RESEARCH

The therapeutic effect of amantadine in influenza occurring during the winter of 1971-2 assessed by double-blind study

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THERE is good evidence of the prophylactic efficacy of amantadine hydrochloride 'Symmetrel' (Togo *et al.*, 1968; Galbraith *et al.*, 1969) in influenza A_2. The therapeutic effect has also been investigated and the drug, taken orally at the onset of influenzal symptoms, produced amelioration of symptoms (Watson, 1970) in the patients treated and significant reduction in the duration of fever (Galbraith *et al.*, 1971).

Method

To assess the value of amantadine in subsequent influenza epidemics, those doctors who had participated in previous studies, the majority of whom were on the register of the Epidemic Observation Unit of the Royal College of General Practitioners, were invited to take part in the 1971–2 therapeutic trial, The practices were in England (53), Wales (seven), Scotland (four), and Ireland (two). Each doctor was asked to include in the study any patients suffering from clinical influenza of not more than 48 hours' duration. He was given enough equipment to treat four patients, and could obtain additional material if he wished to treat more.

All patients who participated in the trial were allocated a code number, and medication, whether drug or placebo, was provided on a random, double-blind basis so that neither doctor nor patient knew of the composition of the capsules. Individuals who had received influenza A_2 virus vaccine during the preceding year were excluded from the study.

Dosage

Amantadine was provided in 100 mg capsules or as a syrup containing 50 mg per 5 ml. Adults received one capsule of soft gelatin containing a suspension of amantadine in oil every 12 hours. Children aged 10–15 years received one capsule every 24 hours and younger children (two–ten years) a proportional dose of syrup. Infants below two years were excluded. Placebo capsules (oil base without drug) and syrup were used with a similar dosage schedule. Active or placebo medication was started when the doctor first saw the patient with influenza and was continued for seven days.

Collection of the specimens

Influenza was diagnosed on clinical and epidemiological grounds. A blood sample was taken when the patient first consulted the doctor and a second two or three weeks later.

The blood specimens were tested at the University of Sheffield Virus Research Laboratory for haemagglutination-inhibiting (HI) antibody with A_2 Hong Kong/68 virus and for complement-fixing (CF) antibody with influenza A ribonucleoprotein (PR 8) using standard methods (Bradstreet and Taylor, 1962).

A fourfold or greater rise in antibody titre in either or both of these tests was taken as evidence of influenza A infection.

Clinical observation

When the doctor first saw the patient, he provided code-labelled capsules or syrup and noted the temperature and the time at which treatment started. Temperature readings were taken thrice in 24 hours and clinical symptoms were recorded daily. The patients were visited by the doctor or a nurse at frequent intervals. The time it took for the temperature to fall below 37.2°C (99°F) was measured in hours.

Results

Observations were made on 112 patients with clinically diagnosed influenza. However, three records were incomplete and 44 patients included in the study did not meet the serological criteria of infection with influenza A_2 virus—namely, a fourfold or greater rise in HI or CF titre in the paired serum specimens.

The results from a total of 65 patients with serologically proven influenza A_2 (Hong Kong/68) infection were analysed. Of these patients, 34 received amantadine and 31 received the placebo. The sex and age distribution of the two groups are shown in Table 1. The mean age of amantadine treated patients was 41.8 years and that of the placebo group 37.3. The differences were not significant and the groups may be considered similar.

TABLE 1

AGES AND SEX OF PATIENTS IN AMANTADINE AND PLACEBO GROUPS

Group	*Total number of patients*	*Number of patients in each age group*							*Mean age (years)*	*Proportion of males and females in each group*	
		10–	20–	30–	40–	50–	60–	70+		*Males*	*Females*
Amantadine	34	2	5	11	5	6	3	2	41·8	23	11
Placebo	31	3	8	8	4	6	1	1	37·3	16	15

Fever

The mean duration of fever in the patients receiving amantadine was 73.6 hours and that of patients on placebo 86.0 hours. This difference is not significant.

Symptoms

The following symptoms were listed on the response card: cough, headache, sore or dry throat, muscle-ache, poor appetite. These were recorded daily as present or absent by each patient. The distribution of symptom-clearance time in the two groups is shown in Table 2.

On average, patients on amantadine took 64 hours for clearance of symptoms while patients receiving placebo took 90 hours—a very significant difference. Furthermore, in the amantadine treated group, 41 per cent cleared in less than two days, 42 per cent took two to four days and only 18 per cent more than four days. In the control group the corresponding percentages were 23 per cent, 29 per cent and 47 per cent took more than four days. These percentage distributions were highly significantly different.

TABLE 2
DISTRIBUTION OF SYMPTOM-CLEARANCE TIME

Group	*Time (in hours) to clear symptoms*							*Total*	*Mean hours**
	24	24–	48–	72–	96–	120–	144–		
	Number %	*Number* %	*Number* %	*Number* %	*Number* %	*Number* %	*Number* %	*Number* %	
Amantadine	2 *6*	12 *35*	8 *24*	6 *18*	3 *9*	— —	3 *9*	34 *101*	63·9
Placebo	3 *10*	4 *13*	4 *13*	5 *16*	6 *19*	1 *3*	8 *25*	31 *99*	90·3

* Difference between groups=26·4 hours : 0·02>P>0·01

Return to work

The time taken from start of treatment to return to full activity, measured in days, was also recorded in this investigation. The mean overall duration of illness in patients on amantadine was 9.2 days while that of patients receiving placebo was 11.8 days. This difference of 2.6 days is statistically significant.

Laboratory results

Of the 112 patients with clinically diagnosed influenza, 55 (49 per cent) had a fourfold or greater rise in HI titre and 48 (43 per cent) a fourfold or greater rise in CF titre between acute and convalescent sera. The antibody responses in patients with serologically confirmed influenza are shown in Tables 3 and 4. There was no significant difference between the amantadine and placebo groups in the degree of antibody response. This finding suggests that the drug did not significantly depress the immunological response to infection.

TABLE 3
H.I. ANTIBODY RESPONSES

Group	*Number of patients with stated antibody rise in H.A. tests*			*Total patients*
	<4 fold	4–24 fold	25–64 fold	
Placebo	23	19	10	52
Amantadine	31	17	9	57
Total	54	36	19	109

No significant difference (P>0.05) was detected between the numbers of placebo and amantadine treated individuals in each of the three groups.

TABLE 4
C.F. ANTIBODY RESPONSES

Group	*Number of volunteers with stated antibody rise in C.F. tests*			*Total patients*
	<4 fold	*4–24 fold*	*25–64 fold*	
Placebo	24	17	7	48
Amantadine	29	21	3	53
Total	53	38	10	101

No significant difference (P>0.05) was detected between the numbers of placebo and amantadine treated individuals in each of the four groups.

Discussion

There was relatively little influenza throughout Great Britain during the winter of 1971–2 and this accounts for the small numbers in this trial compared with the previous studies. Nevertheless, the widely distributed practices enabled the family doctors to include patients to provide enough results for statistical analysis.

While there was no reduction in the duration of pyrexia in the patients taking the active drug compared with those on the placebo, a more rapid clearance of symptoms and a shorter duration of time off work characterised those patients taking amantadine. These findings agree with those reported previously (Hornick *et al.*, 1969; Wingfield *et al.*, 1969; Togo *et al.*, 1970).

The relatively large number of patients diagnosed clinically as suffering from influenza, who subsequently were found not to possess a fourfold or greater rise in antibody seen by a group of experienced practitioners, emphasises the necessity of serological proof of infection in all therapeutic studies of influenza.

In this investigation, as in those performed previously, no evidence of reduction in the levels of circulatory influenza antibodies was demonstrated in infected individuals who received amantadine. The drug appears, therefore, not to possess the disadvantage of inhibiting the development of natural immunity when used as a therapeutic agent.

Summary

In double-blind, placebo controlled study of amantadine (Symmetrel) in the treatment of patients with influenza A_2 Hong Kong, confirmed clinically and serologically, a significant reduction in symptom clearance time and duration off work were demonstrated. There was no evidence that amantadine significantly depressed the levels of circulating influenza antibodies detected in convalescent sera.

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References

Bradstreet, C. M. P. & Taylor, C. E. D. (1962). *Monthly Bulletin of the Ministry of Health* (London), **21**, 96–104.

Galbraith, A. W., Oxford, J. S., Schild, G. C. & Watson, G. I. (1969). *Lancet*, **2**, 1026–1028.

Galbraith, A. W., Oxford, J. S., Schild, G. C., Potter, C. W. & Watson, G. I. (1971). *Lancet*, **2**, 113–115.

Hornick, R. B., Togo, Y., Mahler, S. & Iezzoni, D. (1969). *Bulletin of the World Health Organization*, **41**, 671–676.

Togo, Y., Hornick, R. B. & Dawkins, A. T. (1968). *Journal of the American Medical Association*, **103**, 1089–1094.

Togo, Y., Hornick, R. B., Felitti, V. J., Kaufman, M. I., Dawkins, A. T., Kilpe, V. E. & Claghorn, J. L. (1970). *Journal of the American Medical Association*, **211**, 1149–1156.

Watson, G. I. (1970). *Practitioner*, **205**, 351–357.

Wingfield, W. L., Pollack, D. & Grunert, R. R. (1969). *New England Journal of Medicine*, **281**, 579–584.