Emerging Health Threats Forum
Identifying and assessing emerging threats to human health from pathogens, chemicals, the environment, radiation, and society

Thursday 25 June 2009

Experts urge caution over Tamiflu

Debate rages over possible side-effects in teens as health authorities dole out drug as a precaution against pandemic flu

Source: framucar

Experts meeting in Geneva this week are set to issue World Health Organization (WHO) advisory guidelines for the use of antiviral drugs in the 2009 flu pandemic. The discussions coincide with the publication of new information about the safety of the antiviral drug Tamiflu in teenage children. The fresh analysis[1] of an old dataset from Japan, published online this month by Takashi Yorifuji and colleagues, reignites the dispute over whether the medication can lead some children to behave abnormally.

Japan is the largest consumer of Tamiflu in the world. Prior to the 2009 pandemic, the country consumed 75% of the drug's global supply.

Puzzling evidence

Between 2001 and 2007, the Japanese government received 211 reports of people showing abnormal behaviour soon after taking the drug, according to a review paper published last year. Some of the people affected experienced delirium or hallucinations, and others tried to jump out of windows. According to media reports, at least 18 Japanese children died after taking the drug and while showing these abnormal behaviours.

In response to these reports, in March 2007 Japanese health authorities banned the use of Tamiflu, also known as oseltamivir, in children aged 10–19. The government also funded two epidemiological studies to better understand the effect of the drug on children's behaviour.

The first, led by Rokuro Hama, included around 2800 children and compared the incidence of "adverse" behaviour between those who had taken the drug and those who had not. The authors found the drug was positively associated with abnormal behaviour.

A larger follow-up study involving more than 9000 children was carried out in 2006–7 and found no link between the drug and irrational behaviour. But a re-analysis of these data, published in the July edition of *Epidemiology*, has now reached the opposite conclusion.

Tom Jefferson, of the Cochrane Vaccines Field and lead author of a Cochrane Review on oseltamivir, is surprised that these strange behaviours didn't show up during clinical testing of the drug. "Two Japanese studies, by Hama and Yorifugi, point to frequent and almost instantaneous adverse events," he says. But these effects did not show up in the drug-registration trials where Tamiflu was tested in around 500 children and 2000 adults, he explains. "It is very puzzling."

Back in 2006, the US Food and Drug Administration added a precaution label to Tamiflu after the reports of adverse effects came in from Japan. To get a better idea of the risks, the Agency commissioned a large study of more than 18,000 people, aged between 1 and 21, who took the drug between 2006 and 2007. The research[2], published three months ago in the *International Journal of Adolescent Medicine and Health*, found no evidence that those taking Tamiflu experienced abnormal behaviours.

In fact, these results suggested that using Tamiflu could protect people against abnormal behaviour. Ward Casscells, who led the US study, cannot explain why the findings are so different to the latest results from Japan. Casscells once advised Roche about Tamiflu's effect against heart attack and stroke, and does not recall receiving money from the drug company.

The discrepancy between the US and Japanese studies could lie in differences between the datasets, says Andrew Herxheimer, a pharmacoepidemiologist at the UK Cochrane Review Centre. The data used in the US study came from medical records, which makes them unreliable for this type of research, he explains.

Grounds for precaution?

Herxheimer believes there is a link between Tamiflu and abnormal behaviour. "We just don't know how rare it is," he says. Because of this, he feels that health authorities have made a "mistake" in giving the drug to children amidst school closures to help stem the 2009 pandemic. "In order to use something we have to have some reasonable estimate of the benefits versus harms relationship," says Herxheimer. The benefit of taking the drug is small as it only makes a difference in serious cases, he explains. But the potential for harm is there, and is serious. "The light should be at yellow not green."

Herxheimer says the abnormal behaviours documented in Japan may be triggered only in a small number of children treated with the drug. Or, there could be other factors at play, he points out.

As the debate continues, Chris Del Mar, of Bond University in Queensland, Australia, a member of the WHO advisory panel discussing antiviral-drug guidelines this week, believes that abnormal behaviour should be regarded as an adverse event of oseltamivir. If adverse events do arise from use of the drug, it will be very important to balance the risk of harm against the benefits, he says. “It will be interesting to see if it [the Japanese report of adverse effects] is corrobborated with safety data from other countries now that oseltamivir has been splashed about so much.”

Looking more closely at the Japanese data, other researchers offer further insights into what could be behind the conflicting study results, and look to the months ahead.

Politics come into play

Yukitoshi Izumi, Professor of Psychiatry at Washington University in St. Louis, Missouri, says that politics has played a part in creating the confusing situation that has emerged from the Japanese research. “The background issue is not science, nor even statistics, but politics played in Japan,” he says.

Izumi explains that partway through the large-scale follow-up study commissioned by the Japanese government, it emerged that the leader of the research team, Shumpei Yokota, had received money from a branch of Roche, the pharmaceutical company that makes Tamiflu. He was then replaced by Yoshio Hirota, and the team continued to analyse the data which were already collected by Yokota.

Their initial findings were published at the end of 2007, and indicated that abnormal behaviour was seen in 12% of the patients who took the drug, compared with 13% of those who didn’t. Instead of the drug being associated with abnormal behaviour, the research suggested once again that Tamiflu could have a protective effect.

“Such a strange result was induced by an alteration, or manipulation, of sample numbers,” says Izumi. There were 99 people in the study who showed abnormal behaviour before they had taken Tamiflu, he explains. The researchers had moved these 99 cases into the control group, even though they had received the drug. “This alteration masked the possible positive relation[ship] successfully.”

Original data and new analysis under fire

In their re-analysis of the same data, Yorifugi and colleagues also argue that these 99 cases should be included in the Tamiflu-treated group. Using a statistical technique that accounts for the total number of days that patients used Tamiflu in relation to the incidence of abnormal behaviour, they say the rate of adverse behaviour increased 1.5-fold among people treated with the drug.

Helena Kraemer, Professor Emerita of Biostatistics in Psychiatry at Stanford University in California, says the statistical approach used by Yorifugi and colleagues to re-analyse the data is no more appropriate than the original method used by Hirota and colleagues.

Nevertheless, Yorifugi *et al.* raise some important questions about how the original investigators gathered the data, according to Kraemer. Clearly, the drug cannot be implicated in abnormal behaviour until after it has been given, she says. “It doesn’t matter what analytical method is used if the sample or measurements themselves are flawed.”

Japanese culture could be a factor

Izumi says that exposure to other chemical substances could be interacting with the drug to trigger the strange behaviours seen in Japan. Many Japanese people believe that Chinese herbal medicines are effective against flu, he explains. The most popular of these, called Ma Huang, contains extracts of ephedra — a stimulant linked with serious adverse effects. “Taking ephedra alone [has] made a person jump from a window,” he points out.

Using Tamiflu with alcohol and caffeine, which are readily available to Japanese teenagers, is another possible cause for abnormal behaviour, says Izumi. His research group observed that mice began jumping if they were given combinations of ephedrine, caffeine, ethanol, and Tamiflu.

Test of time

The true test for the safety of Tamiflu will come in the months ahead. Many governments have stockpiled the drug to help prepare for an influenza pandemic, and many have already broken into these stocks during the early stages of the ongoing ‘swine flu’ pandemic. Routine prescriptions of the drug could give rise to more accidents associated with strange behaviour, says Izumi.

Many children in the UK have been given the drug as a precautionary measure if cases of swine flu appeared at their school. Anecdotal reports have suggested that some of these children became tearful or had sleepless nights, says David Tovey, Editor-in-Chief of the Cochrane Library. But these reports are not reliable indications of a link with use of the drug, he explains; they could simply indicate a natural reaction to the news that a classmate was diagnosed with the disease.

Tovey and Herxheimer say that large scale case-control studies designed to look at the effects of oseltamivir on children are needed now.

Earlier this month, researchers serving on a Japanese health ministry panel advised that the 2007 ban on using Tamiflu in teens should **remain in place**. The WHO’s stance is expected to become clear in the coming weeks.

References and link

1. Yorifugi T, Suzuki E, Tsuda T. Oseltamivir and abnormal behaviours. True or not? *Epidemiology* 2009, **20**. **doi**: **10.1097/EDE.0b013e3181a3d3f6**
2. Casscells SW, Granger E, Kress AM, Linton A. The association between oseltamivir use and adverse neuropsychiatric outcomes among TRICARE beneficiaries, ages 1 through 21 years diagnosed with influenza. *Int J Adolesc Med Health* 2009, **21**:79–89. **Abstract**

US government information about pandemic medication

Print Close