GROUP STUDY

A study of 1-adamantamine hydrochloride during the 1970 Hong Kong influenza epidemic

M. SCHAPIRA, M.D., M.R.C.G.P.
Keighley

J. S. OXFORD, B.SC., PH.D.
University Virus Research Laboratory, Lodge Moor Hospital, Sheffield

A. W. GALBRAITH, M.A.M.B., B.S.C.I.R.
Medical Department, Geigy Pharmaceuticals, Macclesfield

DURING the latter part of December 1968, influenza appeared in certain communities in England and the virus was identified as an A_2 strain. It was antigenically similar to that isolated in Hong Kong and which had been responsible for the epidemics in Europe and the United States during the autumn of that year. Vaccine against this strain had been prepared, but reports of its efficacy against the virus in human volunteers were scanty. In early January 1969, a few patients in Keighley reported influenzal symptoms and a prophylactic study of 1-adamantanamine hydrochloride (amantadine) was begun. This was the first winter that the Hong Kong virus variant had appeared in Britain and little was known of the protective value of the drug. Previous studies had shown the drug to possess a prophylactic action (Quilligan, Hirayama and Baernstein 1966, Togo, Hornick and Dawkins 1968). A study carried out in general practice in Great Britain during the winter of 1967–68 showed amantadine to have a protective effect against an influenza virus immunologically related to $A/_2$/England/10/67 (Galbraith, Oxford, Schild and Watson 1969a).

Method

After verification of an influenzal epidemic in Keighley, volunteers were admitted to the study and a blood specimen was taken from each person and sent to the Virus Research Laboratory, Sheffield for antibody estimation. Then a small canister labelled only with a code number and containing 20 capsules of either amantadine (100 mg) or placebo (oil base without drug) was given to each volunteer with instructions to take one capsule twelve hourly.

If symptoms of influenza appeared during the time the individual was taking the capsules, a record was made of the suspected source of infection, the presence or absence of headache, aching limbs, fever, respiratory difficulty, chest pain, shortness of breath and loss of voice. From all persons who reported suffering from symptoms of influenza, a second blood specimen was taken. A four-fold or greater rise in the haemagglutination-inhibiting (HI) antibody to influenza A_2/Hong Kong/1/68 virus was regarded as indicating infection. The volunteers were interviewed on the occasions of the first and second venepuncture. Records were kept of the date of inclusion in the study, symptoms of influenza and the date of completion of the volunteers' participation in the investigation.

Results

Volunteers were included from three independent companies, the staff of a school, a bank, a newspaper, family groups and persons included singly (table I). The total numbered 297 and of these 157 received amantadine and 140 received placebo capsules.

Their ages ranged from 8–81 years with a mean age in the amantadine group of 38 years and in the placebo group 38·5 years.

The initial antibody status of the volunteers is represented in table II. It is shown that of 128 subjects on amantadine whose first blood samples were tested, 83 per cent had an HI titre of less than 1/18, 10 per cent possessed a titre of between 1/18 and 1/72

TABLE I
SOURCES FROM WHICH VOLUNTEERS WERE TAKEN

Source	*No. of volunteers*
A.F. Co.	13
P.S.& S. Co.	20
N.S.F. Ltd.	21
School	17
Bank	18
Newspaper	18
Family groups	87
Singletons	103
	297

TABLE II
INITIAL HI ANTIBODY STATUS

Treatment	*Less than 1/18*	*1/18–1/72*	*1/144 or greater*
Amantadine per cent	*83*	*10*	*7*
Placebo (per cent) ..	*86*	*4*	*10*

and 7 per cent had a titre of greater than 1/144. Of the 124 individuals receiving placebo, 86 per cent had an HI titre of less than 1/18, 4 per cent possessed a titre of between 1/18 and 1/72 and 10 per cent had a titre of greater than 1/144. Thus the groups were matched closely for age and initial antibody status.

During the study, 49 of the 157 individuals given amantadine (31·2 per cent) as against 39 of the 140 given placebo (27·9 per cent) suffered from symptoms of influenza (table III). However, of the 49 drug-treated cases who had symptoms of influenza, 37

TABLE III
INCIDENCE OF SYMPTOMS OF INFLUENZA

Treatment	*Total no. of volunteers*	*Those with symptoms of influenza*	*Paired sera available*	*Serologically confirmed influenba*
Amantadine	157	49	37	8
Placebo	140	39	36	15
Difference 0·1>P>0·05				

paired sera were available and of these only eight showed a four-fold or greater rise in HI titre between first and second specimens.

Of the 39 individuals receiving placebo, 36 paired sera were available and 15 revealed a four-fold or greater rise in HI titre.

Expressed as percentages, 23 per cent on amantadine and 42 per cent on placebo showed serologically proven influenza (0·1>p>0·05). This result is of borderline significance in favour of the group receiving drug protection.

When the different symptoms were analysed separately, no significant difference between the active and placebo-treated groups was noted regarding symptomatology except for shortness of breath. In the drug-treated group, only 14 out of 48 (29 per cent) compared with 23 out of 38 (61 per cent) on placebo, complained of this symptom. This

is a highly significant difference ($p<0\cdot01$) in favour of the drug-treated group.

Discussion

A prophylactic trial demonstrating the efficacy of amantadine was carried out by general practitioners throughout Great Britain during which the drug was administered to familial contacts of serologically proven cases of influenza (Galbraith *et al* 1969a). Subsequently a therapeutic study of amantadine was performed in general practice amongst patients already suffering from clinical influenza (Galbraith *et al* in press).

In contrast to the previous trials, during the present study it was not possible to establish equivocally in each patient the exact time of the initial infection with influenzal virus. Thus amantadine was being tested under both prophylactic and therapeutic conditions. However, the present investigation was particularly interesting because the trial was conducted in a single practice by one doctor. The testing of a potential antiviral compound in such a setting offers the advantage that the compound is assessed under conditions closely related to its possible later use.

Previous studies (Galbraith *et al* 1969a) have emphasized the importance of close laboratory control for the diagnosis of influenza in clinical trials of antiviral agents. It is also necessary for the control and experimental groups to be carefully matched for age, sex and initial antibody levels to influenza virus since these factors may influence the incidence of influenza infection.

A low incidence of HI antibody was found at the beginning of the infection in both control and drug-treated groups confirming the low levels found in the previously reported study in England (Galbraith *et al* 1969b). The marginal effect of amantadine found in the present study may support the suggestion that a combination of influenza antibody and amantadine is required to give effective prophylaxis against influenza. The effect of amantadine in lowering the incidence of shortness of breath has not been recorded previously and future studies might investigate this finding in greater detail.

More recently we have demonstrated that amantadine has some therapeutic activity against influenza A_2 strains (Galbraith, Oxford, Potter, Schild and Watson, in press; Watson, G. I. 1970). Further studies, particularly in general practice, would help to determine the potential value of amantadine and would provide information about the most suitable design of clinical trials to test future chemotherapeutic agents against respiratory viruses.

Acknowledgements

We wish to express our thanks and gratitude to Dr E. Lewis-Faning for the statistical analysis, to Messrs A. Fielding & Company, Platt International Limited, N.S.F. Limited, Whinburn School, Barclays Bank (77 North Street, Keighley, Branch), The Keighley News, to Mrs Constance Schapira, S.R.N., and to Mrs Ann Welham for secretarial help.

References

Quilligan, J. J., Hirayama, M., and Baernstein, H. D. (1966). *Journal of Paediatrics*, **69**, 572.

Togo, Y., Hornick, R. B., and Dawkins, A. T. (1968). *Journal of the American Medical Association*, **203**, 1089.

Galbraith, A. W., Oxford, J. S., Schild, G. C., and Watson, G. I. (1969a). *Lancet*, **2**, 1026.

Galbraith, A. W., Oxford, J. S., Schild, G. C., and Watson, G. I. (1969b). *Bulletin of the World Health Organization*, **41**, 671.

Watson, G. I. (1970). *Practitioner*, **205**, 351.