as these were invariably normal this examination was discontinued.

Sulphanilamide.—Blood concentrations were lower than in the case of sulphaguanidine-treated cases, the highest concentration in the blood being 3.3 mg. and the lowest 0.1 mg. per 100 c.cm. In the main they varied between 1 and 2 mg. Concentrations in the faeces varied between a trace and 840 mg. per 100 c.cm., the average being between 300 and 400 mg.

Toxicity of Drugs

In no case treated with either sulphaguanidine or sulphanilamide was any evidence of toxicity observed, judged by the standards of nausea, cyanosis, vomiting, pyrexia, rash, or haematuria. The urine was examined every second day for blood and albumin, but this practice was later reduced to twice weekly on account of lack of toxic symptoms. Older patients were also questioned with regard to any disagreeable effects, but these were remarkable by their absence.

Gastro-enteritis in Infants

Four cases were treated with sulphaguanidine; 3 of these patients died without any improvement in the stools or in the general condition. All were male babies, varying in age from 1 to 2 months and presenting varying degrees of dehydration, with frequent loose, green, and offensive stools from which no specific organism was obtained. The dosage used was 3 g. during the first 24 hours as a loading dose, followed by 2 g. daily for 4 days, but in none of the cases did the concentration in the blood exceed 0.8 mg. per 100 c.cm., although the concentration in the faeces went as high as 25,000 mg. We can only conclude that the dehydration and the frequency of the stools were so pronounced that the drug had no time to be absorbed and was passed rapidly through the intestines.

Paratyphoid B Fever

Eight cases treated with sulphaguanidine were taken, varying in age from 3 months to 53 years. Sulphaguanidine had no effect on the stools, which remained positive throughout the course and for a considerable time afterwards, although in two cases a distinct improvement in clinical condition was noted. These patients were exceedingly listless, with marked loss of appetite, but within 48 hours of starting treatment with sulphaguanidine their general condition had greatly improved. The dosage varied from 5.25 g. daily for 6 days to a maximum of 10.5 g. daily for 14 days.

Summary

273 cases of bacillary dysentery treated in the City (Infectious Diseases) Hospital, Aberdeen, during 1941-2 are described, together with 4 cases of gastro-enteritis of infants and 8 cases of paratyphoid B fever. Of the cases of bacillary dysentery 140 received no drug, 83 were treated with sulphaguanidine, and 50 had sulphanilamide.

The series receiving no chemotherapy were given 2 drachms of sodium sulphate night and morning for an adult and 1 drachm night and morning for a child. Those receiving sulphaguanidine were given a 5-day course based on body weight, the initial loading dose during the first 24 hours being 0.5 g. per kilo of body weight, followed by a maintenance dose of 0.1 g. per kilo for the next 4 days. Those receiving sulphanilamide were given a dosage amounting to half the quantity of sulphaguanidine.

The tablets were powdered and administered in milk 4-hourly for the first 24 hours and 3 times daily for the next 4 days. Parenteral

fluids were given intravenously in the form of 5% glucose-saline where necessary, and particular stress was laid on fluid intake by mouth—8 to 10 pints for adults and proportionately less for children.

The stay in hospital and the number of days during which the stools remained positive were reduced by half in the sulphaguanidine-treated cases as compared with those receiving no chemotherapy, except in the case of Sonne convalescent carriers, in which both the stay in hospital and the number of days bacteriologically positive were slightly increased. In the sulphanilamide-treated cases both the stay in hospital and the length of time during which stools remained positive were increased, but this may be accounted for by the small dosage of drug and by the small number of cases treated.

Neither sulphaguanidine nor sulphanilamide produced any toxic symptoms or disagreeable effects.

4 cases of gastro-enteritis and 8 cases of paratyphoid B were treated with sulphaguanidine without any improvement.

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REFERENCES

- Anderson, D. E. W., and Cruickshank, R. (1941). *British Medical Journal*, **2**, 497.
 Brewer, A. E. (1943). *Ibid.*, **1**, 36.
 Bulmer, E., and Priest, W. M. (1942). *J. R.A.M.C.*, **79**, 277.
 Buttle, G. A. H., et al. (1938). *Biochem. J.*, **32**, 1101.
 Canizares, O., and Morris, G. E. (1941). *Arch. Derm. Syph.*, Chicago, **44**, 873.
 Fairley, N. H., and Boyd, J. S. K. (1942). *Lancet*, **1**, 20.
 — (1943). *Trans. roy. Soc. trop. Med. Hyg.*, **38**, 253.
 Firor, W. M., and Jonas, A. F. (1941). *Ann. Surg.*, **114**, 19.
 — and Poth, E. J. (1941). *Ibid.*, **114**, 663.
 Hall, W. A. (1941). *New Orleans med. Surg. J.*, **94**, 283.
 Henderson, J. L. (1943). *British Medical Journal*, **1**, 410.
 Levi, J. E., and Willen, A. (1941). *J. Amer. med. Ass.*, **116**, 2258.
 Lyon, G. M. (1941). *Ibid.*, **116**, 2440.
 Marshall, E. K., jun., Bratton, A. C., White, H. J., and Litchfield, J. T., jun. (1940). *Johns Hopk. Hosp. Bull.*, **67**, 163.
 — et al. (1941). *Ibid.*, **68**, 94.
 Roblin, R. O., jun., and Winnek, P. S. (1940). *J. Amer. chem. Soc.*, **62**, 1999.

TECHNIQUE OF INTRAVENOUS DRIP TRANSFUSION IN INFANTS

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The technique of intravenous drip transfusion, or venoclysis, was first applied to the treatment of infants about ten years ago, since when it has established itself as the most effective method of combating severe dehydration due to infantile diarrhoea and vomiting or for the post-operative administration of fluids in babies and small children. But it is much more difficult to carry out than in adults, has more risks, and provides an arduous task for the nursing staff, on whose energies and competence the success of the method chiefly depends. Unfortunately, owing to the frequency with which things can go wrong, it is apt to be regarded as a method that demands a party of experts to run it. It is true there is a real danger of overloading the system with fluid, and judgment in this matter requires experience; but it is as often as not the accumulation of small faults and mishaps, rather than more serious ones, that determines the success or failure of the undertaking. The object of this paper is to discuss the causes of failure and their remedy and to put forward some general principles for running continuous intravenous transfusions in infants with efficiency and safety.

The Technique Normally Adopted

The anterior saphenous vein at the ankle is chosen, as it is very constant in position and has definite surface markings. It lies on the anterior surface of the tibia, running upwards and slightly backwards midway between the tendon of tibialis anticus and the internal malleolus of the tibia, both of which can be felt. It is often visible in thin babies or may be made to stand out, and it is plainly visible in most adults, in whom its position and course may be easily examined.

The diameter of this vein in a 3-months-old baby is between 1 and 2 mm., and although it will stretch to slightly more than this it is difficult to insert a cannula into it of greater thickness than 2 mm. Various types of cannula are used to meet the case, such as a large-sized hypodermic needle with the bevel