

# **A TRIAL OF SULPHAMETHOXYPYRIDAZINE (S.M.P.) IN THE MANAGEMENT OF INFLUENZA**

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Basildon

Sulphamethoxy pyridazine is a sulphonamide that has a prolonged action because the rate of excretion by the kidneys is much slower than that of more conventional sulphonamides<sup>3</sup>. Significant blood levels are maintained for at least twenty-four hours after a single dose. The usual therapeutic dose is 1G. on the first day and 0.5G. (one tablet) daily thereafter. In more serious infections, the daily dose may be increased to about 2G. When taken in doses of 0.5G—1G. a day, there are very few side effects. The drug is excreted by the kidneys to a large extent as the acetylated form and as this is rather insoluble, an adequate fluid intake is necessary.

During January 1959, an outbreak of influenza began at the R.A.F. Training Camp, St. Athan. Influenzal virus B was the causal organism in most of the cases but there were also a few cases due to virus A. S.M.P. was used to treat patients with mild complications and we were impressed by the therapeutic results and also by the relative lack of nausea so often associated with sulphonamide therapy. We therefore decided to do a controlled trial on the use of this drug in the management of influenza. As secondary bacterial infection is the cause of most of the complications and persistent debility of influenza, we hoped that a bacteriostatic agent would reduce their incidence, though of course it would have no effect on the primary illness.

## **Organization of the Trial**

Patients were originally seen by their unit medical officers and were then referred to the sick quarters for admission to the infectious diseases ward. As the patients arrived the receptionist put their names in a register. Later the receptionist put a mark (M) against every second name in the register. The names concerned were then sent to the ward and these patients received an initial dose of 1G. and then a daily dose of 0.5G. of S.M.P. All patients received the

usual treatment with aspirins and inhalations.

It was not always possible to be absolutely accurate in separating influenza cases from other upper respiratory tract infections in the early stages. Whenever the original diagnosis of influenza had to be changed after further observation and investigation, the patient concerned was excluded from the trial. The only other patients excluded were those who were found on admission, to have complications severe enough to warrant special therapy. The accuracy of the final diagnosis was checked by virus complement fixation titres on patients selected at random. Most of those tested showed rising titres for influenza viruses A or B.

Patients were kept in the sick-quarters until they were completely symptom free and until they had been afebrile for at least 48 hours. On discharge, they were considered to be fit to return to normal work.

### Results

The total number of cases in the trial was 120. The treated group contained 58 and the untreated group 62.

TABLE I  
MEAN DURATION OF INITIAL PYREXIA AND STAY IN HOSPITAL

	<i>Treated</i>		<i>Untreated</i>		<i>P</i>
	<i>Mean</i>	<i>Standard deviation</i>	<i>Mean</i>	<i>Standard deviation</i>	
No. of days of initial pyrexia	1.78	$\sqrt{.914}$	2.03	$\sqrt{1.96}$	0.2
Total No. of days in hospital	6.29	$\sqrt{8.4}$	7.7	$\sqrt{16.18}$	0.05

In table I the mean duration of the initial pyrexia and the mean duration of the stay in sick-quarters in the two groups are compared. Though the mean duration of the initial pyrexia in the treated group is slightly less than that of the untreated group, this difference is not significant. This is to be expected because the initial pyrexia is mainly due to the viraemia of influenza. However, there were many cases where the pyrexia was unduly prolonged and one may presume that this was due to a large extent to secondary infection. Prolonged pyrexia was defined arbitrarily as four or more days. There were only four such cases in the treated group compared to eleven in the untreated group. Recurrence of pyrexia may also be presumed to be due to secondary infection and the relevant figures are seen in table II. The treated group show a smaller number of patients

with a recurrence of pyrexia.

On the average, the treated group of patients spent 1.4 days less in the sick-quarters than the patients in the untreated group. This difference is significant statistically and demonstrates that the duration of the illness is definitely shortened in the treated group. The difference in the mean values of 1.4 represents a saving of 81 working days in the treated group of 58 patients.

TABLE II  
NUMBER OF CASES WITH PROLONGED OR RECURRENT PYREXIA

	<i>Treated</i>	<i>Untreated</i>	<i>P</i>
No. of cases with pyrexia of 4 or more days	4	11	0.1
No. of cases with a recurrence of pyrexia	11	20	0.1
No. of cases in sick-quarters 8 or more days	14	29	0.01
No of cases in sick-quarters 10 or more days	7	15	0.1
No. of cases with complications	3	11	0.05

In this epidemic of influenza, the incidence of complications was low and there were no cases of pneumonia. The complications encountered are listed in table III. The incidence of complications

TABLE III  
INCIDENCE OF COMPLICATIONS

<i>Complication</i>	<i>Treated</i>	<i>Untreated</i>
Bronchitis .. .. .	2	2
Sinusitis .. .. .	0	4
Otitis media .. .. .	0	2
Tonsillitis .. .. .	1	3

was much less in the treated group and the difference is statistically significant. The two cases of bronchitis in the treated group were both so mild that they hardly merited the diagnosis. Tonsillitis has been recorded as a complication of influenza only where the tonsillar infection clearly occurred during recovery from what was primarily a case of influenza. In one such case, the clinical diagnosis was tested and confirmed by finding a rising titre of complement.

fixing antibody to influenza virus A. The most troublesome complications proved to be the cases of sinusitis and otitis media and some needed further treatment with antibiotics. No proven case of either otitis media or sinusitis occurred in the treated group.

### Discussion

Recently the routine treatment of colds and similar illnesses with antibiotics has been under discussion. Most people agree that the routine use of antibiotics in illnesses of this type is not justified, the main objections being the possible emergence of antibiotic-resistant organisms and the cost of treatment. However, these arguments do not apply to the same extent to the use of sulphonamides. Treatment with S.P.M. is cheap, easily carried out and carries no risk of producing antibiotic-resistant organisms. Side effects are uncommon<sup>2 5 6</sup> with S.M.P., especially when the lower dosage schedules are used. The low dosage effectively reduces the incidence of gastro-intestinal side effects. Rarely, the other side effects usually associated with sulphonamide therapy, such as headaches, rashes and anaemia, may occur. None were observed in this series. The only patient who had a rash was in the untreated group.

The therapeutic results tabulated above indicate that the treatment is effective both in shortening the course of the illness and in avoiding the complications of influenza. We feel that there is no serious objection to the use of S.M.P., and that it is justifiable on clinical and economic grounds to use it in the routine management of influenza. The average cost of treatment worked out at about four shillings per patient.

Influenza is one of the commonest of the winter illnesses in this country and causes the loss of an enormous number of working days. In this series where the average duration of the illness was 7.7 days in the untreated group, the saving in the treated group was 1.4 days per patient. This represents a decrease of 18 per cent in the days of training lost. The lowered incidence of complications is also important. Conditions such as sinusitis or otitis media contracted during a bout of influenza, can permanently damage the organ involved. This often means recurrent infections and further damage, long after the causal attack of influenza has been forgotten. Contrary to our previous experience this epidemic of influenza produced very few cases of pneumonia so we have not been able to form any opinion as to the effectiveness of S.M.P. in preventing this lesion.

### Summary

S.M.P. was given routinely in an initial dose of 1G. and then 0.5G. daily to 58 of 120 cases of influenza. The remaining 62 acted

as controls.

S.M.P. appeared effective in shortening the duration of the illness and in reducing the incidence of complications.

Treatment is cheap and easy.

#### Acknowledgement

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**Infectious Diseases Today.** G. I. WATSON, M.D., D.T., M. & H.  
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Dr Watson divided infectious diseases into three types: those in which a diagnosis can be made by the family doctor on clinical examination; those which require laboratory techniques for their elucidation; and those ill-defined fevers which remain.

Measles is nowadays mild in infants, especially if they are breast-fed; gamma-globulin has a place in treatment. Influenza has an incubation period of 2 days, and this often results in two attacks in one person causing a biphasic fever; symptomless carriers help to spread the disease. Chickenpox may be caught from patients with herpes zoster, the virus being common to the two diseases. Rubella is particularly prone to do damage in expectant mothers during the earliest months of the pregnancy, and such attacks may cause the baby to be born with cataract, deafness or severe heart lesions. Toxoplasmosis is another damaging disease in early pregnancy and may resemble glandular fever but with a negative Paul Bunnell reaction. Streptococcal sore throat is still common, and may be followed by nephritis.

Pyrexia of uncertain origin was seen frequently from 1959 to 1960 (120 cases in Dr Watson's practice). These were diagnosed as Shere fever (Coxsackie A) (13 cases), PUO + rash (7), Polio virus (4), Adeno-virus (44), Coxsackie B (8), WP/60 (25), Strep M.G. + pneumonia (2), and of unknown origin (17). Details of these were given by Dr Watson.

Finally Dr Watson drew attention to the great differences in the reaction to infection of different subjects.