MEDICATION USE IN BREASTFEEDING WOMEN

Many medicines are safe for use by breastfeeding women
The risks and benefits of each medicine should be evaluated for the individual mother and the infant
Caution is required when prescribing to mothers with premature or low birth weight infants, particularly when multiple medicines are required
Safety information in standard sources may be limited and is often conflicting; the NMIC has access to specialist lactation sources and is well placed to answer any enquiries

INTRODUCTION

The importance of breastfeeding for both infants and mothers is well known. Exclusive breastfeeding for the first 6 months of life, followed by continued breastfeeding while complementary foods are introduced until the child is 2 years of age and beyond, is recommended by many national and international agencies, including the Department of Health and Children. Breastfeeding is particularly beneficial for pre-term infants. The incidence of breastfeeding in Ireland has increased in recent years, even though Ireland has one of the lowest breastfeeding rates in Europe. Figures from 2010 found that 46% of infants in Ireland were exclusively breastfed in the first 48 hours, compared to 81% in the United Kingdom and 87% in Poland. During the post-partum period, women frequently need medical care and may require medications for conditions such as infection, depression and pain. Women with chronic medical conditions may require medication during this period. Evidence suggests that >50% of all breastfeeding women use some medicines. It is generally agreed that all medications transfer into human milk to some extent, however it is usually quite low (<10% of the maternal dose) and is seldom clinically relevant for the infant. The decision to use pharmacological therapy in breastfeeding women must balance the benefits of therapy for the mother and continuing breastfeeding for the mother and infant against the potential risk of drug exposure to the infant. There is a limited number of agents that are absolutely contraindicated in breastfeeding women including anti-neoplastic agents and radioactive pharmaceuticals. However, it can be challenging to determine which medications are suitable for breastfeeding women as different information sources can give conflicting recommendations. Usually there are more data on older medicines, which are generally preferred. This bulletin outlines the points to consider when prescribing for a breastfeeding woman, and addresses some of the frequently asked questions (FAQs) received by the National Medicines Information Centre (NMIC) on this topic.

GENERAL CONSIDERATIONS

Drug, infant and maternal factors are considered when assessing the risks and benefits of prescribing to breastfeeding women.

Drug Factors: The maternal plasma concentration of a drug is one of the most important factors in the exposure of a breastfed infant to the drug; most medicines enter human milk by passive diffusion. As the maternal plasma level of a drug increases, the breast milk level increases, and subsequently falls as the plasma level falls. Drugs with long half-lives are more likely to accumulate in human milk. Exposure of the infant to a drug can be reduced by avoiding breastfeeding at the time the drug reaches its maximum concentration in the plasma and by using drugs with shorter half-lives. Drugs with high molecular weights (e.g. heparins, interferons and insulin) are less likely to pass into breast milk. Highly lipid soluble drugs penetrate into breast milk in higher concentrations than those that are not. Drugs which are highly protein bound (e.g. warfarin) have low levels in breast milk. Breast milk is more acidic than plasma, therefore drugs with a high pH (e.g. barbiturates) may concentrate more in breast milk. Drugs with a low oral bioavailability (e.g. omeprazole) do not enter the infant’s bloodstream via breast milk, however they may affect the gastrointestinal tract causing diarrhoea, constipation and occasionally pseudomembranous colitis. It is important to consider that medications which are lipid soluble and centrally active that produce sedation or other neuroleptic effects in the mother, may produce similar effects in the infant. One of the more popular methods for assessing infant risk is to estimate the Relative Infant Dose (RID), which is available for many drugs. It provides a standardised method of relating the infant’s dose via breast milk to the mother’s dose.
Topical and vaginal formulations of metronidazole are suitable to use in breastfeeding women as maternal macrolides (particularly erythromycin) and pyloric stenosis.

Low levels of the macrolides erythromycin (RID 2%), clarithromycin (RID 2%) and azithromycin (RID 6%) are found in breast milk and are considered by many sources as compatible with breastfeeding (RID 6%) are found in breast milk and are considered by many sources as compatible with breastfeeding. Macrolides: Low levels of the macrolides erythromycin (RID 2%), clarithromycin (RID 2%) and azithromycin (RID 6%) are found in breast milk and are considered by many sources as compatible with breastfeeding women. Adverse events associated with drug exposure via lactation occur most often in infants < 2 months and rarely in infants > 6 months. Newborns and especially premature infants are more at risk due to immaturity of the liver and kidneys and subsequent clearance of some medications; the competency of barriers such as the blood-brain barrier is another factor. In addition, drug metabolites may also have pharmacological effects and medications with long half-lives may accumulate, particularly in younger or premature newborns. Infants can be categorised as low (age 6-18 months), moderate (full-term infants age 2 weeks – 6 months) or high risk (premature, newborn or infants with medical conditions such as renal impairment) of adverse effects from exposure to medications from breast milk. Older infants typically breastfeed less often; this makes it easier to time the administration of the mother’s dose where appropriate. Also, medications that are considered safe for infants (i.e. those that are used therapeutically in the infant), are generally considered to be low risk when given to the breastfeeding woman.

**Maternal factors** to consider include the severity of the condition being treated and the risk to the mother of not receiving medication. It is also important to consider whether the medication is required for short-term or long-term use. Medicines penetrate into milk more during the colostrum period (days 0-3 after parturition) than in mature milk, however the absolute dose transmitted is low due to the low volumes of milk produced during this period (30-100 mL/day). Mature milk volume is usually highest in the early morning while the fat content of milk is usually highest in the late morning. For some medicines e.g. once-daily short acting medicines, mothers are advised to breastfeed first, and then take their medicine, thereby decreasing the likelihood of overexposing the infant to the medicine.

In summary, many medicines are safe to use while breastfeeding; table 1 summarises the key points about medicine use in breastfeeding.

**FREQUENTLY ASKED QUESTIONS ON THE SAFETY OF MEDICINES IN BREASTFEEDING WOMEN**

Many medicines are not authorised for use in breastfeeding, however safety information for most medicines is available. The NMIC frequently receives enquiries on the use of medicines in breastfeeding women from healthcare professionals. The resources that the NMIC use include the Summary of Product Characteristics, standard medicines information sources, specialist lactation sources and the recent literature. The remainder of this bulletin will discuss some FAQs on the use of medicines in breastfeeding women. For additional information on these FAQs or other therapeutic areas, please contact the NMIC.

**Use of antibiotics in breastfeeding women**

Post-partum women may require treatment with antibiotics for conditions such as mastitis, endometritis and urinary tract infection.

**Penicillins and cephalosporins**: Penicillins (RID 1%) and cephalosporins (RID 4%) have been well studied in breastfeeding and are considered safe in breastfeeding women. They are frequently used for the treatment of mastitis. There is less information available with third generation cephalosporins. Adverse events reported in exposed infants include diarrhoea and oral candida infection.

**Macrolides**: Low levels of the macrolides erythromycin (RID 2%), clarithromycin (RID 2%) and azithromycin (RID 6%) are found in breast milk and are considered by many sources as compatible with breastfeeding women. There are some epidemiological data to suggest an association between infants exposed to macrolides (particularly erythromycin) and pyloric stenosis. Metronidazole (RID 13%) is used to treat specific infections in premature neonates, infants and children. Topical and vaginal formulations of metronidazole are suitable to use in breastfeeding women as maternal...
systemic absorption is limited. Breastfed infants receive metronidazole in doses less than those used to treat infections in infants when metronidazole is given orally or intravenously to breastfeeding women. Historically, there has been a concern regarding infant exposure to metronidazole via breast milk, due to the findings of genotoxicity and carcinogenicity in animals, however the relevance of this is unknown in humans. In addition, the routine clinical use of metronidazole suggests that the previous concerns were largely overstated and that short-course maternal metronidazole use in breastfeeding should be well tolerated without the need to discontinue breastfeeding. Some sources do recommend discontinuing breastfeeding for 12-24 hours after oral single-dose (2g) maternal metronidazole treatment. Case reports of candida infections and diarrhoea have been reported in infants exposed to metronidazole.

Tetracyclines: Some sources state that tetracyclines are contraindicated in breastfeeding women due to concerns regarding teeth discoloration or tetracycline bone deposition in the infant. However other sources advise that if other antibiotics are not appropriate, short term use (<3 weeks) may be acceptable, as the transfer into breast milk is low and absorption is inhibited by the calcium in the breast milk (especially for the older tetracyclines). Quinolones: Many sources do not recommend quinolones for breastfeeding women; their use in animal studies has been associated with arthropathy. Short-term use of quinolones may be acceptable (calcium in the milk may interfere with absorption), however it is preferable to use an alternative antibiotic if possible. Quinolones should be avoided in breastfeeding mothers of infants with G6PD deficiency and used with caution where the infant has epilepsy.

Practice point: Breastfed infants exposed to antibiotics via breast milk should be monitored for changes to gastrointestinal flora (e.g. diarrhoea, vomiting, oral candidiasis) and allergic reaction.

Use of antifungals in breastfeeding women

Women frequently require antifungal therapy in the post-partum period. The use of topical antifungal therapy such as clotrimazole and miconazole is considered acceptable in breastfeeding women, as there is minimal maternal absorption. Topical use of ketoconazole and terbinafine if required is considered low risk but should be avoided on the nipples and breast. If local treatment is ineffective; oral fluconazole is the preferred systemic antifungal which is considered acceptable for short-term use. Even though the RID of fluconazole has been estimated to be up to 22%, the amounts excreted in breast milk are less than the neonatal fluconazole dose. One source advises that it should be taken at night after the last breastfeed. The exposed infant should be monitored for gastrointestinal disturbances.

Use of antidepressants in breastfeeding women

Post-partum depression affects up to 20% of mothers and can have devastating effects on the mother-infant relationship if left untreated. Not all women with depression require pharmacotherapy; for those who do antidepressants are an effective option. Most antidepressants are excreted in low concentrations in breast milk. Currently there is little evidence to suggest that exposure to antidepressants through breastfeeding has any serious effects in infants even though long-term neuro-developmental effects have not been adequately studied. Advice from secondary psychiatric care should be considered before starting antidepressants in breastfeeding women. The choice of the antidepressant should be based on clinical factors, including previous effective treatments. The antidepressant should be started at the lowest effective dose and increased slowly. The clinical condition of the mother and infant should be monitored, particularly for low birth weight and premature infants.

Selective serotonin reuptake inhibitors: (SSRIs) are the most frequently prescribed antidepressants and are the class for which the most evidence exists. SSRIs have relatively long half-lives and drug accumulation can occur in neonates and young infants. Many sources recommend sertraline (RID 2%) and paroxetine (3%) as the preferred first choice SSRIs to use during breastfeeding, compared to other SSRIs they have shorter half-lives and lower passage into breast milk. Adverse events associated with infant exposure to SSRIs via breast milk include irritability, decreased feeding and sleep problems. These are more often reported after exposure to fluoxetine (RID 2-15%) (which has a half-life of up to 6 days) and citalopram (RID 4%), both of which are best avoided.

Tricyclic antidepressants (TCAs) are prescribed less often than SSRIs due to concerns about maternal toxicity. TCAs except doxepin can be used to treat depression in breastfeeding women, however the non-sedating TCAs such as nortriptyline or imipramine (not licensed in Ireland) are the preferred TCAs. Other antidepressants: There are less data available on other antidepressants such as venlafaxine (RID 8%), duloxetine (1%) and mirtazapine (RID 6%), which are generally not recommended as first choice antidepressants.

Practice points: If a woman is already on an effective antidepressant, prescribers should continue with that antidepressant rather than switching to an alternative. All infants exposed to antidepressants in breast milk should be monitored for drowsiness, poor feeding, irritability, or behavioural effects.

Use of analgesics in breastfeeding women

Analgesics are one of the most commonly used medications while breastfeeding. Paracetamol is regarded as an acceptable analgesic to use in breastfeeding women. The amount of oral paracetamol in breast milk (RID 9%) is much less than doses given to infants. Some reports suggest that exposure to paracetamol in the first year of life is a risk factor for asthma, but a causal link has not been established.
Non-steroidal anti-inflammatory drugs (NSAIDs) pass into breastmilk in small amounts and are generally considered compatible with breastfeeding. Ibuprofen, which is frequently prescribed for infants and has a short half-life (RID 1%), is preferred to other NSAIDs, such as naproxen (RID 3%), which has a long half-life (there has been a reported case of bleeding and anaemia in an infant exposed to naproxen). 

Aspirin (RID 10.5%) is best avoided as an analgesic in breastfeeding women; aspirin use in children has been associated with Reye’s syndrome. Some experts recommend that low-dose aspirin (75-162mg per day) may be used as antithrombotic therapy in breastfeeding women where indicated; breastfeeding should be avoided for up to 2 hours after administration to reduce the antithrombotic effect in the infant.

Opioids: Maternal use of opioid analgesics during breastfeeding can cause infant drowsiness and central nervous system depression; non-opioids should be used when possible. Newborn infants in particular are sensitive to the effects of opioids, as they have reduced clearance of opioids up to the age of 6 months. If required, opioids should be used with caution in breastfeeding women and at the lowest dose for the shortest duration possible. The infant should be closely monitored for sedation and other adverse effects (e.g. feeding difficulties). Codeine (RID 8%), a mild opioid, is contraindicated in breastfeeding women. There have been adverse events (including apnoea and death) reported in codeine-exposed breastfed infants, particularly in breastfeeding women who are ultra-rapid metabolisers of codeine. Tramadol (RID 3%) is considered by some experts as acceptable to use short-term in breastfeeding women, exposed infants should be monitored for sedation and feeding difficulties.

Use of antihistamines in breastfeeding women

Antihistamines may be required by breastfeeding women for symptoms including pruritus and allergic rhinitis. First generation antihistamines (chlorphenamine and diphenhydramine) should be used with caution as they easily cross the blood-brain barrier and are known for their sedating effects. Second generation non-sedating antihistamines such as cetirizine and loratadine do not cross the blood-brain barrier as readily, and are preferred. Infants should be monitored for signs of excessive irritability, jitteriness and drowsiness.

Use of antihypertensives in breastfeeding women

In the postnatal period some breastfeeding women may require antihypertensive medication. Many of these medications are suitable to use in breastfeeding, however there are some medications which are preferred. Beta (β) blockers: Various sources recommend that propranolol (RID 0.3%), labetalol (RID 0.6%) and metoprolol (RID 1%) are the preferred β blockers for breastfeeding women. Other β blockers such as atenolol which has low protein binding and is primarily renally excreted, have been associated with adverse effects in infants and should be avoided. Monitoring of the infant for hypotension, bradycardia and lethargy is recommended when using β blockers during breastfeeding.

Methyldopa is one of the preferred antihypertensives in breastfeeding women; low levels of methyldopa (RID 0.1-0.4%) are found in breastfed infants and are not expected to cause adverse effects.

Calcium antagonists: Many sources include nifedipine (RID 2.3%), verapamil (RID 0.15%) and diltiazem (RID 0.9%) as the preferred calcium antagonists to use in mothers of breastfed infants. Exposed breastfed infants to calcium antagonists should be observed for bradycardia and hypotension.

Angiotensin converting enzyme inhibitors (ACEIs): The ACEIs with the most amount of data available on breastfeeding are captopril (RID 0.0002%) and enalapril (RID 0.175%), which are amongst the preferred ACEIs in breastfeeding women. They are not recommended however, in the first weeks after delivery due to concerns of profound hypotension, particularly in preterm infants. Infants exposed to ACEIs, should be observed for hypotension.

There is insufficient evidence on the safety of angiotensin receptor blockers (ARBs) in breastfeeding women to recommend their use.

SUMMARY

- The benefits of breastfeeding for mothers and infants are well known and should be promoted
- Many medicines can be used safely in breastfeeding women
- The age and maturity of the infant should be considered when a breastfeeding woman requires pharmacotherapy
- The clinical condition of the mother and infant should be monitored, particularly for low birth weight and premature infants
- There are many sources of information available on the use of medicines in breastfeeding women; the NMIC has access to specialist sources and is happy to answer enquiries on this topic
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