THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA WITH SULFAPYRIDINE*

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FOLLOWING the development of prontosil by Domagk many attempts were made to develop a drug more effective against the pneumococcus. In May, 1938, Whitby,[1] using one of these derivatives ("M. & B. 693"), reported excellent results in protecting mice against pneumococcus infection, and shortly afterward Evans and Gaisford[2] reported a series of 100 cases of pneumococcus pneumonia treated with sulfapyridine (M. & B. 693). In this series there was a mortality rate of 6 per cent in the treated cases as against a mortality rate of 27 per cent in the 100 untreated control cases. In the belief that confirmation of these results would be of interest we are here reporting the use of this drug in 30 cases of pneumococcus pneumonia.

SELECTION OF CASES

All cases of pneumonia admitted to the medical wards of the Royal Victoria Hospital were immediately subjected to the following routine: physical examination, x-ray of chest, sputum typing (Neufeld) and culture, and blood culture. The cases selected for this series were those which showed positive evidence of pneumonia by physical examination, history and by x-ray, and in which the sputum contained pneumococci in sufficient numbers to permit direct typing. Many of these cases were confirmed by culture of the aspirated material obtained by lung puncture in the diseased area; in all cases in which this was done pure growths of pneumococci were obtained in the original culture of this aspirated material. Since we have wished to study the effects of chemotherapy on pure pneumococcus pneumonia it has seemed justifiable to exclude those cases not having sufficient pneumococci in the sputum to permit direct typing, or whose lung puncture did not yield a pure growth of pneumococcus. Blood cultures were done as a routine on admission, using 20 c.c. of blood, but only two positive cultures were obtained. By observing these precautions, we have felt reasonably certain that we were dealing with a pneumococcus pneumonia.

METHOD OF STUDY

X-rays of the chest were taken on admission, shortly after the return of the temperature to normal, and before discharge of the patient. Routine studies were made of the blood and urine, and many of the cases had complete blood studies on admission, just after the return of temperature to normal, and before discharge. The blood level of the sulfapyridine was determined daily in all cases and in the earlier ones twice daily during the period of administration of the drug. The determination of the sulfapyridine level in the blood was done by the modified method of Marshall and Litchfield[4] except that the photoelectric colorimeter[3] was used and sulfapyridine replaced the sulphanilamide in the standards.

METHOD OF ADMINISTRATION OF SULFAPYRIDINE

In general all cases were given 2.0 grams (4 tablets) of sulfapyridine as soon as sputum specimens and blood culture had been obtained. This dose was repeated in four hours, and then the patient was given 1.0 grams every four hours until the temperature had remained normal for forty-eight hours. The dosage was then decreased to 1.0 grams every six hours for another twenty-four hours, and the drug then discontinued. This made an average dose of 27.0 grams per patient.

Those patients who did not show a rapid temperature response, or who developed complications, were given total doses as high as 50 grams without any apparent ill effects. Although Flippen, Lockwood, Pepper and Schwartz[6] recommend a maximum total dose of 25 grams no evidence has been presented to date which would indicate that amounts in excess of this will produce toxic effects.

With each dose of sulfapyridine it has been our practice to give 0.6 gram (10 grains) of

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sodium bicarbonate, in the belief that nausea and vomiting were decreased by this procedure, and Marshall, Bratton and Litchfield[5] have shown that absorption in dogs is more rapid and regular when the drug is given in a sodium bicarbonate solution or in hydrochloric acid. In several cases where vomiting was severe, we attempted to administer the drug per rectum, suspended in water. Although doses as high as 2.0 grams every four hours were given it was found impossible to maintain a blood level of over 2 mg. per 100 c.c. in four cases in which this was done.

In addition to the specific therapy we have used symptomatic measures, such as sedatives, intravenous fluids, and oxygen, whenever such were indicated, but in no case have we used any

TABLE

Case No.	Age	Type	Day of disease admitted	Lobes involved by x-ray	Respiration, pulse and temperature on admission			Complications on admission	Blood concentration of drug in 12 - 18 hours	Total dose (grams)	Number of days to normal temperature	Complications and drug effects	Results
					Resp.	Pulse	Temp.		mg. per 100				
P.G.	21	I	4	R+LLL	40	120	104.8	Left pleural effusion	9.4	10	2	Irrational after 10 grams	C
J.N.	50	I	2	LLL	34	118	102.0	.....	.....	20	2 - 2*	Vomiting; two day relapse when drug stopped	C
M.A.	45	I	2	RLL	40	148	103.3	.....	4.5	34	2	Drug fever	C
D.R.	40	I	3	RUL	30	120	102.0	? Arrested pulmonary tuberculosis	5.9	30	..	Moderate vomiting	C
E.W.	22	II	3 - 6	RLL+LLL	48	130	104.0	Bilateral otitis media	14.2	29	3 - 6*	Pleural effusion (sterile)	C
E.L.	16	II	2	LLL	38	132	104.4	.....	5.5	23	1	Mild vomiting	C
A.D.	34	II	4	LLL	30	116	101.0	Positive blood culture	8.2	30	1	Mild vomiting	C
A.D.	45	II	2	RLL	28	108	100.4	.....	5.4	52	2 - 4*	Pleural effusion (sterile)	C
D.I.	26	II	2	RLL	32	124	101.0	.....	7.2	32	2	Mild vomiting	C
G.Mc.	39	II	4	R+LLL	28	118	102.6	.....	10.5	24	1	.....	C
B.F.	40	III	4	RML	36	120	103.0	.....	3.0	26	1 - 2*	Recurrence when drug stopped first time	C
B.B.	46	III	2	RM+RLL	28	118	101 8	.....	14.0	14	2 - 4*	Recurrence when drug stopped first time	C
R.B.	41	III	2	RUL	36	120	102.4	Right pleural effusion	3.6	46	5	.....	C
N.L.	31	III	2	RLL	24	110	103.0	.....	6.8	9	1	Mild vomiting	C
H.L.	39	III	3	RM+LL	34	120	103.0	.....	8.2	11	2	Severe vomiting	C
R.S	43	III	3	RU+ML	36	118	102.0	.....	10.0	21	3	.....	C
A.C.	42	III	5	RL+LLL	40	120	102.8	.....	5.8	52	8	Severe vomiting	C
A.P.	34	III	2	R+LLL	20	110	103.2	.....	6.2	16	1	Moderate vomiting	C
W.B.	53	IV	4	R+LLL	30	134	104.4	Jaundice	11.2	33	3	Delayed resolution	C
S.M.	18	V	4	RLL	60	120	104.4	Positive blood culture Acute arthritis	4.8	34	1	Mild vomiting	C
A.P.	53	VII	3	RM+LL	28	116	99.4	.....	6.8	31	1	.....	C
G.H.	52	VII	6	LU+LL	28	96	103.4	Asthma	10.4	29	2	.....	C
N.F.	44	VII	5	RU+ML	26	110	103.0	.....	13.0	28	1	Slight cyanosis 0.4 gm./100	C
F.F.	57	VII	6	LUL	22	120	100.6	Diabetes—not controlled	9.2	38	1	Slight delay in resolution	C
H.O.	46	VII	1	RML	32	118	101.0	CNS Syphilis	5.8	20	1	Slight delay in resolution	C
F.H.	45	VIII	3	R+LLL	24	100	101.8	.....	5.8	24	1	.....	C
H.K.	45	VIII	4	RLL	30	85	101.8	Tertiary syphilis	8.4	24	1	Pleural effusion (sterile)	C
J.T.	41	XII	5	RML	40	132	105.0	.....	10.0	31	3	Moderate vomiting	C
W.K.	17	XVIII	1	RLL	34	110	104.0	.....	....	12	1	.....	C
G.S.	81	XX XXII XXIX	1 1	RM+LL LLL	38 ..	112 ...	101.0	Chronic myocarditis. Left bundle branch lesion.	5.8	24 ..	1 ..	....	D

C = Cured. D = Died. *The second figure indicates number of days until normal temperature reached after relapse or complication.

form of treatment which would interfere with or enhance the action of sulfapyridine.

BLOOD CONCENTRATION

We have attempted to find some correlation between the amount of the drug given and the blood level obtained. After four or five grams had been given the blood level was found to vary from 3.6 to 14.2 mg. per 100 c.c. Although the concentration seemed to reach a constant level in any particular patient (modified somewhat by the fluid intake) this was not always the same in different individuals. This variation in concentration reached is not related to the ratio of dosage to kilogram weight. Marshall, Bratton and Litchfield[5] have shown that in man the drug is excreted in the urine both in the form of free sulfapyridine and as the conjugated *p*-acetylaminobenzenesulfamidopyridine. It is quite possible that individual variations in the degree of conjugation and in the rate of absorption of the drug accounts for this lack of uniformity of blood concentration. In this series no attempt was made to determine the ratio of free and conjugated sulfapyridine in the blood or urine.

In general it can be stated that in this series of cases the recommended dosage has given blood levels of 5 to 10 mg. per 100 c.c. in the first 12 to 18 hours, and that the dosage of 1 gram every four hours maintains this level. We have been unable to detect any advantage in maintaining the blood concentration over 10 mg. per 100 c.c. Those patients in whom the blood levels averaged 5 to 9 mg. per 100 c.c. did quite as well as those with higher average concentrations.

RESULTS

In this series of 30 cases of pneumococcic pneumonia there was one death. This occurred in a man of 81 years who was admitted during the first day of disease with pneumonia (types XX and XXII) involving the right middle and lower lobes, and a recent left bundle-branch lesion. His temperature became normal within twenty-four hours after admission and remained so for twelve days. On the twelfth day his respirations and pulse increased and he became quite cyanosed. X-rays taken at this time revealed bronchopneumonic changes in his left lower lobe and his sputum contained a few pneumococci (type XXIX). Sulfapyridine therapy was begun at this time, but in spite of this his temperature and pulse rose steadily and his blood pressure dropped rapidly from 180/100 to 90/70 and he died on the fifth day of his second attack. Autopsy was not obtained, so that the condition of his heart could not be ascertained, but it is our belief that it played a major rôle in causing his death rather than the pneumonic lesion.

It will be seen that the temperature in 21 of the 30 cases shown in the Table returned to normal within forty-eight hours after the administration of sulfapyridine was begun, and in 14 of these it did so within the first twenty-four hours. This fall in temperature was in all cases accompanied by a conspicuous reduction in the pulse and respiratory rates, and the patients were much improved subjectively. Three cases showed some increase in temperature and other signs of recrudescence when the drug was discontinued too early. These symptoms disappeared in several days when moderate amounts of sulfapyridine were given. In five cases more than two days elapsed before the temperature became normal. Of these three had complications on admission (pleural effusion, bilateral otitis media, jaundice) and three had had the disease for five days.

All of the commoner types of pneumococci are represented in the series but there is an unusually large percentage of types III and VII.

COMPLICATIONS AND DRUG EFFECTS

The complications due to the disease were few and of little importance. There were 3 cases of delayed resolution as revealed by x-ray findings and by physical signs. This delay was moderate in degree and prolonged the patients' stay in the hospital by only a few days. Pleural effusion of such an extent as to be appreciable by physical signs was encountered in three cases. In each of these, cultures of the fluid on two or more occasions revealed no organisms, and the fluid soon disappeared without aspiration. In all other cases x-ray findings and physical signs indicated that the pneumonic process resolved at a normal rate.

The most serious difficulty encountered in the use of sulfapyridine was the frequency with which it produced anorexia, nausea and vomiting. Almost all patients complained of anorexia and nausea, and 20 of the 30 vomited one or more times during the course of its administration. In three vomiting was of sufficient severity to require discontinuing the drug and to make necessary the administration of fluids by the intravenous route. This troublesome feature of the drug did not appear to be related to the blood concentration. Many means were tried to circumvent the difficulty but without appreciable success. It is hoped that the soluble sodium salt, which can be effectively administered rectally or intravenously, will correct this.

Methæmoglobin and sulph-hæmoglobin determinations were done on many of the cases, and

in none was the amount of the former over 5 per cent, while sulph-hæmoglobin was not found in any of the cases. One patient (P.G.) became quite irrational after receiving 10 grams of the drug (blood level 9.4 mg. per 100 c.c.), but this condition cleared up within twenty-four hours after discontinuing it. Mild confusion was present, however, in several cases on admission. This did not increase but rather disappeared shortly after administration of the drug was begun.

A moderate fall in hæmoglobin and red cell counts was found in many cases, but in none did this exceed what might be expected in any severe infectious disease. No leucopenia or any suggestion of agranulocytopenia occurred.

Ten cases of pneumonia due to other organisms were studied during this period. In general the response to the drug was not conspicuous or even suggestive, and serious complications occurred quite frequently. In only two cases was there a pronounced drop in temperature within forty-eight hours, so that the contention that the action of sulfapyridine is purely antipyretic seems quite improbable.

CONCLUSION

Sulfapyridine was used in the treatment of 30 cases of pneumococcic pneumonia with a resultant mortality of 3 per cent.

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SULPHANILAMIDE IN THE TREATMENT OF CYSTITIS AND PYELITIS*

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IN previous papers of this series[1, 2] the biochemical response of healthy human subjects and of patients to various doses of sulphanilamide has been described. The present communication outlines briefly the investigations which led to the adoption of what we consider the most satisfactory dosage regimen for the treatment of pyelitis and cystitis with this substance.

When the drug was first introduced into the clinic for the treatment of non-specific urinary tract infections the large initial doses recommended by other workers were used. While these were found to be effective in eliminating the infecting bacteria a large proportion of the patients developed mild reactions, such as headache, nausea and dizziness. Fortunately, in only a few instances were these sufficiently severe to cause any alarm, but the unpleasant subjective symptoms detracted considerably from the therapeutic usefulness of the drug. A search for a method of administration which, while clinically effective, would not produce such undesirable reactions was therefore undertaken. It was felt that the best method would not be found without a very complete clinical, bacteriological and biochemical study of each patient, and, consequently, the following investigations were conducted on certain patients undergoing treatment by the several dosage regimens which were studied.

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EXPERIMENTAL

Methods used in the investigation.—

1. *Clinical.*—Complete physical and urological examination, blood non-protein nitrogen, hæmoglobin, and differential cell count were done and repeated when indicated.

2. *Bacteriological.*—(*a*) Isolation and identification of the infecting micro-organisms.

(*b*) Determination of the *in vitro* bacteriostatic level of the drug for each bacterium found in the urine. This test was conducted by adding to Hartley's broth pure recrystallized sulphanilamide to produce concentrations of 10, 25, 50, 100, 200 and 300 mg. per 100 c.c. A 20-hour culture of the isolated organism in Hartley's broth was diluted in saline to 1:5,000; 1:50,000, and 1:500,000. One loopful of each of these dilutions was transferred to a 5 c.c. portion of each of the above sulphanilamide-broth media. Control tubes containing no sulphanilamide were similarly inoculated. Readings were made by comparing opacities after incubation for 24 hours at 37° C. The tube containing the lowest concentration of sulphanilamide which in any of the culture-dilutions showed definite inhibition of growth was taken as the *in vitro* bacteriostatic level for that particular organism.

(*c*) Cultures and colony counts from the urine at various times during therapy. In order to follow the bacteriological response of the cases undergoing treatment the usual routine cultures were made at from 1 to