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2-*p*-AMINOBENZENESULPHONAMIDO-4 : 6-DIMETHOXYPYRIMIDINE ABSORPTION AND EXCRETION IN MAN

BY

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WITH NOTES ON A CLINICAL TRIAL IN PNEUMONIA

BY

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The work of Gage, Martin, Rose, Spinks, and Tuey (1947) showed that a new sulphonamide, 2-*p*-aminobenzenesulphonamido-4 : 6-dimethoxypyrimidine or sulphadimethoxypyrimidine, had an unusual persistence when administered orally to animals. This fact, in conjunction with the observation that the antibacterial action *in vitro* and *in vivo* was of the same order as that of sulphadiazine, suggested that the compound merited a clinical trial, which was carried out in the medical wards of Crumpsall Hospital, Manchester. It was hoped that a sulphonamide which persisted in the blood for longer periods than other sulphonamides might be effective in the treatment of pneumonia in a single dose, or at most in doses once or twice daily.

METHODS

Sulphadimethoxypyrimidine was first administered to essentially normal patients, mostly convalescing from surgical and skin conditions, in doses ranging from 0.5 to 5 g. These patients were, at the time of testing, in fairly good general health and had no febrile condition ; except in one patient (receiving 0.5 g.) renal function was normal. Blood concentrations and recoveries in the urine are illustrated in the Table and Fig. 1. Two patients only were used for each dose level. The drug was also administered to a series of 80 patients, mostly suffering from pneumonia. One or two of these patients had other conditions normally requiring sulphonamide therapy. The results for 30 of these patients are shown in Figs. 2, 3, and 4 ; those obtained from the rest of the patients were similar although several patients had not received the full course before they were transferred to other treatments, penicillin or sulphamezathine, on clinical grounds.

Blood and urine sulphonamide estimations were made by the method of Rose and Bevan (1944). Twenty-four-hour collections of urine were made without preservative. For the blood urea, protein, phosphatase, and bilirubin estimations the methods of King (1946), slightly modified, were used.

RESULTS

Normal subjects showed a steady increase in maximum blood concentration and persistence with increasing dosage. (Table, Fig. 1.) The maximum was

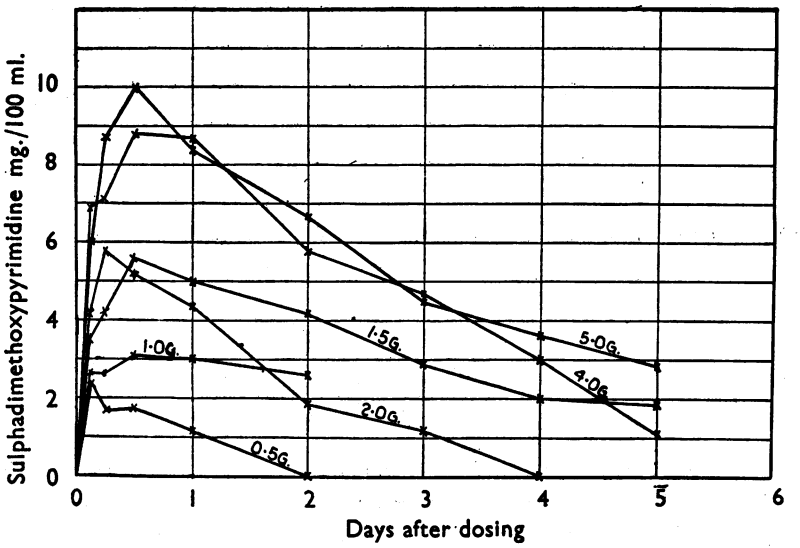

FIG. 1.—Blood concentrations of sulphadimethoxypyrimidine following the administration of single doses to normal subjects.

TABLE

NORMAL PATIENTS: MEAN BLOOD CONCENTRATIONS AND URINE RECOVERIES WITH SINGLE DOSES OF SULPHADIMETHOXYPYRIMIDINE

All readings are means for two patients (5.0 g. dose, one patient only)

Dose g.	Mean blood concentrations of free and, in parentheses, conjugated drug in mg./100 ml.										Total urine recoveries of free and, in parentheses, conjugated drug	
	1 hr.	2 hrs.	3 hrs.	6 hrs.	12 hrs.	24 hrs.	2 days	3 days	4 days	5 days	mg.	Per cent of dose
0.5	1.25	2.05	2.45	1.7	1.75	1.2	Trace				74	14.8
	(0.1)	(0.05)	(0.2)	(0.05)	(1.25)	(0.55)	(0.85)				(18)	(3.6)
1.0	1.4	2.15	2.65	2.65	3.1	3.0	2.6	Trace			218	21.8
	(0.1)	(0.15)	(0.05)	(0.25)	(0.2)	(0)	(0.4)	(1.6)			(46)	(5.3)
1.5	0.4	1.85	3.5	4.2	5.65	5.05	4.2	2.9	2.05	1.9	500	33.3
	(0)	(1.05)	(1.0)	(0.95)	(0.7)	(0.85)	(0.7)	(0.2)	(0.35)	(0)	(77)	(4.4)
2.0	1.85	3.15	4.2	5.85	5.2	4.4	1.9	1.2	0		637	31.8
	(0)	(0)	(0)	(0.5)	(0.6)	(0.35)	(0.2)	(0.25)	(Trace)		(252)	(12.6)
4.0	1.15	4.05	6.0	8.75	10.05	8.45	6.7	4.55	3.65	2.85	835	30.6
	(0.25)	(0.1)	(0.25)	(0.65)	(0.45)	(0.6)	(0.4)	(0.45)	(0.25)	(0.2)	(241)	(6.0)
5.0	3.3	5.0	6.9	7.1	8.8	8.7	5.8	4.7	3.0	1.1	1202	24.0
	(0)	(0)	(0.3)	(0.1)	(0.2)	(0.3)	(0)	(0)	(0)	(0.5)	(415)	(8.3)

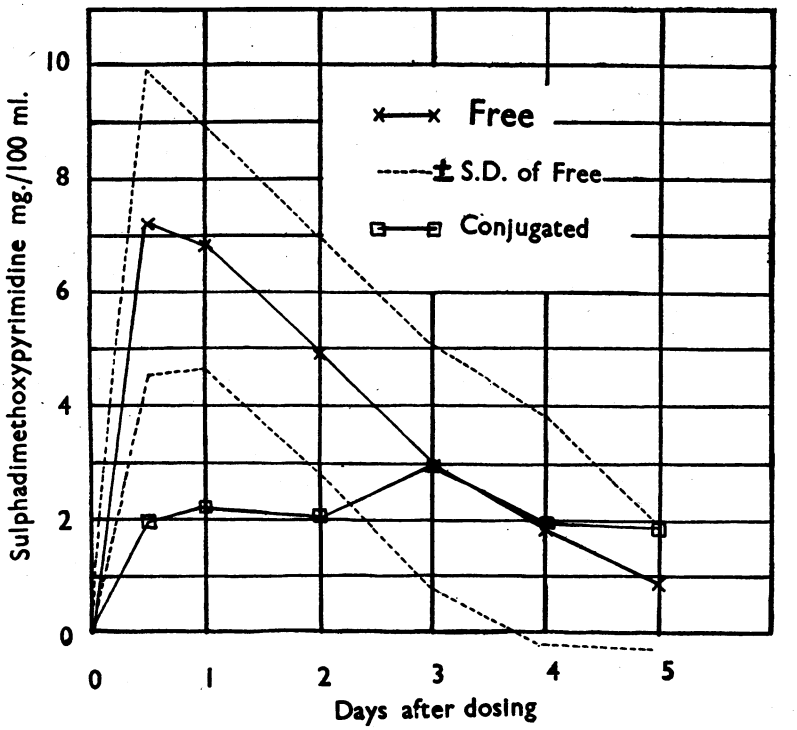

FIG. 2.—Blood concentrations of sulphadimethoxypyrimidine following the administration of a single dose of 5 g. to pneumonia patients.

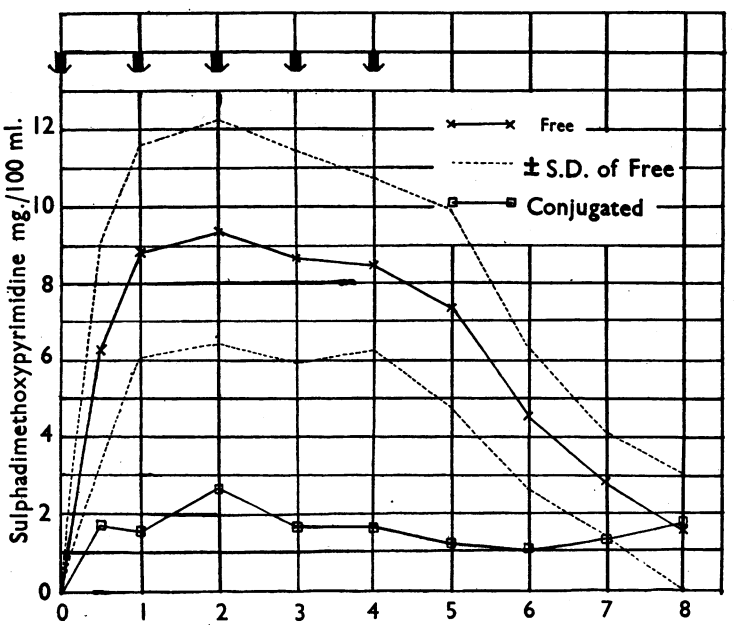

FIG. 3.—Blood concentrations of sulphadimethoxypyrimidine following the administration of an initial dose of 5 g., and then 3 g., daily to pneumonia patients.

attained at three hours after a dose of 0.5 g., but with higher dosage the maximum was at 12 hours. After a single dose of 4 g. a blood concentration of 10.05 mg./100 ml. was attained after 12 hours and 2.85 mg./100 ml. persisted five days after the dose; a similar dose of sulphamezathine gave a maximum of 13.2 mg./100 ml., falling to traces within 24 hours. For patients suffering from pneumonia a single dose of sulphadimethoxypyrimidine gave on the average lower maxima and less well sustained blood concentrations (Fig. 2). The average maximum attained after 5 g. was 8.86 mg./100 ml., and only traces were detected in the blood after four days, although 2 mg./100 ml. were still present after three days.

In patients treated with 5 g. followed by 3 g. every 24 hours, blood concentrations were usually well maintained (Fig 3). In a few cases, however, the drug concentration did not reach a level of 8 mg./100 ml., a concentration usually regarded as effective chemotherapeutically. Patients with a low concentration of free drug usually showed a high percentage of acetylation, a frequent finding with other sulphonamides.

Since clinical results were not completely satisfactory it was decided to try a dose of 5 g. followed by 3 g. every 12 hours (Fig. 4). This dosage gave

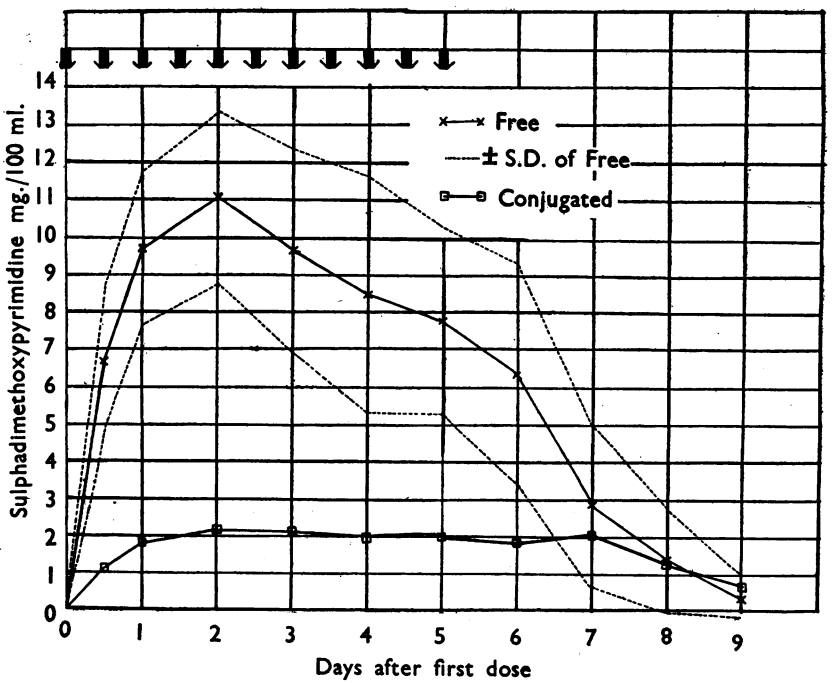

FIG. 4.—Blood concentrations of sulphadimethoxypyrimidine following the administration of an initial dose of 5 g., and then 3 g., at twelve-hourly intervals, to pneumonia patients.

slightly higher blood concentrations. All patients (except one who had only three doses) attained blood concentrations of over 8 mg./100 ml. In nearly all pneumonia patients receiving the drug, whether as single or repeated doses, free sulphadimethoxypyrimidine was still present in appreciable quantities three days after the last dose. In one patient with staphylococcal pneumonia and considerable renal damage (blood urea 100 to 150 mg./100 ml.), sulphonamide was still present in measurable quantities 16 days after the last dose, though the blood urea had fallen slightly.

Samples of cerebrospinal fluid were obtained from two patients and contained sulphadimethoxypyrimidine concentrations, in one case of 58 per cent, and in the other of 31 per cent, of the simultaneous blood concentration.

The blood concentration of sulphadimethoxypyrimidine reached a slightly lower maximum than did sulphamezathine after similar doses, but this maximum was attained later and high blood concentrations persisted for a very much longer period. There was a tendency for the concentrations reached in the controls to be higher than those attained with similar doses of the drug in febrile patients. Persistence of the blood concentrations after the last dose was definitely less in the febrile patients.

The recovery of the drug in the urine was comparatively low. The average recovery was 32.9 per cent, 26.6 per cent being free and 6.6 per cent conjugated in the normal patients, as compared with 86.2 per cent for sulphamezathine (Clark *et al.*, 1943), 68 per cent for sulphadiazine (Reinhold *et al.*, 1941), and 57.3 per cent for sulphapyridine (Long and Feinstone, 1938). The percentage of the drug recovered as acetyl compound, both from blood and urine, was low. These results must in part be interpreted in the light of the results of Gage *et al.* (1947) who record only partial recovery of the drug after acid hydrolysis.

Crystals of the drug were seen in many of the urines passed, but no renal symptoms were observed directly referable to the presence of the crystals. In two patients with severe renal damage this damage could not be definitely assigned to the effect of sulphadimethoxypyrimidine. The crystals took the form of St. Andrew's crosses and were shown chemically to be free sulphadimethoxypyrimidine. When compared with the needle-shaped crystals often observed in the urine of patients receiving other sulphonamides, sulphadimethoxypyrimidine would not be expected to cause such extensive mechanical injury to the renal structures. Confirmatory evidence was provided by estimation of blood urea in 34 patients. The blood urea was usually about 40 mg./100 ml. on admission and in most cases tended to fall as the pneumonic condition improved. In no case was there a significant rise except in one woman dying within 48 hours of admission who was shown at autopsy to have severe chronic nephritis.

In chronic toxicity tests by Gage *et al.* (1947) large doses of sulphadimethoxypyrimidine in rats gave rise to severe central necrosis of the liver lobules, and it

was thought advisable to perform some liver function tests. Estimations of serum bilirubin, protein, and phosphatase were therefore made on nine patients. There was no change in the concentrations of these substances such as would indicate liver damage. It is realized that this series of tests would only show gross liver damage, and that minor impairment of function might pass unnoticed.

Summary

1. Sulphadimethoxypyrimidine in man persists in the blood stream longer than do the other common sulphonamides after similar doses.

2. Acetylation of the drug is slight.

3. Single daily doses of sulphadimethoxypyrimidine will give blood concentrations of an order considered adequate for therapy in pneumonia.

Clinical Trial

Sulphadimethoxypyrimidine was given to 41 patients with pneumococcal lobar pneumonia, whose ages varied between 16 and 78 years.

An initial dose of 3 to 5 g., followed at intervals of 24 hours by two doses of 2 g., was found to give a blood level of 5–13 mg. per 100 ml. which was maintained for 40 to 60 hours. Eighteen patients were treated in this way.

Nine patients were given an initial dose of 5 g., followed by 3 g. at intervals of 24 hours for four doses, a blood concentration of 5 to 14 mg. per 100 ml. being maintained for about 120 hours.

In thirteen patients an initial dose of 5 g. was followed at 12-hour intervals by two doses of 3 g. and then by 2 g. doses for several days, maintaining blood concentrations between 7–16 mg. per 100 ml. for four to six days. This method proved the best for maintaining adequate blood levels.

The drug was well tolerated and showed quite definite therapeutic value, but was not so effective as other sulphonamides used in series of similar cases (Don *et al.*, 1940; Macartney *et al.*, 1942; Ramsay *et al.*, 1945).

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