Oseltamivir and zanamivir are effective for treating influenza, but preventive effects are unclear

Abstracted from: Cooper NJ, Sutton AJ, Abrams KR et al. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomized controlled trials. *BMJ* 2003; 326: 1235.

BACKGROUND Strategies for preventing and treating influenza include immunisation and anti-viral medication. The neuraminidase inhibitors, zanamivir and oseltamivir, may be useful for preventing and treating influenza. However, there is little evidence on the clinical effectiveness of zanamivir and oseltamivir in different at-risk populations.

OBJECTIVE To assess the effectiveness of neuraminidase inhibitors oseltamivir and zanamivir in the treatment and prevention of influenza A and B across three different population groups: children, high-risk adults and otherwise healthy adults.

METHOD Systematic review and meta-analyses of randomised controlled trials.

SEARCH STRATEGY MEDLINE (1966 to December 2001); EMBASE (1980 to December 2001); Integrated science citation index (1981 to December 2001) and manufacturers' trial databases were searched. Bibliographies were hand searched and pharmaceutical companies contacted for information on unpublished trials.

INCLUSION/EXCLUSION CRITERIA Eligible studies were English language randomised controlled, double-blind trials comparing treatment or prevention of influenza with recommended doses of zanamivir or oseltamivir; which reported a minimum of one relevant end-point (see outcomes, below). Three populations were considered: children $\leq$12 years; otherwise healthy people aged 12 to 65 years, and high-risk individuals (defined as people aged $\geq$65 years or those with chronic medical conditions such as respiratory disease, heart disease or pulmonary disorders).

DATA ANALYSIS The methodological quality of the trials was scored using a validated test. Meta-analyses were performed for each neuraminidase inhibitor individually. Results were presented for populations with clinically diagnosed influenza and for those with laboratory-confirmed influenza. A random effects model was used to account for heterogeneity among trials.

OUTCOMES The main treatment outcomes were time to symptom relief and incidence of complications requiring antibiotics. The main prevention outcome was symptomatic, laboratory confirmed influenza at the completion of the trial.

MAIN RESULTS *Treatment*: There was significant heterogeneity across treatment trials. Trials varied in the definition of symptoms and also in the measurement scales used. Eight randomised trials of zanamivir and nine of oseltamivir were identified. Zanamivir and oseltamivir reduced the median time to alleviation of symptoms in each population compared with placebo, although results were more marked in people with laboratory-confirmed influenza (see Table 1). *Prevention*: Three randomised trials of zanamivir and four of oseltamivir were identified. Zanamivir reduced the risk of acquiring influenza in healthy populations by 69%, and in post-exposure households by 81% compared with placebo. Similar results were obtained with oseltamivir (risk of acquiring influenza reduced by 74% in healthy populations reduced and by 90% in people exposed to influenza).

AUTHORS' CONCLUSIONS Treatment of both intention-to-treat and flu-positive populations with neuraminidase inhibitors zanamivir or oseltamivir significantly reduced the time taken for relief of symptoms. Evidence for prophylactic use of neuraminidase inhibitors is lacking in all populations.

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Table 1
Reduction in the time to symptom relief after zanamivir or oseltamivir treatment, in clinically diagnosed and laboratory-confirmed populations

	Reduction in time (days) to symptom relief	
	Zanamivir versus Placebo (95% CI)	Oseltamivir versus placebo (95% CI)
Clinically diagnosed population		
< 12 years	1.00 (0.48 to 1.52)	0.87 (0.26 to 1.49)
Otherwise healthy 12 to 65 years	0.78 (0.26 to 1.31)	0.86 (0.30 to 1.42)
High risk	0.93 (0.05 to 1.90)	0.35 (−0.71 to 1.40)
Laboratory-confirmed influenza population		
< 12 years	1.00 (0.40 to 1.60)	1.49 (0.76 to 2.22)
Otherwise healthy 12 to 65 years	1.26 (0.59 to 1.93)	1.38 (0.80 to 1.96)
High risk	1.99 (0.90 to 3.08)	0.45 (0.97 to 1.88)

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Commentary 1

Seasonal influenza epidemics are associated with considerable morbidity and mortality resulting in three to five million cases of severe illness and 250,000 to 500,000 deaths annually in the industrialised world.[1,2] Vaccination against influenza is the most important intervention to reduce this burden. Nevertheless, neuraminidase inhibitors potentially offer a complementary approach to influenza management.

Treatment

Cooper and colleagues systematically review the clinical evidence on zanamivir and oseltamivir for the treatment or prevention of influenza.[1] The results clearly show that neuraminidase inhibitors can reduce the duration of symptoms of influenza by approximately 1 day in both influenza-positive and ITT populations. Essentially, this means the last day of illness will be averted – when symptoms are at their mildest. Unless clinically significant reductions in the severity of symptoms can be shown, neuraminidase inhibitors may be of limited value. Moreover, evidence on reduction in complications or mortality is sparse. These are the important features of influenza management strategies that need to be addressed.

Prevention

The effectiveness of preventive interventions depends on the prevalence of influenza in the population. Prophylactic use of neuraminidase inhibitors requires either accurate predictions for the optimal timing to gain the maximum benefit from short-term use (i.e. around the peak of the influenza season), or use for extended periods well beyond those observed in clinical trials. Because a few days or weeks within an influenza season does not show the dynamics of influenza, the longer-term effectiveness of these antivirals remains largely unsubstantiated. Similarly, prophylactic antivirals are of no use in countries without distinct influenza seasons.[2]

Costs

The costs of these antivirals are prohibitive for prophylactic use, ranging from £63,000 to £83,000 per quality-adjusted life year gained (QALY) for residential populations, and from £240,000 to £1.9 million per QALY in other populations. The costs per QALY gained from neuraminidase used in treatment of influenza are more acceptable ranging from £17,000 to £31,000.[3]

Compared with vaccination, treatment with neuraminidase inhibitors is approximately 5 and 48 times more costly in healthy populations and high-risk populations respectively.[3] Vaccination in residential elderly is cost-saving, and therefore, any viable alternatives must also be cost-saving.

Implications

Evidence to convince clinicians to prescribe neuraminidase inhibitors for the management of influenza requires improved, larger-scale studies with a focus on events that affect resource use. Future clinical trials must include details of the type and severity of complications such as GP consultations, admissions to hospital, and deaths. One thing this systematic review does show is that these factors are missing from the clinical trials reviewed.

This lack of evidence, compounded with the high costs of these agents, are the key barriers to use.[2] Moreover, the proven effectiveness and cost-effectiveness of vaccination requires that if

neuraminidase inhibitors are going to be viable, as either an alternative to or used with vaccination, a niche must be established with sound evidence to back up this niche. In the interim, the paucity of convincing evidence and lack of demand for neuraminidase inhibitors must eventually drive down the price to levels comparable with M2 inhibitors (e.g. amantadine). Given the burden of illness lies in severe morbidity and mortality it is only fitting that any intervention for the management of influenza is shown to reduce severe illness and death.

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Commentary 2

The neuraminidase inhibitors represent a marked advance in the prevention and treatment of influenza. The M2 inhibitors, amantadine and rimandatine, are clearly established as preventing 70% to 90% of episodes of type A influenza illness. However, in treatment, while they do reduce duration of illness, their exact value has not been well established, nor has their ability to prevent influenza complications. Their inactivity against type B virus is of less concern than the rapid emergence of resistant variants, a limitation in use of the drugs in close environments such as nursing homes.[1]

In contrast, the activity of the neuraminidase inhibitors in treating both type A and B influenza has been well defined in healthy adults, and to a lesser extent, children. Much attention has been given to the time to alleviation of symptoms, but this is an artificial, though useful, end-point and no person with influenza would know that he or she has reached this point.[2,3] Less attention has been paid to the fact that significant reduction in symptom scores in the treated as compared to placebo recipients starts I day after therapy begins. There is also emerging information that treatment with neuraminidase inhibitors reduces the frequency of complications, some of them severe.[4]

As pointed out by Cooper et al, the data for those most likely to develop influenza complications, older persons and those of any age with chronic conditions, are scarce, in part because they were excluded from the initial clinical trials.[5] This has presented policy-makers with a dilemma. Some have elected to allow use of the drugs in the higher risk groups, while discouraging it in the rest of the population. This strikes me as illogical on two grounds, first because it is not strictly evidence based, and second, because complications as well as longer duration of illness are what makes influenza important. Non-high-risk people are by far the larger portion of the population. Thus, even though they have a lower frequency of complications, because of their large numbers, such events can have a public health impact.

There are more limited data on primary prevention produced by the neuraminidase inhibitors.[6,7] However, the caution supported by Cooper et al is not necessary. This is an easier endpoint to study since it is dichotomous. Investigations have been quite consistent in demonstrating a 70% to 90% preventive efficacy, either in seasonal or more targeted time periods. Interestingly, this is similar to the protective efficacy of the M2 inhibitors, and for that matter, vaccine. However, vaccine will remain the preferred means of prophylaxis, except in special situations such as when there is an unexpected change in antigen or in post-exposure prophylaxis.

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