Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments

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STUDY QUESTION

What is the regulatory evidence from randomised controlled trials of effectiveness and harms of oseltamivir for influenza in all age groups?

SUMMARY ANSWER

Oseltamivir shortens the duration of influenza-like illness symptoms in treatment of adults and non-asthmatic children and prevents their appearance in prophylaxis, but also causes vomiting and nausea and increases the risk of headaches and renal and psychiatric syndromes. It has no significant effect on hospitalisations, and its effects on pneumonia are doubtful because of the lack of a verifiable outcome.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Neuraminidase inhibitors are used globally for treatment and prophylaxis of influenza, but the evidence for their effectiveness in preventing complications of influenza is sparse and information regarding their adverse events is lacking. To address reporting bias in trials of oseltamivir, we included only full clinical study reports of randomised controlled trials and relevant regulatory comments (roughly 150 000 pages), the first time that such methods have been used in a Cochrane review to our knowledge.

Selection criteria for studies

We examined clinical study reports of randomised controlled trials testing the effects of oseltamivir for prophylaxis and treatment of influenza in healthy people or the chronically ill who have symptoms of influenza-like illness. These were augmented by regulators' comments and reports during drug registration.

Primary outcome(s)

We considered symptom relief, symptom prevention, hospitalisation, complications, and harms

Main results and role of chance

In trials of treatment of influenza, oseltamivir had modest symptomatic effects. It reduced the time to first alleviation of symptoms in adults by 16.7 hours (95% CI 8.4 to 25.1, P<0.0001). It had no effect in asthmatic children, but did in otherwise healthy children (mean difference 29 hours (12 to 47), P=0.001). There was no difference in hospitalisations in adults, and sparse data in children. Secondary illness data (such as "pneumonia") were captured by participant self reporting to the investigator in 15/20 trials. Oseltamivir reduced investigator mediated, unverified "pneumonia" in treated adults, but the effect was not significant in the five trials that used a more detailed diagnostic form for pneumonia. The effect in children was not significant, and there was no significant reduction in risk of any other self reported, investigator mediated, unverified complication of influenza. In treatment of adults oseltamivir increased the risk of nausea (risk difference 3.66% (0.9 to 7.39)) and vomiting (4.56% (2.39 to 7.58)), and in treatment of children it induced vomiting (risk difference 5.34% (1.75 to 10.29)).

In prophylaxis trials, oseltamivir reduced the proportion of symptomatic influenza in individuals by 55% (risk difference 3.05% (1.83 to 3.88)). However, it also increased the risk of psychiatric adverse events on and off treatment (risk difference 1.06% (0.07 to 2.76)), headaches on treatment (3.15% (0.88 to 5.78)), renal events on treatment (−0.67% (−2.93 to 0.01)), and nausea on treatment (4.15% (0.86 to 9.51)).

Bias, confounding and other reasons for caution

We were relatively inexperienced and unfamiliar in dealing with large quantities of detailed information. There was high risk of bias for included outcomes due to missing data, selective reporting, possibly active placebo, lack of outcome definitions, suboptimal measurement, and incomplete reporting in the clinical study reports.

Study funding/potential competing interests

This project was funded by the NIHR Health Technology Assessment programme (HTA-10/80/01). The views and opinions expressed are those of the authors and do not necessarily reflect those of the Department of Health. TJ receives royalties from his books and is occasionally anonymously interviewed by market research companies; he acted as an expert witness in a litigation case related to oseltamivir in healthcare workers in Canada. PD received €1500 from the European Respiratory Society for a talk on oseltamivir, and is an associate editor of the *BMJ*. CJH receives payment for educational courses and royalties for his books.

Main outcomes of trials of oseltamivir	
Outcome	**Point estimate (95% CI)**
Trials of treatment of influenza in adults	
Reduction in time to first alleviation of symptoms (hours)	16.7 (8.4 to 25.1)
Risk ratio for investigator mediated, unverified "pneumonia":	
Studies using non-specific form	0.50 (0.27 to 0.90)
Studies using specific form for diagnosis of pneumonia	0.93 (0.59 to 1.47)
Trials of prophylaxis	
Psychiatric harms:	
Risk difference (%)	1.06 (0.07 to 2.76)
Number needed to harm	94 (36 to 1538)
Interruption of viral transmission	Unproven

Zanamivir for influenza in adults and children: systematic review of clinical study reports

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STUDY QUESTION

What is the regulatory evidence from randomised controlled trials of effectiveness and harms of zanamivir for influenza in all age groups?

SUMMARY ANSWER

Zanamivir slightly reduces the time to symptomatic improvement in adults (but not children) with influenza-like illness, although this effect is attenuated by symptom relief medication, and has only minor harmful effects (except for bronchospasm). It does not reduce the risk of reported or confirmed pneumonia, and evidence on hospitalisations was unassessible. The results do not support a reduction in asymptomatic influenza and subsequent risk of transmission.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Neuraminidase inhibitors are used for the treatment and prophylaxis of influenza, but the evidence for their effectiveness in preventing complications of influenza is sparse and information regarding their adverse events is lacking. To address reporting bias in trials of zanamivir, we included only full clinical study reports of randomised controlled trials and relevant regulatory comments (roughly 150 000 pages), the first time that such methods have been used in a Cochrane review to our knowledge.

Selection criteria for studies

We examined clinical study reports of randomised controlled trials testing the effects of zanamivir for prophylaxis and treatment of influenza in healthy people or the chronically ill who have symptoms of influenza-like illness.

Primary outcome(s)

We considered symptom relief, symptom prevention, hospitalisation, complications, and harms.

Main results and role of chance

In adult treatment, zanamivir reduced the time to first alleviation of symptoms by 0.60 days (95% CI 0.39 to 0.81, P<0.00001). In children there was no significant effect on time to first alleviation of symptoms. In adult treatment trials, zanamivir did not reduce the risk of patient reported, investigator mediated pneumonia (risk difference 0.17% (−0.70 to 0.73)), nor x ray confirmed pneumonia (−0.06% (−6.56 to 2.11)). The effect on pneumonia in children was also not significant (0.56% (−1.64 to 1.04)). There was no significant effect on risk of otitis media or sinusitis in both adults and children, with only a small effect found for bronchitis in adults (risk difference 1.80% (0.65 to 2.80)). There was insufficient evidence to

Main outcomes of trials of zanamivir	
Outcome	**Point estimate (95% CI)**
Trials of treatment of influenza in adults	
Mean difference in time to first alleviation of symptoms (days)	0.6 (0.39 to 0.81)
Risk difference for "pneumonia" (%):	
Self reported, investigator mediated pneumonia	0.17 (−0.70 to 0.73)
X ray confirmed pneumonia	−0.06 (−6.56 to 2.11)
Trials of prophylaxis	
Symptomatic influenza in individuals:	
Risk difference (%)	1.98 (0.98 to 2.54)
Number needed to treat	51 (40 to 103)
Risk difference for asymptomatic influenza in individuals (%)	0.14 (−1.10 to 1.10)
Interruption of viral transmission	Unproven

assess hospitalisations in adults and children. Zanamivir tended to be well tolerated.

In prophylaxis studies, zanamivir reduced symptomatic influenza in individuals (risk difference 1.98% (0.98 to 2.54), number needed to treat 51 (40 to 103)), but the prophylaxis effect on asymptomatic influenza was not significant in individuals (risk ratio 0.97 (0.76 to 1.24)) or in households (0.88 (0.65 to 1.20)). In households treated prophylactically there was an effect on symptomatic influenza (risk difference 14.84% (12.18 to 16.55)), but this was based on only two small studies including 824 participants. Prophylaxis had a small effect on reducing pneumonia in adults, but not in children, nor on bronchitis or sinusitis in adults or children.

Bias, confounding, and other reasons for caution

Although we might expect clinical study reports to provide the most comprehensive account possible, we encountered difficulties in identifying all relevant information. Incomplete reporting in some of the reports might have influenced our decision making. Knowledge of new potential biases accumulated during the review process.

Study funding/potential competing interests

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Derivation and validation of a clinical prediction rule for uncomplicated ureteral stone—the STONE score: retrospective and prospective observational cohort studies

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STUDY QUESTION

Can a clinical prediction score (STONE) for ureteral stones that cause symptoms be used to identify patients with a very high or very low probability of having uncomplicated ureteral stones?

SUMMARY ANSWER

ive factors predicted the presence of ureteral stones: male sex, acute onset of pain, non-black race, presence of nausea or vomiting, and microscopic hematuria. The STONE score reliably and objectively predicted the probability of uncomplicated ureteral stones, and patients with a high score had a lower prevalence of acutely important alternative causes of symptoms.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Kidney stones are common and though computed tomography (CT) is now the first line diagnostic test, i t has not been shown to improve patient centered outcomes in renal colic. In this study a clinical prediction rule was derived and validated that can identify patients with a high probability of having uncomplicated ureteral stones and the absence of other important cause of symptoms, which may allow more appropriate choices of imaging.
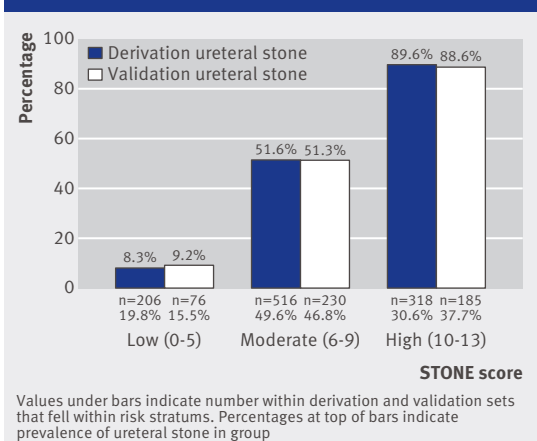
Participants and setting

Patients (1040 in the retrospective cohort and 491 in the prospective cohort) who presented to two emergency departments in the New Haven Connecticut area with suspected kidney stone for whom the clinician ordered a diagnostic CT scan.

Design, size, and duration

The derivation phase involved a retrospective record abstraction of a priori factors from the medical record in patients receiving CT for suspected renal colic, with the presence of ureteral stone separately and blindly derived from dictated CT reports. 1853 records of 5383 CT scans using a renal colic protocol from April 2005 to November 2010 were randomly selected for review, of which 1040 met the inclusion criteria. For prospective validation, study staff collected the elements of the STONE score blinded to the CT results and enrolled 491 patients from May 2011 to February 2013.

Prevalence of ureteral stone by STONE score category in derivation and validation cohorts

Values under bars indicate number within derivation and validation sets that fell within risk stratums. Percentages at top of bars indicate prevalence of ureteral stone in group

Main results and the role of chance

Multivariate logistic regression on factors from the derivation set yielded the five elements of the STONE score, which were converted to an integer scoring system from 0-13 points and stratified as at low (score 0-5), moderate (6-9), and high (10-13) risk of ureteral stones. In the derivation and validation cohorts ureteral stone was present in, respectively, 8.3% and 9.2% of the low risk group, 51.6% and 51.3% of the moderate risk group, and 89.6% and 88.6% of the high risk group. Prevalence of acutely important alternative findings in patients with a high score were less than half (0.3%) the overall group.

Bias, confounding, and other reasons for caution

This study was performed in two emergency departments in a single geographic area, and all patients were scanned by CT. Results may be different in other populations.

Generalisability to other populations

Though the study population was diverse in terms of age, sex, and ethnicity the study was performed at two emergency departments in the same geographic area. Further multicenter validation is warranted.

Study funding/potential competing interests

This study was funded by the Agency for Healthcare Research and Quality.

A population health approach to reducing observational intensity bias in health risk adjustment: cross sectional analysis of insurance claims

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STUDY QUESTION

Is there a more accurate approach to health risk adjustment than that used by US Medicare, which relies on diagnoses from insurance claims?

SUMMARY ANSWER

Five measures of population health—obesity, smoking status, self reported illness, and admission to hospital for hip fractures and strokes—performed much better than the approach used by US Medicare. Together, they explained 65% of residual variation in regional mortality after adjustment for age, sex, and race compared with less than 10% for the Medicare method.
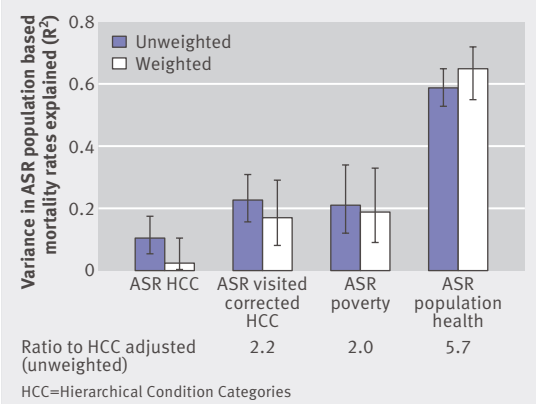
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Standard health risk adjustment methods that use administrative databases are subject to observational intensity bias: higher frequency of patient visits to physicians leads to more diagnoses in the databases, resulting in the population seeming to be sicker. The population health index reduced and explained much more of the variation in regional mortality rates and avoided inappropriate swings in mortality rates in regions with high and low visit rates to physicians than did Medicare's standard administrative database method.

Participants and setting

A 20% sample of fee for service Medicare beneficiaries aged 65 and older residing in one of 306 hospital referral regions in the United States in 2007 (n=5 153 877).

Ability to explain residual variation in age, sex, and race (ASR) adjusted hospital referral regions mortality using four methods of risk adjustment (R^2 statistics and 95% confidence interval; unweighted and weighted)

HCC=Hierarchical Condition Categories

Design

Cross sectional analysis of the Medicare administrative claims database from 2007.

Primary outcomes

The effect of health risk adjustment on age, sex, and race adjusted mortality and spending rates among hospital referral regions using four indices of health: the standard Center for Medicare and Medicaid Services—Hierarchical Condition Categories (HCC) index used by the US Medicare program (calculated from diagnoses listed in Medicare's administrative database), a visit corrected HCC index (to reduce the effects of observational intensity on frequency of diagnoses), a poverty index (based on US census), and a population health index (calculated using data on incidence of hip fractures and strokes, and responses from a population based annual survey of health from the Centers for Disease Control and Prevention).

Main results and the role of chance

The visit adjusted HCC, poverty, and population health indices explained more of the residual variation in age, sex, and race adjusted mortality across regions than did the standard HCC index. The standard HCC index explained more of the residual variation in spending across regions. However, once the observational intensity bias was removed by adjusting the standard HCC for visits, almost none of the variation in spending could be explained.

Bias, confounding, and other reasons for caution

Using mortality as a measure of overall population health may not account for more subtle measures of health status. We used county level measures of health rather than patient level measures.

Generalisability to other populations

This study is representative of the elderly population in the United States. Other healthcare systems, including the English National Health Service, use risk adjustment for allocation of resources, and the findings of this paper may have bearing on their approach.

Study funding/potential competing interests