Q&A 260.4

Are penicillins and cephalosporins safe in breastfeeding?

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

Date prepared: 11 November 2015

Background

Penicillins and cephalosporins are antibiotics used for a wide range of infections. They are considered to be low in toxicity [1].

In general, drugs which are fat soluble, with low protein binding, diffuse passively into breast milk [1]. Acidic drugs pass less readily into breast milk than basic drugs [1]. Both penicillins and cephalosporins are weak acids with low fat solubility and therefore are not thought to pass into breast milk in significant concentrations [1]. With most antibiotics, the breastfed infant receives less than 1% of the maternal weight-adjusted therapeutic dose [2,3].

There are a number of questions which have been raised about the use of penicillins and cephalosporins during breast-feeding [2]:

- Can absorption of the drug via the breast-milk cause side-effects?
- Is the drug absorbed in significant amounts to be bactericidal in the infant?
- Can the infant develop bacterial resistance?

Answer

Penicillins

Penicillins are distributed into milk in low concentrations and are considered compatible with breastfeeding [4, 5, 6]. Low levels of clavulanic are anticipated in milk due to the drug's properties, and therefore co-amoxiclav is considered compatible during breastfeeding [5, 6].

No studies could be located on the use of temocillin during breastfeeding. The manufacturers advise that mothers should not breastfeed their infants whilst receiving temocillin [7]. However, since penicillins are generally considered compatible, temocillin is also likely to be safe [8]. Nevertheless, caution should still be exercised if temocillin is used [8].

There is no information regarding the combination of piperacillin with tazobactam during breast-feeding, however very low levels of piperacillin are found in milk [5, 6]. Only trace quantities of *Timentin*® (ticarcillin with clavulanic acid) have been reported in breast milk [9]. The poor oral bioavailability of both piperacillin/tazobactam and *Timentin*® would also limit oral absorption by the infant [6]. Piperacillin/tazobactam and *Timentin*® are considered compatible with breastfeeding.

No studies could be located on the use of pivmecillinam during breastfeeding. However, the manufacturer's advise that pivmecillinam can be used during lactation and that no adverse effects on the infant would be expected [10].

Cephalosporins

Cephalopsorins are also distributed into milk in low concentrations and are considered compatible with breastfeeding [4, 5]. Cephalosporins are classified as first, second, third, and fifth generation [6].

Out of the first generation, cefadroxil has been found to produce higher milk concentrations than most other cephalosporins [1]. This is because it has a lower rate of elimination and a higher fat solubility [1]. However, it is still considered compatible with breastfeeding [5].

Second generation cephalosporins are also considered compatible with breastfeeding [4, 5].

Oral bioavailability of the third generation cephalosporins is significantly lower than that of the first or second generation [11]. This will limit the amount of drug absorbed orally by the infant [8]. However, the pharmacokinetics of the third generation cephalosporins require special consideration.

When doses of 2g ceftriaxone are used the protein binding capacity of the serum is saturated, leaving more free drug to transfer into breast milk [12]. A study which looked at the penetration of a 2g dose of ceftriaxone found diffusion into the milk to be 4.4% of the maternal weight-adjusted therapeutic dose. However, no adverse effects were noted in the neonate [12]. In another study, the amount of ceftriaxone found in breast milk was low, although the concentrations achieved after intramuscular administration were consistently higher than those achieved after intravenous administration. These differences are not expected to be clinically relevant [13].

In a study which looked at the transfer of ceftazidime into breast milk after multiple doses, results showed higher levels in milk than those reported for other cephalosporins. These higher levels may be due to the pharmacokinetics. Ceftazidime has a low level of protein binding and a relatively long plasma half-life which favours its transfer into breast milk. However, there is no progressive accumulation of ceftazidime with multiple doses [14].

No reports describing the use of cefixime or ceftaroline during lactation could be located and it is not known whether they are distributed into breast milk [5, 15, 16]. However, based on information for other cephalosporins, cefixime and ceftaroline are considered compatible with breastfeeding [5].

Cefpodoxime has been shown to be excreted in breast milk in small amounts, and is also considered compatible with breastfeeding [5, 17].

Table 1 summarises some of the information regarding penicillins and cephalosporins in breast milk.

Antibiotic	Generation of cephalosporin	Expected infant dose (maternal weight-adjusted therapeutic dose)	Maternal dose studied
Amoxicillin	-	1%	1g single dose
Ampicillin	-	0.2–0.5%	4g daily
Benzylpenicillin	-	not reported	2.4g single dose
Co-amoxiclav	-	0.9%	not reported
Flucloxacillin	-	0.4%	250mg single dose
Phenoxymethylpenicillin	-	0.09%	1320mg single dose
Piperacillin as single agent	-	not reported	12g daily
Pivmecillinam	-	no information	no information
Temocillin	-	no information	no information
Ticarcillin as single agent	-	0.2%	15g daily
Cefaclor	2nd	0.4–0.8%	500mg single dose
Cefadroxil	1st	0.8–1.3%	1g single dose
Cefalexin	1st	0.5–1.5%	1g single dose
Cefixime	3rd	no information	no information
Cefotaxime	3rd	0.3–0.5%	4g daily
Cefpodoxime	3rd	0.02%	200mg single dose
Cefradine	1st	0.3%	2g daily
Ceftaroline	5th	no information	no information
Ceftazidime	3rd	0.9%	6g daily
Ceftriaxone	3rd	4.4%	2g daily
Cefuroxime	2nd	0.6–2%	2.25g daily

Table 1: Characteristics of penicillins and cephalosporins in breast milk [5, 6, 11, 13, 18, 19, 20]

Adverse effects

To date, no adverse effects in infants have been proven to be a result of exposure to penicillins or cephalosporins via the breast milk [2].

Although it seems unlikely that the small doses received by the infants could cause direct gastro-intestinal irritability, such amounts may be capable of changing the oral or gastro-intestinal flora [3, 21]. This could lead to oral candida infections, diarrhoea, and possibly effect the absorption of nutrients [3, 21]. The third generation cephalosporins have been found to alter the gut flora with greater potential than other cephalosporins when given directly [22].

In a study of 87 breastfeeding women treated with antibiotics (amoxicillin, erythromycin, co-trimoxazole, cloxacillin, cefalexin, nitrofurantoin, ampicillin, and cefaclor), 15% of mothers reported diarrhoea in their infants [3].

In another study of 105 breastfeeding women treated with either amoxicillin, co-amoxiclav, cefalexin, or cefuroxime, side-effects reported were minor, self-limiting, and did not require interruption of breastfeeding [23]. The incidences of side-effects in the infants were 7.5% for amoxicillin (diarrhoea and rash), 9% for cefalexin (diarrhoea) 2.6% for cefuroxime (diarrhoea) and 22% for co-amoxiclav (constipation, rash, diarrhoea, and irritability). One infant was found to have raised liver enzymes which returned to normal after the mother stopped co-amoxiclav—a causal relationship to co-amoxiclav and the elevated liver enzymes was not confirmed [23].

In another small study in which breastfeeding mothers taking ampicillin monitored their infants for various side-effects, no statistical differences were seen between the infants in the control group (no antibiotic exposure) and those exposed to ampicillin [24].

Theoretically, if the infant has been sensitised to an antibiotic *in utero*, they are likely to exhibit allergic reactions to subsequent exposure, even the very small quantities seen in breast milk [19]. Therefore, the infant should be monitored for rashes or other signs of allergy [2]. However, this issue remains to be evaluated further.

Antibiotic exposure via the breast milk can also alter and interfere with microbiological cultures in infants who are being investigated for sepsis [4, 22].

Bactericidal effect or resistance of cephalosporins and penicillins in the breast-fed infant?

The significance of bactericidal concentrations in breast milk remains to be evaluated [1]. Although some studies have shown that the concentration of the antibiotic in milk could be bactericidal for some organisms, these concentrations are unlikely to correspond to the required bactericidal levels in the infant [1]. Another study has shown that the concentrations of the antibiotic in milk are not bactericidal [21].

There are no studies which discuss whether the concentrations the infant is exposed to are enough to cause bacterial resistance to the antibiotic.

Summary

- Penicillins and cephalosporins are the antibiotics of choice during breast-feeding [25]. Wherever possible, it is preferable to use antibiotics which have been used clinically for longer, for example the second generation cephalosporins [25]. Where necessary, other antibiotics can be chosen, but they should always be used at the lowest possible dose [24].
- Although the concentrations of penicillins and cephalosporins in breast milk are too low to have a bactericidal effect in the infant and too low to cause systemic side-effects, the infant may still experience adverse effects by alteration of the oral and gut flora. This may theoretically lead to oral candida infections and diarrhoea.
- If an infant has been sensitised to a particular antibiotic *in utero,* or as a result of direct therapeutic administration to the infant,, exposure to the antibiotic via breast milk may cause an allergic reaction, no matter how low the breast milk concentration.

- Therefore, although penicillins and cephalosporins are considered compatible with breastfeeding, the infant should still be monitored for adverse effects.
- *Many decisions on the management of infectious diseases in breastfeeding mothers will need to be taken on a case-by-case basis, particularly if there are unusual circumstances e.g. prematurity, infant morbidity, requirement for high doses, or concurrent medication. In these instances, further advice can be sought from the U.K. Drugs in Lactation Advisory Service provided jointly by the Trent Medicines Information Service and the West Midlands Medicines Information Service (Telephone: 0116 258 6491 or 0121 311 1974).*

Limitations

- Evidence relating to the side-effects in infants caused by exposure to penicillins and cephalosporins via the breast milk is limited and has yet to be established. In particular, there is inadequate data to establish if an infant can become hypersensitive to an antibiotic following exposure via the breast milk.
- Many studies investigate the concentration of a drug in breast milk based on a single exposure to that drug. Multiple exposure, as would be seen in clinical practice, is under-investigated. Such exposure could therefore lead to accumulation of the drug in breast milk.
- There is no information available to adequately assess whether the concentrations of the antibiotics in breast milk are enough for the infant to develop bacterial resistance.
- The information above refers to full term and healthy infants only.

References

1. Kafetzis DA, Siafas CA, Georgakopoulos PA et al. Passage of cephalosporins and amoxicillin into the breast milk. Acta Paediatr Scand 1981; 70: 285–288.
2. Lee A, Inch S, and Finnigan D. Therapeutics in Pregnancy and Lactation. Oxon: Radcliffe Medical Press, 2000.
3. Ito S, Blajchman A, Stephenson M et al. Prosepctive follow-up of adverse reactions in breast-fed infants exposed to maternal medication. Am J Obstet Gynecol 1993; 168: 1393–9.
4. Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. 10th edition [on-line]. Philadelphia, PA. Lippincott Williams & Wilkins [updates included quarterly]. Available from www.inkling.com/read [accessed on-line 30/10/15].
5. Drugs and Lactation Database (LactMed). Toxnet Toxicology Data Network, United States National Library of Medicine. Available from http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT [accessed on-line 30/10/15].
6. Hale TW. Medications and Mother's Milk. Online edition. Amarillo, TX. Pharmasoft Publishing. Available at www.medsmilk.com [accessed on-line 30/10/15].
7. Negaban 1g powder for solution for injection/infusion—Summary of Product Characteristics. Eumedica. Revised April 2011. Available at www.medicines.org.uk .[accessed on-line 30/10/2015].
8. Klasco RK (Ed): DRUGDEX® System. Thomson Micromedex (Greenwood Village, Colorado, USA, updated periodically). Available at: www.thomsonhc.com [accessed on-line 30/10/15].
9. Timentin 0.8 G, 1.6 G, 3.2 G —Summary of Product Characteristics. Glaxo Smith Kline. Revised March 2014. Available at www.medicines.org.uk .[accessed on-line 30/10/2015].
10. Pivmecillinam 200mg film-coated tablets—Summary of Product Characteristics. Aurobindo Pharma - Milpharm. Revised October 2015. Available at www.medicines.org.uk .[accessed on-line 11/11/2015].
11. Bar-Oz B, Bulkowstein M, Benyamini L et al. Use of antibiotic and analgesic drugs during lactation. Drug Saf 2003; 26: 925–935.
12. Bourget P, Quinquis-Desmaris V, and Fernandez H. Ceftriaxone distribution and protein binding between maternal blood and milk postpartum. Ann Pharmacother 1993; 27: 294–7.
13. Kafetzis DA, Brater DC, Fanourgakis JE, et al. Ceftriaxone distribution between maternal blood and fetal blood and tissues at parturition and between blood and milk postpartum. Antimicrob Agents Chemother 1983; 23: 870–873.
14. Blanco JD, Jorgensen JH, and Castaneda YS, et al. Ceftazidime levels in human breast milk. Antimicrob Agents Chemother 1983; 23; 479–480.
15. Suprax Tablets 200mg—Summary of Product Characteristics. Sanofi. Revised January 2015. Available at www.medicines.org.uk [accessed on-line 30/10/15].
16. Zinforo 600 mg powder for concentrate for solution for infusion—Summary of Product Characteristics. AstraZeneca. Revised September 2015. Available at www.medicines.org.uk [accessed on-line 30/10/15].
17. Cefpodoxime 200mg tablets—Summary of Product Chracteristics. Aurobindo Pharma-Milpharm. Revised July 2015. Available at www.medicines.org.uk [accessed on-line 30/10/15].

18. Sweetman SC (ed), Martindale: The Complete Drug Reference, updated periodically. London: Pharmaceutical Press. Available from www.medicinescomplete.com [accessed on-line 04/11/15].
19. Matheson I, Samseth M, Loberg R, et al. Milk transfer of phenoxymethylpenicillin during puerperal mastitis. Br J Clin Pharmacol 1988; 25: 33–40.
20. Ilet KF, Hackett LP, Ingle B et al. Transfer of probenicid and cephalexin into breast milk. Ann Pharmacother 2006; 40: 986–989.
21. Kafetzis DA, Lazarides CV, Siafas CA, et al. Transfer of cefotaxime in human milk and from mother to foetus. J Antimicrob Chemother 1980; 6 (Suppl A): 135–141.
22. Mathew JL. Effect of maternal antibiotics on breast feeding infants. Postgrad Med J 2004; 80: 196–200.
23. Benyamini L, Merlob P, Stahl B et al. The safety of amoxicillin/clavulanic acid and cefuroxime during lactation. Ther Drug Monit 2005; 27: 499–502.
24. Campbell AC, McElnay JC Passmore CM. The excretion of ampicillin in breast milk and its effects on the suckling infant. J Pediatr Gastroenterol Nutr 1988; 7: 568.
25. Schaefer C, Peters P, Miller RK. Drugs during pregnancy and lactation. 3rd ed. London: Elsevier, 2015.

Quality Assurance

Prepared by
Laura Kearney, Trent Medicines Information Service, Leicester Royal Infirmary

Date Prepared
11 November 2015

Checked by
Vanessa Chapman, Trent Medicines Information Service, Leicester Royal Infirmary

Date of check
3 December 2015

Search strategy

- Embase and Medline
- UKDILAS database: www.ukmi.nhs.uk/ukdilas
- UKDILAS resources
- Manufacturers (eMC)