Antivirals for treatment and prevention of human seasonal influenza

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While immunisation is the primary public health strategy for prevention of influenza, antivirals are important complementary measures for controlling seasonal/epidemic human influenza, especially when there is a mismatch between circulating and vaccine strains and in at-risk population groups.

Two classes of antivirals are commonly used against influenza infections – the M2 ion-channels inhibitors (adamantanes), and the more recently developed neuraminidase inhibitors (NIs), which Australian researchers contributed to heavily. Some studies from Russia and China suggest that arbidol, an indole compound which inhibits virus membrane fusion with host cells *in vitro* and which has been used clinically in Russia, might be useful for influenza therapy and prophylaxis [1]. Arbidol is not available in Australia.

The adamantanes (amantadine and rimantadine) are effective only against influenza A. Studies showed that amantadine treatment can shorten duration of symptoms by 1 day, and was 61% effective in preventing symptomatic influenza [2]. Rimantadine demonstrated comparable effectiveness in smaller studies [2]. Both agents were associated with significant gastrointestinal adverse effects, and amantadine with neurological toxicity. Adamantane-resistant influenza strains emerge within days of commencing treatment, and are as transmissible and as virulent as the wild-type virus. Increasing adamantane resistance of influenza A viruses has been described, particularly in Asia, and is most likely related to uncontrolled clinical use [3]. Use of these drugs is not widely recommended.

NIs (oseltamivir (Tamiflu) and zanamivir (Relenza)) are effective both for treatment and prophylaxis (short- and long-term) of influenza A and B. A recent systematic review found that when NIs were used for treating 'healthy' adults with influenza, symptoms were 20-24% more likely to be alleviated and in two-thirds of the time compared with placebo [4]. Nasal viral titres were significantly reduced with NI treatment [4].

Oseltamivir treatment of influenza-infected subjects significantly reduced overall antibiotic use by over a quarter and lowered respiratory tract complications by more than half. The risk of hospitalisation possibly caused by influenza was lower in oseltamivir-treated patients, although the difference did not achieve statistical significance. No significant benefits were observed for subjects with an influenza-like illness (ILI) that was not confirmed to be influenza [5]. Commencing oseltamivir treatment earlier (within 12 hours compared to within 48 hours from symptom onset) enhanced clinical efficacy [6, 7]. Oseltamivir is more effective against influenza A than influenza B [8].

When used for (pre-exposure) prophylaxis in community outbreak settings, overall, NIs were 59% efficacious against symptomatic influenza, and 39% against both symptomatic and asymptomatic

influenza. However, there was no protection against ILI from prophylaxis with NIs [4].

In post-exposure prophylaxis in the household setting, compared with treatment of index cases alone, the protective efficacy of oseltamivir against proven influenza was 58.8% for households and 68% for individual contacts (children aged ≥1 year were included) [9]. Protective efficacy of zanamivir for household contacts was 79% (children aged ≥5 years were included), when index cases were also treated [10]. In another randomised controlled study where index cases were not treated, oseltamivir achieved a protective efficacy of 84% for households and 89% for individual contacts (≥12 years) against clinical influenza [11].

In otherwise healthy children with laboratory-confirmed influenza, both NIs reduced the median duration of illness by about 25% (1.25-1.5 days). Oseltamivir reduced complication rates (especially otitis media) significantly [12]. Prophylactic benefits of NIs in children have not been separately studied or analysed, but are reflected in some of the household post-exposure prophylaxis studies.

Although older people in residential care facilities (RCFs) are at high risk of influenza infection and complications, and prophylaxis is often recommended to all residents during epidemics, few studies that specifically address this population group have been conducted. In a case series of influenza A outbreaks in nursing homes, symptomatic residents who received oseltamivir treatment were less likely to be prescribed antibiotics, be hospitalised or die; these benefits remained statistically significant even for vaccinated subjects [13].

A double-blind study with highly-vaccinated RCFs allocated residents aged ≥65 to oseltamivir or placebo as pre-exposure prophylaxis. A 92% reduction ensued in incidence of laboratory-confirmed influenza ($p=0.002$) [14]. Another study, which had some methodical drawbacks, found a statistically insignificant protective efficacy of 29% in poorly-vaccinated RCF residents receiving inhaled zanamivir for post-exposure prophylaxis [15]. No studies have evaluated control strategies in RCFs comparing case-treatment alone to case-treatment with prophylaxis, or with strategies involving staff, or in combination with effective surveillance that allow early antiviral therapy. Such is now underway through the support of the Australian Research Council.

Oseltamivir is administered orally. Its main adverse effects are nausea and vomiting (although these did not contribute to any significant treatment withdrawal in trials [4]), which can be reduced by taking with food. Zanamivir is given by inhalation, and has been associated with bronchospasm and some difficulty of use in the young and elderly. There is limited efficacy data on intravenous NIs, and clinical data on new NIs (e.g. peramivir) are awaited.

Regarding cost-effectiveness, a recent Canadian analysis found that vaccination of institutionalised elderly was the only dominant strategy over standard care (using over the counter medications), when various strategies including vaccination, antiviral prophylaxis, empirical treatment and antiviral treatment following rapid diagnosis were evaluated. Disease prevalence or diagnostic accuracy of influenza strongly influenced the cost-effectiveness of all other strategies. It concluded that antiviral treatment or prophylaxis was likely to be more cost-effective in specific populations at specific times during the influenza season [16].

The Australian Influenza Specialist Group recommends NIs to be prescribed for patients with ILI (within 48 hours of symptom onset) if the rapid antigen test is positive, or if the patient is at high risk of adverse outcome and is also unvaccinated, or when suboptimal vaccine response is expected. Benefits from NIs are deemed unlikely for

vaccinated persons without risk factors. NI use in vaccinated at-risk patients and otherwise healthy unvaccinated subjects is discretionary. Residents of long-term RCFs, healthcare workers and people in contact with high risk individuals are considered appropriate candidates for prophylaxis [17].

Clinical NI resistance is not yet a concern. However, NI usage level worldwide has been low apart from Japan. The global Neuraminidase Inhibitor Surveillance Network demonstrated no primary resistance before the introduction of NIs, and the prevalence of resistance was low (0.33%: 8/2287 isolates) in the first 3 years of NI use. No resistant isolates were from individuals known to have received NIs [18].

In clinical studies, zanamivir-resistance has only been identified from one highly immunocompromised child. Oseltamivir-resistance occurred rarely in immunocompetent adults, but was reported in 5.5-18% of children treated with oseltamivir under different conditions [19, 20]. Resistant viruses appeared to be less transmissible and less infectious in ferret studies [21]. The impact of emergence of NI-resistant influenza is unknown and ongoing vigilant surveillance is warranted. As with antibiotics, indiscriminate use of NIs should be discouraged.

Conclusion

NIs are effective and safe antivirals for early treatment of influenza, and appear to be especially useful and cost-effective in specific high risk settings like RCFs. Early diagnosis of influenza and identification of outbreaks are essential adjuncts to effective control of influenza using NIs. Further studies are necessary to evaluate the additional benefits of more widespread use of NIs for influenza prophylaxis, as well as risks of adverse events and whether clinically-significant resistance emerges.

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