Oseltamivir or zanamivir—can mothers breastfeed after treatment for influenza?

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Date prepared: 20 January 2018

Background

Oseltamivir (Tamiflu®) and zanamivir (Relenza®) are neuraminidase inhibitors licensed for prophylaxis and treatment of influenza. Treatment should be started within 48 hours of onset of symptoms (36 hours for zanamivir in children). Oseltamivir is administered orally whilst zanamivir is administered by inhalation. A treatment course lasts for five days for both drugs.

Oseltamivir is licensed for adults and children older than 1 month for prevention of influenza when influenza virus is circulating in the community. Prophylaxis should be started within 48 hours of exposure (36 hours for zanamivir). Oseltamivir is also licensed for infants under one year, including neonates (but excluding premature infants) for treatment during an influenza pandemic. Zanamivir may be used in adults and children aged 5 years or over (1-3).

Zanamivir solution for IV or nebulised administration is also available as an unlicensed medication for compassionate use for named patients. This method of administration may be required in critical illness for example (4).

In 2009, oseltamivir or zanamivir were designated as the first-line drugs to treat patients with symptoms and their contacts in the event of confirmed H1N1 (Swine flu) or H5N1 (Avian flu) influenza A infection (5,6). The current use of oseltamivir and zanamivir for the prophylaxis and treatment of influenza is covered by guidance from the National Institute for Health and Clinical Excellence (NICE) (7,8), Public Health England (PHE) (4) and the Department of Health (DH) for pandemic flu (9).

The only specific national guidance on the use of antivirals in breastfeeding mothers is contained in the PHE and DH guidance (8,9). The DH guidance (9) states that *'women who are breastfeeding and have symptoms of influenza should be treated with an antiviral medicine. The preferred medicine is Tamiflu, as for other adults. However, if a woman's baby is born and breastfeeding is started while the woman is taking Relenza, she should complete the course of Relenza; it is not necessary to switch to Tamiflu. If it is decided that a woman who is breastfeeding requires prophylaxis because of family or other contact with a novel pandemic virus strain, the preferred antiviral medicine is Tamiflu*'.

Answer

Oseltamivir

Oseltamivir is a prodrug that is readily absorbed after oral administration and converted hepatically into its active metabolite, oseltamivir carboxylate. The oral bioavailability in terms of oseltamivir carboxylate is approximately 75%. Only 5% of a dose is found as oseltamivir in the systemic circulation (2). Oseltamivir carboxylate, if given orally, has very limited bioavailability (10). The manufacturer advises that 'administration of oseltamivir may be considered where there are clear potential benefits to lactating mothers' (2).

In a case report, the mother of a 9-month-old infant was treated with oseltamivir, 75 mg twice daily. She provided 11 milk samples over the 5-day treatment period, during which the infant was not breastfed. Oseltamivir carboxylate was undetectable in the first milk sample, and reached a steady state concentration of 37–39 micrograms/L after 3 days. Concentrations of oseltamivir were significantly lower than those of the carboxylate. The authors calculated that a fully breastfed infant would ingest a maximum of 12 micrograms/kg daily, equivalent to 0.5% of the weight-adjusted maternal dose (11).

In a second report, seven postpartum women who were bottle feeding their infants donated milk samples at intervals from zero to 24 hours after a single 75 mg oral dose of oseltamivir phosphate (12). Both oseltamivir phosphate and its active metabolite, oseltamivir carboxylate, were detected in milk samples. The mean peak milk levels of oseltamivir phosphate and oseltamivir carboxylate were 26.9 microgram/L (at mean 3.4 hours after the dose) and 41.9 microgram/L (at mean 18.9 hours) respectively. Peak oseltamivir phosphate and carboxylate levels appeared in breast milk approximately one and 14 hours after peak maternal plasma levels respectively. Assuming a normal milk intake of 150 mL/kg daily, a fully breastfed infant would receive approximately 0.9 microgram/kg oseltamivir and 3.6 microgram/kg oseltamivir carboxylate daily, although these levels are from administration of half the normal treatment dose. Although this study has some limitations (single dose, non-steady state conditions; half normal daily maternal dose; breastfeeding not established), the amount ingested by an infant would be considerably below the normal infant dose for influenza treatment of 4-6 mg/kg daily (2).

A dose of 4 mg/kg daily has been found to be effective and safe in infants aged less than one year (13). From the levels that have been reported in the literature clinical effects of maternal treatment with oseltamivir on a breastfed infant would not be expected (14).

Zanamivir

Maternal systemic absorption after inhalation of zanamivir is approximately 10–20%, and the oral bioavailability is limited to approximately 1–5% (3). There are no data on the excretion of zanamivir into human breast milk via any route, and the manufacturer advises that 'the use of zanamivir is not recommended in mothers who are breast feeding' (3). However, based on its pharmacokinetic properties (extremely limited oral bioavailability for the infant and short half-life), the exposure of a breastfed infant, when administered to the mother via any route, would be expected to be insignificant (10,14,15).

A review of the use of oseltamivir and zanamivir in breastfeeding mothers (14) concludes:

- Both oseltamivir and zanamivir are considered to be compatible with breastfeeding.
- Continuation of breastfeeding by a woman taking these medications is unlikely to lead to substantial drug exposure to the infant.
- Adjustment of dose because of breastfeeding is not necessary.
- If an infant being breastfed by the mother receiving oseltamivir or zanamivir needs direct treatment or chemoprophylaxis, the recommended dose of oseltamivir or zanamivir for infants should be given.

Summary

- Oseltamivir and its active metabolite, oseltamivir carboxylate, are excreted into human breast milk in very small amounts. Limited data suggest that clinical sequelae from maternal treatment would not be expected in a breastfed infant.
- There are no data on zanamivir use during lactation but based on limited bioavailability the systemic exposure of a breastfed infant from maternal treatment, via any route, is expected to be insignificant.
- The overall consensus is that treatment with either drug is not a reason to discontinue, or put limitations on, breastfeeding full-term or pre-term infants. Due to the very small amounts transferred into breast milk, and the limited oral bioavailability of either drug, the benefits of breastfeeding are considered to outweigh any, albeit unidentified, risks.
- If an infant being breastfed by the mother receiving oseltamivir or zanamivir needs direct treatment or chemoprophylaxis, the recommended dose of oseltamivir or zanamivir for infants should be given.
- The UK Drugs in Lactation Advisory Service (UKDILAS) advises that, as a precaution, infants should be monitored for vomiting and diarrhoea.

Limitations

Data on oseltamivir are limited. The recommendation for zanamivir is based on pharmacokinetic principles only.

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Date Revised
20 January 2018

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Date of check
5 February 2018

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