Can oseltamivir be used in adult patients with renal impairment?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

Before using this Q&A, read the disclaimer at www.ukmi.nhs.uk/activities/medicinesQAs/default.asp

Date prepared: 4th September 2013

Background

Oseltamivir phosphate is a pro-drug which is extensively converted to the active metabolite oseltamivir carboxylate (OC). OC is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body (1).

The normal adult dose of oseltamivir for the treatment of influenza is 75mg twice daily for 5 days (1, 2). The normal adult dose of oseltamivir for post-exposure prophylaxis of influenza is 75mg once daily for 10 days (1, 2). For prevention during an influenza epidemic in the community, the normal adult dose is 75mg once daily for up to six weeks (1, 2).

Answer

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate. At least 75% of an oral dose reaches the systemic circulation as OC. Exposure to the pro-drug is less than 5% relative to the active metabolite (1).

Absorbed oseltamivir is primarily (>90%) eliminated by conversion to OC (1). OC is eliminated entirely (>99%) in the urine (1, 3). Renal clearance (18.8 L/h) exceeds glomerular filtration rate (7.5 L/h) indicating that tubular secretion occurs in addition to glomerular filtration (1). Peak plasma concentrations of OC decline with a half-life of 6 to 10 hours in most subjects (1). The half-life of oseltamivir is prolonged in patients with end stage renal failure (4, 5).

Renal clearance of OC decreases linearly with creatinine clearance (CrCl). Therefore an increase in plasma concentrations of OC can be expected in patients with severe renal impairment (CrCl<30 mL/min) (6).

Oseltamivir is generally well-tolerated, but gastrointestinal side effects and dizziness may appear with increasing doses, particularly in patients with renal failure (7). Oseltamivir has a wide safety margin so one source suggests that there appears to be little risk associated with higher-than-usual concentrations in renal failure (5). However, another source reporting a possible case of oseltamivir-induced angioedema in a patient with chronic renal failure, suggests that it is important to appropriately dose patients with compromised renal function as supratherapeutic dosing increases the risk of drug-related adverse events (8).

In Japan, it was recommended that acute renal failure be added as a clinically significant adverse reaction to product literature for oseltamivir. This was based on reports associating oseltamivir use with acute renal failure. It is recommended that patients be carefully observed upon onset of renal failure and appropriate measures taken immediately if any abnormalities occur (9). Renal failure is not listed as an adverse effect of oseltamivir in UK product literature (1).

Renal Impairment

The manufacturer of oseltamivir revised their dosing recommendations for the use of oseltamivir in patients with renal impairment following a request by the Committee for Medicinal Products for Human Use (CHMP). These changes to the license were based on clinical data from in-house
pharmacokinetic studies and modelling and simulation analysis on pharmacokinetics of oseltamivir in patients with varying degrees of renal function (10). Other reference sources may pre-date this updated information. No dosage adjustment is needed in adults with a CrCl>60mL/min (1). A lower dose is required in severe renal impairment (RI) due to accumulation of OC (4). Where there is any concern about renal function, zanamivir may be the preferred option (11).

**CrCl 30-60mL/min**

The licensed dose for the treatment of influenza in adults with CrCl 30-60mL/min is 30mg twice daily. For prevention of influenza in adults with CrCl 30-60mL/min, the licensed dose is 30mg once daily (1). The manufacturer had previously recommended no dosage adjustment was necessary in this patient group. The Renal Drug Handbook notes that the Renal Association guidance and the American data sheet still suggest that no dosage adjustment is needed in adults with a CrCl>30mL/min (4).

**CrCl 10-30mL/min**

Dose information for this patient group is conflicting. The manufacturer recommends dose adjustment for both treatment and prevention in adults with severe RI (CrCl 10-30mL/min). The area under the plasma concentration-time curve (AUC) of OC was on average increased 10-fold in patients with CrCl<30mL/min as compared with individuals without RI (7). The manufacturer recommends the following dose reductions:

- For treatment of influenza: 30mg once daily (1).
- For prophylaxis of influenza: 30mg every second day (1).

The Renal Drug Handbook follows the manufacturer’s guidance, but additionally describes the higher doses which have previously been safely and effectively used as recommended by the Renal Association and American product literature (4). The Renal Association have previously recommended the following dosing schedules:

- For treatment of influenza: 75 mg once daily, or 30 mg twice daily (12).
- For prophylaxis of influenza: 75mg every second day or 30 mg once daily (12).

**CrCl <10mL/min**

The use of oseltamivir in patients with RI with CrCl<10mL/min is not recommended by the manufacturer because of an absence of data (10). As there are few data available there is no definitive dose guidance available. However anecdotal dosing advice is available which is extrapolated from pharmacokinetic data for CAPD patients (4,12,13).

- For the treatment of influenza, a single dose of 75mg oseltamivir has been suggested by the Renal Association; and a dose of 30mg once a week (2 doses) has been recommended for post-exposure prophylaxis (12).

**Critical Care Setting**

It has been noted that many critical care units are prescribing double the licensed usual dose of oseltamivir for treatment (12). HPA guidance states that: the dose may be increased to 150 mg (this is an off label dosage) in critically ill patients in an attempt to maximise drug levels in the lungs, reduce shedding and prevent viral rebound. However as with complicated influenza, zanamivir should be used when there is suspected poor GI absorption or failure to respond to oseltamivir (15).

The following dosing recommendations have been made for the treatment of critically ill patients.

**For patients with CrCl>30mL/min** oseltamivir 75-150mg twice daily for 5 days (12,14,15).

**For patients with CrCl 10-30mL/min** oseltamivir 75mg once or twice daily for 5 days (12,14).

**For patients with CrCl<10mL/min** oseltamivir 75mg STAT repeated every 5 days if required (14).

For critically ill patients who require prophylactic doses, the following recommendations have been made (14).

**For patients with CrCl>30mL/min** oseltamivir 75 once daily for 10 days (14).

**For patients with CrCl 10-30mL/min** oseltamivir 75mg every second day for 10 days (14).

**For patients with CrCl<10mL/min** oseltamivir 30mg once a week (usually for 2 doses) (14).

It has been noted that these doses have been associated with an increase in adverse effects (16). A study in adults (n=80) and children (n=246) admitted with severe influenza compared double (150mg
twice daily in adults) versus standard dose oseltamivir (75mg twice daily in adults) on viral status and clinical outcomes after 5 days of treatment. Doses were adjusted according to renal function but patients with a CrCl<10mL/min were excluded from the study. Of 53 adults admitted to intensive care, 19 received double dose and 24 received the standard dose of oseltamivir. Overall, the study showed no difference in virological and clinical outcomes between double dose and standard dose of oseltamivir. No differences were found between double and standard dose groups in median days in intensive care (4.5 [interquartile range 3-6] vs. 5 [2-11]). Despite the limitations of the study – the authors caution against extending the results to different patient populations e.g. morbidly obese adults or those with underlying chronic illnesses – the results do not support routine use of double dose oseltamivir to treat severe influenza.

Summary
- Oseltamivir carboxylate (OC) (the active metabolite of oseltamivir phosphate) is excreted entirely in the urine through glomerular filtration and tubular secretion.
- Oseltamivir is generally well-tolerated, but gastrointestinal side effects and dizziness may appear with increasing doses, particularly in patients with renal failure.
- Renal clearance of OC decreases linearly with creatinine clearance (CrCl).
- Adults with mild renal impairment (RI) (CrCl>60mL/min) can receive the normal adult dose.
- The manufacturer of oseltamivir has revised their dosing recommendations for the use of oseltamivir in patients with renal impairment.
- The manufacturer recommends dose reduction for both treatment and prevention in adults with moderate RI (CrCl 30-60mL/min):
  - For treatment of influenza: 30mg twice daily.
  - For prophylaxis of influenza: 30mg once daily.
- The manufacturer recommends dose reduction for both treatment and prevention in adults with severe RI (CrCl 10-30mL/min):
  - For treatment of influenza: 30mg once daily.
  - For prophylaxis of influenza: 30mg every second day.
- Other (unlicensed) dose recommendations exist for patients with CrCl 10-60mL/min (see above) but should be considered with caution as their advice may precede the updated licensed manufacturer’s guidance.
- The manufacturer states that oseltamivir is not recommended in patients with CrCl<10mL/min. In these patients zanamivir is the preferred option for both prophylaxis and treatment. Please see Q&A 270.2 zanamivir in renal impairment for more information about the use of zanamivir in patients with RI or on RRT.
- For patients with CrCl<10mL/min there is no definitive dosage guidance. Anecdotal dosing advice exists:
  - For treatment of influenza: a single dose of 75mg has been suggested.
  - For prophylaxis of influenza doses of 30mg repeated weekly (2 doses) has been suggested.
- The decision to prescribe oseltamivir, and which dose to use, for patients with renal impairment lie with the treating physician and should be based on an appropriate assessment of the likely risk versus benefit ratio. If oseltamivir is prescribed in patients with CrCl<10mL/min or at doses higher than those recommended by the manufacturer (which is outside of the product license) the patient must be monitored closely for efficacy, adverse effects and signs of toxicity.
- For patients in the critical care setting, many units are reported to be prescribing double the usual dose (see above).

Limitations
The manufacturer of oseltamivir has updated their dosage recommendations for patient with renal impairment. Many reference sources precede this information, and therefore caution should be exercised when considering conflicting information from older reference sources. There are very few data available for patients with severe renal impairment receiving oseltamivir. Paediatric patients are outside of the scope of this document. The information in this Q&A relates only to oral oseltamivir, it is not applicable to the use of intravenous oseltamivir. Information relating to the use of oseltamivir in
patients undergoing renal replacement therapies is described in Q&A 390.2 Can oseltamivir be used in adult patients on renal replacement therapies?

References
10) Personal Communication with Medical Information Specialist for Roche Products Ltd. Email, 9th December 2011.

Quality Assurance

Prepared by
Julia Kuczynska (based on earlier work by Michèle Skipp), South West Medicines Information, Bristol

Available through NICE Evidence Search at www.evidence.nhs.uk
Date Prepared
4th September 2013

Checked by
Trevor Beswick, South West Medicines Information, Bristol

Date of check
17th September 2013

Search strategy
- Embase (*Oseltamivir OR oseltamivir.ti,ab) AND (exp*Kidney-Failure OR exp*Renal Replacement Therapy).
- Medline (*Oseltamivir OR oseltamivir.ti,ab) AND (exp*Renal Insufficiency OR exp*Renal Replacement Therapy).
- Manufacturer (Roche Products Ltd, Personal Communication, email 11/11/11).
- Internet search (Cochrane Library, NHS Evidence), search term "oseltamivir renal"; "oseltamivir dialysis".
- Internet search (Google "oseltamivir renal; oseltamivir dialysis").
- In-house database. Keywords – Oseltamivir.
- In-house renal files and texts.
- The Renal Association website: www.renal.org