Tamiflu side effects come under scrutiny

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TOKYO

Japanese paediatricians are studying whether Tamiflu, the drug widely thought to be our best defence against avian flu, might be causing mental instability and suicidal tendencies. An initial study cleared Tamiflu of any link, but that study, as well as a larger one that has just started, are raising concerns about conflicts of interest, as some of the researchers have received large sums of money from the drug's Japanese distributor.

Countries around the world have been stockpiling Tamiflu (oseltamivir) since 2004, in case of a pandemic of avian flu. Japan is by far the biggest user of the drug: in 2005, Japanese doctors wrote 9 million prescriptions for Tamiflu, compared with 3 million for all other countries combined. But concerns about the drug's safety, which is made by Roche, have been growing after some unusual deaths in Japanese teenagers who had taken it. Most recently, a 14-year-old girl and a 14-year-old boy died when they jumped from apartment buildings on 16 and 27 February, respectively.

Tokyo-based Chugai Pharmaceuticals, which distributes the drug in Japan, says that it has reported 289 cases of psychoneurotic effects, including three suspicious deaths, to the Japanese health ministry since the drug was launched there in 2001. Chugai now lists the possibility of severe neurological side effects on the drug's labelling and has distributed a warning note to hospitals. The Japanese health ministry insists that there is no clear evidence of a link, however, and points out that flu itself can cause symptoms such as abnormal behaviour. Roche agrees, adding that the number of suspicious deaths is tiny compared to the number of people who have been prescribed the drug.

Tamiflu was cleared initially when seven paediatricians and a statistician looked at the side effects of it and other influenza drugs, as well as at the symptoms of flu itself. The study, which ended in February 2006, followed up 2,846 children aged mostly ten or younger who had been diagnosed with flu. The frequency of abnormal behaviour in children who took Tamiflu was 11.9%, compared with 10.6% in those who didn't take it, which the researchers concluded was not a significant difference.

Shunpei Yokota, head of the study group and a paediatrician at Yokohama City University's Graduate School of Medicine, admits that the study had shortcomings, including a poor definition for the term 'abnormal behaviour'. So in February, at the government's request, Yokota's team launched a larger study, which will trace 10,000 people aged 0–18 years. The team aims to release the results by this autumn.

Experts call for active surveillance of drug safety

Earlier this month, the US Food and Drug Administration (FDA) cautioned Americans that two classes of drugs in widespread use have serious and sometimes life-threatening side effects that warrant new label warnings.

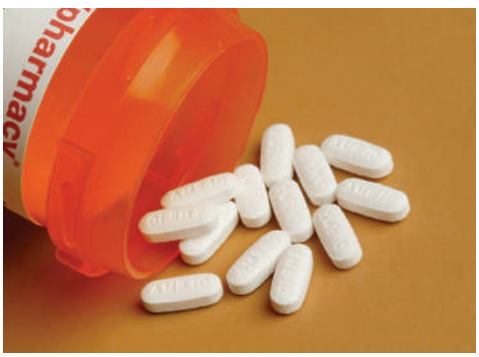
On 9 March, the agency announced that three erythropoietin-type drugs for treating anaemia increase the risk of death, blood clots, strokes and heart attacks, and accelerate the growth of some cancers. Then on 14 March, it asked makers of 13 widely prescribed sedative-hypnotic sleeping pills to toughen label warnings because of reported severe allergic reactions and "complex sleep-related behaviours", including falling asleep while driving.

These warnings, for blockbuster drugs that have been on the market for years, highlight an increasing challenge that confronts the FDA. Side effects may not emerge until new drugs are taken by huge numbers of people. This lesson was driven home by the anti-inflammatory drug Vioxx, which was withdrawn in 2004 after five years on the market, for causing heart attacks and strokes. As a greying America consumes an ever-expanding smorgasbord of medicines, the agency is fighting an uphill battle to catch the next Vioxx before it turns into a fully fledged disaster.

So experts are calling for the FDA to move beyond its current passive system for monitoring the safety of marketed drugs. The Adverse Event Reporting System relies on doctors — if and when it occurs to them — to report suspected side effects to the agency. But doctors filed fewer than 25,000 such reports in 2005, suggesting that the system is capturing only a small fraction of the actual side effects.

"The system in this country for identifying drug safety signals is not nearly as robust as it could be," says Scott Gottlieb, resident fellow at the American Enterprise Institute, a conservative Washington think-tank, and a former deputy commissioner for medical and scientific affairs at the FDA.

Last week, Mark McClellan, a former FDA commissioner, told a Senate committee considering new drug-safety legislation that the system "needs to do better than just seeing the tip of the iceberg of a safety problem after it has already hit us". Health-information



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Side effects often don't emerge until a drug has been on the market for some time.

Suicides in Japanese teenagers have raised concerns about Tamiflu's safety.

But Yokota's team has itself come under fire recently. Last week, it emerged that Chugai paid for paediatric research and teaching by at least two members of the study group, including Yokota, and Tsuneo Morishima of Okayama University.

Chugai gave ten million yen (around US$85,000) to Yokota between 2001 and 2006 and two million yen to Morishima in 2005, prompting criticisms that the researchers had a conflict of interest. "It's quite natural for the public to imagine any interest may have been involved," says Masayuki Shibuya, vice-president at Tokushima University, which has developed model guidelines to manage conflicts of interest in clinical research.

Morishima, Yokota and their universities have defended the donations, saying that all funding was approved by the university, and that the money was used for unrelated work and so did not affect the results of the flu study. Tamaki Fushimi, head of drug safety at the Japanese health ministry, says that the ministry was not aware of the funding when it appointed the study group, and that it has not yet decided whether to allow those who received money from Chugai to continue with the study. Masanori Fukushima, professor of clinical-trial design and management at the Kyoto University Graduate School of Medicine, is one of those who think that the researchers should be removed. "The ministry should care about ethical and regulatory issues more properly," he says.

But Yokota insists he has done nothing wrong. "Tamiflu is an important drug, but we have no standards to tell doctors who can be prescribed it and who can't," he says. "It is our responsibility as paediatricians to create this measurement." ■

Ichiko Fuyuno

technology for drug safety is "an idea whose time has come", he added.

McClellan and others are pushing the idea of data mining of existing health-record databases as an active surveillance system to pick up early warnings of adverse side effects. By pooling existing databases run by private insurance plans, government agencies and industry, information on well over 100 million people could be studied in something much closer to real time, he says. The FDA could then identify priority questions and the mechanisms for answering them. If such a system had been in place when Vioxx came on the market in 1999, that drug's dangers could have been detected in months rather than years, McClellan contends.

The same thinking is gaining currency in Europe. "There is great potential in the use of these healthcare databases," says Panos Tsintis, who oversees the safety of marketed drugs for the European Medicines Agency (EMEA) in London.

Drug makers are also backing the idea of a centralized active surveillance system, which they see as preferable to a duplication of effort in which each insurer, government agency and company invents its own scheme. Such a system "would provide information we crucially currently don't have", said Ron Krall, senior vice-president and chief medical officer for GlaxoSmithKline at an Institute of Medicine (IOM) forum on 12 March in Washington DC. The FDA is testing active surveillance in a pilot programme tracking the side effects of four unnamed, newly approved medicines. "In general, safety information trickles in and the FDA is passive in analysing it," said Ellis Unger, an official from the agency's drug-review centre, at the IOM forum. "In this programme we grab each new product by the horns. It's very resource-intensive."

Those costs present a major problem to the cash-strapped agency, which has no funds even to upgrade its existing surveillance system. But advocates of active surveillance say the country cannot afford not to invest what would probably be tens of millions of dollars. That kind of money, says Garret FitzGerald, head of pharmacology at the University of Pennsylvania in Philadelphia, "is peanuts when you think about the public health". ■

Meredith Wadman