Antivirals in the management of an influenza pandemic

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ABSTRACT

- The Australian Government has an extensive stockpile of antivirals (neuraminidase inhibitors) to be used if an influenza pandemic occurs.
- Neuraminidase inhibitors reduce the duration of the symptoms of seasonal influenza infection by 1 day on average, when used as treatment within 48 hours of disease onset.
- Neuraminidase inhibitors prevent infection in up to 74% of people when administered as prophylaxis.
- Resistance of seasonal influenza viruses to neuraminidase inhibitors is low.
- The safety and efficacy (including resistance) of neuraminidase inhibitors against pandemic influenza or the virus of current concern in pandemic planning, influenza A/H5N1, is not known, and further research is needed.

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A key component of the *Australian health management plan for pandemic influenza* is the targeted use of stockpiled antivirals to contain infection in early pandemic stages by treating clinical cases, providing post-exposure prophylaxis to close contacts of ill patients, and providing longer term prophylaxis to health care workers caring for ill patients.[1] During the pandemic, maintenance of essential health services will include use of antiviral drugs for treatment and longer term prophylaxis for health care workers. The use of neuraminidase inhibitors (NIs) is based on outcomes demonstrated in seasonal influenza; NIs should potentially reduce the duration of illness and prevent further infection in an influenza pandemic. The Australian stockpile currently holds 3.8 million courses of oseltamivir, 50 000 courses of oseltamivir suspension for children and 275 000 courses of zanamivir, all available for use within 24 hours. This stockpile is currently one of the highest per capita supplies of NIs held worldwide, and will increase to a total of 8.75 million courses by early 2007.[1]

Current World Health Organization treatment guidelines for influenza A/H5N1 infection, the strain of concern in current pandemic planning, recommend NIs for treatment and prophylaxis. The guidelines also include a soft recommendation for the use of M2 inhibitors (amantadine and rimantadine) for strains of the virus still susceptible to these drugs. M2 inhibitors have a relatively small role in pandemic planning worldwide because of their adverse effect profile and propensity to produce clinically significant viral resistance.[2] The safety and efficacy of antivirals during an influenza pandemic is unknown, and very little is known about their clinical effectiveness against H5N1. Clinical experience with NIs in the treatment of human H5N1 infection is extremely limited and has often been inconsistent with current guidelines.[3,4]

The uncertainty about the effectiveness of antivirals against H5N1 makes planning for the evaluation of the use of antivirals as part of an overall public health response in an influenza pandemic vital. Given the potentially high pathogenicity of a pandemic strain (H5N1 infection in humans has a mortality rate of 59% in 256 cases worldwide, as of 16 October 2006[5]) and the substantial social upheaval that might arise during a pandemic, it is unlikely that it will be ethically and logistically possible to conduct large randomised clinical trials. This necessitates the use of other research methods, such as observational studies, to assess the safety and effectiveness of NIs early in the course of a pandemic.

Neuraminidase inhibitors

Pharmacology

Neuraminidase inhibitors block the influenza virus neuraminidase, a surface glycoprotein that facilitates the release of newly formed virions from infected cells. As a result, NIs prevent the spread of infection in the respiratory tract.[6] NIs are effective against all the nine antigenic (N1–N9) neuraminidase subtypes and against influenza A and B.

Oseltamivir is an oral preparation (either a capsule or liquid suspension) and after absorption is widely distributed throughout the body. Zanamivir is delivered by inhalation or, rarely, intravenous infusion. When administered through a diskhaler, zanamivir is concentrated in the respiratory tract and is effective within 10 seconds. Because the replication of influenza virus is at a peak from 24 to 72 hours after illness onset, the NIs must be administered as early as possible after symptoms appear.[6] The dosing schedules for oseltamivir and zanamivir are shown in Box 1.

Indications for use

Oseltamivir is licensed in Australia for the treatment and prevention of influenza in adults and children older than 1 year.[7] Zanamivir is licensed for the treatment of influenza in adults and children aged 5 years or older. Zanamivir can be used for the prophylaxis of influenza A and B when vaccine is unavailable.[8]

Clinical efficacy

Both oseltamivir and zanamivir have been evaluated in multiple double-blind, randomised controlled trials as treatment or prophylaxis for seasonal influenza in a variety of different patient populations. A Cochrane review of pooled data from eight trials with a total of 1180 participants found that oseltamivir and zanamivir reduce the duration of symptoms by an average of 1 day.[9] In children, a Cochrane review of pooled data from randomised controlled trials has shown that oseltamivir reduces the median duration of the symptoms of influenza by 36 hours. Oseltamivir also significantly reduces the number of complications, particularly otitis media. There was no significant benefit for children with asthma.[10] When used as prophylaxis for 7–10 days, NIs (compared with placebo) were 74% effective in preventing naturally occurring cases of clinically defined influenza and 60% effective in preventing cases of laboratory-confirmed influenza in household contacts of seasonal influenza index cases. NIs have also been used as long-term (6 weeks) prophylaxis to prevent

1 Dosing schedule of antivirals for the treatment and prevention of influenza, according to patient's age and coexisting illness*

	Recommended dose according to age				Coexisting illness	
Drug	1–6 years	7–12 years	13–64 years	⩾ 65 years	Renal disease	Hepatic disease
Treatment						
Zanamivir	na	10 mg (2 inhalations) twice daily for 5 days for children ⩾ 5 years	10 mg (2 inhalations) twice daily for 5 days	10 mg (2 inhalations) twice daily for 5 days	10 mg (2 inhalations) twice daily for 5 days	na
Oseltamivir	2 mg/kg up to 75 mg twice daily for 5 days	2 mg/kg up to 75 mg twice daily for 5 days	75 mg twice daily for 5 days	75 mg twice daily for 5 days	For adults, reduce dose if creatinine clearance is ⩽ 30 mL/min; if creatinine clearance is 10–30 mL/min, 75 mg once daily†	Not evaluated
Prevention						
Zanamivir	na	na	10 mg (2 inhalations) once daily for 10–28 days	na	10 mg (2 inhalations) twice daily for 5 days	na
Oseltamivir	na	na	75 mg once daily for > 7 days (up to 6 weeks)	75 mg once daily for > 7 days (up to 6 weeks)	If creatinine clearance is 1–30 mL/min, 75 mg every second day†	Not evaluated
Amantadine	na	100 mg once daily for children aged 5–9 years	100 mg twice daily for people > 9 years	100 mg once daily	Not available	Contraindicated during pregnancy

na = not applicable. * The doses listed are according to current Australian product information. † No regimen is available for patients with end-stage renal disease. ◆

infection in at-risk populations, reducing the incidence of influenza by 92% in this setting.[11]

The main adverse effect of oseltamivir is gastrointestinal discomfort, which can be relieved by co-administration of food. As oseltamivir is renally excreted, doses must be modified for patients with renal insufficiency.[7] Inhaled zanamivir has been associated with bronchospasm in people with asthma, and the diskhaler may be difficult for the very young and elderly to manage.

M2 inhibitors (the adamantanes)

There are several concerns with the use of the older class of antivirals, M2 inhibitors (amantadine and rimantadine), for seasonal influenza. These concerns include central nervous system (dizziness, nervousness, and insomnia) and gastrointestinal toxicities, as well as antiviral resistance.[11] However, amantadine might be considered as part of combination antiviral therapy by clinicians treating severely ill patients in a pandemic. Current WHO treatment guidelines for pandemic influenza recommend the use of an M2 inhibitor along with an NI only if administered in the context of prospective data collection and if local surveillance data show that the H5N1 variant of concern is known or likely to be susceptible to this drug.[12] Amantadine is currently licensed for prophylactic use, while rimantadine is not licensed for use in Australia and will not be available during a pandemic.

Mechanism of action

M2 inhibitors act by blocking the influx of hydrogen ions through the M2-proton channel of influenza A, inhibiting the uncoating and release of free viral ribonucleoproteins into the cell cytoplasm. In-vitro and animal models have demonstrated a benefit from M2 and NI therapy in combination.[13]

Efficacy and safety

A Cochrane review of the adamantanes for treatment and prophylaxis examined data from 33 randomised double-blind, placebo-controlled trials.[14] As treatment, amantadine reduced fever duration by 0.99 days compared with placebo, and did not affect viral shedding. There was no difference between inhaled and oral amantadine. When used as prophylaxis, amantadine prevented 61% of serologically confirmed influenza A cases compared with placebo. Adverse effects of amantadine include gastrointestinal upset in up to 10% of patients and central nervous system effects, including insomnia and hallucinations, in more than 10% of patients.

Antiviral drug resistance

Antiviral drug resistance is a major concern when proposing widespread use of antiviral medications. This is particularly evident with the adamantanes, where a single amino acid substitution in the transmembrane portion of the M2 ion channel protein causes amantadine resistance (resistant variants have been detected in up to 80% of patients), leading to treatment failure and transmission of resistant virus to others. Amantadine resistance has been found in human and avian H5N1 strains in China, Thailand, Vietnam and Cambodia, although other variants found in Indonesia, China, Mongolia, Russia and Turkey remain sensitive.[13,15] Worldwide seasonal A/H3N2 and A/H1N1 strains are becoming increasingly resistant to the adamantanes.[16]

Resistance to the NIs is less frequent, occurring in less than 1% of virus isolated from adults and 5%–18% of children treated with these drugs. Resistant strains are not generally associated with clinical deterioration except in rare cases of immunocompromised patients and possibly in patients with H5N1 infection.[15,16] Resist-

2 The PIPET (Pandemic Influenza — Prospective Evaluation of Treatment) projects for neuraminidase inhibitor use in a pandemic

PIPET A: Index case treatment protocol — primary endpoint is mortality.

PIPET B: Long-term prophylaxis protocol — primary endpoint is diagnosis of, or seroconversion to, the pandemic strain of influenza.

PIPET C: Short-term prophylaxis following contact with index case — primary endpoint is diagnosis of, or seroconversion to, the pandemic strain of influenza. ◆

ance *in vivo* is usually due to mutations in the neuraminidase region, and *in vitro* involves the haemagglutinin region, leading to impaired enzyme activity.[13] Although oseltamivir resistance in human H5N1 infection has been documented, these mutations occurred in the context of commencement of oseltamivir after 48 hours of illness and suboptimal dosing regimens.[17] Circulating strains of avian H5N1 remain susceptible to NIs.[13,18] In animal models, oseltamivir resistance mutations lead to reduced viral replication and reduced transmissibility.[13] There is little evidence of clinical zanamivir resistance in seasonal influenza or H5N1 strains,[19] and zanamivir remains active against most oseltamivir-resistant variants.[15]

Use of antivirals in H5N1 infection

The safety and clinical effectiveness of NIs against the H5N1 strain is unknown, and currently published data include a limited number of observational cases from Thailand and Vietnam. The role of NIs in the management of seasonal influenza, and the safety profile of these drugs, is well known. Although H5N1 is susceptible in vitro to NIs,[19] recent studies demonstrate that treatment of human H5N1 infection may require higher doses and longer administration of oseltamivir to be effective.[2,20] The pathogenicity of the currently circulating strain of H5N1 is significant (59% compared with 20% in the 1918 pandemic). The NIs were developed and licensed in the setting of seasonal influenza and geared towards identifying the minimal effective dose and regimen duration. NIs may also be used in conjunction with M2 inhibitors in susceptible strains.[11] There is little evidence to support these approaches, and research is necessary to evaluate NIs in this "off-label" context.

Clinical research during an influenza pandemic

The paucity of information about the safety and efficacy of NIs against H5N1 is a current cause of concern in pandemic influenza planning. The National Centre in HIV Epidemiology and Clinical Research at the University of New South Wales, in cooperation with infectious diseases physicians from major teaching hospitals in NSW, South Australia, Victoria, Western Australia, Singapore and Hong Kong, has developed research protocols designed to assess the safety and efficacy of antiviral medications, specifically NIs, in the event of an influenza pandemic reaching Australia, Hong Kong or Singapore. These studies will also generate a tissue repository (plasma or sera, nasopharyngeal aspirates, and peripheral blood mononuclear cells) for prospective and retrospective laboratory research.

The three Pandemic Influenza — Prospective Evaluation of Treatment (PIPET) studies will examine NI use in pandemic influenza index cases, as prophylaxis in the contacts of individuals with pandemic influenza infection, and in essential workers at high risk of exposure who receive long-term prophylaxis (Box 2). To enrol patients in the index case study, the diagnosis of influenza infection will be made using the applicable clinical case definition. At the time of analysis of study data, more stringent criteria will be used to identify the evaluable populations for the planned research questions. Currently, the necessary laboratory techniques for confirmatory purposes are not available. The planned studies are purely observational, as we took the view that the conduct of randomised controlled trials during pandemic influenza would be operationally problematic. Furthermore, randomisation may not be ethically possible in a study of a disease about which we know relatively little, as it would be difficult to establish clinical equipoise.

To allow the PIPET studies to be conducted by any doctor and in any location where pandemic cases are diagnosed, web-enabled case report forms will be used and data collection will be kept to a minimum. Web-based data collection will allow the study to proceed in the event of restricted movement during a pandemic, as it will be possible to provide support to study centres remotely. Any doctor or study centre with a computer and Internet connection will be able to participate in the PIPET studies.

The PIPET study group aims to capture data on as many as possible of the clinically diagnosed cases of pandemic influenza and individuals receiving prophylaxis during the early stages following a pandemic being declared. To achieve this goal, we are asking that each clinician likely to be managing influenza patients in the early stages of a pandemic in Australia consider participating in this project by contacting one of the authors to receive protocol documents and support in the ethics submission process. The critical aim of this study is to capture data for all patients from their first diagnosis of pandemic influenza, making widespread participation of hospitals vital. It is hoped that early data on antiviral treatment and prophylaxis will be used to inform further policy decisions should pandemic influenza become more widespread in Australia. The data collected in this study will not be the only measure used to determine policy; however, we will be able to demonstrate overall rates of morbidity and mortality with some accuracy, as well as identify subgroups in whom there is evidence of either increased or decreased effectiveness of NIs.

Summary

Pandemic planning in Australia and around the world has required a significant investment, both financial and temporal, to develop national responses to pandemic influenza. A cornerstone of this planning has been stockpiling antivirals for use in both treatment and prophylaxis. It is unknown whether oseltamivir will improve clinical outcomes in infected patients and whether resistance will become a clinically important issue in a pandemic. It is difficult to assess if the average reduction of duration of symptoms of 1 or 2 days will be of overwhelming benefit in a pandemic setting: the effect on mortality and hospitalisation, having not been previously measured in seasonal influenza trials, is entirely unknown. For the more relevant concern of transmission by infected individuals, there is little evidence confirming the relationship between symptom duration and viral shedding, so the benefit in this regard is unknown. It is more likely that a benefit to the community will be

derived from the short-term prophylactic use of NIs in preventing transmission and illness, and long-term prophylaxis in protecting health care and other essential workers. It is crucial, given the likely climate of fear that will exist during a pandemic, that prophylactic use is guided by evidence rather than panic or politics. Although Australia has an extensive stockpile, judicious and evidence-based use is required to best protect the whole population. The ability to make evidence-based decisions through research during a pandemic is vital.

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Competing interests

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