Neuraminidase inhibitors for influenza in healthy adults: What we don’t know

Jefferson T, Jones M, Doshi P, Del Mar C. (Acute Respiratory Infections Group, Cochrane Collaboration, Rome, Italy; University of Queensland, School of Population Health, Brisbane, Australia; Program in History, Anthropology, Science, Technology and Society, Massachusetts Institute of Technology, Cambridge, MA, USA; Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia.) Neuraminidase inhibitors for preventing and treating influenza in healthy adults: Systematic review and meta-analysis. BMJ 2009;339:b5106.

SUMMARY

The authors systematically reviewed and did a meta-analysis of studies that evaluated the efficacy of neuraminidase inhibitors (inhaled zanamivir and oral oseltamivir) for treatment of laboratory-proven cases of influenza, and pre- and post-exposure prophylaxis. Four studies which assessed the efficacy for preventing influenza were included in the study. Two of the 4 studies used oral oseltamivir 75 mg daily while 2 studies used inhaled zanamivir 10 mg daily. The authors found that the current evidence neither supports nor refutes the use of neuraminidase inhibitors for the prophylaxis of influenza (risk ratio 1.28 [CI: 0.45–3.66] for oseltamivir and 1.51 [0.77–2.95] for zanamivir).
for zanamavir). It was also observed that both oseltamivir and zanamavir were efficacious in preventing symptomatic laboratory-proven cases of influenza. In the 4 studies, which evaluated the prophylactic use of neuraminidase inhibitors in household contacts of proven cases of influenza, both oseltamivir and zanamavir provided protective effect (risk ratios range: 0.16–0.42).

Twelve studies which evaluated the benefits of neuraminidase inhibitors for therapeutic purpose were included in the study. Both oseltamivir (hazard ratio 1.24, CI: 1.13–1.36) and zanamavir (hazard ratio 1.20, CI: 1.06–1.35) reduced the duration of illness by 1 day. However, data on the prevention of complications of influenza were lacking. Although a previous meta-analysis has shown benefit in reduction of complications, the authors of this meta-analysis excluded that study due to non-availability of detailed data from studies included in that meta-analysis. The exact role of neuraminidase inhibitors in the 2009 H1N1 pandemic has not yet been evaluated in clinical studies.

Before this meta-analysis, the safety data of neuraminidase inhibitors were limited. Nausea was reported with use of oseltamivir (odds ratio 1.79, CI: 1.1–2.93) and was higher with the dose of 150 mg daily compared with lower doses (odds ratio 2.29, CI: 1.34–3.92). Neuropsychiatric events were observed at a rate of 0.5% with oseltamivir in prospective clinical trials. Retrospective studies suggest an incidence of 20–27 neuropsychiatric adverse events per 1000 adults at 14 days and 30–40 neuropsychiatric adverse events per 1000 adults at 30 days. No serious adverse events were noted with zanamavir in clinical trials.

COMMENT
Till recently, neuraminidase inhibitors were accepted as a therapeutic modality and incorporated into various national and international guidelines. Use of neuraminidase inhibitors for treatment of patients with influenza who have other risk factors such as extremes of age, pregnancy, pre-existing co-morbid conditions and immune-suppression is well accepted and non-controversial. Similarly, they have been used for prophylactic purposes. The current study strengthens the practice of chemoprophylaxis in household contacts. Recent recommendations suggest the use of neuraminidase inhibitors in high risk individuals with recent contact and close follow up for otherwise healthy individuals.1

In this study the use of neuraminidase inhibitors for treatment of influenza in healthy adults was also evaluated. The results suggest a modest reduction of hospital stay by 1 day. The efficacy of neuraminidase inhibitors in preventing complications of influenza was not proven in this meta-analysis and the results neither support nor refute this notion. More importantly, the results are in contrast with the findings of Kaiser et al.,2 who had concluded that treatment with oseltamivir in influenza illness reduces lower respiratory tract complications (LRTC) by 55% (4.6% vs. 10.3% with placebo; p<0.001), antibiotic use by 26% (14% vs. 19.1% with placebo; p<0.001), and hospitalization by 59% (0.7% vs. 1.7%; p=0.02) in both healthy adults as well as adults with co-morbid conditions.2

The study by Kaiser et al. has been the basis for many national guidelines and healthcare policies.3 Many countries have made huge stockpiles of oseltamivir costing billions of dollars for epidemic preparedness in view of H5N1 outbreaks and 2009 H1N1 influenza pandemic.4 On the request of Dr Hiyashi, a Japanese paediatrician who was not convinced by the meta-analysis conducted by Kaiser et al., and the Cochrane review which included the study by Kaiser et al., the Cochrane group conducted the current meta-analysis.5 The contrasting results of the current study and the study by Kaiser et al. have opened up a pandora’s box and left many questions unanswered pertaining to the conduct and publishing of studies, regulations regarding availability of data pertaining to drug trials and public health planning.

The study by Kaiser et al. included data from 10 studies, all of which were funded by Roche Pharmaceuticals and were authored by Roche employees and paid consultants.6 Only 2 of the 10 studies were published in peer-reviewed journals. The 8 unpublished studies included 2691 of 3564 patients.26 Further, in the study by Kaiser et al., the incidence of LRTC was much higher than the incidence one encounters in clinical practice.2 What is even more disturbing than the methodology and results of the study is the stance taken by Roche Pharmaceuticals. They were not ready to provide complete data for all unpublished studies, neither the authors of the studies could provide the same. This led to an investigation by BMJ and Channel 4, which brought out some startling facts and raised more questions on the conduct of the studies and the handling of data by Roche.7 Roche have tried to reply and justify their act of not providing the raw data to the practice prevalent at that time, which did not mandate the study protocols and reports to be made public, as it is now. However, they are silent on inclusion of non-published data in the meta-analysis, where guidelines to the contrary have long been available.8 Even if their objection about involvement of a commercial television channel in the entire episode may have some merit, the questions raised about the validity of the meta-analysis conducted by Kaiser et al. and the equivocal results of the current meta-analysis, benefits of neuraminidase inhibitors for therapeutic use in otherwise healthy adults stands to further scrutiny and need to be confirmed in an independent review of the raw data of studies conducted by Roche and well designed randomized controlled trials in the future.

The serious adverse events of neuraminidase inhibitors have not been studied in detail till now. The current study suggests 20–27 neuropsychiatric adverse events per 1000 adults at 14 days and 30–40 neuropsychiatric adverse events per 1000 adults at 30 days. With strong evidence lacking for the therapeutic use of neuraminidase inhibitors in healthy adults and emerging data of serious adverse events, one needs to re-evaluate the benefits and risks of the use of neuraminidase inhibitors. In view of the current pandemic of 2009 H1N1 where large population of healthy adults are at risk of acquiring influenza and a low incidence of severe influenza (LRTC) with 2009 H1N1 in healthy adults, the findings of the current study have great importance. The US Food and Drug Administration (FDA) and WHO guidelines do not support the use of neuraminidase inhibitors for therapeutic use in healthy adults with mild disease.28 It needs to be seen whether these new findings lead to any further amendments in healthcare policies and, more important, any changes in the principles which guide the role of pharmaceutical companies in the conduct of clinical trials, analysis of data and preparation of manuscript. It is important to stress that trial data should be available for public scrutiny which would provide credibility both to the clinical trials and healthcare policies based on these trials.

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