Prophylactic use of amantadine in a boarding school outbreak of influenza A

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SUMMARY. Amantadine was used in a boarding school to control an outbreak of influenza A H3N2. Of 859 pupils 79% took amantadine and almost all of them completed the course (100 mg per day for 15 days). While amantadine was being taken the number of clinical cases of influenza was considerably fewer than that predicted on the basis of previous outbreaks of influenza A at the school. However, during the month following the course of amantadine, the outbreak continued with many clinical cases confirmed by virus isolation. The advantages and limitations of amantadine prophylaxis are discussed.

Introduction

Outbreaks of influenza can cause severe disruption to life in boarding schools and much effort has gone into trying to identify ways to prevent or reduce these outbreaks. Christ's Hospital, a boarding school for approximately 800 pupils aged 11–18 years, has been the subject of a long-term study of influenza. Between 1970 and 1986 there have been 11 outbreaks at the school — six were caused by influenza A, three by influenza B and in the remaining two both types were involved.

Inactivated vaccines are the traditional form of prophylaxis in such communities but the results have been disappointing. At this school no long-term benefit to the individual was observed and at another boarding school severe outbreaks were experienced despite routine annual vaccination of 85–90% of the pupils. Amantadine has been used with some success to control epidemics of influenza A in schools and Payler calculated that the drug was 90% effective in preventing symptoms. Several problems have beset studies of the efficacy of amantadine. First, the compound is only effective against strains of influenza A; it has no activity against influenza B. Thus, it is important to establish the strain of influenza virus which is responsible for the outbreak. Secondly, the outbreak must be recognized early enough to achieve a benefit from prophylaxis, and to be effective it is essential that the capsules are taken regularly.

The long-term study of influenza at Christ's Hospital has revealed certain characteristics of outbreaks of influenza A in this population. The actual epidemic is preceded by several 'forerunner' cases which occur over one or two weeks, and then, the number of pupils with clinical influenza increases sharply with most cases occurring during the next two weeks. The whole epidemic is short-lived and lasts between three and five weeks. These characteristics make it possible to predict with some certainty the beginning of an epidemic. With this knowledge a study was set up at the school to assess the efficacy of amantadine used prophylactically to control influenza A. The objective was to prevent clinical influenza, thereby reducing a potentially large outbreak to one of manageable proportions.

Method

Study design

Consent to treat pupils with amantadine in the event of an influenza epidemic was sought from parents of all children aged under 16 years at the school. Those who were aged 16 years or over were allowed to make their own decision.

The criteria for using amantadine were: influenza A virus should be identified in throat swabs or nasopharyngeal aspirates from early clinical cases; and there should be an increase in cases of clinical influenza with a minimum of 10 cases on one day, 15 over two days or 20 over three days. Apart from children who refused consent and those for whom amantadine was contraindicated, the whole school was scheduled to receive a 100 mg capsule once per day with the midday meal for two weeks. A random control group was not included. Other studies have demonstrated the benefit of amantadine and therefore there were no grounds for withholding prophylaxis from those who had given consent.

The criteria for the use of amantadine were satisfied and prophylaxis was commenced on 5 February 1986 and continued until 19 February. On the afternoon of 20 February the children went home for a mid-term break, returning on 23 February. A check list for each pupil was maintained; these were inspected daily by the school medical officer (T.W.H.) and retained by him for analysis at the end of the study. Urine samples were collected on a random basis from children who attended the infirmary for any reason, for example, regular prescriptions and sports injuries, as well as those with minor ailments, influenza or other acute illnesses. The amantadine concentration was determined to assess compliance.

Investigation of illness

For the purpose of this study the definition of clinical influenza was an illness with an elevated temperature and respiratory symptoms without clinical signs indicating another diagnosis, for example, streptococcal pharyngitis. Nasopharyngeal aspirates and/or throat swabs were collected from pupils with clinical influenza. The aspirates were examined by immunofluorescence for the presence of influenza viruses A and B and other respiratory viruses. The swabs and aspirates were cultured for viruses and haemolytic streptococci.

Acute and convalescent blood samples were investigated for evidence of influenza infection by radial haemolysis using current strains of influenza A H3N2, A H1N1 and B.

Results

Amantadine uptake and compliance

Amantadine was taken by 680 of the 859 pupils in the school (79.2%) and 93.1% of those who took it received all 15 doses or only missed one. Urine samples from 64 pupils were tested...
and amantadine was detected in all those who were receiving capsules and in none of those who were not. None of the side effects associated with amantadine were reported. Although pupils who developed clinical influenza continued to take amantadine no effect on the duration or severity of symptoms was observed.

The outbreak

The time course of the epidemic is shown in Figure 1. The first cases of influenza occurred on 29 January. Influenza A virus was detected by immunofluorescence in five of eight nasopharyngeal aspirates collected on 4 February. The virus was subsequently isolated and identified as influenza A H3N2. There had been 17 cases of clinical influenza by 4 February and on 5 February there were 23 new cases. Amantadine prophylaxis was commenced on 5 February with the midday meal. There were a further 16 new cases on 6 February but thereafter numbers declined. Only 36 pupils were diagnosed as having clinical influenza between 7 and 19 February when prophylaxis ceased — 23 of these had been taking amantadine. One child developed symptoms on 20 February and a further 12 during the mid-term break. Between 24 February and the end of term on 26 March there were 76 more cases of clinical influenza with the last case occurring on 24 March. No prophylaxis was used during this period and the number of new cases reached double figures on one day only. Although not all of these 76 late clinical illnesses were associated with influenza A infection (six children were known to have been infected earlier in the outbreak and two were infected with influenza B) 53.9% had laboratory evidence of infection with influenza A H3N2.

Comparison of influenza A outbreaks

The outbreak in 1986 was compared with other outbreaks of influenza A in the school in 1976, 1978, 1980 and 1983. The outbreak in 1972 had to be omitted because the records were inadequate. The outbreaks were divided into three periods: (1) from when the first cases occurred until the time at which amantadine would have been given and become effective, that is 24 hours after the first dose; (2) the 14 days after period 1, that is the period when amantadine would have been given; (3) after period 2.

The numbers of clinical cases that occurred in the three periods are shown in Table 1. A similar pattern was observed in all the outbreaks when amantadine was not being used, irrespective of the size of the outbreak. The pattern in 1986 was clearly different.

<table>
<thead>
<tr>
<th>Year of outbreak</th>
<th>No. (%) of cases in period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1976 (n = 203)</td>
<td>43 (21.2)</td>
</tr>
<tr>
<td>1978 (n = 418)</td>
<td>86 (20.6)</td>
</tr>
<tr>
<td>1980 (n = 203)</td>
<td>43 (21.2)</td>
</tr>
<tr>
<td>1983 (n = 253)</td>
<td>38 (15.0)</td>
</tr>
<tr>
<td>1986 (n = 181)</td>
<td>56 (30.9)</td>
</tr>
</tbody>
</table>

n = total number of cases in outbreak.

The effect of amantadine was calculated by comparing the observed distribution of cases in 1986 with the expected distribution based on the cumulative data from the other outbreaks (Table 2). During period 2 the difference between the observed cases of influenza and the expected number was 185, which gives a protection rate for the whole school of 83.7%. A similar calculation based on those who took amantadine gives a protection rate of 88.3%.

Discussion

Amantadine prophylaxis may be used to protect individuals at risk from influenza A or to reduce the impact of an epidemic on a community. It was not the intention of this study to perform a controlled trial but to assess the effect of amantadine
Table 2. Comparison of 1986 outbreak with cumulative data from the previous outbreaks of influenza A.

<table>
<thead>
<tr>
<th>Total no. of cases</th>
<th>1 (%)</th>
<th>2 (%)</th>
<th>3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous outbreaks</td>
<td>1077</td>
<td>210 (19.5)</td>
<td>829 (77.0)</td>
</tr>
<tr>
<td>1986 outbreak</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed</td>
<td>181</td>
<td>56 (30.9)</td>
<td>36 (19.9)</td>
</tr>
<tr>
<td>Expected</td>
<td>287</td>
<td>56 (19.5)</td>
<td>221 (77.0)</td>
</tr>
</tbody>
</table>

* Calculated assuming 68 is 19.5% of outbreak. Protective effect: (no. of expected cases – no. of observed cases)/no. of expected cases x 100.

by comparing the epidemic in 1986 with other outbreaks of influenza A at the school. Our objective was to reduce a potentially large outbreak to manageable proportions and to achieve this we had to ensure a high uptake. Parental consent was obtained well in advance of the influenza season and supplies of amantadine sufficient to treat the whole school were obtained and stored at the infirmary. A system for administration was agreed between the medical officer and the rest of the staff. Thus, as soon as the criteria were fulfilled treatment could start.

In 1986 there was no rapid increase in the number of cases once amantadine prophylaxis had started, although amantadine did not give total protection. After the mid-term break clinical cases continued to occur, though not at a rate that caused us to consider restarting treatment. In spite of this second wave the total number of cases in the outbreak was 106 fewer than predicted and the protection afforded by amantadine was similar to that observed by Payler. These findings suggest that amantadine could be used to modify an outbreak of influenza A in a boarding school. Inevitably, cases will occur before it can be established that an outbreak is imminent and with a dose of 100 mg per day it may be 24 hours before an effective concentration is present in the tissues. In addition, it is unlikely that everyone will take amantadine or that it will be 100% effective.

The decision on when to start using amantadine depends upon several factors including the demonstration of influenza A virus in the general population and the occurrence of clinical influenza associated with the virus in a closely defined community which favours rapid spread. In this study long-term monitoring of influenza at the school enabled the start of the outbreak to be recognized. In other populations where such information is not available the criteria used here may not be suitable and Rose has commented that not all cases may come to the attention of the medical officer. Early recognition of outbreaks is essential to achieve benefit from prophylaxis.

How long prophylaxis should continue is a more difficult decision. Payler observed a small number of cases of laboratory confirmed influenza A after a 14 day course of amantadine when approximately half the school received prophylaxis. He suggested that the outbreak might have died out within a few days had the entire school been given amantadine and also that medication should continue for at least four days after the last identified case. From our earlier experience at Christ’s Hospital we believed that a two-week course would span the body of the epidemic. In the event a mid-term break immediately followed the treatment and it was hoped that these two events together would bring the outbreak to an end. Nevertheless, nearly half of the total clinical cases occurred in the second half of the term. It is possible that amantadine, by suppressing symptoms or infection reduced the opportunities for transmission during prophylaxis leaving sufficient susceptible individuals available for infection when further challenged. However, a longer course of prophylaxis is likely to result in problems of compliance among the young and healthy.

Perhaps our experience illustrates why, some 25 years after amantadine was first shown to have a prophylactic effect against influenza A, it is not used more widely. However, we would use it again in similar circumstances to those described here. If there were an antigenic shift and an impending pandemic of influenza A, amantadine would merit serious consideration along with other control measures in the general population or in selected groups.

References


Acknowledgements

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Early application is advised but by the latest by 1 October 1988. Section 63 approval is being sought.