Review: Antiviral agents reduce risk for influenza in healthy adults and alleviate symptoms faster than placebo

Jefferson T, Demicheli V, Rivetti D, et al. **Antivirals for influenza in healthy adults: systematic review.** Lancet. 2006;367:303-13.

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QUESTION

In healthy adults, do antiviral agents reduce risk for influenza and improve outcomes in affected persons?

METHODS

Data sources: MEDLINE (August 2005), EMBASE/Excerpta Medica (June 2005), Cochrane Central Register of Controlled Trials (issue 3, 2005), and bibliographies of relevant systematic reviews and retrieved trials.

Study selection and assessment: Randomized controlled trials (RCTs) that compared the prophylactic or treatment effects against influenza of amantadine, rimantadine, or neuraminidase inhibitors (oseltamivir and zanamivir) with placebo, no treatment, or symptomatic treatment in otherwise-healthy persons 16 to 65 years of age. 53 RCTs met the selection criteria. Quality assessment of trials included randomization method, allocation concealment, blinding, and follow-up.

Outcomes: Cases of symptomatic or asymptomatic influenza (confirmed by laboratory testing) and influenza-like illness (clinical criteria only), alleviation of symptoms and viral shedding or load in affected persons, and adverse effects.

MAIN RESULTS

In prophylaxis trials, amantadine, but not rimantadine, reduced influenza and influenza-like illness more than placebo; neither drug reduced risk for asymptomatic influenza (Table). In treatment trials, both drugs reduced risk for fever at 48 hours (Table), but did not differ from placebo for viral shedding at 5 days. Both amantadine and rimantadine increased risks for adverse effects. In prophylaxis trials, the neuraminidase inhibitors reduced influenza, but not influenza-like illness or asymptomatic influenza, more than placebo (Table). In treatment trials, these drugs increased the likelihood of symptom alleviation (Table) and decreased the mean nasal viral titer at 24 hours by 0.62 (95% CI 0.41 to 0.82). Neuraminidase inhibitors as prophylaxis increased risk for nausea but as treatment did not increase adverse effects.

CONCLUSIONS

Amantadine and neuraminidase inhibitors reduce risk for symptomatic influenza in healthy adults. Antiviral agents alleviate influenza symptoms faster than placebo.

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Antiviral agents vs placebo for prophylaxis and treatment of influenza in healthy adults*

Type of trial	Antiviral agent	Outcomes	Number of trials (*n*)	RRR/RRI (95% CI)
Prophylaxis	Amantadine	Influenza	11 (4645)	RRR: 61% (35 to 76)
		Influenza-like illness	15 (17 496)	RRR: 25% (13 to 36)
		Asymptomatic influenza	4 (963)	RRR: 15% (–80 to 60)
	Rimantadine	Influenza	3 (688)	RRR: 72% (–8 to 92)
		Influenza-like illness	3 (688)	RRR: 35% (–20 to 65)
		Asymptomatic influenza	1 (265)	RRI: 39% (–55 to 327)
	Neuraminidase inhibitors	Influenza	7 (3549)	RRR: 59% (35 to 75)
		Influenza-like illness	7 (3549)	RRI: 20% (–23 to 87)
		Asymptomatic influenza	4 (2974)	RRR: 7% (–51 to 43)
Treatment	Amantadine	Fever at 48 hours	2 (85)	RRR: 79% (34 to 93)
	Rimantadine	Fever at 48 hours	4 (122)	RRR: 84% (47 to 95)
				Hazard ratio (CI)†
	Neuraminidase inhibitors	Time to alleviation of symptoms	9 (4985)	1.22 (1.14 to 1.31)

*Abbreviations defined in Glossary; RRR, RRI, and CI calculated from data in article using a random-effects model.
†Hazard ratio > 1 favors treatment.

COMMENTARY

Antiviral medications for influenza are most commonly used for prophylaxis of exposed vulnerable persons or treatment of those at high risk for complications. Widespread use of antiviral drugs for seasonal or "interpandemic" influenza has only been described in Japan, where rapid diagnosis and treatment within 48 hours of symptom onset optimize the efficacy of the drug. Antivirals are the only intervention for prophylaxis and treatment in years when there is a poor match between vaccine and the circulating viral strain, when no vaccine is yet available, and for persons who cannot be routinely immunized (e.g., anaphylactic egg allergy) or who have poor immunologic response. In the 2005–06 season, only neuraminidase inhibitors could be used because the circulating H3N2 strain was highly resistant to amantadine (1).

The review by Jefferson and colleagues showed that antiviral drugs prevent laboratory-confirmed influenza and improve clinical outcomes. Not surprisingly, they are less effective for illness without virologic confirmation, since noninfluenza viruses are probably also responsible.

The reader may be puzzled by the authors' conclusions that the evidence does not support use of adamantines for influenza and that there is no role for neuraminidase inhibitors in seasonal influenza. Taken in isolation, these conclusions do not reflect the complexity of the decision making required to use antiviral agents wisely. Although these drugs are effective in the prevention and treatment of seasonal influenza, not all situations in which they can be used will be equally compelling and the individual patient's risk–benefit ratio should be considered. There are also other issues for antiviral drug use. How will we understand the most effective use of antiviral drugs if they have only been used in the artificial environment of a blinded clinical trial? How will clinicians become familiar with these drugs if they never use them? These issues are, no doubt, among the concerns that led the World Health Organization to call for enhanced utilization of antiviral agents in the interpandemic period (2).

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References

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2. **Stöhr K.** Vaccine. 2003;21:1744-8.