Use of amantadine in influenza: a second report

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SUMMARY. Clinical influenza attacked 304 out of 576 boys at a west country boarding school. Influenza A/ENG/333/80 (H_1N_1), a drift from A/USSR/92/77, was isolated from 14 out of 40 throat swabs. Pre-epidemic sera from 64 new boys showed that 54 already had antibodies to H_1N_1 and 40 of them had antibodies to this novel variant. Nevertheless, when their serum was re-examined post-epidemically, 36 showed a rise in antibody, indicating that infection had occurred.

One hundred and twenty-six junior boys were given amantadine and, of these, 22 (17.4 per cent) developed influenza, whereas 218 (57 per cent) of 382 boys who did not take amantadine had influenza. The immune status was known for 64 boys, 43 of whom were given amantadine. Only five (11.6 per cent) became clinically ill while taking the drug, whereas 10 (47.6 per cent) of the remaining 21 boys became ill. When their serum was re-examined, it was found that 20/43 of those taking amantadine and 5/21 of those not taking the drug had subclinical infection. The two groups were comparable in their pre-epidemic antibody status and all lived within the same environment during the outbreak.

It is concluded that amantadine secured a reduction in clinical influenza without protecting significantly against subclinical infection, thus allowing subtype specific immunity to develop.

Introduction

THE schoolboys in this study are all boarders at a public school in the west country. There are 576 boys, aged between 12 and 18 years, most of whom live under one roof. Influenza is the major illness affecting the school and information about these epidemics is collected by the Study of Influenza in Residential Schools (SIRS) team. Serum was taken from most of the new entrants (84 boys) to the school in September 1980, and post-epidemic sera was taken in January 1981 to give a cohort of 64 paired sera.

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On 24 November 1980, a feverish illness broke out, and by 28 November it was clear that there was an epidemic of influenza. The numbers of sick rapidly increased, and the more seriously ill senior boys and all the junior boys were taken into emergency sick-bays. By 7 December, when the term ended, all had recovered sufficiently to go home.

The previous report on the value of amantadine did not include immunological confirmation of the findings.[1] Most other studies on the use of amantadine have used clinical measurements, and there has been scepticism of its value.[2]

Method

Boys in the school are not routinely vaccinated against influenza. Those who fall ill are treated in an infirmary, although in this epidemic so many were ill that only the junior boys were closely supervised by a nurse day and night in emergency sick-bays. They were treated by rest in bed, with aspirin or paracetemol and, for cough, codeine linctus.

Throat swabs from 40 boys and taken to the Public Health Laboratory (PHL) at Bath, 14 miles away. The isolates were further typed and characterized by the influenza centre at the central Public Health Laboratory at Colindale, London.

Of the original 84 new entrants, post-epidemic sera was taken in January 1981 from 70. Five were excluded because they were day boys (three of these boys had influenza but did not take amantadine). One boy was away during the epidemic with appendicitis, 10 boys refused, and two had left the school; all except two of these boys had not had influenza. Sixty-four paired sera could be used, but there were technical difficulties with two. These 64 paired sera were examined by haemagglutination inhibition (HI) and radial haemolysis (SRH) with strains of A/USSR/92/99 and A/ENG/333/80, both H_1N_1 influenza virus, by the Influenza Research Unit at Guildford Public Health Laboratory.

From 29 November until 7 December 1980, as they went to bed, amantadine 100 mg was given daily by mouth to all the boys (126 boys) in the junior houses who were not already ill, by their house masters or dormitory prefects. In the subsequent analysis of the effects of giving amantadine, only those ill after 27 November are compared. Those in the senior houses (64 boys) and those in the junior houses (four boys) who were ill before 27 November were excluded from subsequent analysis. In this way it was hoped to compare groups with the same susceptibility to the virus. Although the school is all under one roof, of the 18 boys ill on 24 November, nine were in the same coach for a rugby fixture on 22 November and five of these were in the same house. These differences between senior houses had disappeared by 27 November.

Results

Clinical influenza developed in 304 (52.7 per cent) of the boys.

Table 1 shows the analysis of those boys who had not already become ill before 27 November, the date amantadine was started. It excludes 64 boys from the senior houses and four from the junior houses. There is a suggestion of an association between the taking of amantadine and protection against the clinical symptoms of influenza. Of the 40 throat swabs taken for viral studies, 14 revealed isolates of influenza H_1N_1, characterized as A/ENG/333/80, a variant drifted from A/USSR/92/77 (H_1N_1).

Table 2 shows the antibody status of the 64 boys for whom paired sera were available in relation to treatment with amantadine and clinical influenza throughout the epidemic. The following notes are evident from the Table:

1. Without amantadine: infection rate was 71.4 per cent, illness rate 47.6 per cent. With amantadine: infection rate was 58 per cent, illness rate 11.6 per cent. Using Cochrane tests: illness rates for those with and those without amantadine, critical ratio = 3.1, $P<0.01$. Similarly the infection rates, as indicated by a rise in antibodies, for those with and those without amantadine, critical ratio = 0.7, $P<0.05$

2. Infection rate as indicated by a rise in antibodies was highest in those boys with no pre-epidemic antibody and least in those with homologous antibody. Within each antibody grouping—None, A/USSR/92/77, and A/ENG/333/80 plus A/USSR/92/77—amantadine had no significant effect on the infection rate.

3. In all antibody groups, the rate of clinical influenza was lower in the boys who were taking amantadine.

Table 1. Influenza rates after 27 November, the date amantadine was started.

	Treatment of boys still well on 27 November (number of boys)	
	With amantadine	Without amantadine
Developed influenza	22	218
Did not develop influenza	104	164
Total	126	382

$\chi^2 = 59$, $P<0.001$.

Discussion

This report suggests that taking amantadine prevented the clinical illness of influenza H_1N_1, but without preventing a rise in antibodies. Amantadine caused no undesirable side effects. It can be seen from Table 2 that the two groups of junior boys, those taking amantadine and those not taking it, had similar pre-epidemic antibody to the H_1N_1 influenza virus. Some boys avoided the handout of pills of amantadine because they were absent from the dormitory for one reason or another. Several of those who missed the drug, even one dose, became clinically ill. A dosage of 100 mg may have been too low for some of the larger boys. Clearly, if amantadine is not taken regularly it is ineffective.

This study supports other reports from the United States,[3,4] showing that amantadine renders clinical type A influenza shorter in duration and less serious.

Influenza vaccines are made less effective by the mutability of the influenza virus and are unlikely to contain the right antigens when there is a major shift. Exposure to novel variants is unavoidable.[5] However, amantadine appears to offer protection even if there has been a major shift in the antigens of the virus.

The clinical problem remains. Does the patient have influenza, and is it virus A or B? New methods of pharyngeal and nasal aspirations and the development of immunofluorescent techniques can clarify the diagnosis within three hours, before the inappropriate use of amantadine. This technique is the subject of a further study.

The percentage of new boys who had antibody to influenza H_1N_1 before the epidemic is similar to that found in other schools in the SIRS survey of the same age group.

Table 2. Antibody status of the 64 boys for whom paired sera were available.

Prechallenge antibody to H_1N_1	Without amantadine			With amantadine		
	Number of boys	Antibody rise	Clinical symptoms	Number of boys	Antibody rise	Clinical symptoms
Antibody group						
None	4	4	4	6	6	1
A/USSR/92/77	6	5	2	8	6	5
A/ENG/333/80 + A/USSR/92/71	11	6	4	29	13	3
Total	21	15	10	43	25	5

The re-emergence of influenza A H_1N_1 as a virulent virus poses many questions. Was the earlier infection different, and was the naturally occurring antibody response to the first infection not protective against a second attack? Are two attacks needed to boost the antibody response, or three as with the triple vaccine used in babies? Is there another mechanism at work, such as in shingles, or is there some latent process as described by Hope Simpson.[6] Continued studies over long periods, together with documented epidemiological studies, may answer these questions.

References

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Withdrawal of diazepam

Forty-one outpatients who were longterm consumers of diazepam in therapeutic dosage were gradually withdrawn from the drug over 3 months by stepwise reduction. In a double-blind procedure half the patients began withdrawal immediately and half after 8 weeks. Of 36 patients who completed treatment, 16 (44.4 per cent) experienced true withdrawal phenomena on reducing their drugs, but eight other patients had pseudo-withdrawal reactions at a time when their drug treatment was unchanged. The pseudo-withdrawal reactions consisted of an increase in anxiety symptoms only, whereas true withdrawal symptoms also included perceptual changes and psychotic symptoms.

Source: Tyrer P, Owen R, Dawling S. Gradual withdrawal of diazepam after long-term therapy. *Lancet* 1983; **1**: 1402.