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Research articles

ADVERSE DRUG EFFECTS FOLLOWING OSELTAMIVIR MASS TREATMENT AND PROPHYLAXIS IN A SCHOOL OUTBREAK OF 2009 PANDEMIC INFLUENZA A(H1N1) IN JUNE 2009, SHEFFIELD, UNITED KINGDOM

M Strong (m.strong@sheffield.ac.uk)¹, J Burrows¹, E Stedman², P Redgrave³

1. School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom
2. Medical School, University of Sheffield, Sheffield, United Kingdom
3. NHS Sheffield, Sheffield, United Kingdom

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During the containment phase of the 2009 influenza A(H1N1) pandemic, mass treatment and prophylaxis with oseltamivir was used to control an outbreak of pandemic influenza in a primary school in Sheffield, United Kingdom, where ten cases of pandemic influenza had been laboratory confirmed over a three day period in June 2009. A subsequent cross-sectional survey showed that 51 of 297 (17%) pupils and 10 of 58 (17%) reported an influenza-like illness. The most common symptoms were headache, cough, fever, tiredness, sore throat and nausea. Fifty-three staff and 273 pupils took oseltamivir for treatment or prophylaxis. Of this group, 41% (113/273) of pupils and 47% (25/53) of staff reported adverse effects. Overall, 14% (37/273) of pupils and 20% (11/53) of staff did not complete the course of oseltamivir, primarily due to adverse effects. Nausea, vomiting and rash were statistically significantly associated with failing to complete the course of oseltamivir. Given the potential for side effects from oseltamivir, particularly among those without influenza who receive the drug for prophylaxis, our findings have two important implications. Firstly, the benefits of mass treatment in an outbreak setting must clearly be greater than the benefits of targeted treatment. Secondly, any large scale regional or state level system for distribution of antiviral drugs for treatment should ideally include a robust quantification of an individual's probability of infection with influenza virus in order to avoid unnecessary treatment.

Introduction

An outbreak of 2009 pandemic influenza A(H1N1) occurred in a Sheffield junior school in June 2009, during the United Kingdom pandemic influenza containment phase. Over a three day period a seasonally unusual number of pupils and staff became unwell with influenza-like illness. Ten cases were laboratory confirmed as pandemic influenza and a decision was taken to close the school for one week and offer oseltamivir (unless contraindicated) to pupils and staff regardless of their being symptomatic or not.

As with any drug, oseltamivir is associated with adverse effects. In clinical trials including adults and adolescents with influenza, nausea and vomiting were statistically significantly more common in those who took the treatment dose of oseltamivir compared with those who took placebo (11% versus 7% for nausea alone, and 8% versus 3% for vomiting) [1]. Anecdotal evidence at the time of the outbreak described, suggested that the prevalence of adverse gastrointestinal effects could be somewhat higher than this, and subsequent studies in other outbreaks with pandemic influenza in England have confirmed this [2,3].

The prevalence and severity of adverse drug reactions, whether perceived or experienced, are important factors in patients' adherence to medication, and adherence is improved if the benefit of a drug is perceived to outweigh potential harm [4]. The balance between benefit and potential harm is particularly important where a drug is taken prophylactically for a disease that is considered to be mild. In such situations harm may easily outweigh benefit and lead to poor compliance. Poor compliance with prophylaxis in the context of a communicable disease outbreak is of public health concern if the drug is being used not only to protect the individual from disease, but also to reduce person-to-person transmission.

Our study aimed to determine the prevalence of adverse effects from treatment and from prophylaxis with oseltamivir, and whether these were associated with failure to complete the course of oseltamivir.

Methods

The school was closed at the end of the school day on Friday, 12 June and reopened on the morning of Monday, 22 June. Oseltamivir was offered to all staff and pupils at the school by local NHS Sheffield and Health Protection Agency staff. The medication was distributed at the school on the evening of 12 June, and the morning of 13 June. Those reporting fever plus two other influenza associated symptoms were considered clinical cases of influenza, and were prescribed an age appropriate treatment dose (60mg for school pupils and 75mg for adults) twice daily for five days. Laboratory confirmation was not routinely undertaken on the clinical cases reported during the mass treatment phase of the outbreak. Those who did not fit this case definition were prescribed the same dose as for treatment, but once daily for 10 days.

Questionnaire

We conducted a cross-sectional survey and approximately two weeks after the end of the outbreak, a questionnaire was distributed via the school to all pupils and staff to be filled in anonymously. The questionnaire asked for the following information: whether or not the respondents had been 'poorly with flu symptoms', which symptoms they had experienced, any past medical history, whether they had taken oseltamivir and how long they had taken it for, any adverse effects they had experienced, and if they had stopped taking oseltamivir, why had they done so. Finally, respondents were asked if there was anything else they would like to tell us (Figure 1).

Figure 1. Questionnaire on influenza-like illness and oseltamivir use, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009





Statistical analysis

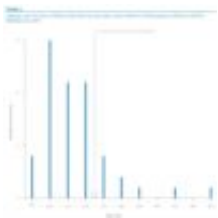
Data were analysed in R 2.9.1 [5]. For proportions we calculated 95% confidence intervals (CI) using the exact binomial method. Association between failure to complete the course of oseltamivir and the presence or absence of adverse effects was explored using multivariate logistic regression. We retained in the model those adverse effect covariates that were significantly associated, at $p < 0.05$ level, with failure to complete the course. For the included adverse effect covariates we present odds ratios (OR) as the measure of association, along with 95% CI.

We tested for a difference in the proportions of respondents with and without influenza-like illness reporting adverse effects using a chi-square test for homogeneity with a null hypothesis of no difference and a significance level of $p < 0.05$. We tested for a difference in the proportions of respondents with and without influenza-like-illness who failed to complete the course of oseltamivir in the same way.

Results

The epidemic curve shows the number of new cases of influenza-like illness by day over the period of the outbreak from June 9 to June 19, 2009; fewer cases occurred with a reported onset date after the school closure compared with the time before (Figure 2).

Figure 2. Epidemic curve of cases of influenza-like illness by onset date, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009



The response rate to the questionnaire was 84% (58/69) among staff and 62% (297/476) among pupils. Pupils who responded were between seven and twelve years old with a mean age of 9.5 years. Staff were asked to indicate which 10-year age band they fell in and 64% (37/58) staff were aged between 40 and 59. Of the 341 respondents who indicated their sex, 45% (129/288) of pupils and 91% (48/53) of staff were female.

Influenza-like illness

Influenza-like illness was reported by 51 pupils (17%; 95% CI: 13-22%) and 10 staff (17%; 95% CI: 9-29%). Pupils who indicated that they were 'generally fit and well' in terms of their overall health were less likely to report that they had had influenza (OR=0.45; 95% CI: 0.22-0.98; $p=0.038$). In staff, no such association was seen.

The most common symptoms reported by the 61 persons with influenza-like illness, were headache (84%; 95% CI: 72-92), cough (80%; 95% CI: 68-89), fever (69%; 95% CI: 56-80), tiredness (69%; 95% CI: 56-80), sore throat (52%; 95% CI: 39-65) and nausea (51%; 95% CI: 38-64) (Table 1).

Table 1. Symptoms in people reporting influenza-like illness, Sheffield, England, June 2009 (n=61)^{a,b}

Symptom	n	%	95% CI
Cough	50	82	71-91
Sore throat	48	79	68-88
Runny nose	47	77	66-86
Headache	33	54	43-64
Fatigue	32	53	42-62
Loss of appetite	28	46	35-55
Stomach pain	27	44	33-53
Diarrhoea	26	43	32-52
Nausea	26	43	32-52
Shortness of breath	25	41	30-50
High fever	25	41	30-50
Low fever	25	41	30-50
Chills	25	41	30-50
Joint pain	25	41	30-50
Muscle aches	25	41	30-50
Loss of consciousness	2	3	0-6
Other	2	3	0-6
None	1	2	0-4

Uptake, adverse effects and adherence to oseltamivir

Fifty-three staff (91%; 95% CI: 81-97) and 273 pupils (92%; 95% CI: 88-95) took up the offer of taking oseltamivir.

Adverse effects were reported by 113 pupils (41%; 95% CI: 35-47) and 25 staff (47%; 95% CI: 33-61). The most commonly reported adverse effects, mentioned by over 10% of the sample were nausea (26%; 95% CI: 22-32), abdominal pain (20%; 95% CI: 15-24), and headache (12%; 95% CI: 8-16) (Table 2). While the majority of adverse effects were physical in nature, two respondents, one staff and one pupil, reported a number of symptoms related to disturbed mood and 19 reported insomnia. There were no life-threatening adverse effects reported (Table 3).

Table 2. Adverse effects reported by >1% of people taking oseltamivir, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009 (n=326)

Adverse effect	n	%	95% CI
Nausea	84	26	22-32
Abdominal pain	65	20	15-24
Headache	39	12	8-16
Insomnia	19	6	3-9
Disturbed mood	2	1	0-2
Other	2	1	0-2
None	1	0	0-1

Table 3. Adverse effects reported by <1% of people taking oseltamivir, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009 (n=326)

Adverse effect	n	%	95% CI
Life-threatening	0	0	0-0
Other	2	1	0-2
None	1	0	0-1

Among those with influenza-like illness, 46% (95% CI: 31-61) of pupils and 56% (95% CI: 21-86) of staff reported adverse effects. In those who were well, 40% (95% CI: 34- 47) of pupils and 45% (95% CI: 30-61) of staff reported adverse effects. There was no significant difference in the proportion reporting adverse effects between those with influenza-like illness and those without (chi-square=0.26, df=1, p=0.6), or between pupils and staff (chi-square=0.33, df=1, p=0.57).

Thirty-seven pupils (14%; 95% CI: 10-18) and 11 staff (20%; 95% CI: 11-34) did not complete the full course of oseltamivir. The most common reasons given were 'it made me feel ill' (50%; 95% CI: 35-65), 'I didn't think it would help' (17%; 95% CI: 7-30) and 'I forgot to take it' (15%; 95% CI: 6-28). In a logistic regression model, stopping oseltamivir was significantly associated with the presence of nausea (OR=2.4; 95% CI: 1.2-4.9; p=0.013), vomiting (OR=3.5; 95% CI:

1.3-9.3; $p=0.014$) and rash (OR=13.0; 95% CI: 1.1-299.3; $p=0.046$). There was no significant difference in the proportion between those with influenza-like illness and those without (chi-square=0.062; $df=1$; $p=0.8$), or between pupils and staff (chi-square=0.58; $df=1$; $p=0.45$).

Among those with influenza symptoms who did not complete a full course of oseltamivir the median number of days taking the drug was three (interquartile range (IQR) 3-4.5). Among those without influenza-like illness who did not complete a full course of oseltamivir the median number of days taking the drug was seven (IQR 5-8).

Reasons for choosing not to take oseltamivir

Twenty-four pupils (8%; 95% CI: 5-12) and five staff (9%; 95% CI: 3-19) chose not to take any oseltamivir. The most common reason given was 'I didn't think it was needed' (45%; 95% CI: 26-64%) (Table 4).

Table 4. Reasons for not taking oseltamivir, school outbreak of 2009 pandemic influenza A(H1N1), Sheffield, June 2009 (n=29)

Discussion and conclusion

In a primary school outbreak of 2009 pandemic influenza A(H1N1), 41% of pupils and 47% of staff who took oseltamivir for either treatment or prophylaxis reported adverse effects. Overall, 48 of 355 (15%) pupils and staff stopped taking oseltamivir, primarily due to adverse effects. Nausea, vomiting and rash were statistically significantly associated with failing to complete the course of oseltamivir.

We were able to distribute our questionnaire to an entire school population who had been offered oseltamivir irrespective of symptoms, and our response rate was high among staff (84%), and moderately high among pupils (62%). We received a considerable number of positive comments regarding the handling of the outbreak in response to the open question 'anything else you would like to tell us'. This suggests that there was general support for our intervention in the school. However, as with any study that does not have a 100% response rate, we cannot fully exclude that those who did not respond may have been systematically different from those who did. In particular, we might expect those who had experienced drug-associated adverse effects to be more likely to participate than those who had not, introducing a bias in our findings. Moreover, one difficulty with our questionnaire (and with this type of observational study in general) is in determining whether symptoms in those who reported influenza-like illness were a result of the oseltamivir used to treat the illness, or the disease itself. Furthermore, we did not ask about the severity of any influenza-like symptoms or adverse effects experienced, and to some extent this is a limitation of our study as we are unable to test for a relationship between oseltamivir dose (expressed, ideally, as dose per unit of child's weight) and the severity of the adverse effect. We were, however, able to determine through our contact with local paediatric services that there had been no reports of any life threatening or serious adverse effects associated with oseltamivir use in our cohort.

Due to the difficulties of obtaining accurate retrospective information from junior school aged children we do not know the degree to which our results may have been biased. We tried to reduce any such bias by asking parents to assist their children in filling the questionnaire, but we are aware that obtaining accurate information can be a problem in retrospective questionnaire studies, irrespective of the age of the respondents. In order to maximise the accuracy of the recall of symptoms and adverse effects we conducted our study as soon as possible following the reopening of the school.

Our study in the context of previous studies

Two studies similar to ours have been published recently in the United Kingdom, one following an outbreak of 2009 pandemic influenza in a school in South West England [2], and the other following outbreaks in three London schools [3]. The South West study reported adverse effects associated with oseltamivir and compliance with prophylaxis in 11-12 year old pupils in a single school year, whereas the London study involved pupils from one primary school (4- to 11-year-olds), and two secondary schools (11- to 14-year-olds).

The findings of our study are broadly consistent with those found in the two studies. Adverse effects were reported by 51% of 247 pupils in the South West, and 53% of 85 pupils in London, compared with 41% in our study. The majority of children in the previous studies were of secondary school age, and therefore older than our cohort. It is possible that older children are more likely to either experience, or report experiencing adverse effects following the use of oseltamivir. Interestingly, a trend in our study showed that a greater proportion of adults reported adverse effects than children, although this difference was not statistically significant.

The prevalence of adverse effects associated with a drug is reported in its Summary of Product Characteristics (SPC). The SPC for oseltamivir draws on adverse event data from treatment and prophylaxis trials and from post marketing surveillance [1]. Table 5 shows the comparative prevalence of adverse reactions (for those reactions reported in all studies) between the SPC and the school based studies amongst those taking oseltamivir for prophylaxis.

Table 5. Prevalence of adverse effects in people taking oseltamivir prophylactically

Adverse Reaction	SPC	South West	London	Our Study
Headache	10%	15%	12%	18%
Nausea	8%	10%	9%	11%
Dizziness	5%	7%	6%	8%
Stomach pain	3%	4%	3%	5%
Other	14%	19%	16%	20%

The school based studies fairly consistently report a higher prevalence of adverse effects than the trials that informed the SPC. This may be due to the inevitable differences in methods for eliciting adverse event information between highly structured and regulated clinical trials and more informal questionnaire surveys. It is possible that the presence of 'tick box' options for reporting a number of specific adverse reactions may have encouraged over reporting in our survey and also could have favoured symptoms and adverse effects listed over those not listed. Moreover, the anxiety generated by the arrival of a pandemic may have led to a greater attention towards adverse effects.

Reported adherence to oseltamivir for prophylaxis varied between the three school studies, with 66% of pupils in the London schools completing the full ten day course compared with 80% in the South West. Of the 271 asymptomatic pupils in our study 230 (85%) completed the full ten day course. It could be that older children are less likely to complete a course of medication, although we did not find this age effect within our data.

Conclusion

In our study, conducted in the context of a school outbreak of 2009 pandemic influenza, mass treatment and prophylaxis with oseltamivir was associated with adverse effects in a considerable proportion of pupils and staff. Despite this, adherence to the antiviral medication regime was generally good. Given the potential for side effects from oseltamivir, particularly among those without influenza who receive the drug for prophylaxis, our findings have two important implications. Firstly, the benefits of mass treatment in an outbreak setting must clearly be greater than the benefits of targeted treatment. Secondly, any large scale regional or state level system for distribution of antiviral drugs for treatment should ideally include a robust quantification of an individual's probability of infection with influenza virus in order to avoid unnecessary treatment.

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