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Editorial

As editor it is a pleasure for me to remind the reader that with this first issue of Volume 20 we commemorate the fact that it is 20 volumes ago that the founding editor of this journal, the esteemed Dr. M.N.G. Dukes, launched *The International Journal of Risk & Safety in Medicine*. This is neither the place nor the time to give a resume of all the professional activities Graham has been involved with over the years. However, it has always astonished me that, at a time when he was very busy with Meyler's Side Effects of Drugs and with the Side Effects of Drugs Annuals, he had the energy to add the responsibilities of a new journal's editor to his workload. Although we introduced the titles for the subsections of the journal recently, the ambitions have always been the same. And a journal that has the aspiration to cover safety in medicine from the perspectives of three different disciplines, i.e. patient safety, pharmacovigilance and medical law, is definitely going off the beaten path. But Graham did well, actually he did very well.

We celebrate this anniversary with a double issue which features the first in depth review of the safety aspects of oseltamivir. And for making a risk-benefit analysis for this antiviral agent, such a review is timely, given the fact that the United States and many other countries have been stockpiling oseltamivir in the face of the risk that avian flu will spark a pandemic [7].

Oseltamivir is a prodrug of oseltamivir carboxylate, a potent and selective inhibitor of the neuraminidase glycoprotein essential for replication of influenza A and B viruses. It is orally active and significantly reduces the duration of symptomatic illness when initiated promptly in patients with naturally acquired seasonal influenza [5]. Oseltamivir is currently marketed by Hoffmann–La Roche under the trade name Tamiflu. In Japan, it is marketed by Chugai Pharmaceutical Co., which is more than 50% owned by Roche. Tamiflu is prescribed for the common flu. Roche estimates that 50 million people have been treated with oseltamivir. The majority of these have been in Japan, where an estimated 35 million have been treated.

A systematic review of four prophylaxis, 13 treatment and four post-exposure prophylaxis trials with the neuroamidase inhibitors oseltamivir and zanamivir in adults can be found in the Cochrane Database. The authors conclude that because of their low effectiveness neuroamidase inhibitors should not be used in routine seasonal influenza control [3]. Another systematic review deals with three trials involving 1500 children with a clinical case definition of influenza of whom 977 had laboratory confirmed influenza [4]. Oseltamivir reduced the median duration of illness by 26% (36 hours) in healthy children with laboratory confirmed influenza (P value less than 0.0001). The reduction was only 7.7% (10 hours) in 'at risk' (asthmatic) children, and this did not reach statistical significance (P value $= 0.54$).

Human cases of avian influenza A (H5N1) infection have remained rare and sporadic, but the disease is very severe and the case fatality is high. In March 2006, the World Health Organization assembled an international panel of experts to develop rapid advice for the pharmacological management of patients with H5N1 infection [8]. Now WHO strongly recommends the use of oseltamivir both as first-line treatment for H5N1 avian flu and to prevent pandemic influenza infection, with zanamivir as the second choice. The WHO guidelines do not say that treatment must be started within the first 2 days of illness to be effective. The Organization admits that in view of the fact that there were no clinical trials in patients with avian influenza H5N1 disease, the overall quality of evidence on which to base recommendations

was very low. Dr. Nguyen Tuong Van, who runs the intensive care unit of the Center for Tropical Diseases in Hanoi concluded after treating 41 patients with avian flu that oseltamivir had no effect on the disease [10].

Enough about the effectiveness of oseltamivir for the treatment of influenza A infections. What can we say about its safety? Nausea and vomiting are the most commonly reported adverse events and Roche denies any dangerous side effects of its drug. However, there are concerns that oseltamivir may cause dangerous psychological side effects in some people. These concerns have focused on teenagers, but problems have also been reported in children and adults. In 2004, Japan's Health Ministry decided to change the labelling of oseltamivir to include neurological and psychological disorders as possible adverse effects, mentioning impaired consciousness, abnormal behaviour and hallucinations. In 2007, the Ministry warned that oseltamivir should not be given to children aged 10 to 19 [1]. In November 2006, the United States Food and Drug Administration amended the oseltamivir warning label to include the possible side effects of delirium, hallucinations or other related behaviour [6]. The details of this occasionally fatal neurotoxicity can be read in this issue of the Journal.

There is still another concern. In the event of an avian flu pandemic, the current WHO strategy [9] recommends that all infected individuals ($>$1 year of age) receive a 5-day course of 750 mg oceltamivir. This quantity will also be needed for a 10-day prophylaxis course which could be extended for several weeks until there is no further risk of exposure. Up to 80% of an oral dose of oceltamivir can be excreted as oseltamivir carboxylate, the active antiviral metabolite of oceltamivir. Oseltamivir carboxylate is not removed in normal sewage water treatments and is not degraded substantially by UV light radiation and thus the active substance is released in waste water leaving the plant. It is therefore reasoned that a ubiquitous use of oseltamivir may result in selection pressures in the environment that favor development of drug-resistance [2,7].

When we keep all this in mind we inevitably have to come to the conclusion that the final question has to be "are we betting on a crippled horse?".

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Editor

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